Clinical Trial Protocol

Trial Title:	**PRO**phylaxis for pa**T**i**E**nts at risk of **C**OVID-19 infec**T**ion (PROTECT-V)**.**
Protocol Number:	CCTU0307
EudraCT Number:	2020-004144-28
Investigational Product:	Niclosamide, Ciclesonide, Sotrovimab
Protocol Version:	11
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Protocol Signatures:

I give my approval for the attached protocol entitled ***"PROphylaxis for paTiEnts at risk of Covid-19 infecTion (PROTECT-V)"*** Dated 05 SEP 2023

Chief Investigator

Name: Dr Rona Smith

Signature: 

Date: 05/09/2023

Site Signatures

I have read the attached protocol entitled **"PROphylaxis for paTiEnts at risk of COVID-19 infecTion. (PROTECT-V)"** dated 05 SEP 2023 and agree to abide by all provisions set forth therein.

I agree to comply with the conditions and principles of Good Clinical Practice as outlined in the European Clinical Trials Directives 2001/20/EC and 2005/28/EC, the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) and any subsequent amendments of the clinical trial regulations, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

Principal Investigator

Name: _____

Signature: _____

Date: _____

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1. ABBREVIATIONS

AE	Adverse Event
AKI	Acute Kidney Injury
ALT	Alanine aminotransferase
AR	Adverse Reaction
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate aminotransferase
CA	Competent Authority
CCTU	Cambridge Clinical Trials Unit
CI	Chief Investigator
CI	Confidence Interval
CKD	Chronic Kidney Disease
Con Med	Concomitant Medication
COVID-19	Coronavirus Induced Disease 2019
CRF	Case Report Form (when used for data collection)
CRF	Clinical Research Facility
CTA	Clinical Trial Authorisation
CTAP	Coronavirus Treatment Acceleration Program
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic Case Report Form
FDA	Federal Drug Agency
FSGS	Focal Segmental Glomerular Sclerosis
GP	General Practitioner
GFR	Glomerular Filtration Rate
GCP	Good Clinical Practice
GN	Glomerulonephritis
HCW	Healthcare workers
HD	Haemodialysis
IB	Investigator Brochure
ICF	Informed Consent Form
ICNARC	Intensive Care National Audit and Research Centre
IDMC	Independent Data Monitoring Committee
IgA	Immunoglobulin A
IMP	Investigational Medicinal Product
IRR	Infusion Related Reaction
ITT	Intention to Treat
LFT	Lateral Flow Test
MERS	Middle East Respiratory Syndrome, MERS-coronavirus (MERS-CoV)
MHRA	Medicines and Healthcare products Regulatory Agency
NAFLD	Non alcoholic fatty liver disease
NASH	Non alcoholic steatohepatitis
NIHR	National Institute of Health Research
ONS	Office National Statistics

PCR	Polymerase chain reaction
PHE	Public Health England
PI	Principle Investigator
PID	Patient Identifiable Data
PIS	Patient Information Sheet
PK	Pharmacokinetic
PTO	PROTECT-V Trial Office
R&D	Research and Development
RA	Regulatory Agency
RCT	Randomised Control Trial
REC	Research Ethics Committee
RRT	Renal Replacement Therapy
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome coronavirus 2
SD	Standard Deviation
SKP2	S--Phase Kinase Associated Protein 2
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TNF	Tumour Necrosis Factor
TPM	Trial Procedure Manual
TSC	Trial Steering Committee
UKHSA	UK Health Security Agency
WHO	World Health Organisation
WOCBP	Woman of child bearing potential

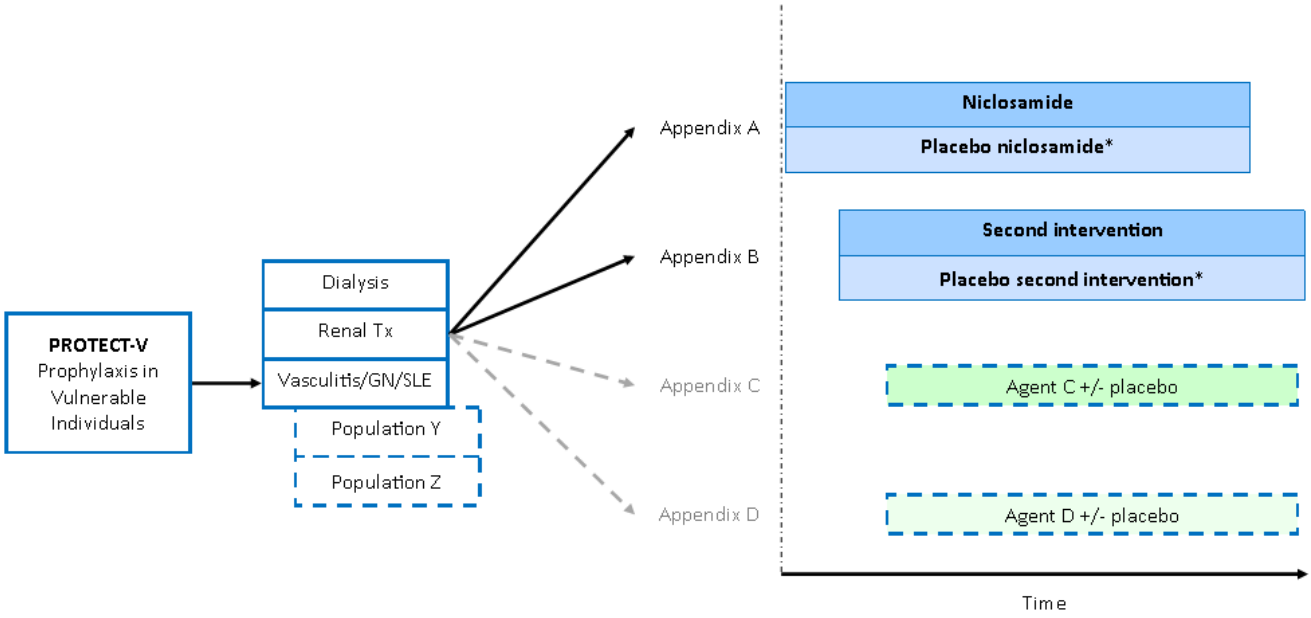
2. INTRODUCTION

PROTECT-V is a platform trial to test prophylactic interventions against SARS-CoV2 infection in vulnerable patient populations at particularly high risk of COVID-19 and its complications, seeking to identify treatments that either might prevent the disease from occurring or may reduce the number of cases where the disease becomes serious or life-threatening. In PROTECT-V, multiple agents can be evaluated on the same platform across multiple vulnerable populations, with the option of adding additional treatments at later time points as these become available. The expectation is for as many sites as possible to recruit to all available trial treatments at any time, however, the platform structure and randomisation/data collection systems allow sites to open the trial treatment arms according to their capacity.

The trial commenced with the first intervention, nasal niclosamide and matched placebo from February 2021.

Potential future prophylactic agents will be introduced either through the CTAP pathway, or if identified by the PROTECT-V study investigators, which will be discussed with the Prophylaxis Taskforce. PROTECT-V is also able to restrict interventions to particular subpopulations or patient groups, as well as adding additional vulnerable patient groups at a later stage. The trial started by enrolling vulnerable patients with kidney or autoimmune diseases, including patients in receipt of dialysis, kidney transplant recipients, individuals with vasculitis and glomerular disease receiving immunosuppression.

Study Schema



*** Individuals will be randomised 1:1 niclosamide placebo at the start of the study. When the second intervention is added, the placebo groups will be merged, and therefore patients will be randomised 2:1 active either active treatment:matching placebo**

3. BACKGROUND AND RATIONALE

3.1. Setting

In December 2019, a respiratory disease causing severe respiratory tract infection a novel coronavirus-induced disease (COVID-19) emerged in Wuhan, China.[1] A month later the Chinese Centre for Disease Control and Prevention identified a new beta-coronavirus (SARS coronavirus 2, or SARS-CoV-2) as the aetiological agent and the disease now called COVID-19. COVID-19 was declared a global pandemic by the WHO on 11th March 2020. To date, there have been > 157 million cases worldwide with 3.27 million deaths (WHO figures 9th May 2021).

3.2. Clinical Course and current treatment options

The clinical manifestations of COVID-19 range from asymptomatic infection to mild, upper respiratory tract infections to severe viral pneumonia with associated respiratory failure and death. Some patients will also go on to develop multi-organ failure, with kidney, cardiac and neurological complications of SARS-CoV-2. The frequency of severe disease in hospitalised patients can be as high as 30%. Many potential treatments are being assessed in randomised treatment trials. The UK RECOVERY trial has demonstrated that dexamethasone reduced deaths by one-third in ventilated patients (rate ratio 0.65 [95% confidence interval 0.48 to 0.88]; p=0.0003) and by one fifth in other patients receiving oxygen only (0.80 [0.67 to 0.96]; p=0.0021). There was no benefit in patients not requiring ventilatory support. The ACCT-1 trial showed a shorter recovery time 11 days (95%CI, 9 to 12) versus 15 days

(95% CI, 13 to 19) in remdesivir-treated patients. A number of other treatment options have demonstrated no benefit, including hydroxychloroquine and lopinavir-ritonavir.

In contrast, there are no drugs proven to *prevent* COVID-19 or to reduce the severity of illness if given as prophylaxis. Although vaccines are now available, there remains a need for other prophylactic agents until vaccine use becomes widespread globally and effectiveness and durability is established, particularly in immunocompromised individuals for whom vaccine responses may be suboptimal. Efforts are underway to repurpose established drugs with well understood drug interactions and safety profiles.

3.3. Rationale for a trial

A considerable number of trials have been established at great speed in the wake of the global SARS-CoV-2 outbreak. However, most assess treatments for established COVID-19.. Boulware and colleagues evaluated hydroxychloroquine versus placebo after known exposure to a confirmed case of COVID-19.[2] This trial failed to show benefit from hydroxychloroquine, but the trial had serious methodological limitations, provided prophylaxis post-exposure and for a short duration, and excluded patients with significant kidney disease. A proposal to conduct a pre-exposure prophylaxis trial with hydroxychloroquine in patients with chronic kidney disease (CKD) receiving dialysis was rejected by the UK MHRA on safety grounds. Headline results from the PROVENT trial, published July 2021, a Phase III, randomised, double-blind, placebo-controlled, multi-centre trial assessing the safety and efficacy of a single IM 300mg dose of AZD7442 (tixagevimab (AZD8895) and cilgavimab (AZD1061)) compared to placebo for the prevention of COVID-19 met its primary endpoint a statistically significant reduction in the incidence of symptomatic COVID-19.

Several patient groups appear to be vulnerable to COVID-19 infection by virtue of demographics, underlying health conditions or as a consequence of treatments for these conditions, and they are at exceptionally high risk of adverse outcomes. Such vulnerable patients include those with kidney disease requiring dialysis, in receipt of a kidney transplant, or with auto-immune diseases that might affect kidney function and require immunosuppression (e.g. vasculitis and glomerular diseases). Despite the introduction of widespread vaccination, there remains a need for antigen independent prophylactic agents. No vaccine is completely effective, new variants of SARS CoV-2 are emerging, and many vulnerable individuals are immunocompromised, either as a result of underlying disease or treatments, and are known to mount a suboptimal response to vaccination against viruses. Individuals with kidney disease – those requiring dialysis, in receipt of a kidney transplant, or with auto-immune diseases that might affect kidney function and require immunosuppression (e.g. vasculitis and glomerular diseases) - are vulnerable to COVID-19 and at high risk of adverse outcomes. These patient groups are also known to mount a sub-optimal responses to vaccination against viruses[3-5.]

Dialysis patients typically need to attend their dialysis centre 3 times per week for at least 4 hours at a time and travel to dialysis centres by ambulance, car or taxi. It is impossible for them to self-isolate. Further, patients receiving dialysis may be less likely to benefit from admission to intensive care due to their comorbidity and the perceived prognostically deleterious impact of end-stage kidney disease. Those dialysis patients contracting COVID-19 have a 26% risk of death from the disease. To date, 11% of the UK's in-centre dialysis population has contracted COVID-19.

Kidney transplant recipients are immunosuppressed and are at increased risk of infections (including viruses) with attendant morbidity.[3] Chronic Kidney Disease is itself recognised as a risk factor for severe infections. The combination of immunosuppression and reduced GFR render kidney transplant recipients at particular risk of COVID-19 since regular healthcare contact is imperative for most patients. Most kidney transplant recipients have been shielding during the pandemic to date, but the need for monitoring and easing of shielding advice make exposure to COVID-19 a real risk. There have already been 1129 confirmed cases among transplant patients in England despite shielding (UK Renal Registry report 28 July 2021) with 158 deaths (14% case fatality rate).

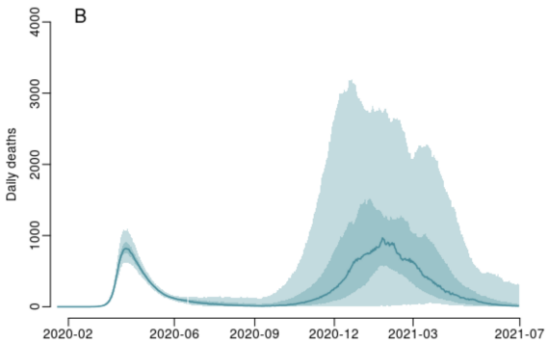
Vasculitis patients suffer with serious relapsing remitting auto-immune disease that results in the requirement for a considerable burden of immunosuppression. The disease itself often results in organ damage, particularly renal and pulmonary damage, and individuals have significant comorbidity. Whilst individual vasculitis

syndromes remain generally rare, the pool of vasculitides represent a considerable patient population thought to be at high risk of contracting COVID-19 leading to severe disease, and even death. There is a paucity of data on the occurrence of COVID-19 in this patient population to date, but of the 64 cases reported by mid June, 17 have died, equating to a 27% case fatality rate.

Despite vaccination against SARS CoV-2, and the third dose and booster vaccination campaign, sub-optimal vaccine response and vulnerability to Covid-19 infection remains a major issue in clinically extremely vulnerable individuals, including immunocompromised renal patients. In July 2021, a synthesised review of 35 studies looking at vaccine response in renal patients demonstrated 89% (85-91%) response in dialysis patients, and 35% (29-42%) in individuals with a renal transplant after two doses of SARS CoV-2 vaccine.[6] The literature on vaccine response in individuals with autoimmune disease is more complicated in view of disease and treatment heterogeneity, but responses are also sub-optimal to healthy individuals. Data on the effect of third doses in the immunocompromised patient population is emerging, and approximately 50% of those individuals not protected after 2 doses mount a response after an additional dose.[7,8] It is important to note that the majority of studies report absolute antibody titres, which does not indicate the functionality and neutralising capacity of the antibodies. In a study of 178 dialysis patients in the UK, AZD1222 alone in sero-naive individuals induces suboptimal neutralising antibody titres against all variants of concern (VOCs), including the delta variant that is dominant globally.[9] As such, a greater proportion of the patient population other than those without detectable antibodies remain highly vulnerable to SARS CoV-2 infection. Furthermore, the occurrence of breakthrough infections, with some studies reporting that immunocompromised persons account for a high proportion (≥40%) of infections among fully vaccinated hospitalized persons is further evidence of sub-optimal vaccine response.[10,11]

Addition of further vulnerable patient cohorts to the PROTECT-V trial platform is possible at later time points as wider networks are established.

The urgent need for interventions that provide effective prophylaxis against SARS-CoV2 is emphasised by a recent report commissioned by the UK Government projected 119,000 in-hospital deaths from COVID19 between September 2020 and June 2021 (95%CI 24,500 - 251,000).[12] This suggests a 'second wave' could be considerably worse than the first. Outside the United Kingdom the pandemic is still accelerating. An effective prophylactic treatment could save thousands of lives.



3.4. A pre-exposure prophylaxis trial in vulnerable populations

PROTECT-V aims to enrol patients at particularly high risk of COVID-19 and its complications, seeking to test whether intranasal niclosamide might prevent the disease from occurring. The PROTECT-V trial platform brings greater efficiency, running multiple sub-trials within one master protocol. The core components of the PROTECT-V trial platform include:

- Central coordination trial management team
- Single data system, with linkage to UKHSA (formerly PHE), ONS, HES and ICNARC datasets
- Sponsor and regulatory oversight
- Single contract with participating sites for multiple interventions/populations
- Statistical efficiency – depending on specific interventions/populations, it may be possible to use Bayesian analysis methods that allow adaptive borrowing of information across populations. This will

mean in the case that there is a consistent effect across populations, the trial will have greater power to find significant differences for individual patient groups.

Initially, participants will be randomised 1:1 to niclosamide or matching placebo. Additional treatment arms may be added if further promising treatments become available.

4. DESIGN AND PROCEDURES

4.1. Trial Population

Participants will be enrolled from three vulnerable patient populations: dialysis patients, kidney transplant recipients and those with vasculitis or other auto-immune kidney disease such as systemic lupus erythematosus (SLE) or glomerulonephritis (GN).

The provisional distribution between trial populations will be 1:1:1 (dialysis:transplant:vasculitis/SLE/GN). No capping for a specific subgroup will be implemented but it is expected to have a minimum of 150 patients in each subgroup per arm, or 300 patients per intervention plus placebo. However, the proportion of the total trial population represented by each subgroup may be adjusted depending on the event rate of the primary outcome measure within each patient group. The subgroup-specific event rate will be monitored monthly.

4.2. Eligibility

4.2.1. Inclusion Criteria

To be included in the trial the participant must:

- Be aged 18 years or older
- Have given written informed consent
- Be a member of one of the following vulnerable patients populations
  - ***Dialysis*** – including in centre haemodialysis, home haemodialysis and peritoneal dialysis
  - ***Kidney transplant*** receiving at least one of the immunosuppressive medications listed in the table below
  - ***Vasculitis*** (according to Chapel Hill Consensus Conference 2012 definitions) or systemic lupus erythematosus (SLE) receiving at least one of the immunosuppressive medications listed in the table below
  - ***Glomerulonephritis**** receiving at least one of the immunosuppressive medications listed in the table below

* Glomerulonephritis includes prior histological confirmation of any of the following conditions - minimal change nephropathy, focal segmental glomerulosclerosis (FSGS), IgA nephropathy, primary membranous nephropathy, membranoproliferative glomerulonephritis or lupus nephritis.

Inclusion criteria	**Dialysis**	**Kidney Transplant OR Vasculitis OR Glomerulonephritis or SLE** *receiving* ***at least one*** *of the following immunosuppressive medications*
Aged 18 years or older	✓	✓
Written Consent	✓	✓
In-centre haemodialysis or home haemodialysis or peritoneal dialysis	✓	-
Ciclosporin	-	✓
Tacrolimus	-	✓
Azathioprine	-	✓
Mycophenolate Mofetil or Mycophenolic Acid	-	✓
Belatacept	-	✓
Methotrexate	-	✓
Tocilizumab	-	✓
Abatacept	-	✓
Leflunomide	-	✓
Prednisolone (current dose) > 20mg daily for 8 weeks	-	✓
Anti-TNF (infliximab, adalimumab, etanercept)		✓
Belimumab		✓
Cyclophosphamide (within the last 6 months)	-	✓
Rituximab (in the last 12 months) or Rituximab in the last 5 years and IgG level <5g/l	-	✓
Alemtuzumab (in the last 12 months)	-	✓
Sirolimus		✓

4.2.2. Exclusion Criteria

The presence of any of the following will preclude participant inclusion:

- Inability to provide informed consent or to comply with trial procedures
- COVID-19 at time of enrolment – either positive SARS CoV-2 swab (PCR or lateral flow test; LFT) or symptoms highly suggestive of COVID-19 infection
- Allergy or hypersensitivity to any of the active IMPs, or to any of the excipients used
- Pregnant, trying to conceive, unwilling to use contraception or breastfeeding
- Current participation in another interventional prophylactic or vaccine trial* against COVID-19.

***Patients remain eligible for enrolment if they have received SARS-COV-2 vaccination as part of routine care.**

Additional exclusion criteria specifically related to individual intervention or IMPs will be listed in the relevant appendices.

4.3. Participant Identification and Consent

Potential participants can be identified via a number of avenues including advertisements, word of mouth, trial specific invitation letter, face to face and existing cohort studies.

- The PROTECT-V website will contain a video where one of the central trial physicians explains the study.
- Additional information, including the detailed Participant Information Sheets will be available from the local site study team and on the study website.

Consent will be obtained by the Principal Investigator at each trial site or by a suitably qualified and delegated health professional and member of the research team at each site.

- Potential participants will be given a copy of the Patient Information Sheet to read through thoroughly, including the opportunity to take it home and discuss the trial with relatives/friends and other medical professional eg GP.
- The Principal investigator or a suitably qualified and delegated health professional will explain the aims, methods, anticipated benefits, potential hazards and risk benefit balance of the intervention.
- The participant will be allowed as much time as they need to consider all the information.
- The Investigator will explain that participants are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason.
- No trial specific procedures will be conducted prior to the participant giving consent by signing the Consent form.
- Participants will be given a copy of their signed PIS and Informed Consent form to retain at home for future reference. Contact details for the local study team are included in the PIS should the participant have any further questions.

If further safety information becomes available, the PIS and Informed Consent Form (ICF) will be reviewed and updated and submitted to the REC for approval. All participants that are actively enrolled in the study

will be informed of the updated information and will be required to sign the revised copy of the PIS/ICF in order to confirm their wish to continue on the study.

The Informed Consent form must be approved by the REC and must be in compliance with GCP, local regulatory requirements and legal requirements. The investigator or designee must ensure that each trial participant is fully informed about the nature and objectives of the trial and possible risks associated with their participation.

4.4. Screening

4.4.1. Screening Assessment – in person consultation

The screening and baseline visits may be readily combined in those patients who agree to participation in the trial. Screening will be conducted at participating sites. Participants attending the screening visit will be given a unique ID number to be used in all CRFs.

All eligible participants who proceed to randomisation will be provided with the trial specific Patient ID Card which includes details of the trial IMPs and contact details of the local study team and Sponsor.

4.5. Randomisation

The PI or suitably qualified and delegated member of the study team will confirm the eligibility of a participant by entering their screening data into the PROTECT-V eCRF web portal. Once the full screening details have been entered and eligibility confirmed, the participant will be randomised.

Randomisation will be carried out using a web-based randomisation system (Sealed Envelope) accessible via password-protected access. Randomisation will be stratified by PROTECT-V disease sub-group, age and site using a stratified block randomisation method.

Immediate allocation of treatment will be performed, with documentation of the decision in a blinded confirmatory email. The notification will state what intervention a participant has been randomised to but not whether active or placebo drug has been assigned. The system will allocate the participant treatment pack code(s) which will relate uniquely to the first supply of IMP. Different treatment pack code(s) for every subsequent order of IMP supply will be allocated by the randomisation system.

4.6. Blinding

PROTECT-V will commence as a double blind placebo controlled study where neither the participant nor clinician will be aware of treatment allocation (whether active or placebo). As additional IMPs are added to the platform, the practicalities of blinding treatment and the need/availability of matched placebo will be evaluated on an individual basis. It may be necessary to restrict the number of IMPs in the platform if blinding is to be maintained. The independent DMC will regularly review the event rate in individual placebo arms to ensure they are comparable. In the participant's information sheet, participants will be clearly informed that they will be blinded until the end of the trial or until a new standard care has been established, whichever occurs first.

4.6.1. Emergency unblinding

Treatment code break and unblinding must only occur in exceptional circumstances when knowledge of the actual treatment is essential for further management of a participant and their safety. If the investigator or

treating clinician deems unblinding to be necessary, the web-based randomisation system can be used by designated local investigators to unblind. The unblinder will not be shown the treatment allocation on-screen. Instead the allocation will be sent by email to the treating clinician and the unblinding notification without allocation should be printed and retained within the Investigator Site File. An email stating that an unblinding has taken place will be automatically sent to the coordination team and CI for oversight purposes.

Unless it is necessary for the safety of the participant, the actual allocation must not be disclosed to the participant or other site personnel, either verbally or by any written correspondence. The CI/PI will also notify the Sponsor and the relevant authorities as necessary.

4.6.1. Schedule of Assessments

Assessment Schedule	Screen/ Baseline visit	Weekly (±3 days) %	2-weekly (±3 days) %	As required	data linkage	Final assessment
Eligibility check	X					
Medical history	X					
Concomitant Medications	X	X	X			
Symptom checker questionnaire$	X	X	X			
SARS-CoV2 PCR or lateral flow test	X			X		
Serum sample for SARS-CoV2 Total Ab assay	X					X
ALT/AST&	X					
Pregnancy test#	X					
SAR/SAE/SUSAR Reporting				X		X
Randomisation	X					
COVID-19 infection					X	

#A pregnancy test is required for WOCBP within 14 days prior to starting trial treatment. Women are considered WOCBP following menarche and until becoming post-menopausal unless permanently sterile (previous hysterectomy, previous bilateral salpingectomy and or oophorectomy). A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A serum pregnancy test is required for all WOCBP participants.

% Weekly for one month and 2-weekly thereafter. Any participant testing positive for SARS-CoV-2 without symptom will be required to complete a COVID-19 symptom assessment at least weekly for 4 weeks after diagnosis, unless hospitalised.

$ Telephone consultation will occur for the first 6 weeks. More details in sections 4.7.1.2 and 4.7.1.3.

[&] Routine ALT/AST tests performed up to 2 week before screening visit will be accepted to assess liver function

Refer for each appendix for additional intervention specific assessments.

4.7. Trial assessments

The following sections describe the schedule of assessments that will be completed by participants. The Schedule of Assessments is shown in the table below. Further details are available in the trial procedures manual (TPM).

PROTECT-V is a pragmatic trial. In view of the challenges of conducting clinical trials in a pandemic, research-specific face-to-face visits as part of their trial participation will be kept to a minimum and aligned with routine clinical follow up whenever possible, as healthcare contact needs to be minimised during the COVID-19 pandemic. Therefore, telephone follow-up and self-reporting of symptoms will be utilised.

Data on the primary endpoint (COVID-19 infection) will be captured on a monthly basis via linkage with UKHSA (formerly PHE), and by direct reporting by sites or by participants. All subsequent assessments will consist of self-completed questionnaires online or post, or through telephone calls from the local trial team. Where possible, data will be collected in real time through linkage with NHS Digital or equivalent, ONS, ICNARC or other routine data sources as necessary. Data on death will be reported by sites or obtained via linkage.

4.7.1. Timing of assessments

4.7.1.1. Screening/Baseline 'visit' 1 (face to face)

- Eligibility
- Randomisation
- Baseline data collection
  - Medical history
  - Current medications
  - Vaccination history
  - Symptom checker self-assessment questionnaires
- Research serum sample collection to detect anti SARS-COV-2 antibodies
- IMP courier delivery arrangements (if necessary) and instruction on IMP administration, storage, dose recording (if necessary).

4.7.1.2. Telephone consultations - weeks 1,2,3, 4 and 6 (±3 days)

Participants will be telephoned by a member of the local research team and asked about the treatment received and symptoms suggestive of potential side effects of the trial treatment or of COVID-19 infection, once every week for the first 4 weeks and then again on the sixth week from the start of the trial treatment. If concerns are raised about potential side effects of the IMP received, the information will be reviewed by the PI and a decision made whether to continue IMP. Participants will be asked to keep a diary of IMP administration (if self-administering) with reasons for any missed doses.

4.7.1.3. Two-Weekly self-reporting - week 8 onwards

Participants will be asked to complete a short questionnaire regarding COVID-19 self-assessment/reporting and potential side effects of the IMP received, once every two weeks during trial conduct via email, in paper form via mail, or via telephone interview. Participants receiving in centre haemodialysis may be assessed during their dialysis sessions. The intention of two-weekly self-reporting is to provide participants with the opportunity to

- indicate any symptoms suggestive of COVID-19 infection,
- side effects of IMP administration,
- report new concomitant medications
- report vaccination against COVID-19

If a participant has not submitted data for a period of approximately 6 weeks, they will be contacted by the local study team for a telephone interview to minimise loss to follow up. Failure to follow up a participant for more than 6 consecutive weeks will halt their trial treatment dispensation until communication has been restored. Failure to follow up a participant for more than 12 consecutive weeks will be considered loss of follow up and conclude their participation in the trial.

Unscheduled assessment – "suspected COVID-19 infection"

Should an individual develop symptoms suggestive of COVID-19 infection, which are listed in the Participant Information Sheet, they must inform the site team of their symptoms so these can be followed up and recorded within the electronic case report form (eCRF) pages. The participant should also take a COVID-19 lateral flow test (LFT), or preferably a PCR test if possible, depending on the tests available via the NHS.

If they encounter any issues with organising the PCR or LFT, the participant should get assistance from the site team. Swabs (PCR or LFT) for COVID-19 (and swabs for influenza – see text below) should be performed as soon as possible after onset of symptoms. As soon as the result of the COVID-19 swab (PCR or LFT) and the influenza swab (if applicable) are known, the participant should inform the site team of these results.

Importantly, if the participant's LFT appears positive, the participant should:

- Take a photograph of the LFT result including the QR code
- Forward this photograph together with the date of the test and Trial ID number to the participating site team.
- Report their LFT result on the government website (currently this is https://www.gov.uk/report-covid19-result.)

The site team should then file a copy of the LFT result in the participants' medical notes and within the ISF. If the LFT shows a positive result, a PCR test may also be arranged if these are available. Participants will also be required to notify their trial physician.

Where possible, if the LFT is negative but the patient has symptoms consistent with COVID-19 infection, the team may then try to arrange a COVID-19 PCR test.

For the niclosamide/matched placebo arm only, patients may also be swabbed for influenza at the same time, if they present to hospital. If this is not done routinely with the COVID-19 test in their area, the influenza test does not have to be completed. Where influenza swabs are available, the participant can self-swab, or ask a relative, or the individual performing the COVID-19 swab (PCR or LFT) may perform the test according to the instructions provided. The swab should be placed in the stamped addressed envelope and placed in a post box immediately to return to local site laboratories for testing.

The individual should contact their local site to

- Inform the site team of their symptoms so that these can be followed up and recorded in the eCRF pages
- Get assistance should they be having difficulty organising a test (PCR or LFT) themselves. Swabs (PCR or LFT) for COVID-19 and swabs for influenza should be performed as soon after onset of symptoms as possible.

Inform the site team of the result of the COVID-19 swab (PCR or LFT), and receive the result of the influenza swab. If LFT is used, the individual should forward a photograph of the LFT result including the QR code, date of the test and their Trial ID number to the site trial team. The LFT result should also be reported on the government website (https://www.gov.uk/report-covid19-result). The site team may assist the patient with reporting their LFT result on the government website as necessary.

Participants should continue taking trial medication (if self-administering medication) until advised to stop by a member of the trial team or admitted to hospital.

Participants must follow the public health guidance for "suspected COVID-19 infection" current at that time

Any participant testing positive for SARS-CoV-2 will be required to complete a COVID-19 symptom assessment at least weekly for 4 weeks after diagnosis, unless hospitalised.

4.7.1.4. Final safety assessment

PROTECT-V is an event driven platform trial. The anticipated median treatment duration per participant is 6 months. However, the individual arm may conclude while some participants are in the trial for less than 6 months if the required number of events are observed. Upon completion of the trial, participants randomised to the active IMP and matching placebo will be notified by email or by telephone depending on participant preference. Participants will be asked to stop taking IMP (if self-administering) and acknowledge receipt of end-of-trial arm notification. Patients will remain blinded.

A final safety assessment will be conducted in person, 4-6 weeks after the final treatment (defined as date of last dose of IMP administered). Participants will be asked to return all completed medication diaries and IMP containers, if self-administering, for compliance assessment at this visit. Participants will be asked a series of questions to identify any additional adverse events or adverse reactions experienced since their last follow up assessment and a blood sample will be taken for a SARS-CoV2 total antibody assay, to detect asymptomatic cases of COVID-19 infection.

At the final assessment, patients may be re-screened for consideration of enrolment (under a new subject ID) into one of the other arms of the PROTECT-V trial platform. It is not permitted for re-enrolment into the originally assigned arm.

4.8. Duration of study

PROTECT-V is an event driven trial. Duration for each IMP will be detailed in the relevant appendix.

4.9. Treatment withdrawal

Participants will be withdrawn from trial treatment at the discretion of the PI/CI if continuation in the trial is deemed to be against the participant's best interest.

Treatment will be withdrawn if:

- Participants become pregnant
- Participant is hospitalized for COVID-19
- Participant experiences unacceptable drug reaction
- Participant has not been followed up for more than 6 consecutive weeks (temporary halt) or for more than 12 consecutive weeks (loss of follow up and trial withdrawal).

Participants who have been withdrawn from the trial treatment and are experiencing ongoing toxicity will be followed up until the adverse reaction comes to its conclusion. In the event of a Participant being withdrawn from the trial treatment, they will continue to receive the most appropriate standard of care treatment available under the guidance of their treating clinician.

Following treatment withdrawal, at the final assessment, patients may be re-screened for consideration of enrolment (under a new subject ID) into one of the other arms of the PROTECT-V trial platform.

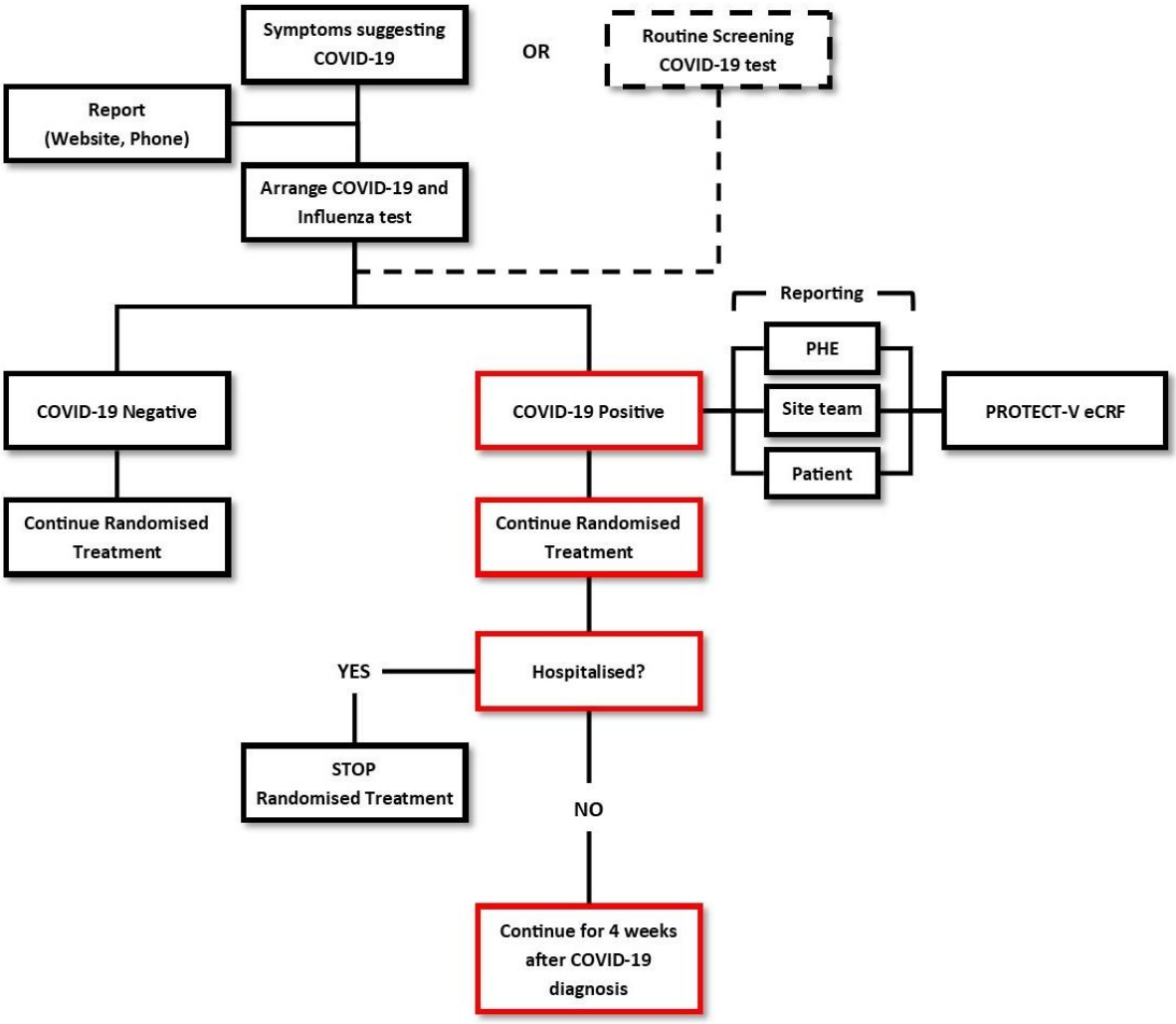
4.9.1. Treatment period

Participants will continue allocated treatment until one of the following occurs:

a. The required number of the primary outcome events have occurred (for each intervention)
b. The participant is hospitalised with COVID-19 (see 4.10.2.)
c. 28 Days after a diagnosis of COVID-19 if hospitalisation is not required

4.9.2. Diagnosis of COVID-19

Participants may receive a diagnosis of COVID-19 during the course of participation in the trial, either as a result of routine testing or prompted by suggestive symptoms. Any participant diagnosed with COVID-19 should continue self-administering their randomised treatment, if applicable, for 28 days after the date of diagnosis, unless hospitalised. Participants hospitalised with a diagnosis of COVID-19 should stop the randomised treatment immediately.



Participants receiving a diagnosis of SARS-CoV-2 infection who are asymptomatic (most likely after routine screening) will be required to follow the above algorithm, continuing with treatment for 4 weeks unless hospitalised. If such participants remain asymptomatic, they will be judged not to have reached the primary endpoint for the trial. If they become symptomatic after diagnosis, they will be judged to have reached the primary endpoint of the trial. Under these circumstances, the primary endpoint date will remain the date of confirmed SARS-CoV-2 (the date of the test).

Any participant testing positive for SARS-CoV-2 will be required to complete a COVID-19 symptom assessment at least weekly for 4 weeks after diagnosis, unless hospitalised.

4.10. Withdrawal of consent

Participants may withdraw consent for continuation in the trial at any point. Participants may choose to withdraw only from active trial participation (trial treatment and self-reporting questionnaires), allowing continuation of data collection through data linkage, or may choose to withdraw both from the trial and all further data linkage.

No further trial procedures will be undertaken and no data or samples will be collected from the time of consent withdrawal, in line with the participant's wishes. However, data and samples collected up to the time of consent withdrawal will be included in the data reported for the trial. The Investigator should inform the coordination

team as soon as possible and complete the End of Treatment Case Report Form (CRF), Trial Endpoint CRF and withdrawal CRF page if no further follow up is planned.

Please note that the participant will be contacted for a safety assessment 4-6 weeks from last IMP dose regardless whether the participant withdrew from the further assessment.

4.11. Objectives

4.11.1. Primary objective

The primary aim of the trial is to determine if prophylactic treatment reduces the risk of confirmed symptomatic COVID-19 infection in vulnerable renal and immunosuppressed patients participating in the study.

4.11.2. Secondary objectives

The trial also aims to:

1) Determine if prophylactic treatment increases the time to confirmed SARS-Cov-2 infection from the date of randomisation including incidental asymptomatic cases in the vulnerable populations taking part in the study.

2) Determine the safety of prophylactic treatments in this patient population

3) Determine if prophylactic treatment reduces mortality and severity of COVID-19 infection in the vulnerable populations taking part in the study.

4.11.3. Exploratory objectives

Determine if prophylactic treatment increases the proportion of individuals with antibodies to SARS-Cov-2 at the end of the trial in the vulnerable populations taking part in the study.

4.12. Outcomes

4.12.1. Primary Outcome

The primary outcome for PROTECT-V is confirmed symptomatic COVID-19 infection during treatment.

4.12.1.1. Definition of the primary outcome event

The primary outcome event is defined as the presence of both

- Confirmed SARS-CoV2 (by either PCR or lateral flow) and
- One or more symptoms in keeping with COVID-19, including:
  - Respiratory (Cough +/- sputum and shortness of breath)
  - Constitutional (Pyrexia/chills, myalgia/arthralgia, fatigue, rash, headache, confusion)
  - Gastrointestinal (nausea/vomiting, diarrhoea, abdominal pain, loss of appetite)

The date (time) of the primary outcome event is defined as the date of the confirmed COVID-19 test.

4.12.2. Secondary Outcomes

Secondary outcomes include

a. Time to confirmed SARS-Cov-2 infection from the date of randomisation including asymptomatic cases

b. Safety and All-cause mortality
c. Severity of COVID-19 disease (assessed by PI 28 days after date of positive test)
    i. Adapted WHO ordinal scale (defined as the **worst category** 28 days from date of positive test or until date of discharge from hospital, whichever occurred later)
        1. Healthy carriers - confirmed SARS-CoV2 infection, no symptoms
        2. Very mild symptoms, no limitations
        3. Mild, limitations on activities
        4. Mild, hospitalised, no oxygen requirement
        5. Moderate, hospitalised, oxygen via mask or nasal cannulae
        6. Severe, non-invasive ventilation or high flow oxygen
        7. Very severe, intubation and mechanical ventilation
        8. Critical, ventilation and additional organ support (RRT/ECMO)
        9. Death
    ii. Length of inpatient stay
    iii. Common COVID-19 complications (including ARDS, viral pneumonitis, myocarditis/myocardial injury, AKI)

Additional information on longer term outcomes may be collected through review of medical records or linkage to medical databases such as those managed by NHS Digital, ICNARC, and UKHSA (formerly PHE).

4.12.3. Exploratory Outcomes

Exploratory outcomes will include

1. Occurrence of antibodies to SAR-CoV-2 at the end of the trial

4.13. Sample management

Only authorised staff will have access to the trial samples. Full instructions for the collection, labelling and storage of samples are provided in the Trial Procedure Manual.

4.13.1. SARS-Cov-2 antibody testing

Serum samples will be taken at baseline and final assessment visits to test presence of antibodies against SARS-Cov-2. Samples will be stored and analysed in batch. Refer to laboratory section of trial procedure manual for full details of sample processing.

4.14. Methods of analysis of each prophylactic intervention

4.14.1. Analysis populations

The following populations will be defined for efficacy and safety analyses for each of prophylactic intervention.

4.14.1.1. Intent-to-treat population (ITT)

The ITT population is defined as all participants randomised between the prophylactic intervention and the randomised placebo, regardless of whether they actually received trial treatment. The treatment group will be analysed as randomised.

4.14.1.2. · Safety population

The safety population comprises all participants randomised between the prophylactic intervention and the placebo, and having received as least one dose of trial treatment. The treatment group will be analysed as treated.

4.14.2. Efficacy Analysis

The primary outcome measure, symptomatic COVID-19 infection, will be compared between each prophylactic treatment and the randomised placebo groups in the ITT population using a Cox proportional hazards model, considering adjustment for the following fixed effects

- Age
- Sex
- Ethnicity
- Patient population (dialysis, vasculitis/glomerulonephritis, transplant)
- Known high-risk pre-existing conditions (e.g. cardiovascular disease, hypertension, diabetes mellitus), vs not.
- Detectable anti SARS-COV-2 antibodies at baseline
- Receipt of Covid-19 vaccination (a time-dependent covariate)
- Randomisation option (one prophylactic treatment vs two prophylactic treatments)

The hazard ratio will be determined and statistical significance will be declared using a 2-sided alpha-level of 0.045 (adjusting for interim analyses, see sample Size section for details). There is no need to use a multiplicity adjustment for the treatment arms as these are considered independent comparisons. A 95% confidence interval for the hazard ratio from the Cox model will be provided. The estimand properties of the primary and sensitivity analyses of the primary endpoint will be detailed in the Statistical Analysis Plan

Participants who did not develop symptomatic COVID-19, withdrew from the study, are lost to follow-up or died prior to developing symptomatic COVID-19 will be censored at the date of last treatment administered (for self-administered IMP, otherwise last follow-up for all other participants). Further detail will be included in statistical analysis plan (SAP). Asymptomatic confirmed COVID-19 (either by PCR or LFT) participants will be followed up for a maximum of 4 weeks (this is consistent with the maximum of 4 week treatment after positive COVID-19). If any protocol specified symptoms have occurred, the date of the positive COVID-19 test is the date of primary endpoint event; otherwise, the participant will be censored at the date of last follow up, or last treatment administered, if self-administering IMP.

For the secondary outcome measure of time-to-confirmed SAR-Cov-2 infection (either by PCR or LFT) in the ITT population, the analysis will use a Cox proportional hazards model as described for the primary outcome measure. The median, 25th and 75th percentile and 95% Cis for time to confirmed SARS-CoV-2 infection (either by PCR or LFT) will be provided. The severity scale of COVID-19 disease will be compared using a proportional odds model for all COVID-19 infected participants. Length of inpatient stay will be compared using Fine and Gray approach with discharge alive as event of interest and hospital death as competing event for all hospitalised participants.. Common COVID-19 complications for all COVID-19 infected participants in the ITT population will be analysed using the standard chi-square test. The comparisons on the secondary outcome measures will be compared according to a pre-specified hierarchal order. Details will be included in the SAP.

Different efficacy analysis will be included in an Appendix if required.

4.14.3. Safety Evaluation

The safety analyses will be based on the safety population for each prophylactic treatment. All safety parameters will be summarised. Summary tables will be presented for incidence rates of AEs, ARs, SAEs and SARs.

A full statistical analysis plan will be written before any analyses are undertaken.

4.15. Method of analysis at the end of trial

If efficacy is observed for more than one prophylactic intervention, comparisons between different prophylactic treatments will be performed at the end of trial in an exploratory manner.

4.16. Sample size

Details for each intervention will be included in the relevant appendix. The impact of vaccine response and infections rates in this patient population remains uncertain, and the assumption used in the sample size estimation will be monitored by the DMC. Sample size re-estimation will be considered with the process detailed in the DMC Charter.

4.17. Criteria for the premature termination of a prophylactic treatment

Each prophylactic intervention will be reviewed individually every 2 months by the Independent Data Monitoring Committee (DMC) for safety, combined primary outcome measure event rate and making a recommendation for performing efficacy analyses. A prophylactic treatment arm will be stopped early if there are any safety concerns. Depending on the specific requirements of each prophylactic treatment specified in the corresponding Appendix, a treatment could be stopped early for efficacy should there be sufficient evidence of beneficial effect comparing to the randomised placebo, or for futility if there is sufficient evidence of futile effect comparing to the randomised placebo. These decision will be based on the recommendation of independent Data Monitoring Committee with the detailed process included in the DMC charter and the approval from the Trial steering committee.

Should one treatment arm be stopped earlier, future participants would be randomised between the remaining active prophylactic treatments and their matching placebos.

4.18. Trial restrictions

Women of childbearing potential are required to use effective contraception for the duration of the trial and for 28 days after the completion of the last treatment. This includes:

- Intrauterine Device (IUD)
- Hormonal based contraception (pill, contraceptive injection or implant etc.)
- Barrier contraception (condom and occlusive cap e.g. diaphragm or cervical cap with spermicide)
- True abstinence (where this is in accordance with the participant's preferred and usual lifestyle)

5. SAFETY MONITORING AND REPORTING

All Adverse Events (AEs) and Adverse Reactions (ARs) will be recorded in the medical notes and in the appropriate section of the CRF. SAEs and SARs should be reported to the sponsor as detailed in section 5.3.

5.1. Adverse Event Definitions

TABLE 1	
Term	**Definition**
Adverse event	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which is not necessarily caused by or related to this treatment.
Adverse Reaction	All untoward and unintended responses to an investigational medicinal product related to any dose administered. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression 'reasonable causal relationship' means to convey, in general, that there is evidence or argument to suggest a causal relationship.
Unexpected Adverse Reaction	An adverse reaction, the nature, or severity of which is not consistent with the applicable reference safety information (RSI). When the outcome of the adverse reaction is not consistent with the applicable RSI this adverse reaction should be considered as unexpected.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	Any untoward medical occurrence that at any dose: - results in **death**, - is **life-threatening** - requires **hospitalisation** or **prolongation** of existing inpatient hospitalisation - results in persistent or significant **disability or incapacity**, - is a congenital anomaly or birth defect. - is another important medical event Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information set out in the RSI.

NB: to avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

5.2. Expected AEs or ARs

The Sponsor expects that adverse events are recorded from the point of Informed Consent regardless of whether a participant has yet received a medicinal product. Individual adverse events should be evaluated by the investigator. This includes the evaluation of its seriousness, and any relationship between the investigational medicinal product(s) and/or concomitant therapy and the adverse event (causality). All expected Adverse Reactions are listed in the latest MHRA approved version of the RSI as specified in section 5.4.2 This must be used when making a determination as to the expectedness of the adverse reaction. If the adverse reaction meets the criteria for seriousness, this must be reported as per section 5.3.

All AEs and ARs, which are new or significantly worse since commencing the trial, should be recorded on the symptom checker questionnaire in the CRF and sent to the trial coordination centre within one month of the investigator becoming aware of the event.

5.3. Recording, Evaluating & Reporting of Serious Adverse Events / SARs

The Chief Investigator or PI is responsible for ensuring that the assessment of all SAEs for expectedness and relatedness is undertaken, (except for elective overnight admissions for pre-existing medical conditions, or complications directly related to vascular access, such as fistula thrombosis or central venous catheter infection or malfunction, or renal transplantation), and the onward notification of all SAEs and SARs to the Sponsor immediately but not more than 24 hours of first notification. A further review of expectedness will be undertaken by the Chief Investigator. The sponsor has to keep detailed records of all SAEs and SARs reported to them by the trial team.

The Chief Investigator is also responsible for prompt reporting of all Serious Adverse Reactions to the competent authority (MHRA) if they could:

- adversely affect the health of participants
- impact on the conduct of the trial
- alter the competent authority’s authorisation to continue the trial in accordance with Directive 2001/20/EC

Details of where to report SAEs and SARs can be found in the PROTECT-V trial manual and on the front cover of the protocol.

It will not be a requirement to report any SAE which occurs between final study visit in one arm of the trial, and date of consent to a subsequent arm of the trial.

5.3.1. Assessment of Seriousness

Seriousness is assessed against the criteria in the table 1 above.

5.3.2. Assessment of Causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definition:

Not related – where an event is not considered to be related to the IMP

Related – the known effects of the IMP, its therapeutic class or based on challenge testing suggest that the IMP is the most likely cause.

5.3.3. Clinical Assessment of Severity

Mild	The participant is aware of the event or symptom, but the event or symptom is easily tolerated
Moderate:	The participant experiences sufficient discomfort to interfere with or reduce his or her usual level of activity
Severe:	Significant impairment of functioning; the participant is unable to carry out usual activities and / or the participant's life is at risk from the event.

5.4. Assessment and onward reporting of SUSARs

All suspected adverse reactions related to study IMP which occur in the PROTECT-V trial, and that are both unexpected and serious (SUSARs) are subject to expedited reporting.

5.4.1. Who should report and whom to report to?

The Sponsor delegates the responsibility of notification of SUSARs to the Chief Investigator. The Chief Investigator must report all the relevant safety information previously described, to the:

- Sponsor
- Competent authorities in the concerned member states (e.g. MHRA)
- Ethics Committee in the concerned member states

The Chief Investigator shall inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

5.4.2. Reference Safety Information (RSI)

RSI is a list of medical events that defines which reactions are expected for the IMP within a given trial and thus determining which Serious Adverse Reactions (SARs) require expedited reporting.

RSI will be specified in each specific appendix.

5.4.3. When to report SUSARs

5.4.3.1. Fatal or life-threatening SUSARs

The CI must inform the Sponsor of any fatal SUSAR immediately but within 24 hours of the site investigator awareness of the event. The MHRA and Ethics Committee must be notified as soon as possible but no

later than 7 calendar days after the trial team and Sponsor has first knowledge of the minimum criteria for expedited reporting. In each case relevant follow-up information should be sought and a report completed as soon as possible. It should be communicated to all parties within an additional 8 calendar days.

5.4.3.2. Non-fatal and non-life-threatening SUSARs

All other SUSARs and safety issues must be reported to the Sponsor immediately but within 24 hours of the site investigator awareness of the event. The MHRA and Ethics Committee must be notified as soon as possible but no later than 15 calendar days after first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be given as soon as possible.

5.4.4. How to report SUSARs?

5.4.4.1. Minimum criteria for initial expedited reporting of SUSARs

Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports should be submitted within the time limits as soon as the minimum following criteria are met:

a) a suspected investigational medicinal product
b) an identifiable participant (e.g. trial participant code number)
c) an adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship
d) an identifiable reporting source
and, when available and applicable:
- a unique clinical trial identification (EudraCT number or in case of non-European Community trials the sponsor's trial protocol code number)
- a unique case identification (i.e. sponsor's case identification number)

5.4.4.2. Follow-up reports of SUSARs

In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality should be actively sought from the reporter or other available sources. Further available relevant information should be reported as follow-up reports.

In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction.

5.4.4.3. Format of the SUSARs reports

Electronic reporting is the expected method for expedited reporting of SUSARs to the competent authority. The format and content as defined by the competent authority should be adhered to.

5.5. Pregnancy Reporting

All participant pregnancies within the trial or up to 1 month after the last dose should be reported to the Chief Investigator and the Sponsor using the relevant Pregnancy Reporting Form within 24 hours of notification.

Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE.

6. TRIAL COMMITTEES

6.1. Trial Management Group (TMG)

The TMG will meet on a weekly basis during initial set up, and then two weekly face to face or by teleconference to oversee the running of the trial. TMG members will review SAEs which have occurred in the trial. If there are specific safety concerns these may be raised with the TSC and IDMC. TMG members will include co-investigators, trial statistician, trial pharmacist, the trial co-ordinator and data manager at the Cambridge Clinical Trials Unit (CCTU).

6.2. Trial Steering Committee (TSC)

The Trial Steering Committee (TSC) is responsible for the review of the trial and related activities at regular intervals. The TSC also provides overall supervision for the trial, to ensure that it is conducted in accordance with the protocol and GCP and to provide advice through its independent chairman. The committee will aim to convene at regular intervals to review the data and discuss the recommendations from the Independent Data Monitoring Committee (IDMC). The details of the TSC are set out in the PROTECT-V Trial Steering Committee Charter.

6.3. Independent Data Monitoring Committee (IDMC)

The IDMC will comprise an unblinded independent group, as defined in the PROTECT-V Data Monitoring Committee Charter document, which will define the role of the IDMC. The IDMC will be responsible for the review of all safety (but not exploratory) data and will meet regularly whilst the trial is ongoing, from opening to recruitment until the final visit of the last participant.

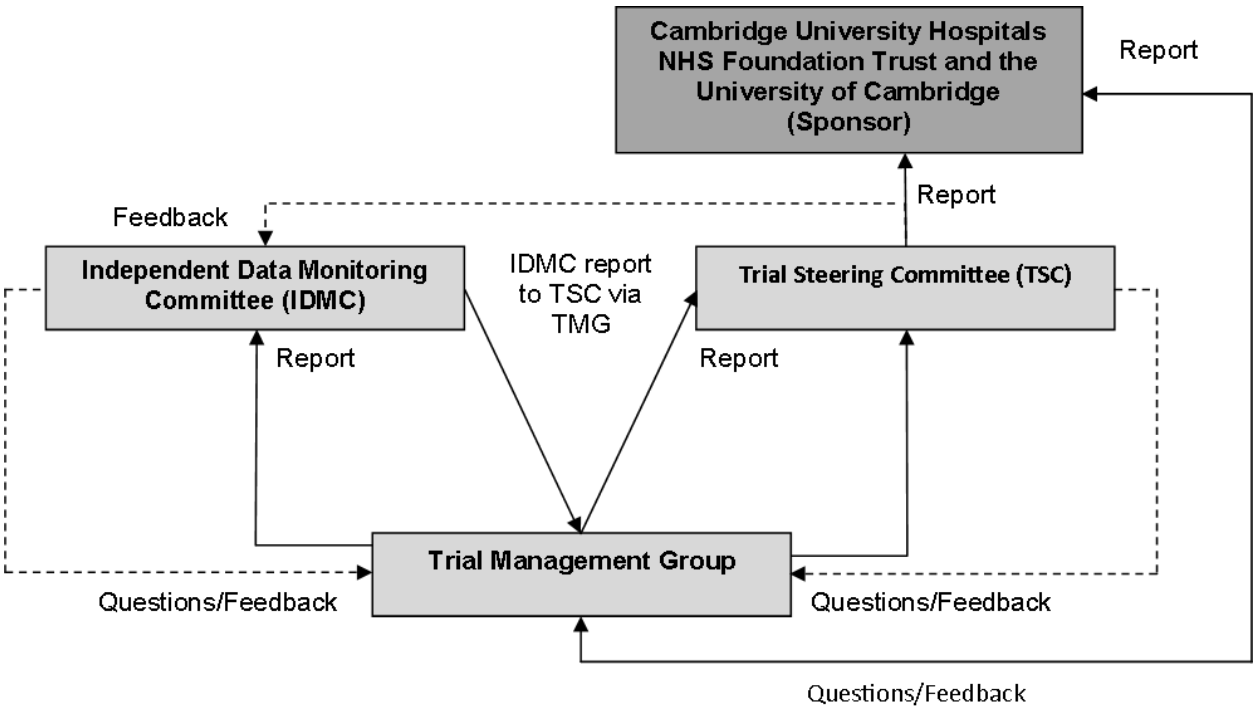


Diagram of Relationships between Trial Committees and Group

7. DATA HANDLING AND RECORD KEEPING

All data will be transferred into an electronic Case Report Form (eCRF) which will be anonymised. All trial data in the CRF must be extracted from and be consistent with the relevant source documents. The eCRFs must be completed in a timely manner. Completeness and accuracy of the eCRF is the responsibility of the investigator. The eCRF will be accessible to trial coordinators, data managers, the Investigators, Clinical Trial Monitors, Auditors and Inspectors as required.

Investigators must ensure that trial related documentation sent to the trial coordination centre contains no participant identifiable data. A trial specific data management plan will describe in detail the data management processes using the eCRF and the trial database.

All trial assessments, including the questionnaires and the medication diary, will be emailed securely (using nhs.net email) to the local PI to enable records to be stored at participating sites.

A copy of the data associated with a trial participant will be provided to the local PI at the end of the trial.

All data entries will be made in the eCRF. It will not be possible to edit any data fields already marked as complete. Requests for corrections or additions will need to be made using the data change request form or logging a data change request in the eCRF.

Study participants will provide explicit consent to the use of identifiable data for the purposes of the conduct of the study. The PROTECT-V trial management team will hold identifiable data on all participants including name, date of birth, gender, NHS number or equivalent, home address and postcode, telephone number and email address where applicable.

Personal identifiable data (PID) will be stored separately from anonymised study data on a secure server hosted within University of Cambridge School of Clinical Medicine Secure Data Hosting Service. PID will be accessible to the PROTECT-V trial team within the Cambridge Clinical Trials Unit, monitors, auditors and inspectors as required. It is necessary to 1) perform validation of NHS numbers and linkage to routinely collected datasets (NHS Digital, ONS), and 2) to generate datasets with participant details for mail merge creation of questionnaires, and is therefore imperative to the conduct of the study.

7.1. Source Data

To enable peer review, monitoring, audit and/or inspection, the investigator must agree to keep records of all participants (sufficient information to link records e.g., CRFs, hospital records and samples), all original signed informed consent forms and copies of the CRF pages.

Source data may include but is not limited to:

- Informed Consent Form
- Relevant sections of the Case Report Form (written or electronic), as defined by the TPM
- Medical Records (written or electronic)
- On-line laboratory test results systems
- Photograph of the Lateral Flow Tests, together with the test date and patient Trial ID
- Participant Questionnaires (written or electronic)

7.2. Data Protection & Participant Confidentiality

All investigators and trial site staff involved in this trial must comply with the requirements of the Data Protection Act 2018 and Trust Policy with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

8. ETHICAL & REGULATORY CONSIDERATIONS

The consent information and consenting procedure is described under section 2.2, and will be approved by the REC.

8.1. Ethical committee review

Before the start of the trial or implementation of any amendment we will obtain approval of the trial protocol, protocol amendments, informed consent forms and other relevant documents e.g., advertisements and GP information letters if applicable from the REC. All correspondence with the REC will be retained in the Trial Master File/Investigator Site File. Annual reports will be submitted to the REC in accordance with national requirements. It is the Chief Investigator's responsibility to produce the annual reports as required.

8.2. Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments. Development Safety Update Reports (DSURs) will be submitted to the MHRA in accordance with national requirements. It is the Chief Investigator's responsibility to produce these reports as required.

8.3. Protocol Amendments

Protocol amendments must be reviewed and agreement received from the Sponsor for all proposed amendments prior to submission to the REC and/or MHRA. The only circumstance in which an amendment may be initiated prior to REC and/or MHRA approval is where the change is necessary to eliminate apparent, immediate risks to the participants (Urgent Safety Measures). In this case, accrual of new participants will be halted until the REC and/or MHRA approval has been obtained.

8.4. Peer Review

The PROTECT-V trial protocol has been peer-reviewed by the CUH COVID-19 Trials Prioritisation Group, and independently peer reviewed by the COVID19 Research Committee of the UK Kidney Research Consortium..

8.5. Declaration of Helsinki and Good Clinical Practice

The trial will be performed in accordance with the spirit and the letter of the declaration of Helsinki, the conditions and principles of good clinical practice, the protocol and applicable local regulatory requirements and laws.

8.6. GCP Training

All trial staff must hold evidence of appropriate GCP training or undergo GCP training prior to undertaking any responsibilities on this trial. This training should be updated every 2 years or in accordance with local Trust policies.

9. SPONSORSHIP, FINANCIAL AND INSURANCE

The trial is sponsored by Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge.

The study will be funded by LifeArc, Addenbrooke's Charitable Trust and Kidney Research UK. Additional funders are acknowledged at the appendices.

Cambridge University Hospitals NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the clinical trial caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the trial, but no-one has acted negligently. The University of Cambridge will arrange insurance for negligent harm caused as a result of protocol design and for non-negligent harm arising through participation in the clinical trial.

10. MONITORING, AUDIT AND INSPECTION

The investigator must make all trial documentation and related records available should an MHRA Inspection occur. Should a monitoring visit or audit be requested, the investigator must make the trial documentation and

source data available to the Sponsor's representative. All participant data must be handled and treated confidentially.

The Sponsor's monitoring frequency will be determined by an initial risk assessment performed prior to the start of the trial. A detailed monitoring plan will be generated detailing the frequency and scope of the monitoring for the trial. Throughout the course of the trial, the risk assessment will be reviewed and the monitoring frequency adjusted as necessary.

On-site or remote monitoring will be conducted for all participating sites. The scope and frequency of the monitoring will be determined by the risk assessment and detailed in the Monitoring Plan for the trial.

11. PROTOCOL COMPLIANCE AND BREACHES OF GCP

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used. Protocol deviations, non-compliances, or breaches are departures from the approved protocol. They can happen at any time, but are not planned. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately. Deviations from the protocol which are found to occur constantly again and again will not be accepted and will require immediate action and could potentially be classified as a serious breach. Any potential/suspected serious breaches of GCP must be reported immediately to the Sponsor without any delay.

12. PUBLICATIONS POLICY

On completion of each intervention of the trial the data will be analysed and tabulated and an Intervention Specific Final Trial Report prepared. The results of this trial may be published or presented at scientific meetings. Any reported serious breaches will be detailed in all publications in line with regulatory requirements.

Authorship of final trial outputs will be assigned and funding acknowledged in accordance with guidelines set out by the International Committee of Medical Journal Editors.

The statistician will also provide the Chief Investigator with the full summary of the trial results. The investigator is encouraged to share the summary results with the trial participants, as appropriate. The Trial team will provide the investigator with the randomisation codes for their site only after completion of the full statistical analysis.

Trial information from this protocol will be posted on publicly available clinical trial registers before enrolment of participants begins. A results summary will also be posted to publicly available clinical trial registers and a manuscript developed for publication in a peer reviewed journal after completion of the trial.

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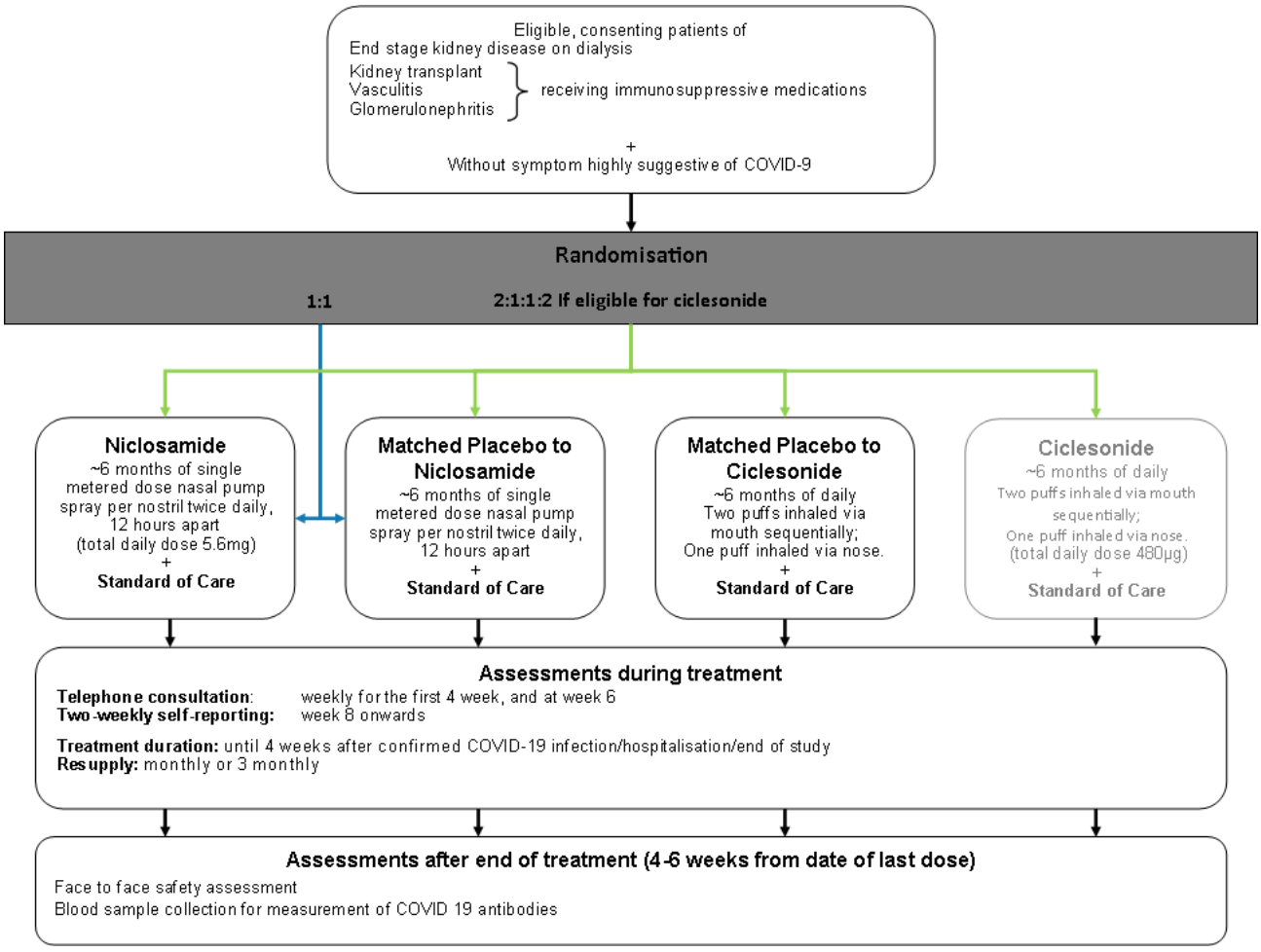
APPENDIX A: NICLOSAMIDE

Trial flowchart



1. INTRODUCTION

The trial commenced with the first intervention, nasal niclosamide and matched placebo from February 2021. The intended second intervention is nasal and inhaled ciclesonide. Participants are being randomised in a 1:1 ratio until the second intervention is introduced. Once ciclesonide is introduced, participants who are eligible for ciclesonide will be randomised to niclosamide, ciclesonide, niclosamide matching placebo or ciclesonide matching placebo in a 2:2:1:1 ratio. The net result will be a 1:1:1 distribution between niclosamide, ciclesonide and placebo, with niclosamide-matching placebo and ciclesonide-matching placebo pooled for the analysis. In

this way, the PROTECT-V platform gains efficiency by reducing the overall sample size required to assess niclosamide and ciclesonide by around 25% from what would be required to conduct two independent trials. There will be a very small proportion of participants who will be not eligible for ciclesonide as there are additional exclusion criteria for this arm; these participants will be randomised to niclosamide and niclosamide matching placebo in a 1:1 ratio.

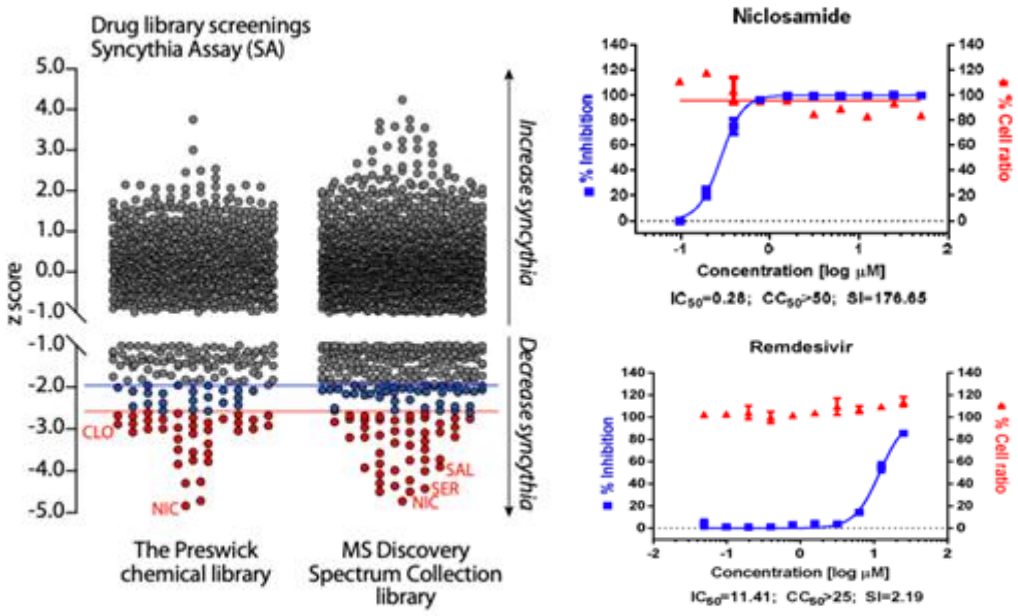
2. BACKGROUND

2.1. Rationale for niclosamide as a prophylactic measure

Niclosamide is a derivative of salicylic acid. It is a cheap, safe drug that has been used for tapeworm infestations for decades and is on the WHO's List of Essential Medicines. Although the exact target and mechanism of action is uncertain, niclosamide has pleiotropic activities and in vitro activity against a range of viruses and bacteria has been reported, including inhibition of SARS-CoV-1 replication, totally abolishing viral antigen synthesis.[7] Potential mechanisms of action for niclosamide on SARS-CoV-2 include modulation of the pH gradient across endosomal membranes inhibiting viral escape, as well as autophagy related mechanisms[8] In the case of MERS, it is thought that niclosamide acts via SKP2 inhibition to reinstate autophagy.[9]

Prior to the emergence of COVID-19, studies had suggested that niclosamide may have broader clinical applications aside from treatment of parasitic disease, such as a role inmalignancy, bacterial and viral infections, metabolic diseases (including Type II diabetes, NASH and NAFLD), and inflammatory conditions (rheumatoid arthritis, systemic sclerosis and atopic dermatitis).[10]

In the context of COVID-19, niclosamide has been identified as the leading candidate for activity against SARS-CoV-2 in two separate library screens of existing approved drugs (Giacca et al; 2020. Unpublished data). Furthermore, researchers at Institut Pasteur Korea have reported niclosamide as one of the most potent FDA approved inhibitors of SARS-Cov-2 in in vitro assays using vero cells, with IC_{50} of 0.28µM >25x higher than that of chloroquine and >40x higher than that of remdesivir.[11]



Left panel: drug library screens using syncythia assay showing that niclosamide is the most potent inhibitor of SARS-CoV2. NIC - niclosamide. CLO - chloroquine. Right panel: Dose-response of SARS-CoV-2 inhibition by niclosamide and remdesivor in vitro. The blue squares represent inhibition of virus infection (%) and the red triangles represent cell viability (%). Institut Pasteur Korea March 20, 2020.

However, oral niclosamide is poorly absorbed from the gut with low bioavailability, thus meaning that re-purposing as a therapy for COVID-19 is tricky, since the dose required to achieve sufficient exposure in target tissues is unknown. However, there are currently five clinical trials registered for testing oral niclosamide in COVID-19 infection, using the doses used to treat parasitic infection.

Niclosamide primarily undergoes hepatic clearance after oral administration with the majority eliminated via the feces. When used to treat tapeworm infection, the dose of niclosamide is not adjusted in renal impairment. In humans, following a single oral dose of 2 grams of carbonyl ^{14}C-niclosamide, only 2% to 25% is excreted in the urine over a 4-day period with the remainder eliminated in faeces.[11] Excretion was essentially complete within 1-2 days. In urine, the glucuronides of 1) niclosamide, 2) 4'-nitro-reduced metabolite (2',5-dichloro-4'-amino-salicylanilide), and 3) the N- acetylated metabolite (2',5-dichloro-4'-acetamino-salicylanilide) were reported by Andrews et al., 1982.[12] The glucuronide metabolites found in urine are similar to those found in rats after oral administration of radiolabeled niclosamide (Griffiths and Facchini 1979), a species where oral doses up to 5000 mg/kg/day have been administered for 4 weeks without adverse findings.[13]

Since aqueous solubility and oral bioavailability of niclosamide is poor there is reason to believe that other formulations, such as an inhaled preparation, would be advantageous for treating COVID-19. Union Therapeutics has developed a new stable liquid formulation (UNI911) of niclosamide. Related formulations have been tested topically in clinical trials for atopic dermatitis in over 600 subjects. These preparations have been re-purposed into an intranasal and nebulised formulation. A phase I escalating dose study in healthy volunteers using these formulations has recently been completed, with a favourable safety profile.

In-vitro data indicating potent inhibition of SARS-COV2 replication and cellular penetration, together with evidence that SARS-COV2 initially replicates predominantly in the nasal epithelium, suggests nasal niclosamide is best placed as a prophylactic agent or for treatment of early stage COVID-19 disease when the viral load is a main issue.

The PROTECT-V trial will administer 1% niclosamide ethanolamine solution via a nasal spray pump twice daily (140µL of a 1% niclosamide ethanolamine solution, equivalent to 1.4mg of niclosamide ethanolamine salt per nostril twice daily; total daily dose 5.6mg niclosamide ethanolamine salt (4.7mg free niclosamide acid). Even in a highly conservative approach, where 100% of the administered dose would be assumed to permeate and reach blood circulation, the maximal systemic exposure would still be approx. 40 times lower than the one reported with oral niclosamide at the approved dose (Yomesan chewable tablets) of 2g/day (based on the reported 10% bioavailability of oral niclosamide by Chang et al. 2006,[14] i.e. 200 mg day^{-1} / 5.0 mg day^{-1} = 40).

Based on 1) hepatic clearance as the primary mechanism for elimination of niclosamide, 2) the low human intranasal dose, 3) anticipated low bioavailability, 4) the lack of reported toxicity at high doses in animals, and 5) a reported half-life of niclosamide of 1.3 to 5.6 hours, which suggests that steady state levels are reached within a few days, the proposed nasal application of UNI911 to renally impaired patients will not lead to appreciably high levels of niclosamide or its metabolites outside of those previously evaluated in animals following a single or short-term human dosing regimen and thus no dose adjustments are recommended for patients with renal impairment.

UNI911 has been developed to maximise delivery of niclosamide to local tissues. In a non-clinical PK study UNI911 was administered by nebulisation to the lungs of sheep and sequential bronchoalveolar lavages were performed over a period of 8 hours after dosing. The study demonstrated a local exposure in the epithelial lining fluid in the deep lung above the SARS-CoV-2 IC50 value of niclosamide for the full 8 hour duration

supporting a twice daily regimen. On this basis, the proposed twice daily intranasal administration of UNI911 to the nasal cavity should deliver a therapeutically active dose, considering that the dose delivered per surface area to the nasal cavity by intranasal spray pump exceeds that delivered to the lungs in the sheep PK study by nebulisation. The PK findings from the non-clinical study in sheep is also in agreement with PK findings in a recently completed Phase 1 study using UNI911 administered both by nebulisation to the lungs and intranasal spray pump to the nasal cavity.

3. TRIAL TREATMENT - NICLOSAMIDE (UNI911)

3.1. Niclosamide Name and description

INN:	Niclosamide Ethanolamine
Chemical name (IUPAC):	5-chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide.2 aminoethanol
CAS registry number:	1420-04-8
Lab code:	UNI911

The IMPs niclosamide Nasal Spray 1% and matching Nasal Spray Placebo will be provided in 20 mL amber glass vials with nasal spray pumps, containing 8.5 mL of the respective solution, delivering 140 µL per spray shot. It is an isotonic and euhydric aqueous solution with red colour.

3.2. Niclosamide Legal status

Niclosamide is currently approved and marketed for the oral treatment of tapeworm infections in several European and developing countries but not the UK. Niclosamide ethanolamine has not previously been approved as a pharmaceutical drug and is used in this trial as an unlicensed product.

3.3. Niclosamide Supply, dispensing and accountability

Niclosamide Nasal Spray 1% and matching Nasal Spray Placebo will be provided by UNION therapeutics A/S, DK-Hellerup. Supply of the finished product to participating site pharmacies will be overseen by the trial co-ordinator and distributed by a sponsor-appointed third party. Upon initial authorisation by the sponsor, an initial supply will be sent to sites; supplies thereafter will be distributed as detailed in the pharmacy manual.

IMP will be dispensed at appropriate intervals, supplying the bottles labelled with kit numbers allocated. Full accountability records will be completed to document receipt, dispensing and destruction of expired and unused IMP at the end of the study. Further details of dispensing are detailed in the pharmacy manual.

IMP will be collected by the participant during dialysis sessions or sent by courier to the participant.

IMP for the trial will be provided free-of-charge for participating sites.

3.4. Niclosamide Packaging and Labelling

The IMPs niclosamide Nasal Spray 1% and matching Nasal Spray Placebo are packaged and labelled in single packs with one unit each. The outer carton and bottle label are blinded as to whether niclosamide or its

matching placebo is contained and complies with regulatory requirements. Each unit is labelled with an individual unique treatment pack number. The same number will appear on the bottle and carton label.

3.5. Niclosamide Storage

The IMPs niclosamide Nasal Spray 1% and matching Nasal Spray Placebo must be stored as per labelled storage conditions. Participants must only use each spray for a total of 14 days, even if there remains liquid in the bottle.

3.6. Niclosamide Treatment Duration

PROTECT-V will be an event driven trial, and continue until the required number of events are accrued. It is anticipated that the median treatment duration will be 6 months for each participant with a maximum treatment period of 9 months.

3.7. Niclosamide Dose

140µL of a 1% niclosamide ethanolamine solution in each nostril twice daily, equivalent to 1.4mg of niclosamide ethanolamine salt per nostril twice daily, approximately 12 hours apart. Total daily dose 5.6mg niclosamide ethanolamine salt (4.7mg free niclosamide acid).

No dose modifications are permitted.

3.8. Niclosamide Administration

Single metered dose nasal pump spray per nostril twice daily.

3.9. Niclosamide Missed or Replacement Doses

Missed doses will not be replaced. A dose will be considered missed after 6 hours of usual administration time.

3.10. Niclosamide Contraindications

Niclosamide and placebo to match are contraindicated in subjects allergic or hypersensitive to niclosamide, its derivatives or any formulation excipients.

3.11. Niclosamide side effects and concomitant medications

The overall results from a phase 1 study in healthy volunteers receiving single or multiple escalating doses of the nebulized solution plus 150 µL of the intranasal formulation via spray showed no Serious Adverse Events and no early discontinuations. The Adverse Events, the most common of which was upper respiratory tract

irritation, were mild in intensity. After multiple dosing with 3 mL (Cohort 7) and 6 mL (Cohort 5) of inhaled niclosamide 1% there were some subjects who showed repeated asymptomatic drops in FEV1 (defined as a drop in FEV1 with more than 200 mL and 12%). These drops were all reversible, spontaneously or following dosing with short-acting beta2-agonist.

The nasal administration was well tolerated with mild nasal irritation commonly reported. The irritation could be sensed as mild pain and/or a light burning sensation in the nose, sneeze or runny nose. The nasal irritation, with few exceptions, disappeared spontaneously within one hour after the administration. There was no moderate or severe pain or nosebleed reported. The nasal application was associated with some unpleasantness that became less evident as the multiple dosing progressed. It is highly unlikely that the nasal administration contributed to the decrease in FEV1 since there was an increase in these events with the inhaled dose level and because of the much lower drug administered through the nasal route.

No formal drug-drug interaction studies with inhaled or intranasal niclosamide have been conducted. Given the expected low systemic exposure the risk for drug interactions is considered low. As a matter of precaution, administration of niclosamide should be made separately from any other drug administration.

All standard of care medicines are to continue as per standard practice and will be recorded by the study team as described.

3.12. Placebo to match niclosamide

Placebo to match niclosamide will be supplied, stored, labelled, dispensed and dosed as for the active formulation. The placebo product is formulated to have the same appearance as the active solution.

3.13. Treatment Period

The median anticipated treatment period is 6 months with a maximum treatment period of 9 months. Last follow-up visit will be scheduled 4-6 weeks after last dose. After the end of the trial, Union Therapeutics will endeavour to make available to trial participants further supplies of the IMP in the event that the trial demonstrates benefit but this cannot be guaranteed.

3.14. Treatment Withdrawal

Unacceptable drug reactions for niclosamide include:

- Moderate or severe pain in the nose
- Severe itch or burning sensation in the nose
- Spontaneous nose bleeding as result of nasal ulceration
- Oedema that prevents breathing through the nose

4. ELIGIBILITY

Specific additional exclusion criteria

- Significant structural nasal disease in the opinion of the investigator

- Prior participation in the niclosamide arm of the trial (if being re-screened for participation in a second interventional arm).

5. BLINDING

PROTECT-V-niclosamide will be a double blind placebo controlled study where neither the participant nor clinician will be aware of treatment allocation.

6. RANDOMISATION

A participant will be randomised to:

- niclosamide vs ciclesonide vs matching placebo to niclosamide vs matching placebo to ciclesonide in a 2:2:1:1 ratio, or
- niclosamide vs matching placebo to niclosamide in a 1:1 ratio if a participant is eligible for niclosamide but not ciclesonide, or
- ciclesonide vs matching placebo to ciclesonide in a 1:1 ratio if the recruitment of niclosamide intervention is completed as it is the first treatment commenced.

The system will allocate the participant treatment pack code(s) which will relate uniquely to the first supply of IMP. Different treatment pack code(s) for every subsequent order of IMP supply will be allocated by the randomisation system.

Participants and site teams will remain blinded to treatment allocation, i.e. whether active or placebo within a stated intervention. The allocated blinded IMP supply will be collected by participants when possible or sent at suitable intervals to their home by courier.

7. SCHEDULE OF ASSESSMENTs

Assessment Schedule	Screen/ Baseline Visit	7 (±3) days PK *	Weekly (±3 days) %	2-weekly (±3 days) %	14 (±3) days PK *	21 (±3) days PK *	As required	data linkage	Final assessment&
Eligibility check	X								
Medical history	X								
Concomitant Medications	X		X	X					
Symptom checker questionnaire$	X		X	X					
SARS-CoV2 PCR or lateral flow test	X						X		
Serum sample for SARS-CoV2 Total Ab assay	X								X
Medication diary£	X								
Influenza PCR							X		
ALT/AST	X								
Pregnancy test#	X								
SAR/SUSAR Reporting							X		X
Randomisation	X								
IMP supplied							X€		
COVID-19 infection			X	X				X	
PK		X			X	X			

* PK Cohort only

A pregnancy test is required for WOCBP within 14 days prior to starting trial treatment. Women are considered WOCBP following menarche and until becoming post-menopausal unless permanently sterile (previous hysterectomy, previous bilateral salpingectomy and or oophorectomy). A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A serum pregnancy test is required for all WOCBP participants.

% Weekly for one month and 2-weekly thereafter. Any participant testing positive for SARS-CoV-2 without symptom will be required to complete a COVID-19 symptom assessment at least weekly for 4 weeks after diagnosis, unless hospitalised.

$ Telephone consultation will occur for the first 6 weeks.

[&] Final assessment visit will occur 4-6 weeks after end of treatment

[€] IMP will be supplied at least 3-monthly, either at the dialysis centre or by courier.

[£] Local teams will instruct the participant on how to use the medication diary and add enough copies with each IMP dispensation to cover the treatment period

7.1 PHARMACOKINETIC ASSESSMENT

Population Pharmacokinetic (PK) assessment will be conducted in the first 30 participants receiving niclosamide for safety purposes, to exclude the unlikely possibility of accumulation of niclosamide during the course of the trial in patients receiving dialysis only. Given that participants and investigators will be blinded to treatment allocation, PK samples will maintain blinding by including the first 70 dialysis patients in the PK sampling cohort. Including 70 participants is necessary to exclude the scenario where a chance imbalance in treatment allocation early in the study results in fewer than 30 participants allocated to niclosamide. These participants will be identified as the 'PK Cohort'.

The PK Cohort will have a blood sample taken at the start of dialysis, before taking the IMP. PK Cohort participants receiving dialysis in the afternoon or evening may take the morning dose of IMP, but should omit the evening dose until the PK sample has been obtained. The procedure for obtaining PK samples is described in the trial procedures manual.

PK samples will be obtained 7 (±3) days after the date of first IMP dose (or coincident with the 3rd dialysis session post-dating randomisation), 14 (±3) days and 21 (±3) days after date of first dose.

8. ADDITIONAL OBJECTIVES

8.1. Exploratory Objectives

1) Determine if nasal niclosamide reduces the occurrence of other influenza infections in the vulnerable populations taking part in the study

9. ADDITIONAL OUTCOMES

9.1. Exploratory Outcomes

1) Occurrence of other influenza infection (swab confirmed)
2) Occurrence of other respiratory viral infections (aside from COVID-19 and influenza)
3) Staphylococcus aureus infections (dialysis population only)

10. SAMPLE SIZE

For each prophylactic intervention, it is planned initially to randomise 1500 subjects between the prophylactic treatment and the placebo or the shared placebo for patients randomised to more than one prophylactic treatments option. This was based on that the estimated 6-month rate of confirmed symptomatic COVID-19 infection was around 15% in the placebo group, and 10% in each treatment arm; this would correspond to a

hazard ratio of 0.648. With a 0.045 significance level (for an overall significance level of 0.05 with two interim analyses using a Lan-DeMets error-spending approach corresponding to symmetric 2-sided O'Brien-Fleming boundaries (https://doi.org/10.1002/sim.4780131308) and 90% power, the maximum total number events required would be 235. With a 3 month recruitment and a further continuation of 8 months (a total of 11 months), the number of events required would be observed with a total of 1275 subjects, allowing for a 15% noncompliance, a total of 1500 subjects. With a 6 month recruitment and a further continuation of 7 months (a total of 13 months), the number of events required will be observed with a total of 1278 subjects, allowing for a 15% noncompliance, a total of 1500 subjects. There are uncertainties and changes with the sample size assumptions with the development of the COVID 19 pandemic. Recruitment period will not be restricted by the assumptions. These assumptions are therefore monitored regularly by the independent data monitor committee (IDMC). Sample size re-estimation will be considered with the recommendation from the IDMC.

11. CRITERIA FOR EARLY TERMINATION

The study will be reviewed every 2 months by the independent Data Monitoring Committee (DMC) for safety, combined primary outcome measure event rate and making a recommendation for performing efficacy analyses. Should there be sufficient evidence of a difference in the primary outcome measure between the niclosamide arm and the matched placebo arm at one planned interim analysis, the DMC may consider recommending early termination of the study. As a guide to the DMC, considering the total duration of study is around 1 year, a maximum of two formal interim analyses, based the number of primary endpoint events, are to be performed using a Lan-DeMets error-spending approach corresponding to symmetric 2-sided O'Brien-Fleming boundaries (https://doi.org/10.1002/sim.4780131308). The study will only be stopped earlier if there is sufficient evidence of benefit using the O'Brien-Fleming boundaries, that is, the value of the test statistic crosses the O'Brien-Fleming boundary of beneficial effect of niclosamide.

As a potential pivotal study, it is not planned to stop the study for futility. The study will be stopped early if there are any safety concerns based on the recommendation of the independent Data Monitoring Committee and the approval from the Trial Steering Committee. As guidance, the study might be stopped early for safety concerns

- if the rate of unacceptable toxicity in the niclosamide arm is over 20%, that is, the estimated lower limit of a 95% confidence interval is greater than 20%. In general, local intolerance should only be regarded as an unacceptable toxicity if the event fulfils criteria for a serious adverse event or is severe.

- if the incidence of moderate/severe adverse events/symptoms is 15% more in the niclosamide arm with a minimum of 200 participants in each arm at a significance level of 0.05.

12. SAFETY REPORTING

12.1. Recording, Evaluating & Reporting Serious Adverse Events / SARs

The Chief Investigator will ensure that all safety information is reported to Union Therapeutics when sponsor review is complete.

12.2. Reference Safety Information (RSI)

For this trial the Reference Safety Information is: Union Therapeutics Investigator Brochure for UNI911 (Niclosamide nasal spray), Version 1.0, 26th August 2020 section 6.1.

12.3. Pregnancy Reporting

The Chief Investigator will then report the pregnancy to UNION within 24 hours of notification

13. ADDITIONAL FINANCIAL SUPPORT

Trial medications and financial contributions are provided by UNION Therapeutics.

14. INTERNATIONAL PARALLEL PROTOCOL

A parallel niclosamide arm of the PROTECT-V study will be conducted in India. The George Institute for Global Health, India will sponsor PROTECT-V protocol in India. Trial medications and funding for the Indian arm of the study are provided by UNION Therapeutics. The overarching trial eCRF, statistical support and trial committees will be provided by the UK PROTECT-V infrastructure. Data on patients recruited in India will be entered directly into the PROTECT-V study database, and cumulative data from the parallel trial will contribute to the overall sample size and primary endpoint events. The study data from the parallel PROTECT-V protocols conducted in India and the UK will be shared via the trial eCRF throughout the trial and be reviewed by the trial committees listed in section 6 of the core protocol. The George Institute for global health, as Indian sponsor, is responsible for reporting all safety data to local authorities in accordance with local regulatory requirements and to Cambridge University Hospitals in periodic safety reports. This data will then be shared with Union therapeutics according to section 12.1 of Appendix A of the protocol.

15. PUBLICATIONS POLICY

All manuscripts or abstracts which present data from the niclosamide arm of the trial must be made available for review by Union Therapeutics before submission. This is to protect proprietary information and to provide comments.

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APPENDIX B: CICLESONIDE

Appendix B Protocol Contributors

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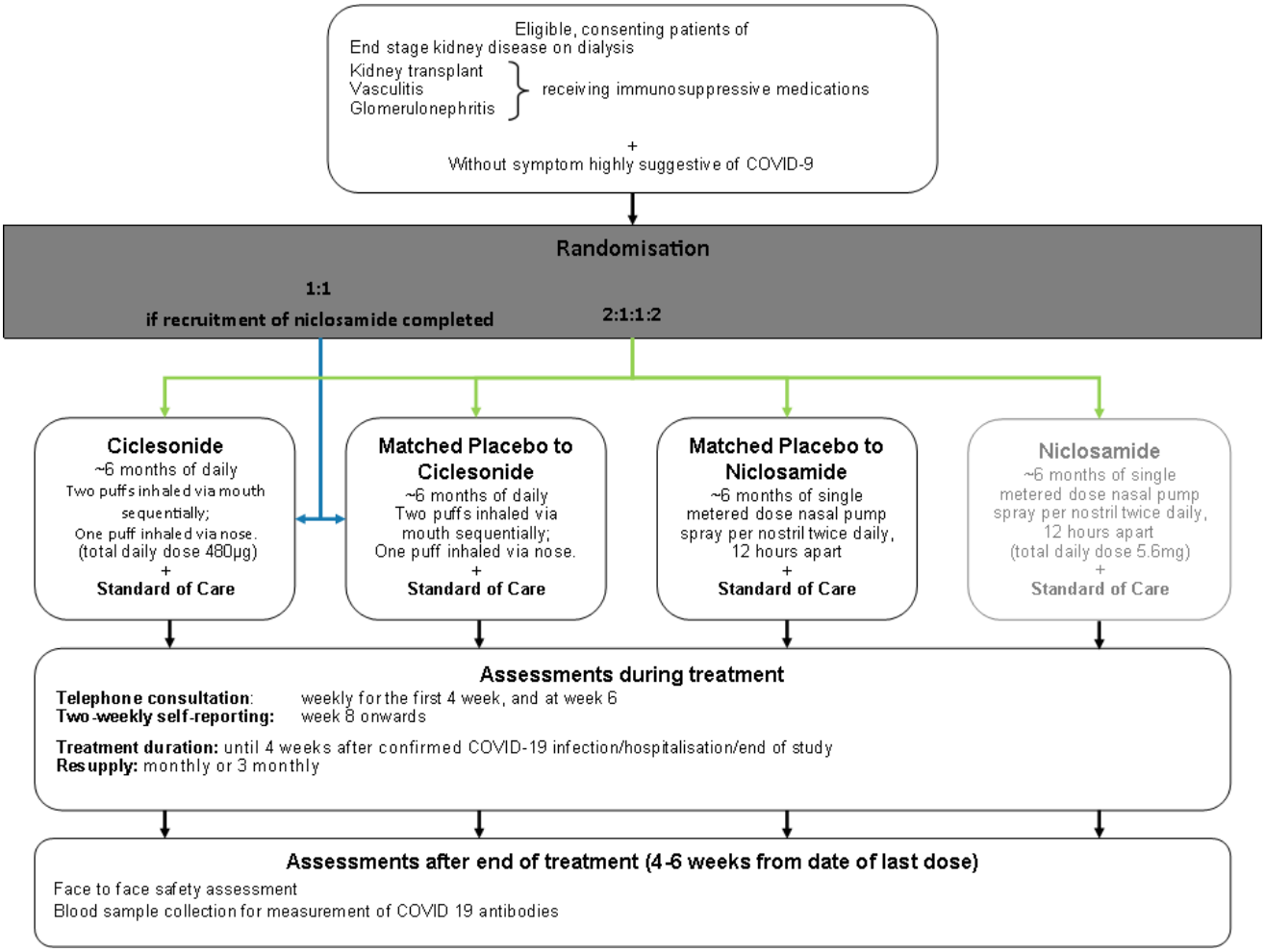
Prof Graeme Devereux	Professor of Respiratory Medicine, Liverpool School of Tropical Medicine

Trial Flowchart



1. INTRODUCTION

The trial commenced with the first intervention, nasal niclosamide and matched placebo from February 2021. The intended second intervention is nasal and inhaled ciclesonide. Participants are being randomised in a 1:1 ratio until the second intervention is introduced. Once ciclesonide is introduced, participants who are

eligible for ciclesonide will be randomised to niclosamide, ciclesonide, niclosamide matching placebo or ciclesonide matching placebo in a 2:2:1:1 ratio. The net result will be a 1:1:1 distribution between niclosamide, ciclesonide and placebo, with niclosamide-matching placebo and ciclesonide-matching placebo pooled for the analysis. In this way, the PROTECT-V platform gains efficiency by reducing the overall sample size required to assess niclosamide and ciclesonide by around 25% from what would be required to conduct two independent trials. There will be a very small proportion of participants who will be not eligible for ciclesonide as there are additional exclusion criteria for this arm; these participants will be randomised to niclosamide and niclosamide matching placebo in a 1:1 ratio.

2. BACKGROUND

2.1. Rationale for using ciclesonide for COVID-19 prophylaxis

Inhaled corticosteroids (ICS) that are commonly used to treat asthma, COPD and allergic rhinitis have been proposed as a novel way of treating and preventing early COVID-19[1,2]. Ciclesonide is an easily administered ICS licensed for the treatment of asthma and allergic rhinitis that has been shown to possess in vitro anti-SARS-CoV-2 activity but has negligible systemic bioavailability even at higher doses. Consideration of these properties make it a leading candidate for testing as a COVID-19 primary prophylaxis intervention in vulnerable patient groups.

Ciclesonide inhibits *in vitro* SARS-CoV-2 replication in cultured human bronchial epithelial cells via a novel mechanism on non-structural protein 15 (NSP-15)[3,4,5]. This effect is not seen with dexamethasone or commonly used ICS such as budesonide. Notably this effect was seen for SARS-CoV-2 but not other respiratory viruses such as influenza or respiratory syncytial virus (RSV). Ciclesonide has also been shown to form intracellular fatty acid conjugates[6], which may help to inhibit viral lipid dependent attachment to host cells[7].

As an ICS, ciclesonide will also have pertinent class effects. Angiotensin converting enzyme 2 (ACE2), and transmembrane protease serine 2 (TMPRSS2) expression mediate SARS-CoV-2 infection of host respiratory epithelial cells. ICS, particularly at higher doses, have been shown to reduce expression of ACE2 and TMPRSS2 receptors[8]. ICS have also been shown to inhibit *in vivo* production of IL-6[9], a key pro-inflammatory cytokine in COVID-19 and a major predictor of severe disease and poor outcomes[10,11,12].

After inhalation, the major site of initial SARS-CoV-2 infection is the nasopharynx with subsequent micro-aspiration leading to infection of the lower respiratory tract[13]. Reflecting this pattern of clinical disease ACE2 expression is highest in the nose and decreases throughout the lower respiratory tract and is accompanied by a commensurate gradient of SARS-CoV-2 infection early on in the disease[14,15]. The proposed combination of prophylactic inhaled and intranasal ciclesonide will deliver early infection modifying therapy covering the entire respiratory epithelium, critical in the early stages of COVID-19[16]. A further advantage of ciclesonide is that due to its extra fine particle formulation and a particle size of 1.1um, ciclesonide achieves high levels of lung deposition especially in the peripheral airways and alveoli which is not seen with conventional ICS[17]. Hence unlike other ICS higher doses of inhaled ciclesonide are not needed to achieve adequate alveolar deposition.

Ciclesonide has several novel pharmacological properties that distinguish it from other ICS commonly used to treat asthma and COPD. Ciclesonide is an inactive prodrug with low receptor binding affinity, which is activated on site by esterases within the respiratory mucosa to the highly potent active metabolite des-ciclesonide[18],Both ciclesonide and des-ciclesonide have been shown to bind to the active site of NSP-15[5]. Des-ciclesonide forms intracellular lipid conjugates that promote pulmonary retention. It has a high a relative receptor binding affinity of 1200 compared to 100 for dexamethasone, consequently ciclesonide is licensed

for once daily dosing[18]. Ciclesonide and des-ciclesonide exhibit 99% first pass hepatic inactivation for the swallowed fraction and this, combined with 99% plasma protein binding (with no apparent saturation at high doses), results in negligible systemic effects at high inhaled doses (up to 1280µg/day), such as adrenal or bone suppression, even in the long term [19-22]. Administration of supra-therapeutic doses of ciclesonide (2880 µg) to healthy volunteers resulted in very low interstitial concentrations of unbound des-ciclesonide in skeletal muscle and adipose tissue below the lower limit of detection (<0.025 µg/L)[18]. In addition, because the active metabolite des-ciclesonide is generated on-site in the respiratory mucosa, there is minimal presence in the oropharynx or larynx, explaining the very low rate of local adverse effects such as oropharyngeal or laryngeal candidiasis when compared with conventional ICS[18,23].

Several uncontrolled case series of ciclesonide use in COVID-19 have been reported, but the lack of control groups, small size and concurrent testing of other potential antiviral agents limit interpretation[8-10]. A large retrospective study linking inhaled ICS usage with subsequent death from COVID-19 suggested that ICS-users with COPD or asthma were at increased risk of death even after multiple covariate adjustment; nevertheless residual indication bias and lack of adequate adjustment mean that ICS may yet have a protective effect[11,12]. Several small-to-medium-sized trials of inhaled ciclesonide are planned or ongoing for the prevention or treatment of COVID-19.

2.2. Dosing and administration of ciclesonide

The maximal recommended daily dose of inhaled ciclesonide for asthma is 640µg with no adjustment for renal or hepatic impairment. The proposed inhaled dose of ciclesonide of 320µg once daily for the inhaled route has not been shown to be associated with any systemic adverse effects in patients with asthma in the long term[19,20,24]. A dose of 160µg once daily for the intranasal route will be used, which is similar to the recommended 200µg aqueous nasal spray dose, this also has no detectible systemic effects[25]. Nose bleeds are the most common adverse effect (4.9% 200µg ciclesonide vs 2.9% placebo) which is a dose related class effect of intranasal corticosteroids due to thinning of the nasal mucosa especially in the valve area albeit with the aqueous nasal spray [26]. The doses of inhaled and intranasal ciclesonide have been chosen to achieve high local drug concentrations and are both in keeping with usual clinical recommended doses for asthma and allergic rhinitis.

We propose to employ a pragmatic, easy to use delivery method for ciclesonide pMDI via Aerochamber spacer and facemask with mouth breathing for the inhaled route and nose breathing for the intranasal route. The proposed delivery devices will simplify drug administration and has been used as a technique to improve adherence[27,28]. Hence patients will not have the inconvenience of having to use two separate devices, one for the nose and one for the lungs. Administration of intranasal budesonide via spacer and nasal adaptor has already been shown, in two separate studies in adults and children with allergic rhinitis and asthma, to improve nasal peak inspiratory flow and nasal symptoms, thus proving that particles emitted from the spacer are trapped in the nose[27,28]. In both studies, asthma symptoms and oral peak expiratory flow also improved showing that, as expected, there is indeed some overspill of budesonide into the lungs.

Ciclesonide and its active metabolite des-ciclesonide are metabolised and excreted by hepatic mechanisms. No dose modification is required for patients with renal disease.

3. TRIAL TREATMENT - CICLESONIDE

3.1. Ciclesonide Name and description

Chemical name (IUPAC): 2-[(1S,2S,4R,8S,9S,11S,12S,13R)-6-cyclohexyl-11-hydroxy-9,13-dimethyl-16-oxo-5,7-dioxapentacycloicosa-14, 17-dien-8-yl]- 2-oxoethyl 2-methylpropanoate
CAS registry number: 141845-82-1

Matched placebo contains the same solvent and propellant as the active product but no drug substance.

3.2. Ciclesonide Legal status

The ciclesonide product being supplied for use in the trial is an unlicensed formulation identical to that of the UK licensed formulation. Ciclesonide (by inhalation of aerosol) is currently licensed in the UK as a treatment to control persistent asthma in adults and adolescents (12 years and older). It is a pressurised solution, intended for inhalation use and commercialised under the brand Alvesco. The recommended dose of ciclesonide is 160µg once daily, which leads to asthma control in the majority of patients. However, this may be increased if necessary to 320µg twice daily, in severe asthma.

3.3. Ciclesonide Supply, dispensing and accountability

Ayrton Saunders will distribute supplies of ciclesonide and matched placebo to a sponsor appointed third party who will be responsible for the labelling and final packaging of the product into clinical trial supplies. Supply of the finished product to participating site pharmacies will be overseen by the trial co-ordinator and distributed by a sponsor-appointed third party. Upon initial authorisation by the sponsor, an initial supply will be sent to sites; supplies thereafter will be distributed as detailed in the pharmacy manual.

IMP will be dispensed at appropriate intervals, supplying the inhalers labelled with allocated kit numbers. Full accountability records will be completed to document receipt, dispensing and destruction of expired and unused IMP at the end of the study. Further details of dispensing are detailed in the pharmacy manual.

IMP will be collected by the participant during dialysis sessions or sent by courier to the participant.

IMP for the trial will be provided free-of-charge for participating sites.

3.4. Ciclesonide Packaging and Labelling

The IMPs ciclesonide and matching placebo are packaged and labelled in single packs with one unit each. The outer carton and bottle label are blinded and complies with regulatory requirements. Each unit is labelled with an individual unique treatment pack number. The same number will appear on the inhaler and carton label. Each patient will also require a single AeroChamber Plus spacer with attached face mask for administration of the IMP throughout the entire study.

3.5. Ciclesonide Storage

The IMPs ciclesonide and matching ciclesonide Placebo must be stored as per labelled storage conditions. Store below 25°C out of direct sunlight in accordance with the manufacturer's instructions. Do not use or

store near open flame or heat; do not puncture canisters. Exposure to temperatures >49°C may cause canister to burst; do not throw canister into fire or incinerator.

3.6. Ciclesonide Treatment Duration

PROTECT-V will be an event driven trial, and continue until the required number of events are accrued. It is anticipated that the median treatment duration will be 6 months for each participant with a maximum treatment period of 9 months.

3.7. Ciclesonide Dose and Administration

Participants will be prescribed ciclesonide once daily, administered as follows:

- Two puffs (320 µg) inhaled via mouth sequentially.
- One puff (160 µg) inhaled via nose.

No dose modifications are permitted.

3.8. Ciclesonide Missed or Replacement Doses

Missed doses will not be replaced. A dose will be considered missed after 12 hours of usual administration time.

3.9. Ciclesonide Contraindications

Ciclesonide and placebo to match are contraindicated in subjects allergic or hypersensitive to ciclesonide, its derivatives or any formulation excipients.

3.10. Ciclesonide side effects and concomitant medications

The following are known side-effects (taken from Summary of Product Characteristics for ciclesonide inhaler and aerosol) and will be collected within the case report form:

Incidence	Side-effect
Uncommon (>1/1,000, <1/100)	Nausea, vomiting*, bad taste, application site reactions (including nasal discomfort and epistaxis), application site dryness, oral fungal infections*, headache*, dysphonia, cough after inhalation*, paradoxical bronchospasm*, eczema and rash

Rare or very rare (>1/10,000 – 1/1,000)	Palpitations**, abdominal pain*, dyspepsia*, angioedema, hypersensitivity, hypertension
Unknown	Psychomotor hyperactivity, sleep disorders, anxiety, depression, aggression, behavioural changes (predominantly in children)

* similar or lower incidence when compared with placebo

** palpitations were observed in clinical trials in cases mostly confounded with concomitant medication with known cardiac effects (e.g. theophylline or salbutamol)

All standard of care medicines are to continue as per standard practice and will be recorded by the study team as described.

3.11. Placebo to match Ciclesonide

Placebo to match ciclesonide will be supplied, stored, labelled, dispensed and dosed as for the active formulation.

4. ELIGIBILITY

4.1. Additional Exclusion Criteria

In addition to the core exclusion criteria in the master protocol, the presence of any of the following will preclude participant inclusion:

1. Significant structural nasal disease in the opinion of the investigator
2. Prior participation in the ciclesonide arm of the trial (if being re-screened for participation in a second interventional arm).
3. Currently taking inhaled corticosteroids - beclometasone dipropionate (aerosol inhaler and dry powder inhaler), budesonide (dry powder inhaler and single-dose units for nebulization), ciclesonide (aerosol inhaler), fluticasone propionate (dry powder inhaler, aerosol inhaler, and single-dose units for nebulization), mometasone furoate (dry powder inhaler).
4. Received a live vaccine within last 14 days - ciclesonide increases risk of generalised infection: influenza, MMR, rotavirus, typhoid, varicella-zoster (shingles), yellow fever.
5. Taking one of the following medications
    - Systemic Ketoconazole, itraconazole, ritanovir, nelfinavir

5. BLINDING

PROTECT-V-ciclesonide will be a double blind placebo controlled study where neither the participant nor clinician will be aware of treatment allocation.

6. RANDOMISATION

A participant will be randomised to:

- niclosamide vs ciclesonide vs matching placebo to niclosamide vs matching placebo to ciclesonide in a 2:2:1:1 ratio, or
- niclosamide vs matching placebo to niclosamide in a 1:1 ratio if a participant is eligible for niclosamide but not ciclesonide, or
- ciclesonide vs matching placebo to ciclesonide in a 1:1 ratio if the recruitment of niclosamide intervention is completed as it is the first treatment commenced.

The system will allocate the participant treatment pack code(s) which will relate uniquely to the first supply of IMP. Different treatment pack code(s) for every subsequent order of IMP supply will be allocated by the randomisation system. Participants and site teams will remain blinded to treatment allocation, i.e. whether active or placebo within a stated intervention. The allocated blinded IMP supply will be collected by participants when possible or sent at suitable intervals to their home by courier.

7. SCHEDULE OF ASSESSMENTs

Assessment Schedule	Screen/ Baseline visit	Weekly (±3 days) %	2-weekly (±3 days) %	As required	data linkage	Final assessment&
Eligibility check	X					
Medical history	X					
Concomitant Medications	X	X	X			
Symptom checker questionnaire$	X	X	X			
SARS-CoV2 PCR or lateral flow test	X			X		
Serum sample for SARS-CoV2 Total Ab assay	X					X
ALT/AST	X					
Pregnancy test#	X					
Medication diary€	X					
SAR/SAE/SUSAR Reporting				X		X
Randomisation	X					

IMP supplied				**X€**		
COVID-19 infection		**X**	**X**		**X**	

#A pregnancy test is required for WOCBP within 14 days prior to starting trial treatment. Women are considered WOCBP following menarche and until becoming post-menopausal unless permanently sterile (previous hysterectomy, previous bilateral salpingectomy and or oophorectomy). A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A serum pregnancy test is required for all WOCBP participants.

% Weekly for one month and 2-weekly thereafter. Any participant testing positive for SARS-CoV-2 without symptom will be required to complete a COVID-19 symptom assessment at least weekly for 4 weeks after diagnosis, unless hospitalised.

$ Telephone consultation will occur for the first 6 weeks.

& Final assessment visit will occur 4-6 weeks after end of treatment

€ Local teams will instruct the participant on how to use the medication diary and add a copy with the first IMP dispensation

8. SAMPLE SIZE

For each prophylactic intervention, it is planned initially to randomise 1500 subjects between the prophylactic treatment and the placebo or the shared placebo for patients randomised to more than one prophylactic treatments option. This was based on that the estimated 6-month rate of confirmed symptomatic COVID-19 infection was around 15% in the placebo group, and 10% in each treatment arm; this would correspond to a hazard ratio of 0.648. With a 0.045 significance level (for an overall significance level of 0.05 with two interim analyses using a Lan-DeMets error-spending approach corresponding to symmetric 2-sided O'Brien-Fleming boundaries (https://doi.org/10.1002/sim.4780131308) and 90% power, the maximum total number events required would be 235. With a 3 month recruitment and a further continuation of 8 months (a total of 11 months), the number of events required would be observed with a total of 1275 subjects, allowing for a 15% noncompliance, a total of 1500 subjects. With a 6 month recruitment and a further continuation of 7 months (a total of 13 months), the number of events required will be observed with a total of 1278 subjects, allowing for a 15% noncompliance, a total of 1500 subjects. There are uncertainties and changes with the sample size assumptions with the development of the COVID 19 pandemic. Recruitment period will not be restricted by the assumptions. These assumptions are therefore monitored regularly by the independent data monitor committee (IDMC). Sample size re-estimation will be considered with the recommendation from the IDMC.

9. CRITERIA FOR EARLY TERMINATION

The study will be reviewed every 2 months by the independent Data Monitoring Committee (DMC) for safety, combined primary outcome measure event rate and making a recommendation for performing efficacy analyses. Should there be sufficient evidence of a difference in the primary outcome measure between the ciclesonide arm and the placebo arm at one planned interim analyses, the DMC may consider recommending early termination of the ciclesonide arm of the study. As a guide to the DMC, considering the total duration of study is around 1 year, a maximum of two formal interim analyses, based the number of primary endpoint

events, are to be performed using a Lan-DeMets error-spending approach corresponding to symmetric 2-sided O'Brien-Fleming boundaries (https://doi.org/10.1002/sim.4780131308). The study will be stopped earlier if there is sufficient evidence of benefit using the O'Brien-Fleming boundaries, that is, the value of the test statistic crosses the O'Brien-Fleming boundary of beneficial effect of ciclesonide. Condition power and predictive power will also be estimated and reviewed by the independent DMC, the study might be stopped early for futility. The detailed stopping guidance will be included in the DMC charter.

The study will be stopped early if there are any safety concerns based on the recommendation of the independent Data Monitoring Committee and the approval from the Trial Steering Committee. As guidance, the study might be stopped early for safety concerns

- if the rate of unacceptable toxicity in the ciclesonide arm is over 20%, that is, the estimated lower limit of a 95% confidence interval is greater than 20%
- if the incidence of moderate/severe adverse events/symptoms is 15% more in the ciclesonide arm with a minimum of 200 participants in each arm at a significance level of 0.05.

10. SAFETY REPORTING

10.1. Recording, Evaluating & Reporting of Serious Adverse Events / SARs

The Chief Investigator will ensure that all safety information is reported to Ayrton Saunders at the same time as notification to the Sponsor.

10.2. Reference Safety Information (RSI)

For this trial the Reference Safety Information is section 4.8 of the Alvesco (160mcg ciclesonide) summary of product characteristics. The applicable SmPC version will be the latest version that has been approved by the MHRA for use in this trial.

10.3. Pregnancy Reporting

The Chief Investigator will ensure that all pregnancies are reported to Ayrton Saunders when sponsor review is complete.

11. RISK/BENEFIT ASSESSMENT

1. Is there still a need to add another agent to a pre-exposure prophylaxis platform study in light of the Covid-19 vaccination program (including third primary doses and booster doses)?

The PROTECT-V study protocol is clear that all patients should receive SARS CoV-2 vaccination as part of standard of care, and that includes third primary dose and/or booster doses as appropriate. However, many studies have shown that immunocompromised renal patients mount sub-optimal responses to vaccination.

In July 2021, a synthesised review of 35 studies looking at vaccine response in renal patients demonstrated 89% (85-91%) response in dialysis patients and 35% (29-42%) in individuals with a renal transplant after two doses of SARS CoV-2 vaccine[29]. Although, third doses lead to a response in approximately 50% of those individuals not protected after 2 doses, a considerable number of immunocompromised patients remain vulnerable to SARS CoV-2 infection[30,31]. The literature on vaccine response in individuals with autoimmune disease is more complicated in view of disease and treatment heterogeneity, but responses are also sub-optimal to healthy individuals. Table 1 shows the vaccine response from 695 patients in Cambridge, UK (unpublished data) and demonstrates not only the proportion of patients responding to vaccination, but the sub-optimal magnitude of response (threshold of protection for this assay 1896; healthy control titres >30,000).

It is also important to note that the majority of studies report absolute antibody titres, which does not indicate the functionality and neutralising capacity of the antibodies. In a study of 178 dialysis patients in the UK, AZD1222 alone in sero-naive individuals induces suboptimal neutralising antibody titres against all variants of concern (VOCs), including the delta variant that is dominant globally[32]. As such, a greater proportion of the patient population other than those without detectable antibodies who remain highly vulnerable to SARS CoV-2 infection. Furthermore, the occurrence of breakthrough infections, with some studies reporting that immunocompromised persons account for a high proportion (≥40%) of infections among fully vaccinated hospitalized persons is further evidence of sub-optimal vaccine response[33,34].

Therefore, despite vaccination, and the third dose and booster vaccination campaign, sub-optimal vaccine response and vulnerability to Covid-19 infection remains a major issue in immunocompromised renal patients.

Table 1: Vaccine response in three groups of immunocompromised renal patients in Cambridge. Threshold of protection for this assay is 1896.

	Dialysis (N=258)	Autoimmune (N=228)	Transplant (N=209)
% response post dose 1	81	45	34
% response post dose 2	96	70	56
Median (IQR) S antibody titre post dose 1	7578 (3023 – 20898)	1327 (155 – 12659)	568 (193 – 3916)
Median (IQR) S antibody titre post dose 2	30806 (26385 – 31951)	19935 (1203 – 30558)	4286 (295 – 26230)

2. Addition of systemic lupus erythematosus to inclusion criteria

Systemic lupus erythematosus patients are another sub-group of the vulnerable renal patient population, receiving the very similar immunosuppressive agents as the renal transplant and vasculitis/GN patients. They will be stratified within the Vasculitis/GN cohort.

3. Rationale for using unlicensed formulation of ciclesonide; the dose and route of administration

We considered using a licensed form of ciclesonide for the PROTECT-V trial, but since Ayrton Saunders were able to provide matched placebo, we opted for this formulation, as placebo control is so important in these prophylaxis studies.

The maximal recommended daily dose of inhaled ciclesonide for asthma is 640µg with no adjustment for renal or hepatic impairment. The proposed inhaled dose of ciclesonide of 320µg once daily for the inhaled route has not been shown to be associated with any systemic adverse effects in patients with asthma in the long term[19,20,24]. A dose of 160µg once daily for the intranasal route will be used, which is similar to the recommended 200µg aqueous nasal spray dose, this also has no detectible systemic effects[25]. The proposed combination of prophylactic inhaled and intranasal ciclesonide will deliver early infection modifying therapy covering the entire respiratory epithelium, critical in the early stages of COVID-19[16]. Furthermore, ciclesonide has a high relative receptor binding affinity and is licensed for once daily dosing[18].

We propose to employ a pragmatic, easy to use delivery method for ciclesonide pMDI via the standard of care Aerochamber spacer and facemask with mouth breathing for the inhaled route and nose breathing for the intranasal route. The proposed delivery devices will simplify drug administration and has been used as a technique to improve adherence[27,28]. Hence patients will not have the inconvenience of having to use two separate devices, one for the nose and one for the lungs.

4. Justification for the intensity of scheduled follow up

The intensity and manner of follow up for the ciclesonide arm has been carefully considered to minimise healthcare interactions with clinically extremely vulnerable individuals, but to ensure that there is sufficient monitoring to ensure patient safety. Ciclesonide is widely used for the treatment of asthma at doses greater than those proposed for this study, and for a longer duration without major adverse effects. The safety profile is well established and we believe the proposed remote follow-up schedule provides sufficient safety monitoring. Subjects are seen in person at the screening/baseline visit to discuss the trial, provide informed consent, undergo screening blood tests and be educated about the IMP and trial. All patients then have a weekly telephone call with a member of the study team to ask about potential adverse events related to the IMP for the first 6 weeks of the study. Follow up questionnaires are then completed every 2 weeks throughout the study by the patient and submitted/returned to the trial team.

5. Justification for use of Alvesco SMPC as reference safety information

The IMPD describes the product development strategy taken by Ayrton to demonstrate therapeutic equivalence to the Reference Medical Product (RMP), Alvesco®, via *in vitro* data only, in line with section 5.2 of CPMP/EWP/4151/00 Rev.1. This includes testing to justify a waiver from conducting in vivo studies. A Quality Target Product Profile is outlined (Table 2.1-1), defined after analysis of the SmPC, PIL and applicable patents of the RMP, and Critical Quality Attributes were considered and evaluated to identify product characteristics that might impact quality (Table 2.1-2). A Control Strategy has been developed to ensure manufacturing consistency of a product of required quality. It is therefore, considered that use of the SmPC for Alvesco® is acceptable for use in this study. Section 4.8 of the Alvesco is stated as the reference safety information in Section 10.2 of appendix B.

12. ADDITIONAL FINANCIAL SUPPORT

Trial medications are provided by Department of Health and Social Care funding, and this arm of the trial is supported by funding from the National Institute of Health Research.

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APPENDIX C: SOTROVIMAB

Appendix C Protocol Contributors

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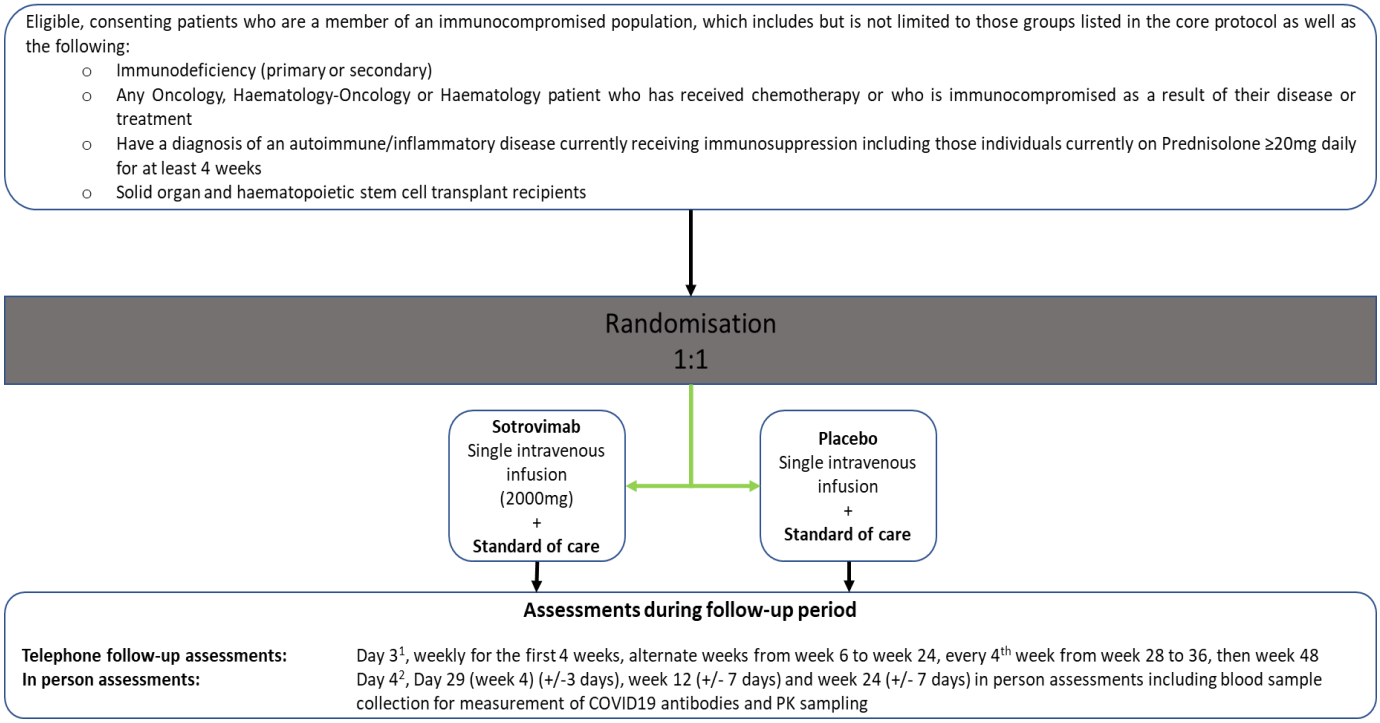
Trial Flowchart



[1]Day 3 (24-72 hours post infusion) telephone call only necessary for lead-in cohorts
[2]Day 4 (48-96 hours post-infusion) in person assessment will only be done for lead-in cohort one and will be a home-visit

1. BACKGROUND

1.1. Rationale for using sotrovimab for COVID-19 prophylaxis

Sotrovimab is a fully human IgG1κ monoclonal antibody (mAb) derived from the parental mAb S309, a potent neutralising mAb directed against the spike protein of SARS-CoV-2 (1). S309 binds to a highly conserved epitope of the SARS-CoV and SARS-CoV-2 spike protein receptor binding domain (RBD) and inhibits SARS-CoV-2 infection in vitro (1). The amino acid sequence of the complementarity determining regions of sotrovimab is identical to the parent molecule S309, with the exception of one amino acid modification (N55Q) introduced to aid antibody developability.

Sotrovimab demonstrates high affinity binding to the SARS-CoV-2 spike RBD. Sotrovimab neutralises SARS-CoV-2 virus in vitro with a half maximal effective concentration (EC_{50}) of 100.1 ng/mL and effectively neutralises pseudotyped virus containing the SARS-CoV-2 spike.

Sotrovimab was also examined for the potential for antibody dependent enhancement (ADE) using a series of in vitro studies. Using moDCs, PBMCs, and U937 cells sotrovimab showed no enhancement of viral uptake, no enhancement of viral replication, and no effect on infection-associated cytokine production. These in vitro data did not identify an elevated concern that sotrovimab will demonstrate ADE in a clinical setting. In addition, in vivo antiviral activity was evaluated in a hamster model of SARS-CoV-2 infection using a

version of the mAb that lacks the 'LS' modification (VIR-7831-WT). VIR-7831-WT showed a dose-dependent improvement in all measured outcomes, with no evidence of disease exacerbation that would indicate a potential for ADE at fully neutralising and sub-neutralising doses.

Clinical Trial data: COMET-ICE

This is a Phase II/III randomised, double-blind, placebo-controlled study which evaluated sotrovimab as treatment for COVID-19 infection in non-hospitalised patients at high risk of medical complications of the disease. Patients included were aged 18 years and older with at least one of the following comorbidities: diabetes, obesity (BMI>30), chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, moderate to severe asthma, or were aged 55 years and older. The study included patients with symptoms for ≤ 5 days, oxygen saturation on room air ≥94% and SARS-CoV-2 infection, as confirmed by local laboratory tests and/or point of care tests. Patients with severe COVID-19 requiring supplemental oxygen or hospitalisation were excluded from the trial. Patients were treated with a single 500 mg infusion of sotrovimab (N=291) or placebo (N=292) over 1 hour (Intent to Treat (ITT), [interim analysis (IA)] population). The median age of the overall randomised population was 53 years (range: 18-96). The three most common pre-defined risk factors or comorbidities were obesity (63%), 55 years of age or older (47%) and diabetes requiring medication (23%). The efficacy of sotrovimab was evaluated in a pre-planned interim analysis and the study was recommended to be stopped by the Independent Data Monitoring Committee (IDMC) for profound efficacy. The primary endpoint, progression of COVID-19 at Day 29, was reduced by 85% compared with placebo (adjusted relative risk reduction) in recipients of sotrovimab vs placebo (p=0.002). Hospitalisation for more than 24 hours or death occurred in 1% (3 out of 291) of patients who received sotrovimab and 7% (21 out of 292) of those who received placebo. The adjusted relative risk reduction for the full ITT (Day 29) population (sotrovimab: 528; placebo: 529) was 79% (p<0.001). Risk reduction was consistent in magnitude between the ITT (IA) and ITT (Day 29) populations. The proportion of patients reporting adverse events was similar between treatment groups; sotrovimab was well tolerated, and no new safety concerns were identified.

Monoclonal antibodies as prophylactic agents in COVID-19

Other monoclonal antibodies have been investigated for their use as prophylaxis against COVID-19 infection and have been proven to be effective.

The PROVENT Phase III prophylaxis trial met its primary endpoint in preventing COVID-19 infection, with administration of Evusheld (tixagevimab/cilgavimab, AZD7442) reducing the risk of developing symptomatic COVID-19 by 77% compared to placebo at 6 months, though the data is yet to be published or independently peer-reviewed (2). Evusheld has now been issued with Conditional Marketing Authorisation by the UK MHRA for pre-exposure prophylaxis of COVID-19 in adults who are not currently infected with SARS-CoV-2 and who are unlikely to mount an adequate immune response to COVID-19 vaccination, or for whom COVID-19 vaccination is not recommended (3). Of note, the MHRA recognises that the duration of protection provided by Evusheld for the Omicron BA.1 and BA.1.1 variants is currently not known.

Ronapreve (casirivimab/imdevimab) has been authorised for use by the MHRA as a prophylactic agent against COVID-19 based on the Phase III COV-2069 trial which demonstrated an 81% relative risk reduction in the development of COVID-19 with Ronapreve versus placebo in individuals who had experienced exposure to COVID-19 from a household contact (4).

Rationale for using sotrovimab in PROTECT-V trial platform

Sotrovimab may have advantages as a prophylactic agent, compared to the other available monoclonal antibodies that target COVID-19:

- **Prolonged half-life**: The Fc domain of sotrovimab includes the 2 amino acid "LS" modification that extends antibody half-life and is also expected to enhance distribution to the respiratory mucosa

(5-7), thus the LS modification allows for less frequent dosing, an important characteristic for a product intended to be used in the prophylaxis setting.

- **Increased respiratory mucosal distribution**: Transcytosis of IgG across mucosal surfaces including respiratory epithelium has been shown to be FcRn dependent (8, 9), and therefore the LS modification may also increase respiratory mucosal distribution, an important consideration in respiratory diseases (10) such as COVID-19. Moreover, FcRn can also play an important role in processing of endocytosed multimeric IgG immune complexes by dendritic cells, thereby contributing to CD4+ and CD8+ T cell responses (11, 12).
- **Effective against all known COVID-19 variants of concern**: Sotrovimab targets a highly conserved spike epitope, with amino acid conservation > 99.99% for all amino acids based on >2,100,000 available sequences. Variants at two positions, E340 and P337, resulted in significant half maximal effective concentration (EC50) shifts indicating reduced susceptibility to sotrovimab. E340 and P337 are >99.99% conserved among sequences in the GISAID database (16 July 2021). In vitro neutralization data using pseudotyped virus carrying mutations from the B.1.1.7 (Alpha, UK origin), B.1.351 (Beta, South Africa origin), P.1 (Gamma, Brazil origin), B.1.427/B.1.429 (Epsilon, California origin), B.1.526 (Iota, New York origin), B.1.617.1 (Kappa, India origin), B.1.617.2 (Delta, India origin), AY.1 (Delta Plus, India origin), AY.2 (Delta Plus, India origin), C.37 (Lambda, Peru origin), B.1.621 (Mu, Colombia origin), and B.1.1.529 (Omicron, South Africa origin) variants demonstrated fold-changes in sotrovimab EC_{50} values of less than 3-fold as compared to WT spike, suggesting sotrovimab retains antiviral activity against variants of concern. Note that EC_{90} values were not calculated from pseudotype virus testing. Additionally, in vitro neutralisation data from authentic SARS-CoV-2 variant viruses indicate sotrovimab retains activity against the B.1.1.7, B.1.351, P.1, B.1.617.1, and B.1.616.2 variants.
- **High barrier to viral resistance**: Sotrovimab neutralised SARS-CoV-2 live virus with an average EC_{90} value of 186.3 ng/mL (range: 125.8 – 329.5 ng/mL) (PC-7831-0105). In resistance analyses, no viral breakthrough was observed through 10 passages at fixed concentrations of antibody, indicating the potential for sotrovimab to have a high barrier to resistance (PC-7831-0109). Using an increasing concentration selection method to force resistance emergence, E340A was identified as a monoclonal antibody-resistant mutant (MARM) conferring a >100-fold reduction in susceptibility to sotrovimab. Notably, E340 is 99.9% conserved among available SARS-CoV-2 sequences.

The PROTECT-V team is aware of other studies assessing the efficacy of both Ronapreve and AZD7442 in similar patient groups. These are not related to this study.

1.2. Dose Rationale

A single dose of 2000 mg was selected for the study based on pseudotype and live virus neutralisation data, and sotrovimab clinical PK data from multiple clinical studies evaluating the 500 mg IV dose.

A preliminary population PK model was developed using data across several studies including COMET-ICE, COMET-PEAK, BLAZE-4 and a PK study in individuals of Japanese and Caucasian descent. The predicted median (10^{th}, 90^{th} percentile) serum concentrations of sotrovimab at week 12 following a single 2000 mg IV dose are 84.3 (52.8, 126.7) µg/mL.

A 2000 mg IV dose was selected to ensure that sotrovimab concentrations in the lung tissue are maintained at or above levels anticipated to be neutralising for the duration of the treatment window. Live virus assays indicated that, compared to wild type EC_{90} (0.288 µg/mL), Omicron BA.1 and BA.2 confer a 3.5-fold and 35-fold shift in EC_{90}, respectively (PC-7831-0155) (13). Results from in vitro pseudotyped virus assays indicated that, compared to wild type EC_{90}, BA.3 confers a 9-fold shift in EC_{90}. Tissue-adjusted EC_{90} values were calculated using two different assumptions for lung:serum ratio of 25% (based on measured data (Report:

2021N472605) (14-17) and 10% (based on literature reports for mABs in general (18-23)); and were used to estimate coverage above tissue-adjusted EC_{90} following a 2000 mg IV dose of sotrovimab.

When assuming a lung:serum ratio of 25%, a 2000 mg IV dose is expected to provide coverage against BA.1, BA.2 and BA.3 with serum concentrations achieving 13x, 1.4x and 5.6x lung tissue adjusted EC_{90} in 90% of patients at Week 12, respectively. When we use a more conservative lung:serum ratio of 10%, a 2000 mg IV dose is expected to maintain serum levels at or above 5.3x, 0.56x, and 2.23x lung tissue adjusted EC_{90} at Week 12 in 90% of patients for BA.1, BA.2 and BA.3 variants, respectively.

Under the 10% and 25% lung:serum ratio assumptions, concentrations of sotrovimab at week 12 following a 2000 mg IV dose are expected to provide adequate protection in ≥ 90% of patients against variants that confer up to 20-fold and 49-fold shift in EC_{90} compared to WT, respectively. Similarly, this dose of sotrovimab at week 12 is expected to achieve adequate coverage for ≥50% of patients against variants that confer up to 31- and 78-fold shift in EC_{90} compared to WT when lung:serum ratio are assumed to be 10% and 25%, respectively.

There is currently no available PK or immunogenicity data on a 2000 mg IV dose. Since sotrovimab exhibits dose proportional PK, exposures would be expected to be dose proportional between a 500 mg and 2000 mg IV doses. In the GLP repeat dose IV monkey toxicology study there were no toxicity findings at doses up to 500 mg/kg, the highest dose tested and the NOAEL [TX-7831-0102]. Assuming dose proportional increase in exposures at 2000 mg, sotrovimab Cmax and AUC in patients are expected to be 15.5 and 13.5-fold lower than Cmax and AUC values from the toxicology study at the NOAEL, supporting the evaluation of sotrovimab at the higher clinical dose of 2000 mg IV. The 500 mg IV dose is being evaluated in the clinical studies: COMET-ICE and ACTIV-3-TICO (NCT04501978).

The overall rate of AEs in COMET-ICE was similar in those treated with sotrovimab compared to placebo (sotrovimab: 114/523 [22%]; placebo: 123/526 [23%]). Serious AEs were numerically more common in the placebo arm than in the sotrovimab arm (32 of 526 [6%] vs., 11 of 523 [2%] respectively). The difference in SAE rates between the arms was mostly due to hospitalisations due to COVID-19–related causes, which were reported more frequently in the placebo group. The nature of SAEs was generally consistent with that expected in the COVID-19 population being evaluated and/or the underlying co-morbidities in the study population. No deaths and no SAEs considered related to treatment by the investigator were reported in the sotrovimab arm of the study. The 250 mg and 500 mg IM doses are evaluated in COMET-TAIL (NCT04913675). So far, reported AEs were not found to be dose-dependent, suggesting a large increase in rate of AEs with 2000 mg IV of sotrovimab is unlikely.

Immunogenicity data at doses higher than 500 mg IV are not available. Sotrovimab is considered low risk for immunogenicity based on intrinsic product characteristics (i.e. quality of GMP manufacturing controls and release specifications), extrinsic factors (i.e. administered as a single dose) and patient population (i.e. no apparent heightened risk of immune response). Limited preliminary analysis of immunogenicity data through Day 29 is available from 391 and 38 subjects given 500 mg IV in COMET-ICE and Japan-PK studies, respectively [ref EUA 000100, Response to FDA Feb 03, 2022 Clin Pharm IR, submitted Feb 08, 2022, Seq No. 0090]. In COMET-ICE, the post-dose rate of antibodies to sotrovimab was 3% (10/391 participants) by Day 29 of the study. Four of the 10 participants were positive for anti-sotrovimab antibodies (ADA) at baseline with no boosting in titre values at Day 29 and therefore were not considered to have treatment-induced ADA. In the Japan-PK study, no post-dose treatment-emergent ADA responses have been observed. To date, the incidence of treatment-emergent ADA responses has remained low, with no detectable impact on safety or efficacy. These clinical findings align with the low immunogenicity risk profile and the risk prediction would not be expected to change substantially at higher doses when the product is administered as a single dose by the same route and for the same intended patient population and indication. Therefore, the current risk-based bioanalytical strategy for immunogenicity analysis (i.e. screening, confirmation, titration and neutralisation assays) is considered appropriate for higher doses as well.
No metabolism studies have been conducted with sotrovimab. As a human IgG1 monoclonal antibody, sotrovimab is expected to be eliminated via catabolism in the same manner as endogenous IgG. No active

metabolite is expected for sotrovimab. As such no dose modification is recommended in individuals with renal or hepatic disease.

2. TRIAL TREATMENT – SOTROVIMAB

The trial treatments in this study are sotrovimab and placebo to match.

2.1. Sotrovimab Name and description

Name	Sotrovimab, VIR-7831, GSK4182136
Dosage Form	Sterile solution for intravenous infusion
Concentration	62.5 mg/mL
Route of administration	Intravenous infusion
Physical description	Colourless or yellow to brown, liquid solution
Formulation	20 mM histidine, 7% sucrose (w/v), 0.04% PS80 (w/v), 5 mM L-methionine at pH 6.0

Sotrovimab drug product is provided as a sterile solution and contains no preservatives. Each single-use, 8 mL vial contains 500 mg of sotrovimab. Four vials will be required for a 2000 mg dose.

2.2. Placebo to match sotrovimab

This will be in the form of 0.9% sodium chloride 100mL for infusion and will be sourced from commercially available stock by the site. It may be procured and stored as per sites usual procedures and only requires handling as an IMP upon dispensing and labelling. Please refer to the pharmacy manual for bag material compatibility information.

2.3. Sotrovimab Legal status

Sotrovimab has received provisional marketing approval in Australia and Special Approval in an Emergency in Japan. Emergency use authorisation has been granted in the United States of America on 26 May 2021 (Emergency Use Authorization). Temporary authorisations have also been approved in Canada (interim Order), Singapore (pandemic Special Access), Italy, United Arab Emirates, Bahrain, Kuwait, Oman, Qatar Brazil, Switzerland, Thailand and Egypt.

In the European Union (EU) a procedure similar to an application for an emergency use/temporary authorisation was initiated on 14 April 2021. This was a referral procedure under Article 5(3) of Regulation 726/2004. This procedure concluded on 20 May 2021 with a positive scientific opinion being issued by the Committee for Medicinal Products for Human Use (CHMP) and a Conditions of Use document is in the process of being issued.

The UK MHRA has issued a Conditional Marketing Authorisation for sotrovimab for the treatment of symptomatic adults and adolescents (aged 12 years and over and weighing at least 40kg) with acute COVID-19 infection who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19 infection (26).

2.4. Sotrovimab Supply, dispensing and accountability

Vir Biotechnology will distribute supplies of sotrovimab to a sponsor appointed third party who will be responsible for labelling and QP release of the final product. Supply of the finished product to participating site pharmacies will be overseen by the trial co-ordinator and distributed by a sponsor-appointed third party. Upon initial authorisation by the sponsor, an initial supply will be sent to sites; supplies thereafter will be distributed as detailed in the pharmacy manual.

IMP will be dispensed by delegated pharmacy staff that will either be responsible for preparing the product in the aseptic unit or dispensing vials directly to an unblinded nurse for ward level preparation as per the sites' own policies and procedures with regards to preparation of mAbs. No unblinded members of staff will have direct contact with the participant. The IMP will be administered by a blinded member of staff.[1] Full accountability records will be completed to document receipt, dispensing and destruction of expired and unused IMP at the end of the study. Further details of dispensing are detailed in the pharmacy manual.

Active IMP for the trial will be provided free-of-charge for participating sites. Placebo will need to be sourced by site. All IMP received by site will be unblinded. Blinding will only occur once the product is prepared in the final IV bag.

[1]Where site policies and procedures require that the individual who prepared an IV drug also attaches it to the patient, an exception may be permitted. In such instances, sites should contact the PROTECT-V Trial Office providing their policy/Site unblinding plan before commencement of recruitment to the sotrovimab arm.

2.5. Sotrovimab Packaging and Labelling

Sotrovimab will be provided in single-use vials in an individual carton and labelled as required in accordance with MHRA requirements for clinical trials. The primary container closure system consists of a Type I glass vial, a Teflon-faced chlorobutyl 20mm stopper, and a flip-off aluminium seal.

2.6. Sotrovimab Storage

The drug product should be stored upright in the carton at 2-8 °C and protected from light.

Investigative site staff must confirm appropriate temperature conditions have been maintained during transit for all active study drug received. All active study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised investigative site staff. All excursions from specified storage requirements should be notified to the sponsor.

2.7. Sotrovimab Treatment Duration

There will be a single infusion of sotrovimab or placebo administered at the beginning of the study. Based on the pharmacokinetics of the drug, it is predicted that the single infusion will remain efficacious for approximately 16 weeks, and possibly up to 48 weeks.

2.8. Sotrovimab Dose and Administration

2000mg of sotrovimab solution (32mL) will be diluted in 68mL of 0.9% sodium chloride and administered by intravenous infusion. The IMP should be infused with a 0.2 μm inline filter. The giving set should be flushed after the infusion is completed to ensure the entire IMP is administered.

Placebo will be in the form of 100mL 0.9% sodium chloride.

No dose modifications are permitted. Please refer to the pharmacy manual for dose preparation, equipment and drug compatibilities.

There will be three lead-in cohorts to establish the most appropriate infusion time (See Figure A1).

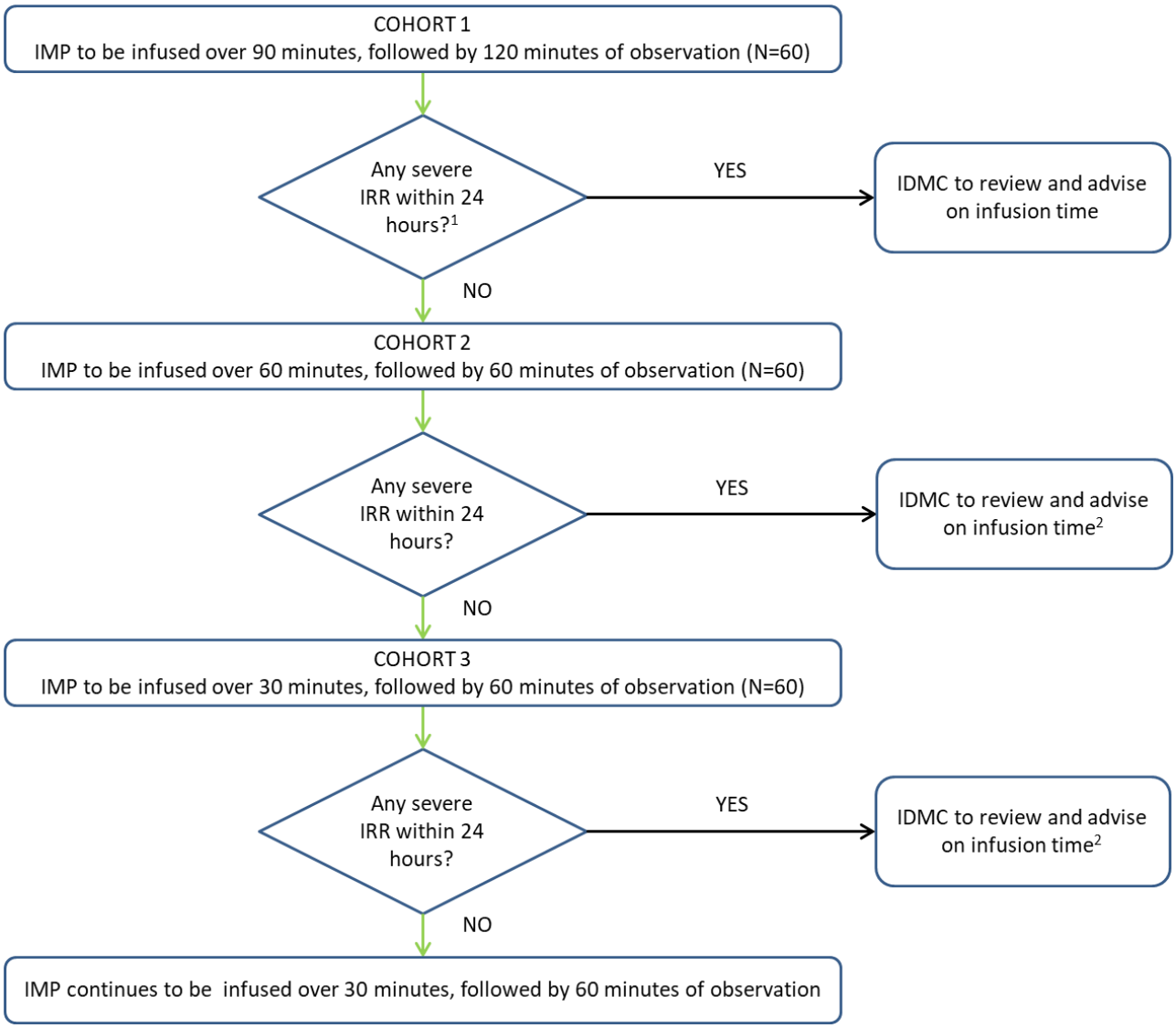


Figure A1. Infusion and observation timings for each lead-in cohort. IMP: Investigational medicinal product. IRR: Infusion related reaction.
[1]Day 4 post-infusion, routine haematology and biochemistry results will also be used to inform this decision.
[2]Post-infusion observation period to remain at 60 minutes.

The time provided in this protocol for infusions length for cohorts 1, 2 & 3 and onwards are approximate (90, 60 and 30 respectively). Infusion time windows are: 10 minutes under cohort infusion time to up to 60 mins over the cohort infusion time.

Infusion and observation times will begin as per Cohort One in Figure A1. After 60 patients have been recruited a safety analysis will be carried out assessing whether any participants had suffered from a severe IRR.

A severe IRR is defined as 1) requiring IMP treatment termination or 2) requiring hospitalisation for interventional management of an IRR within 24 hours. Admission to hospital for observation after a mild/moderate IRR and completion of the infusion will not meet this definition of a severe IRR.

Any severe IRR in Cohort One will be reviewed by the IDMC to evaluate the IRR, and make recommendations to the TMG regarding whether to adjust the infusion time further, implement any other measures, or delay progress to Cohort Two. If no severe IRRs are noted from the first 60 patients recruited, and the Day 4 routine haematological and biochemical assessments do not demonstrate any clinically significant abnormalities, then sites will be instructed to alter the IMP infusion time in-line with Cohort Two.

After 60 patients have been recruited to Cohort Two, data will be reviewed by the IDMC to evaluate the IRR, and make recommendations to the TMG regarding whether to adjust the infusion time further, implement any other measures, or delay progress to Cohort Three. If there is no severe IRR, then sites will be instructed to alter the IMP infusion time in-line with Cohort Three.

After 60 patients have been recruited to Cohort Three, data will be reviewed by the IDMC to evaluate any IRR, and make recommendations to the TMG regarding whether to adjust the infusion time further, or implement any other measures. If there are no severe IRRs then the infusion and observation times will remain as per Cohort Three for the remainder of the study.

There will be no pause in recruitment whilst the safety analyses are being carried out between cohorts. Progression to the next Cohort will not occur until the safety analysis has been reviewed by the IDMC.

2.9. Sotrovimab Contraindications

Sotrovimab is contraindicated and should not be used in subjects with a history of anaphylaxis to sotrovimab or any of the excipients present in the investigational product. Individuals with these conditions will not be eligible for the study.

2.10. Sotrovimab side effects and concomitant drug interactions

The known side-effects of sotrovimab are hypersensitivity (such as skin reactions, bronchospasm, and infusion-related reactions) and anaphylaxis.

There have been two episodes of anaphylaxis for patients who have received sotrovimab 500mg IV. One incident was as part of the ACTIV-3-TICO study evaluating sotrovimab in patients with COVID-19 that required hospitalisation, and the other was following administration as treatment under Emergency/Temporary authorisation of use. Both individuals had COVID-19 infection at the time of drug administration. Both reactions were within 4 hours of receiving sotrovimab.

No pharmacokinetic drug interaction studies have been conducted with sotrovimab. In vitro combination experiments using sotrovimab and remdesivir showed an additive antiviral effect. Notably, no antagonism was observed between the two agents.

There are no safety concerns associated with co-administration of sotrovimab and any vaccine (including COVID-19 vaccines).

Whilst there are no concerns regarding interaction between sotrovimab and chimeric antigen receptor T-cell (CAR-T) therapy infusions, due to the risk of cytokine release syndrome associated with CAR-T therapy, it is advised to wait 4 weeks from a CAR-T therapy infusion before administering sotrovimab.

3. ELIGIBILITY

3.1. Additional Inclusion Criteria

- Be a member of an immunocompromised population, which includes but is not limited to those groups listed in the core protocol as well as the following:
  - Immunodeficiency (primary and secondary immunodeficiencies)*
  - Any Oncology, Haematology-Oncology or Haematology patient who is currently receiving or has received chemotherapy or who is immunocompromised as a result of their disease or treatment
  - Have a diagnosis of an autoimmune/inflammatory disease currently receiving immunosuppression including those individuals currently on Prednisolone ≥20mg daily for at least 4 weeks. Those who have received Rituximab or Alemtuzumab within the last 12 months would also be eligible.
  - Solid organ and haematopoietic stem cell transplant recipients

If a participant is not eligible for the sotrovimab arm, but still wishes to take part in the PROTECT-V study, their eligibility may be assessed for the other available arms of the PROTECT-V platform. The participant should be re-screened using a new subject ID.

No capping for a specific subgroup will be implemented.

3.2. Additional Exclusion Criteria

In addition to the core exclusion criteria in the master protocol, the presence of any of the following will preclude participant inclusion:

- If in the opinion of the PI it is not in the best interests of the participant to take part in the study - for example due to limited life expectancy (≤12 months) due to pre-existing co-morbidities
- History of hypersensitivity reaction to sotrovimab, one of its excipients or any other monoclonal antibody targeting SARS CoV-2
- Known chronic liver disease or hepatic dysfunction as evidenced by ALT or AST > 3x upper limit of the normal range
- History of receiving any monoclonal antibody targeting SARS CoV-2 within the last 6 months
- Admission to hospital for acute, unplanned care at the time of randomisation or in the two weeks prior to screening
- History of receiving chimeric antigen receptor T-cell (CAR-T) therapy less than 4 weeks prior to consenting to take part in the study

*If a potential participant is using any prophylactic agent for COVID-19 other than a licensed SARS-CoV-2 vaccination, their participation must be discussed with the CI prior to randomisation.

4. BLINDING

PROTECT-V-Sotrovimab will be a double blind placebo controlled study arm where neither the participant nor clinician will be aware of treatment allocation. Sites will need to have unblinded members of the study team in order to dispense and prepare the IMP. Only blinded members of staff will have contact with the participants and administer the IMP dose (see section 2.4). A site blinding plan should be in place to cover the methods used by the site to ensure the blinded study team members are not inadvertently informed of the treatment allocation.

4.1. Emergency unblinding

Please refer to section 4.6.1. of the core protocol for details of the emergency unblinding procedure.

5. RANDOMISATION

At sites where the sotrovimab arm of the study is running, participants wishing to take part in the study will be assessed for eligibility for the sotrovimab arm first. If deemed eligible, they will be recruited to and screened for this arm of the trial. If they remain eligible after screening assessments, participants will be randomised to sotrovimab vs matching placebo in a 1:1 ratio.

At sites where the sotrovimab arm is not running, or if a participant is not eligible to take part in the sotrovimab arm, participants can be screened for the other available arms of the PROTECT-V platform.

Randomisation will be carried out using a web-based randomisation system (Sealed Envelope) accessible via password-protected access. Randomisation for the sotrovimab arm will be stratified by PROTECT-V disease sub-group, age and site using a stratified block randomisation method.

Immediate allocation of treatment will be performed, with documentation of the decision in a blinded confirmatory email to blinded staff and an unblinded email to unblinded staff. The system will specify whether the participants are allocated to sotrovimab or placebo.

Participants and blinded members of the site teams will remain blinded to treatment allocation, i.e. whether active or placebo within a stated intervention.

If a patient declines to participate in the sotrovimab arm or has consented to the sotrovimab arm but then is deemed a ‘screen-fail’, then their eligibility for the other open arms of the trial can still be assessed. Participants may be consented for screening, and if eligible, randomised into one of those arms of the study. Participants will be allocated a new subject identifier if they are being re-screened for another arm.

6. SCHEDULE OF ASSESSMENTS

Assessment Schedule	Screening visit	Day 1[1]	Day 3[2] (±1 day)	Day 4[3] (±1 day)	Day 8 (±3 days)	Day 15 (±3 days)	Day 29 (±3 days)	Every 14 days (±7 days)	Day 85 (±7 days)	Every 28 days (±7 days)	Day 169 (±7 days)	Every 28 days (±7 days)	Day 253 (±7 days)	Day 337 (±7 days) Final Study Visit	Confirmed COVID19 infection[5] (+4 days)	28 days post COVID19 infection[17] (±7 days)	28 days post COVID vaccine[6] (±7 days)	As required
Eligibility check	X																	
Medical history	X																	X
Concomitant Medications[4]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
SARS-CoV-2 PCR	X																	
Serum sample for central SARS-CoV-2 ab assay	X						X		X		X				X	X	X	
Blood tests (FBC, U+E, LFTs[19], clotting, immunoglobulins)	X[20]			X			X		X		X				X	X		
ECG	X						X											
Pregnancy status assessment	X[7]										X[14]		X[15]	X[15]				
Urine ACR	X						X		X		X							
Randomisation		X[8]																
Experimental Work Bloods		X[9]													X	X		
Vital signs (HR, Temp, BP, RR, Sats)		X[10]					X		X		X							
IMP administration		X																
Follow-up questionnaire, AE/SAE collection[4, 11]		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK Sampling		X[12]					X		X		X				X[17]	X		
Anti-drug antibody assessment		X					X				X				X[17]	X		
SAR/SUSAR Reporting																		X
Weekly SARS-CoV-2 PCR until tests negative[4]															X			
COVID19 severity assessment questionnaire[4,13]															X			
Saliva samples[16]		X					X		X		X							
Stool Samples[18]															X	X		

[1]Day 1 visit to take place within 14 days of the screening visit. Day 1 procedures may take place on the same day as screening if all required screening investigations are available prior to randomisation.
[2]Day 3 visit only required whilst lead-in cohorts are being assessed. May be done 24-72 hours post-infusion. Sites will be informed when this visit is no longer required.
[3]Day 4 visit only required for lead-in Cohort 1, and will be a home-visit. May be done 48-96 hours post-infusion. Sites will be informed when this visit is no longer required.
[4]Assessment can be carried out remotely (by phone or video-link) if no other assessment requires on-site presence.
[5]PCR or LFT confirmed COVID19 infection at any point after randomisation into the trial, during the follow-up period.
[6]Only applicable if patient received COVID19 vaccination after randomisation into the trial.
[7]A serum pregnancy test is required for WOCBP within 14 days prior to starting trial treatment. Women are considered WOCBP following menarche and until becoming post-menopausal unless permanently sterile (previous hysterectomy, previous bilateral salpingectomy and or oophorectomy). A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
[8]Randomisation may occur prior to day 1, assuming the participant has met the eligibility criteria, as assessed at the screening visit and following central laboratory SARS CoV-2 antibody assessment.
[9]Experimental medicine samples to be taken prior to IMP administration.
[10]Observations to be taken pre-infusion, at the end of infusion, 1 hour post-infusion and for lead-in cohort 1, 2 hours post the infusion (see Figure A1).
[11]All Adverse Events will be collected up to and including Day 28. Following Day 28, only SUSARs, SARs, SAEs and adverse events of special interest (AESIs) will be collected. See section 12 of Appendix C for further detail.
[12]PK sample to be taken within 1 hour of end of IMP infusion.
[13]To be completed by all participants who have a positive PCR test for COVID19. If symptomatic, to be completed weekly until resolution of COVID19-related symptoms, until 28 days after PCR confirmation of infection or hospitalisation, whichever is sooner. If asymptomatic, to be completed weekly for two weeks. If asymptomatic, but then becomes symptomatic, to be completed weekly until resolution of COVID19-related symptoms, until 28 days after PCR confirmation of infection or hospitalisation, whichever is sooner.
[14]Urine pregnancy test is adequate.
[15]Pregnancy assessment based on history from participant is adequate.
[16]These samples will only be taken at Cambridge & University Hospitals Birmingham NHS Foundation Trust sites.
[17]PK and ADA samples at the time of PCR-confirmed COVID19 infection will only be taken from participants who will be attending site for this visit.
[18]Stool samples only to be taken where possible and feasible to do so
[19]Routine ALT/AST tests performed up to 2 week before screening visit will be accepted to assess liver function
[20]see section 6.1.1.

6.1. Trial Assessments

6.1.1. Screening

In addition to the core components of the screening visit listed in section 4.7.1.1. of the master protocol, the following will be conducted:

- ECG
- Serum antibody sample for Roche Elecsys® Anti-SARS-CoV-2 assay. This will be processed in a central laboratory (refer to trial procedure manual for further details)
- Full blood count, clotting profile, renal and liver function
- serum pregnancy test in women of child bearing potential
- Urine albumin:creatinine ratio
- Immunoglobulins

Results of liver function test (permitted within the preceding 2 weeks), pregnancy test and COVID PCR/Lateral Flow test are required prior to eligibility confirmation, randomisation and IMP administration.

The screening assessment should be less than 14 days prior to date of planned IMP administration.

It is permissible for screening investigations that are not essential for determining eligibility (such as ECG, full blood count, clotting profile, renal function, urine albumin creatinine ratio and immunoglobulins) to be taken on Day 1 **prior to IMP infusion**, although every effort should be made to take at screening visit. It is permitted to conduct a screening and Day 1 visit on the same day, provided the site has facility to obtain results of essential screening investigations, randomise the patient and administer IMP on the same day.

6.1.2. Day 1 infusion visit

Prior to commencing the IMP infusion, a blood sample to measure ADA will be collected. Blood samples (up to 70mL in total), will be taken for the additional experimental medicine work packages. Saliva samples will be taken at selected sites local to Cambridge and Birmingham only. Refer to the sample collection section of the trial procedure manual and Section 9 of Protocol Appendix C. Where possible, blood will be drawn at the time of intravenous cannula insertion, or from pre-existing vascular access lines.

Observations (pulse, blood pressure, temperature, respiratory rate and oxygen saturations) must be taken prior to infusion, at the end of infusion, 1 hour after infusion and for lead-in Cohort One, at 2 hours after infusion. All observations must be recorded in the eCRF.

PK samples to be taken within 1 hour after end of infusion (see PK section 6.1.15).

6.1.3. Day 4 safety bloods visit

A blood sample will be taken for all participants enrolled into lead-in Cohort One, 48-96 hours (3-5 days) post-infusion for FBC, renal and liver function tests and clotting profile. This will be a home-visit and will consist of a single blood-draw only. Sites must book this visit with the home-nursing team (see PROTECT-V Sotrovimab arm Trial Procedure Manual and Homecare Manual). Sites should continue to book the Day 4 visit with the home-nursing team until they have notification from the PROTECT-V Trial Office that these assessments are no longer necessary.

6.1.4.Remote follow-up assessments

Please refer to section 4.7.1.2 of the core protocol.

Remote assessments will be made at week 1 (day 8 +/- 3 days from the day of IMP dose), week 2 (day 15 +/- 3 days), every 2 weeks from week 6 (day 43 +/- 7 days) to week 12 (day 85+/- 7 days), and every 4 weeks from week 12 (day 85+/- 7 days) to week 36 (day 253 +/- 7 days). The final telephone assessment will take place at week 48 (day 337 +/- 7 days).

An additional Day 3 telephone assessment (24-72 hours (1 to 3 days) after the infusion) for adverse events only will be required for participants within the lead-in cohorts. Sites should continue performing Day 3 telephone assessments until they have notification from the PROTECT-V Trial Office that these assessments are no longer necessary.

Telephone, email or electronic medical record communication systems (such as MyChart via EPIC) can be used according to local site preference.

While week 12 is the primary endpoint (efficacy of sotrovimab in prevention of symptomatic confirmed COVID-19 (either by PCR or lateral flow test; LFT) over 12 weeks), and primary endpoint efficacy analyses will commence following the last subject reaching week 12 or the last infection + 28 days for WHO severity determination, whichever is later - the week 48 phone call is intended to assess safety, concomitant medications, and pregnancy status in WOCBP.

See section 4.7.1.2 of the core protocol. All data will be collected as specified in the core protocol, but the PI will not need to make a decision regarding continuation of IMP since it is a single IV infusion. The follow up assessment will collect information on COVID-19 infection status, new medications and vaccinations.

6.1.5. Day 29 (week 4) (+/- 3 days), week 12 (+/- 7 days) and week 24 (+/- 7 days) in- person assessments

Activities as detailed in the schedule of assessments will be conducted including:

- Blood draw (for routine blood tests, PK sampling and ADA sampling [ADA sampling week 4 and week 24 only]),
- ECG (day 29 only)
- Urine sample for albumin/creatinine ratio
- Saliva sample collection (for selected sites local to Cambridge and Birmingham only, please see trial procedure manual for further details)
- Vital signs
- Adverse event check

6.1.6. PK and ADA assessment

Refer to trial procedure manual and schedule of assessments for full details. All equipment for collecting PK and ADA samples will be supplied to site.

6.2. Assessments in the event of a patient developing symptomatic, confirmed COVID-19 infection (either by PCR or lateral flow test)

If COVID-19 infection is confirmed either by PCR or lateral flow test (LFT):

a) Participants will be asked to complete a COVID-19 severity assessment questionnaire. This should be completed weekly, via a telephone call with the local research team, until symptoms have resolved, until 28 days following COVID-19 infection confirmation, or until hospitalisation, whichever is sooner.
b) Participants will be asked to undergo blood-sampling for routine safety investigations as well as immunoprofiling work, as set out in sections 7.1 and 9 below.
c) Participants who are attending sites for this assessment will also have PK and ADA samples taken.
d) Participants will be supplied with COVID-19 PCR swabs to be completed weekly and returned to the central study laboratory for viral load determination and sequencing to evaluate viral evolution until the PCR result is negative.
e) Where possible a stool sample will also be collected.

Participants should continue to attend scheduled study visits (in person and telephone).

In the event of discordant PCR/LFT results, the result of the positive test, whichever that may be, will be used to trigger the primary endpoint of the study.

Participants will be eligible to receive established standard of care treatments for SARS-CoV-2 infection (e.g. dexamethasone, anti-SARS-CoV-2 mAb, remdesivir or other antivirals) at the discretion of the local investigator or their usual practitioner.

28 days post confirmed infection, all participants will undergo blood-sampling for SARS-CoV-2 antibody titres, PK and ADA measurement, and where possible, will also have stool samples collected.

6.3. Trial Restrictions (monoclonal arm)

Women of childbearing potential are required to use effective contraception for the duration of the trial for at least 48 weeks after treatment infusion. This includes:

- Intrauterine Device (IUD)
- Hormonal based contraception (pill, contraceptive injection or implant etc.)
- Barrier contraception (condom and occlusive cap e.g. diaphragm or cervical cap with spermicide)
- True abstinence (where this is in accordance with the participant's preferred and usual lifestyle)

Where possible the administration of prophylactic agents for COVID-19, should be deferred until at least 12 weeks after IMP infusion. In the event that a randomised participant commences a prophylactic agent for COVID-19 other than a licensed SARS-CoV-2 vaccination, their ongoing participation must be discussed with the CI. It is at the discretion of the CI as to whether the participant is to continue in the study, or whether they must be withdrawn.

7. ADDITIONAL OBJECTIVES

7.1. Additional exploratory objectives

a) To describe the effect, if any, of sotrovimab therapy on SARS-CoV-2 viral evolution, and monitor for any emergence of a variant of concern as a result of sotrovimab therapy
b) To describe the development of anti-sotrovimab antibodies (immunogenicity) in this patient group and their potential association with PK levels and efficacy
c) To describe the PK of sotrovimab over a 24 week period
d) Immunoprofiling of individuals who develop COVID-19 infection despite sotrovimab therapy pre-, during and post-SARS CoV-2 infection
e) To describe the effect of antibody titre on rates of SARS CoV-2 infection

8. ADDITIONAL OUTCOMES

8.1. Primary Outcomes

The primary outcome for the PROTECT-V sotrovimab arm is confirmed symptomatic COVID-19 infection at 12 weeks (85±7 days) from date of IMP administration.

The primary outcome event (symptomatic COVID-19 infection) is defined in section 4.12.1.1 of the core protocol.

8.2. Secondary Outcomes

In addition to secondary outcomes referenced in section 4.12.2 of the core protocol, the following additional outcome will be assessed:

Confirmed, symptomatic COVID-19 infection at 16 weeks (113±7 days) from date of IMP administration.

Confirmed, symptomatic COVID-19 infection at 24 weeks (169±14 days) from date of IMP administration.

Confirmed, symptomatic COVID-19 infection at 36 weeks (253±14 days) from date of IMP administration.

Confirmed, symptomatic COVID-19 infection at 48 weeks (337±14 days) from date of IMP administration.

8.3. Additional exploratory outcomes

In addition to those outcomes listed in the core protocol, the following exploratory outcomes will be evaluated:

a) Viral load and sequencing in patients who develop SARS-CoV-2 infection by week 48
b) Occurrence of anti-drug antibodies in trial participants (immunogenicity)
c) Description of the PK profile of sotrovimab over a 24 week period
d) Description of individual participant's immunological profile at baseline, the time of SARS-CoV-2 infection and 1 month post-infection, in participants who developed infection by week 48
e) Serum antibody titres to SARS-CoV-2 at baseline will be correlated with the development of SARS CoV-2 infection

9. EXPERIMENTAL MEDICINE SAMPLES

These samples will be used to address exploratory outcomes in section 8.3 above.

Please refer to the sample section of the trial procedure manual (includes details about sample collection, preparation, storage and transport) and the experimental medicine SOP for further details.

Saliva samples will only be collected at sites local to Cambridge and Birmingham.

Where possible the following samples will be collected at the Day 1 infusion visit in all participants in the sotrovimab arm, and in those subjects that develop COVID-19 infection and 28 days later:

Serum, plasma, PBMC, DNA, RNA (up to 70mL blood in total).

Samples will be collected as close as possible to when the participant tests COVID-19 positive (either by PCR or LFT) (ideally within 96 hours) and then 28 days (+/- 7 days) later.

Samples will be labelled with the subject's unique trial identifier. These samples will be shipped immediately for centrally processing at the University of Cambridge or the University of Birmingham, and appropriately stored for future analyses including but not confined to B and T cell immunophenotyping, functional B and T cell assays, anti-cytokine assays, evaluation of the role of mucosal immunity and neutrophil function analyses.

Hypotheses include:

1. Is there an immunological signature associated with SARS CoV-2 infection in individuals who have failed to mount a protective vaccine response?

2. Can this signature also be identified at baseline in individuals treated with sotrovimab, who develop SARS CoV-2 infection?

3. How does the immune profile of individuals who develop infection change from baseline?

4. What is the impact of sotrovimab on the immediate immune response to SARS CoV-2 infection?

5. Is the longer term immune response to SARS Cov-2 infection influenced by sotrovimab?

10. STATISTICS

10.1. Statistical methods

Please refer to section 4.14 of the core protocol for 4.14.1 Analysis populations and 4.14.3 Safety evaluation.

10.1.1. Efficacy Analyses

10.1.1.1. Primary Efficacy Analysis

The primary efficacy analysis of this trial will be a analysis for the difference in the distribution of symptomatic COVID-19 infection at 12 weeks between the sotrovimab group and the placebo group (two-sided at an α-level of 5%), that is, to test the following hypotheses:

H_0: there is no treatment difference between sotrovimab and placebo in proportion of patients who develop symptomatic COVID-19 infection

Vs.

H_1: there is a treatment difference between sotrovimab and placebo in proportion of patients who develop symptomatic COVID-19 infection

The odds ratio or the relative risk with the corresponding 95% confidence interval will be presented as appropriate. The disease sub-group and age at randomisation will be adjusted for as fixed effects in the analyses.

Primary efficacy analyses will be performed according to ITT in participants who have received any IMP.. If the statistical significance at a 2-sided 0.05 level is established for the primary efficacy outcome measure, a hierarchical testing procedure will be applied to the key secondary efficacy outcome measures at a 2-sided 0.05 significance level. The order of testing sequence for key secondary outcome measures is 1) Confirmed, symptomatic COVID-19 infection at 16 weeks (113±7 days) from date of IMP administration 2) Confirmed, symptomatic COVID-19 infection at 24 weeks (169±14 days) from date of IMP administration; 3) Confirmed, symptomatic COVID-19 infection at 36 weeks (253±14 days) from date of IMP administration; 4) Confirmed, symptomatic COVID-19 infection at 48 weeks (337±14 days) from date of IMP administration. Further detail will be documented in the Statistical Analysis Plan (SAP).

Every effort will be made to reduce missing data and it is anticipated that missing data on the primary outcome measure will occur in a very small proportion of participants as the primary endpoint data will also be obtained via linkage to UK Health Security Agency (UKHSA; formerly PHE) data. Methods to assess missing data and missing data sensitivities will be detailed in the analysis plan. The estimand properties of the primary and sensitivity analyses of the primary endpoint will be detailed in the Statistical Analysis Plan.

10.2. Number of patients to be enrolled

The primary outcome measure is symptomatic COVID-19 infection at 12 weeks (85±7 days) from the date of IMP administration. It is anticipated that there will be a reduction of 75% in symptomatic COVID-19 infection with sotrovimab treatment compared with the placebo arm. With the estimated symptomatic COVID-19 infection rate at 12 weeks around 5% to 9% in the placebo arm using currently available blinded data from this arm and unblinded data from the niclosamide arm of PROTECT-V (Appendix A), the table below is a range of sample sizes using the Fisher's exact test with a 5% significance level, 90% power and two-sided test to detect a 75% reduction.

Symptomatic COVID-19 infection rate at 12 weeks		Total number of patients required	Total sample size allowing for 10% non-compliance
placebo arm	Sotrovimab arm with a 75% reduction		
5%	1.25%	932	1036
6%	1.5%	772	858
7%	1.75%	658	732
8%	2%	574	638
9%	2.25%	506	562

Considering the significant uncertainty in the anticipated infection rate during the study period, the sample size assumption will be monitored and reviewed regularly by the independent Data Monitoring Committee (IDMC) in a blinded manner. The study team will consult with the IDMC regarding timing of performing efficacy analyses with consideration of an event driven strategy (Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol. 2004;159(7):702-6.). Approval will be obtained from both the IDMC and TSC prior to performing the primary endpoint analysis.

10.3. Interim Analyses

An independent Data Monitoring Committee (IDMC) will review data, by treatment group on safety of patients in the trial. The IDMC will meet approximately every two months until the end of the trial. In addition, during the initial three lead-in cohort period and prior to the final infusion time being established, the IDMC will review severe Infusion related reaction (IRR) events whenever they are observed and have additional meetings as required.

There are no plans to stop the trial early for efficacy and therefore no interim analyses for efficacy or futility. Efficacy data, by treatment arm, will therefore not be routinely provided. The IDMC can request efficacy data, by treatment group, confidentially from the Trial Steering Committee (TSC) if changes to the protocol are considered and these data are required by the IDMC in order to reach decisions about the ongoing risk/benefit to patients in the trial. If efficacy data are reviewed, a Haybittle-Peto boundary may be used. Full details will be given in the IDMC charter.

11. CRITERIA FOR EARLY TERMINATION

The study will be reviewed approximately every 2 months by the independent Data Monitoring Committee (IDMC). The detailed stopping guidance will be included in the IDMC charter.

The study will be stopped early if there are any safety concerns based on the recommendation of the independent Data Monitoring Committee and the approval from the Trial Steering Committee. As guidance, the study might be stopped early for safety concerns

- if the rate of unacceptable toxicity attributable to study drug in the sotrovimab arm is over 20%, that is, the estimated lower limit of a 95% confidence interval is greater than 20%

- if the incidence of moderate/severe adverse events in the sotrovimab arm is 15% greater than that of the placebo arm, at 12 weeks (85±7 days from date of randomisation) at a significance level of 0.05 for the first 20% patients recruited and followed up for 12 weeks from the date of IMP administration.

12. SAFETY REPORTING

12.1. Recording, Evaluating & Reporting Serious Adverse Events / SARs

The Chief Investigator will ensure that all safety information is reported to GSK at the same time as notification to the Sponsor. The Sponsor will be informed of any SAE/SAR reported to the CI immediately but not more than 24 hours after the CI is first notified. GSK will be informed of any SAE/SAR reported to the CI not more than 72 hours after the CI is first notified.

All AEs (serious and non-serious) will be reported until Day 29 of the study as these are most likely to be potentially related to study drug. Data regarding any AE reported prior to Day 29 will be gathered until resolution of the AE. The population that will take part in this study are multi-morbid and suffer from numerous fluctuating chronic symptoms. Recording all symptoms as possible AEs beyond day 29 would likely lead to an inability to identify any meaningful trends in the AE analysis.

Beyond Day 29, all SAEs and adverse events of special interest (AESI) (whether serious or non-serious) will continue to be assessed until the final study visit on week 48 or day 337. All of these events will be followed to resolution, are otherwise explained or the patient is lost to follow-up. These have been defined based on potential risks associated with the mAb class of therapeutics administered via intravenous infusion and the data available from the COMET-ICE study, and include the following:

- Hypersensitivity reactions (including skin reactions and bronchospasm) at any time after IMP infusion – will be solicited through week 12.
- Infusion-related reactions within 24 hours after IMP infusion (including pyrexia, chills, dizziness and dyspnoea)
- Antibody dependent enhancement (ADE) of disease in those who reach the primary end-point will be assessed

  ADE is a theoretical risk with vaccines and antiviral antibodies and has been best described in association with some vaccine development programs. ADE can occur via one of three previously described mechanisms:

  - By facilitating viral entry into host cells and enhancing viral replication in these cells;
  - By increasing viral fusion with target host cells, enhancing viral replication in these cells;
  - By enhancing disease pathology from viral antigen-antibody related immune complex deposition or complement activation and immune cell recruitment in target organs.

  The first two mechanisms are hypothesised to occur at sub-neutralising antibody concentrations. The third mechanism is hypothesised to occur at high levels of antigen (i.e., viral load) and antibody potentially leading to immune complex deposition and complement activation in tissue sites of high viral replication. This may manifest as acute deterioration in clinical status temporally associated with sotrovimab infusion or as increased severity or duration of illness in sotrovimab-treated participants who reach the primary end-point, compared to what would be clinically expected.

New SAE reporting for patients enrolled to the sotrovimab arm will stop at the time of the final study visit. However, for those who withdraw from the trial prior to the final study visit, new SAE reporting will cease at Day 29 or date of withdrawal, whichever is the latter. SAEs reported prior to these dates will be followed up to closure.

12.2. Reference Safety Information (RSI)

For this trial the Reference Safety Information is:

1. VIR Investigator's Brochure for VIR-7831 – Treatment and prevention of COVID-19, Edition 3, November 2021, Section 6.6.2.

12.3. Pregnancy Reporting

The Chief Investigator will ensure that all pregnancies of female participants are reported to Sponsor and GSK within 24 hours of awareness.

13. JUSTIFICATION OF STUDY DESIGN AND RISK/BENEFIT ASSESSMENT FOR ADDITION OF SOTROVIMAB TO THE PROTECT-V PLATFORM

13.1. Is there still a need for an additional arm in the PROTECT-V platform in light of the COVID-19 vaccination program (including third primary doses and booster doses) as well as other non-vaccine agents?

Preventing infection due to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the cause of COVID-19, is an urgent public health priority. Prevention of COVID-19 with therapeutic interventions has the potential to significantly reduce disease-associated morbidity and mortality, as well as transmission in the community. A number of vaccines for the prevention of COVID-19 have been approved globally. While these currently available vaccines have been shown to be highly efficacious in the general patient population in which the clinical trials were conducted, there are limited data on efficacy in patient populations where immunogenicity may potentially be impaired.

Patients who receive systemic immunosuppression or have an underlying immunodeficiency are at high risk of morbidity and mortality from COVID-19. Solid organ transplant recipients had a 3.53 (95% CI 2.77-2.49) increased risk of COVID-19-related death in the first wave in the UK, the highest increased risk of all medical conditions incorporated in the OpenSAFELY analysis (27). A case series undertaken by the UK Primary Immunodeficiency network found that infection-associated fatality rates were significantly higher in primary immunodeficiency (20%) and secondary immunodeficiency (33.3%) than the general population (28).

In addition, there is mounting evidence that many of these individuals mount sub-optimal responses to vaccines. In July 2021, a synthesised review of 35 studies looking at vaccine response in renal patients; only 35% (29-42%) of individuals with a renal transplant mounted a protective response after two doses of

SARS CoV-2 vaccine (29). Although, third doses lead to a response in approximately 50% of those individuals not protected after 2 doses, a considerable number of immunocompromised patients remain vulnerable to SARS CoV-2 infection (30, 31).

Less data is available on patients with autoimmune disease. Figure A2 compares SARS CoV-2 vaccine responses in patients also with malignancy or receiving immunosuppressive therapies (32). The literature on vaccine response in individuals with autoimmune disease is more complicated in view of disease and treatment heterogeneity, but responses are also sub-optimal compared to healthy individuals. Table A1 shows the vaccine responses from 695 patients in Cambridge, UK (unpublished data) and demonstrates not only the proportion of patients responding to vaccination, but the sub-optimal magnitude of response (threshold of protection for this assay 1896; healthy control titres >30,000).

It is important to note that the majority of studies report absolute antibody titres, which does not indicate the functionality and neutralising capacity of the antibodies. In a study of 178 dialysis patients in the UK, the Astra-Zeneca vaccine (AZD1222) when administered alone in sero-naive individuals induced suboptimal neutralising antibody titres against all variants of concern (VOCs), including the delta variant that is currently dominant globally (33). We considered using a neutralising measure as an eligibility criterion rather than antibody titres alone. However, as a screening tool, this is not possible due to limited availability and high cost. It is also unlikely to become routinely available which would limit rapid translation into practice, should the trial show a positive result.

	Dialysis (N=258)	Autoimmune (N=228)	Transplant (N=209)
% response post dose 1	81	45	34
% response post dose 2	96	70	56
Median (IQR) S antibody titre post dose 1	7578 (3023 – 20898)	1327 (155 – 12659)	568 (193 – 3916)
Median (IQR) S antibody titre post dose 2	30806 (26385 – 31951)	19935 (1203 – 30558)	4286 (295 – 26230)

Table A1: Vaccine response in three groups of immunocompromised renal patients in Cambridge. Threshold of protection for this assay is 1896.

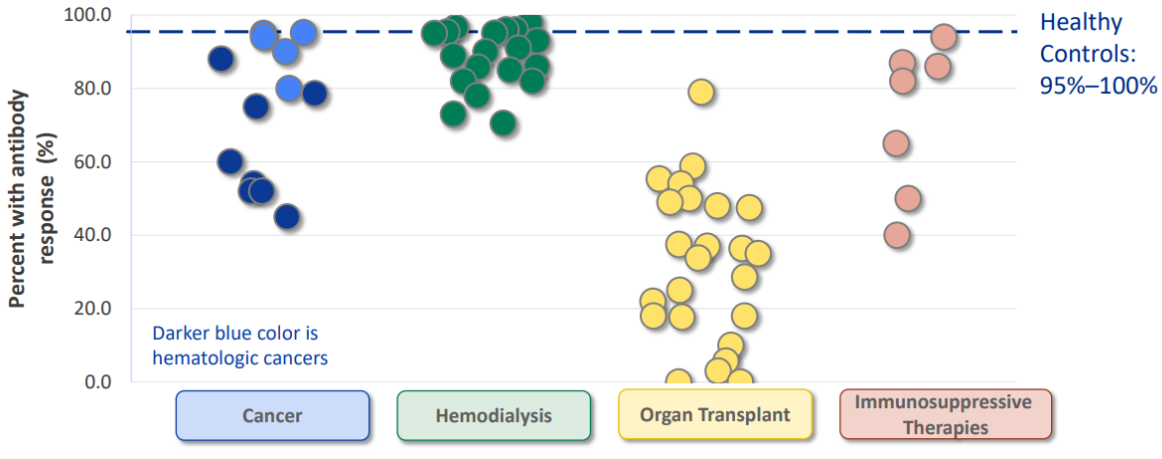


Figure A2: Percent of subjects with antibody response after two mRNA vaccine doses by immunocompromising condition and study (n=63) (32).

Furthermore, some studies have reported that immunocompromised persons account for a high proportion (≥40%) of infections among fully vaccinated, hospitalised persons, providing further evidence of sub-optimal vaccine response (34, 35).

Therefore, despite vaccination, and the third dose and booster vaccination campaign, sub-optimal vaccine response and vulnerability to COVID-19 infection remains a major issue in immunocompromised patients.

There are currently limited non-vaccine agents that are approved for use in immunocompromised patients. In the UK, the anti-SARS-CoV-2 mAb casirivimab/imdevimab (Ronapreve) recently received a conditional marketing authorisation for the prevention and treatment of COVID-19. Use of Ronapreve for prophylaxis was based on efficacy shown in an RCT trial evaluating the subcutaneous administration of Ronapreve for prevention of SARS-CoV-2 infection in seronegative individuals with a household exposure (36). Notably, this study was conducted during a time period with less widespread vaccination and less circulation of COVID-19 variants of concern.

Evusheld has now been issued with Conditional Marketing Authorisation by the UK MHRA for pre-exposure prophylaxis of COVID-19 in adults who are not currently infected with SARS-CoV-2 and who are unlikely to mount an adequate immune response to COVID-19 vaccination, or for whom COVID-19 vaccination is not recommended, though we are not aware of any published data evaluating its efficacy as a prophylactic agent in the patient population being evaluated in this study, or against the Omicron variants that are currently prevalent in the UK.

Some novel oral antiviral agents targeting COVID-19 are being developed. Molnupiravir (Lagevrio), has recently been approved by the UK's MHRA for the treatment of mild to moderate COVID-19 disease (37). Paxlovid (PF-07321332; ritonavir) has also recently been reported to reduce the risk of hospitalisation or death by 89% compared to placebo in non-hospitalised high risk adults with COVID-19. Data is only available on the efficacy of these drugs in patients with confirmed COVID-19 disease, and their efficacy as a prophylactic agent is currently unknown (38).

Therefore, there is an urgent need for development of effective modalities for pre-exposure prophylaxis with conserved activity against emerging SARS-CoV-2 variants in the immunocompromised patient population.

13.2. Broadening inclusion criteria to include non-renal patients who have mounted sub-optimal vaccine responses

The PROTECT-V trial platform is designed to study agents for pre-exposure prophylaxis in vulnerable individuals. The trial commenced prior to the COVID-19 vaccine program, and as such vaccine response was not considered in eligibility criteria. The trial commenced recruiting renal patients, as dialysis patients were severely impacted early in the pandemic, and were unable to shield. Furthermore, an existing network of renal sites and investigators were selected to facilitate rapid set-up, and renal transplant patients and individuals with autoimmune renal disease were also included as they were managed by the same clinicians and identified as being clinically extremely vulnerable.

Response to vaccination has clearly modified the risk profile of COVID-19 infection. Defining vaccine response is complicated but serological tests are now available to measure antibody titres, and identify those individuals with sub-optimal or absent serological responses. Although neutralisation assays would offer a functional measure, they are not practical screening tests for a clinical trial, and are unlikely to become widely available as part of routine care to guide the use of monoclonal antibodies should they demonstrate benefit.

Now that the platform is established, a network has been developed with clinicians beyond the renal community enabling the following clinically extremely vulnerable patients to be enrolled

- Primary immunodeficiency
- Any Oncology, Haematology-Oncology or Haematology patient who has received chemotherapy or who is immunocompromised as a result of their disease or treatment
- Have a diagnosis of an autoimmune/inflammatory disease currently receiving immunosuppression
- Solid organ and haematopoietic stem cell transplant recipients

Inclusion of these vulnerable patients at this stage of the pandemic is also a timely intervention. Due to relaxation of UK-government COVID-19 restrictions, these patients are no longer shielding to the same extent that they were at the beginning of the pandemic, when PROTECT-V was first launched, increasing the possibility of COVID-19 disease in this patient cohort.

In order to effectively expand recruitment into these patient groups, a strategy to recruit from these new patient cohorts has been implemented. National leads have been appointed to drive recruitment across all centres for their allocated patient cohorts. The individuals are leading physicians in their respective fields and have established links with physicians across the country who would be able to recruit these patients. Individual sites will take different approaches to recruitment, however, we recommend identifying clinician sub-investigators at each site with expertise in managing patients from each cohort in order to create an effective recruitment strategy.

13.3. Justification for the intensity of scheduled follow up

The intensity and manner of follow up has been carefully considered to minimise healthcare interactions with clinically extremely vulnerable individuals, but to ensure that there is sufficient monitoring to ensure patient safety. Since an antibody titre is required for eligibility, and a central laboratory is being used to standardise the assay, it is not possible to conduct the screening and infusion on the same day. Three further in person visits at weeks 4, 12 and 24 are required for safety monitoring in order to draw blood samples for safety bloods and PK assays. All other assessments will be conducted via telephone (online and postal questionnaires are not permitted for this arm, as sotrovimab is a novel drug, and this approach is being taken to minimise any loss to follow up) initially weekly for the first 4 weeks, fortnightly during weeks 4-24 and then 4 weekly until week 36 with a final call at week 48.

This study will be the first time a 2000 mg dose will be used in humans. There are no theoretical safety concerns for the use of this dose, based on the NOAEL data. Data from previous in-human studies using a 500mg dose of sotrovimab suggests infusion-related reactions are the most likely adverse events to occur. Given this, we have introduced three lead-in cohorts with consecutive reductions in infusion times to evaluate the most appropriate rate of drug infusion as well as the observation period thereafter (see Figure A1). There will also be an additional telephone assessment 24-48 hours after the infusion for participants within these three lead-in cohorts. For lead-in Cohort One, there will also be an additional set of routine safety bloods on Day 4. Progression of recruitment from one cohort to the next will not occur until independent review of the safety data by the IDMC.

13.4. Collection of Adverse Events up to Day 29 only

Sotrovimab has been administered to tens of thousands of individuals and has a very favourable safety profile. However, it is a novel agent, and therefore all adverse events (AEs) (new symptoms or clear deterioration of pre-existing symptoms) will be collected up until day 29 post dose. The population that will take part in this study are often multi-morbid and suffer from numerous chronic symptoms (e.g. fatigue, nausea). Recording all symptoms as possible AEs beyond day 29 would likely lead to an inability to identify any meaningful differences in the AE analysis. Therefore, only SAEs and AESIs will be collected from Day 29 onwards.

13.5. Rationale for revision of event rate (symptomic COVID-19 infection)

Predicting the event rate is extremely difficult as it is affected by so many variables – public health measures, circulating levels of virus, and variants. Furthermore, the event rate is non-linear. Public Health England data from existing patients recruited to PROTECT-V indicates a 13% attack rate in the last 24 weeks. These patients do tend to shield when able, but as the pandemic continues, many are of working age with dependents, and cannot continue formal shielding, especially as current government guidance does not recommend continuation of shielding. It must also be noted that there has been a reduction of mask-wearing and loss of other public health measures designed to reduce COVID-19 transmission. These changes must be counter-balanced with the shortening in primary end-point from 24 weeks to 12 weeks. Given this level of uncertainty, we believe having a range of 5-9% event rate at 12 weeks within the protocol to be the most appropriate way of representing the recruitment target for this study.

The study is powered to detect a 75% risk reduction of symptomatic COVID-19 infection. The event rate will be monitored by the independent Data Monitoring Committee (IDMC), who within their charter can make recommendations regarding sample size re-calculation should the event rate be different than anticipated. Together with the recruitment monitored regularly, the IDMC will also make recommendations regarding the timing of performing efficacy analyses with consideration of an event driven strategy.

13.6. Justification of a 12-week primary endpoint

The primary outcome measure and clinical study report (CSR) will be based on the data from the first 12 weeks of study. The primary endpoint was updated based on new population PK analyses that incorporated data across several studies evaluating a sotrovimab 500 mg IV dose. Based on these preliminary PK analyses, as well as the shift in EC_{50} with the Omicron sub-variants, the predicted median (5^{th}, 95^{th} percentile) serum concentrations of sotrovimab at 12, 16 and 24 weeks following dosing were evaluated. While the 2000 mg IV dose is expected to maintain adequate coverage above tissue-adjusted EC_{90} (for WT and for variants with <22-fold shift in potency) through 24 weeks, the primary endpoint was changed from 24 weeks to 12 weeks to ensure the highest likelihood of demonstrating efficacy, particularly with the current BA.2 variance predominance. PK sampling will be conducted within 1 hour post-infusion and at days 29, 85 and 163 in the trial to provide further supporting evidence. Secondary endpoint analyses will include time to event and response at 16 week, 24 week, 36 week and 48 week measures, so these analyses coupled with the PK data will be able to demonstrate any waning effect of sotrovimab. There will be an additional addendum to the CSR, including all safety and follow-up data collected up until week 48 of the study.

13.7. Management of individuals who develop COVID-19 infection during the study

Individuals who develop COVID-19 infection during the trial should be treated according to standard of care at that time, including the receipt of monoclonal antibody therapy if it is indicated. If it is possible, the remaining protocol assessments should be assessed for patients with positive 'COVID19'.

We considered unblinding patients that develop COVID-19 during the study, and administering sotrovimab to those who had received placebo. However, we felt that it is ethically sound and logistically more straightforward to recommend standard of care treatment, without unblinding, especially given the rapidly changing nature of COVID-19 therapeutics. There is no theoretical safety concern of interaction between two anti-SARS-CoV-2 monoclonal antibodies, and it may be determined to be beneficial by a patient's treating clinician to administer another mAb as standard of care, even in those who were previously randomised to sotrovimab. In the BLAZE-4 study (NCT04634409), a clinical trial with multiple arms evaluating anti-SARS-CoV-2 mAbs from Eli Lilly and Company and GSK/Vir, sotrovimab was used in combination with bamlanivimab in one arm.

Given sotrovimab's mode of action, there is no theoretical indication that it would interact with the oral anti-SARS-CoV-2 agents mentioned above.

There is also no theoretical risk of receiving a further 500mg dose of sotrovimab having received 2000mg already (according to the available NOAEL data).

13.8. Concerns about monoclonal antoantibodies driving viral evolution

Immunocompromised individuals may be slow to clear the virus, and have been reported to shed virus for many weeks, allowing opportunity for development of mutations. Therefore, the prevention of COVID-19 infection in these individuals is key. However, since there is concern that monoclonal antibodies such as sotrovimab may drive this process, a robust viral screening process is integrated into the protocol. Individuals who develop COVID-19 infection will continue weekly nasopharyngeal PCR swabs, which will undergo deep sequencing to address the question of viral evolution, until PCR negative.

13.9. Concerns about waning of sotrovimab concentrations as the study progresses

The dose of sotrovimab (2000mg) and anticipated duration of efficacy (12 weeks) have been calculated using intensive PK analysis and advanced modelling taking into account the Omicron (B.1.1.529) VOC (as described in 'Section 1.2 Dose Rationale'). In order to ensure sotrovimab levels remain at the anticipated concentrations, we plan to undertake PK sampling at days 1, 29, 85 and 169. This will allow us to confirm sotrovimab concentrations remain at therapeutic levels throughout the study period. In case of unexpected early falls in sotrovimab levels, the efficacy at earlier time points will be investigated guided by the PK sampling results. We will also be measuring PK levels in some patients who develop symptomatic COVID-19 infection in order to assess sotrovimab concentrations in those with break-through infection.

13.10 Removal of antibody threshold of <400 IU/ml as an inclusion criterion

When the sotrovimab arm of PROTECT-V was designed in 2021, the majority of potential participants had received just 2 doses of vaccine against SARS CoV-2. Based on the data available at the time, an antibody threshold of <400 IU/mL was set for inclusion into the study, with the rationale that those with a titre less than this would be most at risk of developing symptomatic COVID-19 infection. However, as of January 2023, most patients have received at least 4 vaccine doses if not 5 or 6. Despite vaccination, the immunocompromised populations remain at risk of symptomatic infection with worse outcomes, but antibody titres have been higher than anticipated, leading to a higher screen fail rate in those who have been enrolled

to the sotrovimab arm of PROTECT-V thus far. In addition, there is no data to suggest that anti-spike antibody levels are a correlate of protection in the immunocompromised population.

There is a balance between timely recruitment to the trial, and the theoretical risk of dilution of an effect size with a higher antibody threshold (though a direct clinical correlate of antibody titres and different thresholds is yet to be established in the literature). Furthermore, the situation is complicated with emerging variants, where higher antibody titres may be required to have a comparable neutralising effect. It is becoming clear that rather than a definitive threshold of complete protection vs no protection, there is a spectrum of protection, and PROTECT V is in an ideal situation to evaluate this spectrum within the trial design.

Therefore, given the lack of evidence for antibody levels being a direct correlate of protection, the antibody titre as a requirement for inclusion has been removed. All those in an at-risk groups currently included in the PROTECT-V trial would be eligible, regardless of their antibody level. The antibody levels would still be measured at recruitment in order to enable a pre-defined, secondary analysis of efficacy effect according to antibody titre. Once implemented, those previously screened and deemed ineligible due to raised antibody titre may be re-approached and re-screened using a new study ID number.

14. ADDITIONAL FINANCIAL SUPPORT

Trial medication and additional funding for this arm of this trial is provided by GSK and Vir Biotechnology.

As part of this support GSK will be provided the following:

- All DMC/TSC aggregated anonymised open session reports related to the Sotrovimab protocol will be shared within 30 days of the meetings.
- Any emerging safety findings with the IMP identified by the DMC meetings will be reported to GSK within 24 hours
- The study database on the date of database hardlock, in a link anonymised form, to GSK, at the end of the study for regulatory filings, for further research or other purposes.

15. PUBLICATIONS POLICY

The analysis of the primary outcome measure will be performed when all randomised patients have completed week 12 or up to 4 weeks post the date of the last confirmed positive COVID-19 result to allow for symptom collection, for those cases that occur between week 8 and week 12. The efficacy on key secondary outcome measures analyses will be when there are a sufficient number of patients that have completed week 16, week 24, week 36 and week 48 (or up to 4 weeks post the date of last confirmed positive COVID-19 result), using a hierarchical testing procedure. The details will be documented in the SAP. The results will be published as soon as possible.

Individual clinicians must not publish data concerning their patients that are directly relevant to questions posed by the trial until the report on the trial is published. The Appendix C Management Group will form the basis of the writing group and advise on the nature of publications. All requests for data will be approved by the TSC.

All publications shall include a list of all investigators. The members of the TSC and IDMC will be listed with their affiliations in the Acknowledgements/Appendix of the main publication.

All manuscripts or abstracts which present data from the sotrovimab arm of the trial will be made available for review by GSK/Vir. These will also be made available for review prior to publication to the TMG and IDMC members. This is to protect proprietary information and to provide comments.

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