Master protocol:

Finding treatments for COVID-19: A phase 2 multi-centre adaptive platform trial to assess antiviral pharmacodynamics in early symptomatic COVID-19 (PLATCOV)

Short title: Finding treatments for COVID-19: A phase 2 platform trial of antiviral pharmacodynamics in early symptomatic COVID-19 (PLATCOV)

Acronym: PLATCOV

OxTREC Ref: 24-21

Trial Registration Number: NCT05041907

Protocol number: VIR21001

Date and Version No: Version 7.0 / 07 August 2024

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Funder: Wellcome Trust Grant ref: 223195/Z/21/Z through the COVID-19 Therapeutics Accelerator

Investigators' contributions:

NJW conceived of the study and initiated the study design with other investigators. WS, JW, CC, JC, NPJD, WRJT, and AMD supported development of protocol and implementation. JW provided statistical expertise in clinical study design.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committee and Regulatory Authorities unless authorised to do so.

Investigator Agreement and Declaration of Interests

"The undersigned has read and understood the trial protocol detailed above and:

- agrees to conduct the trial in compliance with the protocol.
- agrees to comply with the principles of the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice.

and declare no conflict of interest, according to the current version of the Declaration of Helsinki"

Dr William Schilling ……

Co-Principal Investigator Signature Date

Professor Sir Nicholas J White ……

Co-Principal Investigator Signature Date

Table of Contents

1. SYNOPSIS

Study Title	Finding treatments for COVID-19: A phase 2 multi-centre adaptive platform trial to assess antiviral pharmacodynamics in early symptomatic COVID-19 (PLATCOV)
Protocol no.	VIR21001
Rationale	Quantitative evidence of antiviral activity in patients with COVID-19 is required to justify phase 3 clinical trials of putative antivirals
Study Design	Randomised, open label, group sequential adaptive platform trial
Inclusion and Exclusion Criteria	**Inclusion criteria:** • Patient understands the procedures and requirements and is willing and able to give informed consent for full participation in the study • Previously healthy adults, male or female, aged 18 to 60 years at time of consent with early symptomatic COVID-19 • SARS-CoV-2 positive by lateral flow antigen test OR a positive PCR test for SARS-CoV-2 within the last 24hrs with a Ct value of less than 25 (all viral targets) • Reported symptoms of COVID-19 (including fever, or history of fever) for less than 4 days (96 hours) • Oxygen saturation ≥96% measured by pulse oximetry at time of screening • Able to walk unaided and unimpeded in ADLs • Agrees and is able to adhere to all study procedures, including availability and contact information for follow-up visits **Exclusion criteria:** • Taking any concomitant medications or drugs (see appendix 4)† • Presence of any chronic illness/ condition requiring long term treatment, or other significant comorbidity (see appendix 4 for full list) • Laboratory abnormalities discovered at screening (see appendix 4) • For females: pregnancy, actively trying to become pregnant, or lactation • Contraindication to taking, or known hypersensitivity reaction to any of the proposed therapeutics (see appendix 4) • Currently participating in another COVID-19 therapeutic or vaccine trial • Evidence of pneumonia (although imaging is NOT required) † healthy women on the oral contraceptive pill are eligible to join the study.
Planned Sample Size	Continuously running group sequential adaptive platform trial. There is no fixed sample size (see section 10.1 for further discussion). Maximum sample size is 200 patients per intervention arm (excluding negative control (no study drug/no antiviral treatment)) and positive control e.g. nirmatrelvir/ritonavir, ensitrelvir etc), although further recruitment can occur on consultation with the DSMB or TSC, if it is felt that more precision of the result is beneficial.

	This study is expected to enroll approximately 3,800 total participants from up to six countries (Thailand, Brazil, Pakistan, Laos, Nepal and yet unconfirmed site/sites).
Planned Study Period	6 years for total duration of the trial and 120 days for individual patients' involvement
Interventions	The platform trial will assess drugs with potential SARS-CoV-2 antiviral activity of three general types: A. Small molecule drugs: currently nitazoxanide, nirmatrelvir/ritonavir, hydroxychloroquine, atilotrelvir/ritonavir and metformin. B. Monoclonal antibodies: Sotrovimab and any other monoclonal antibodies that become available. C. Dose finding study for the constituent parts of nirmatrelvir/ritonavir
Control	1. Negative control: No antiviral treatment (although local hospital supportive treatment will remain the same e.g. antipyretics, anti-tussives, antihistamines, vitamins etc as per the treating Physician's judgement). 2. Positive control: currently nirmatrelvir/ritonavir at standard dose
Rationale	Each intervention type has a different objective: A. Small molecule drugs: Newly available and repurposed drugs are already used and recommended in some countries. Showing that they do not have significant antiviral activity is as important as showing that they do. For the newly approved antivirals, comparing antiviral activities in-vivo will inform health authorities' recommendations. B. Monoclonal antibodies: There is good evidence from phase 2 studies that monoclonal antibodies reduce viral load in COVID-19 with evidence that they reduce hospitalisation in high-risk individuals. However, monoclonal antibodies are vulnerable to viral escape mutations. Tracking their performance over time is important to characterise the impact and inform the therapeutics of mutant SARS-CoV-2 strains. This will also be important for other antivirals. Monoclonal antibodies are expensive and cannot be produced at large scale currently, but this may change in the near future. Not all these therapeutics may be available, and will be included if there is local availability and regulatory approval. C. Dose finding study: dose finding of the separate components of ritonavir and nirmatrelvir will be highly beneficial. Nirmatrelvir/Ritonavir has shown clinical efficacy in phase III studies. It is widely considered the most effective COVID-19 medication. However, there are disadvantages to using the drug. There are many drug-drug interactions from ritonavir which prevents many of the highest risk individuals from accessing the medication. Dysgeusia and diarrhoea associated with ritonavir may affects patient uptake and reduces adherence or compliance. Furthermore, it is very expensive ($500/course), and may be associated with viral rebound phenomenon. In the urgent context of the pandemic, a higher dose of ritonavir was chosen to guarantee maximum boosting effect. We do not know if the maximal boosting effect could have been achieved with less, or even without Ritonavir. This study will aim to investigate

	whether changing the doses of ritonavir and nirmatrelvir would provide efficacy whilst balancing the negative aspects.	
	Objectives	**Endpoint**
Primary	<u>For all interventions trialled, there are two primary objectives:</u> 1. To evaluate SARS-CoV-2 antiviral efficacy in-vivo (accelerated viral clearance relative to the no study drug arm). This is a superiority comparison. 2. To compare SARS-CoV-2 antiviral efficacy with current best antiviral treatment option (accelerated viral clearance relative to the positive control arm). This is a non-inferiority or superiority comparison.	Rate of viral clearance- estimated from the log_{10} viral density derived from qPCR of standardised duplicate oropharyngeal swabs/ saliva taken daily from baseline (day 0) to day 5 for each therapeutic arm compared with the contemporaneous no antiviral treatment control/ positive control
Secondary	To characterise the determinants of viral kinetics in early COVID-19 disease	Rate of viral clearance (as for primary endpoint)
	To determine optimal dosing regimens through pharmacometric assessment for antiviral drugs with evidence of efficacy (e.g. Nirmatrelvir/ritonavir, Ensitrelvir etc)	
	Characterise viral rebound of studied treatment arms in comparison to contemporaneous controls (e.g. no study drug arm, positive control)	After stopping treatment for at least 24 hours (or 5 days if no drug is given or a single dose monoclonal antibody is given) rebound is defined as a oropharyngeal eluate viral density estimate >1000 genomes per ml for at least 1 timepoint (average 2 swabs), after <u>≥</u>2 consecutive days of average daily viral density estimate less than 100 genomes per ml
	To compare rates of fever clearance and rates of symptom resolution with respect to no treatment	The following comparisons will be made: • Time to resolution of fever • Area Under the Curve of recorded temperature • Time to resolution of symptoms

Tertiary	Characterise the relationship between viral clearance and hospitalisation (hospitalisation for clinical reasons)	Hospitalisation for clinical reasons up to day 28
	Characterise the relationship between viral clearance, randomisation arm and other measures (covariates) and development of post-acute COVID-19 (i.e. long COVID)	Score on post-acute COVID-19 (i.e. long COVID) questionnaire at day 120 – modified COVID-19 Yorkshire Rehabilitation Scale (*C19 YRSm*)

2. ABBREVIATION

ACT	Access to COVID-19 Tools
ADLs	Activities of daily living
AE	Adverse event
AR	Adverse reaction
ARI	Acute Respiratory Infection
BD	Twice a day / twice daily / 2 times daily
C19 YRSm	The modified COVID-19 Yorkshire Rehabilitation Scale
COVID-19	Coronavirus disease of 2019
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTSG	Clinical Trials Support Group
CYP450	Cytochromes P450
DSMB	Data Safety Monitoring Board
EC	Ethic Committee
EDTA	Ethylenediaminetetraacetic acid
FBC	Full blood count
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IL	Interleukin
IM	Intramuscular
IMP	Investigational Medicinal Product
IV	Intravenous
LDH	Lactate dehydrogenase
LFT	Liver function test
MORU	Mahidol Oxford Tropical Medicine Research Unit
NGS	Next Generation Sequencing
OxTREC	Oxford Tropical Research Ethics Committee
PD	Pharmacodynamic
PI	Prinicipal investigator
PK	Pharmacokinetics

POC	Point-of-care
PPE	Personal protective equipment
RDT	Rapid diagnostic test
REGN	Regeneron
RT-qPCR	Real-time quantitative polymerase chain reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SARS-CoV2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TNF	Tumor necrosis factor
TMG	Trial Management Group
TSC	Trial Steering Committee
U&E	Urea and Electrolytes
VTM	Viral transport medium
WHO	World Health Organization

3. BACKGROUND AND RATIONALE

There are many potential therapeutics for COVID-19 and a much larger number of vaccines are in development. Vaccines were given to individuals with the primary aim of reducing morbidity and mortality and the secondary objective of generating herd immunity in the hope of bringing the pandemic to an end. However, there is widespread vaccine inequality. As of 31 December 2023, the WHO states that only 44% of the total global population have been vaccinated against COVID-19 (1). Vaccinations have protected many from severe disease but importantly it is now clear that they provide incomplete protection, and vaccinated or previously infected individuals can still get infected and vulnerable individuals can still become ill. The rapid evolution of more transmissible and potentially vaccine resistant mutant strains (highlighted by the Omicron variant (B.1.1.529), and future variants (which may not be as comparatively mild) is worrying. We know that vaccine and disease-induced immunity is imperfect and short-lived so identifying active antiviral drugs is extremely important. Many people over the next 2-3 years will get COVID-19 with substantial morbidity and hundreds of thousands of deaths. There will always be people, due to their age, comorbidities or being immunocompromised that will need early antiviral therapy. For all these reasons effective therapeutics are needed urgently.

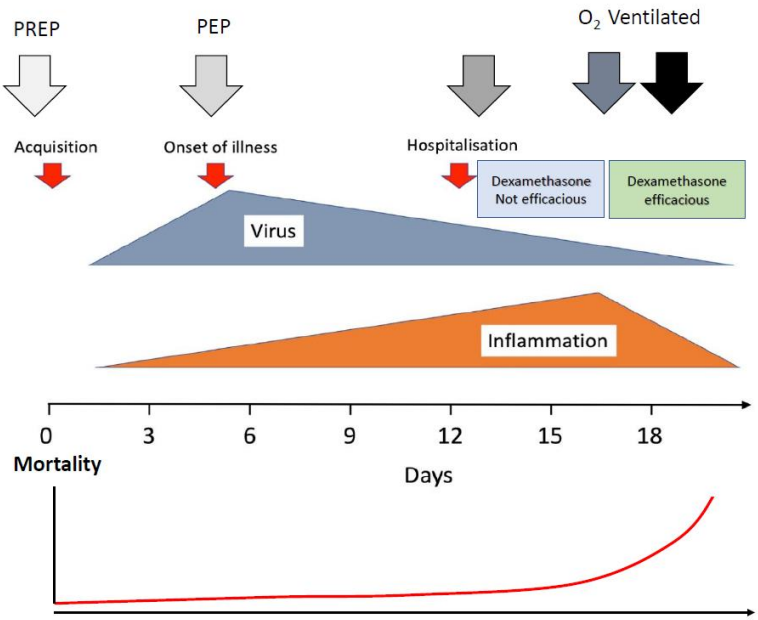

Figure 1 Simplified paradigm of COVID-19 infection and disease. There are two main stages of disease and antiviral therapies should be most effective early on.

Symptomatic COVID-19 infection has two overlapping phases (Figure 1). In the first phase, there is rapid viral replication with peak viral loads in the pharynx occurring approximately at the time of symptom onset. Thereafter viral burdens decline. In this second phase, the viral load decreases (the decline is first order, and the rate of decline is slower in sicker patients) (2-6). During the second phase, a small minority of individuals (particularly the elderly and those with co-morbidities) progress to severe illness (severe pneumonia) and some die. Hospital admission is usually about one week after the onset of illness (7). In those patients requiring respiratory support, low dose dexamethasone reduces mortality substantially (8). At this late stage of the illness inflammatory processes predominate, and antivirals are less likely to be of benefit (9). Antiviral treatments are most likely to be of benefit when given early in the illness. Accelerating viral clearance should reduce the subsequent inflammatory pathology, a hypothesis which is supported by studies of monoclonal antibody therapies and data from hospitalised patients (10, 11). At the time of writing the initial protocol, there were promising monoclonal antibody therapies with evidence of viral clearance acceleration.

Hospitalisation rates in RCTs were lower in the patients receiving these antibodies. However, monoclonal antibodies are currently expensive and difficult to deploy at scale (although this could change rapidly in the near future) and the continued efficacy of monoclonal antibodies is threatened by the evolution and spread of spike protein mutants (12, 13). This has been seen recently with the spread of the Omicron variant, and successive waves of its descendants, which has led, on the basis of in-vitro studies demonstrating decreased neutralization, to curtailment of their use. Two small molecule antivirals (molnupiravir, nirmatrelvir boosted by ritonavir) have completed phase 3 testing, and shown in-vivo benefits in COVID-19. They are already licensed for clinical use in some countries. However, further studies are needed, for better characterisation of the phenomenon of 'viral rebound', where there is a recrudescence of active infection which has implications for transmission. In-vivo synergy testing of combinations of antivirals will be important to assess the effects on viral rebound. This could prevent development of mutations during treatment (i.e. combination therapies given in HIV), for the severely immunocompromised and if more severe variants appear. More antivirals are following, and comparisons of their antiviral effects, as well as the risk of viral rebound and other characteristics, will help healthcare systems decide on their purchase and use.

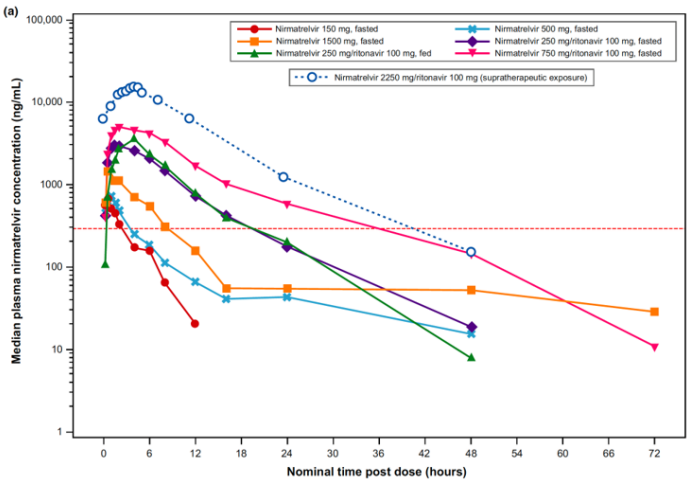

Figure 2 Median plasma nirmatrelvir concentration-time profiles (semi-log scales) for single-ascending dose and supratherapeutic exposure cohorts

Another important area of research is regarding Nirmatrelvir/Ritonavir, which is widely considered the most effective COVID-19 medication. It comprises of Nirmatrelvir (an oral 3CL protease inhibitor of SARS-CoV-2) and Ritonavir (a CYP450 inhibitor which inhibits the metabolism of Nirmatrelvir). The dose of Ritonavir chosen to boost Nirmatrelvir was at the upper end of the range used to boost other protease inhibitors, such as in HIV (100mg BD). This guaranteed maximal boosting and Nirmatrelvir levels. However, dose-finding studies with lower dose or no Ritonavir were not conducted. It is unknown whether the maximum boosting effect could be achieved with less Ritonavir, or even without it. Many protease inhibitors are boosted equally well at lower doses of Ritonavir than 100mg BD e.g., saquinavir, fosamprenivir and darunavir are boosted equally well with a dose as little as 50mg/day (14). A phase I study in healthy volunteers did demonstrate rapid elimination, and low peak levels of Nirmatrelvir given without Ritonavir, although without a pharmacodynamic measure of efficacy. At a dose of 150mg (half the current dose of Nirmatrelvir used in PAXLOVID), the drug levels surpass the EC90 for several hours, which suggests that the drug will have some efficacy (see Figure 2) (15). If a lower dose of Ritonavir and/or Nirmatrelvir is found to still give the levels required for comparable viral clearance, then this could lead to more people being able to take the drug.

There is no optimised or validated approach to rapidly assess potential antiviral therapeutics in COVID-19. Drugs are currently being selected for clinical study on the basis of activity in cell culture systems (in-vitro) and animal models in-vivo. Unfortunately the animal models are not sufficiently good to be included in the drug development critical pathway. Some manufacturers (e.g. Pfizer) have decided not to try and assess antiviral activity of candidate drugs in these animal models. Thus drugs currently under consideration are justified only on the basis of antiviral activity in cell cultures. In order to identify effective antivirals and optimise their dosing, and therefore ensure that phase 3 studies are designed appropriately, and progress is as rapid as possible, in-vivo antiviral effects must be characterized adequately. This can be achieved in natural COVID-19 infections at an early stage of the disease using the following design. Additionally, phase 3 studies looking at the endpoints of hospitalisation and death now need to be prohibitively large, due to the scarcity of these

events compared to earlier in the pandemic (16). Phase 3 studies need to be very large to be adequately powered and this means they are costly and slow to give answers. The trial will develop and validate a platform for quantitative assessment of antiviral effects (5) in low-risk patients with high viral burdens and uncomplicated COVID-19. As the assessment is of the antiviral effect on the virus, as distinct from the outcome on the clinical course of the infection, the results are applicable to all stages of disease where viral replication occurs (including prophylaxis), and can give answers as to the comparative antiviral effect of drugs quickly and with smaller numbers of patients recruited, than studies with clinical endpoints of hospitalisation and death. The role of viral burden and viral load reduction in the development of post-acute COVID-19 sequelae is incompletely understood, but there is evidence that there may be benefit which can be assessed prospectively in this study. The estimated burden of post-acute COVID-19 in terms of quality of life and economic impacts from days lost to work are huge (17).

3.1. Proposal

In this randomised open label, controlled, group sequential adaptive platform trial, we will assess the performance of three distinct types of intervention relative to control (no treatment):

A. Small molecule drugs
B. Monoclonal antibodies
C. Dose finding for Nirmatrelvir/Ritonavir

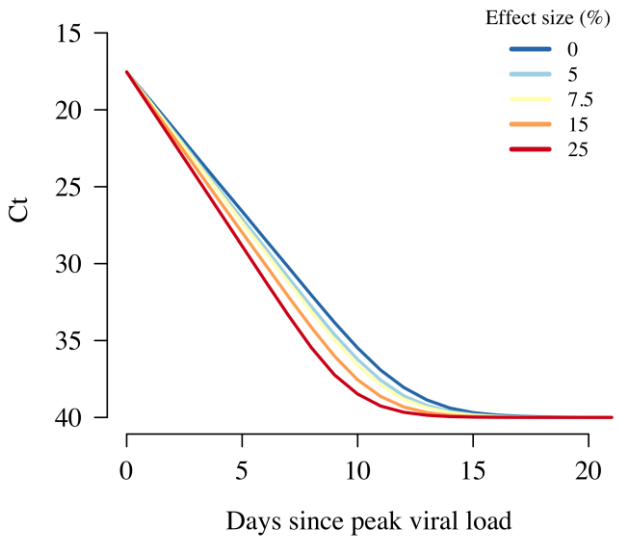

Figure 32. Acceleration of viral clearance rates by different amounts

The trial initially focused on repurposed drugs as they were available at the time, and some are used widely without good evidence of benefit. Subsequently newly developed small molecule antiviral drugs have become available (e.g. molnupiravir and nirmatrelvir/ritonavir). For these newly available and repurposed drugs under consideration (type A interventions i.e. small molecule drugs), the platform trial is designed based on the premise that showing clear evidence of an antiviral effect is as important for medicine and public health as proving there is no significant effect.

Antivirals showing evidence of an antiviral effect in the study, will enter a comparison with the positive control and may subsequently be chosen to be the positive control (such as with standard dose nirmatrelvir/ritonavir) (see Figure 5). Proving that a drug does not accelerate viral clearance in-vivo should provide evidence to stop clinical recommendations based on claims of putative antiviral activity in ex-vivo cellbased assays. Monoclonal antibodies (to be defined as type B interventions) were initially included as a "positive control" until evidence showed loss of activity and the effectiveness of nirmatrelvir/ritonavir. This is beneficial to demonstrate that the method does identify active compounds. It will be important to calibrate and compare the effects of these validated effective therapies relative to the newly identified small molecule antiviral drugs. In addition, for monoclonal antibodies it is also important to characterise waning efficacy over time resulting from novel spike protein mutants (12,13).

For the final group, C, it is important to discover whether there are optimal doses of Ritonavir and Nirmatrelvir which would allow it to be effective whilst reducing some of the drawbacks to the medication

(expense, drug-drug interactions, side effects), thus giving more people access to it. The ritonavir levels have been chosen based on the levels used for HIV and the nirmatrelvir based on the phase 1 study (15). They are as follows –

- Nirmatrelvir 300mg + Ritonavir 100mg twice daily for 5 days (standard dose and positive (+ve) control)
- Nirmatrelvir 300mg + Ritonavir 50mg twice daily for 5 days
- Nirmatrelvir 150mg + Ritonavir 50mg twice daily for 5 days
- Nirmatrelvir 300mg alone twice daily for 5 days.

We aim to rapidly identify the best candidates of the novel small molecule drugs. The distinct objectives for each of these intervention types requires different stopping rules and design features. The rapid turn-round in quantitative PCR measurements is key to the success of this project. Analysis of these results will allow for frequent interim analyses with the aim of halting study arms early for futility, or triggering an intensive nested PK-PD study if there is evidence of clinically significant antiviral activity, although early interim analyses are not likely to yield efficacy assessments, and are aimed primarily at validation of the methodology. This will speed up the identification of antivirals to be assessed in phase III studies. The key metric is the rate of viral clearance (5) (Figure 3).

3.2. Pharmacodynamic assessment

We used prospectively collected serial viral load data from 46 individuals infected with SARS-CoV-2 and an accompanying pharmacodynamic model to simulate different trial designs for putative antiviral drugs using either time-to-clearance or rate-of-clearance as the primary trial endpoint (18). This model was then tested on data from a small pilot study of 24 patients with early symptomatic COVID-19 who were randomised to either ivermectin or placebo (19). **Rate-of-clearance was shown to be a uniformly better endpoint in terms of type 2 error (i.e. results in increased power) than the widely used and reported time-to-clearance (4).** Rate of decline in oropharyngeal qPCR estimates of viral density measured daily also allows shorter and more efficient evaluation of viral clearance (Figure 4). Our simulations (Appendix 3) show that the proposed trial design can identify an effective therapy rapidly in the setting of a platform trial and quickly discard ineffective therapies (both of which are the primary objectives of the trial).

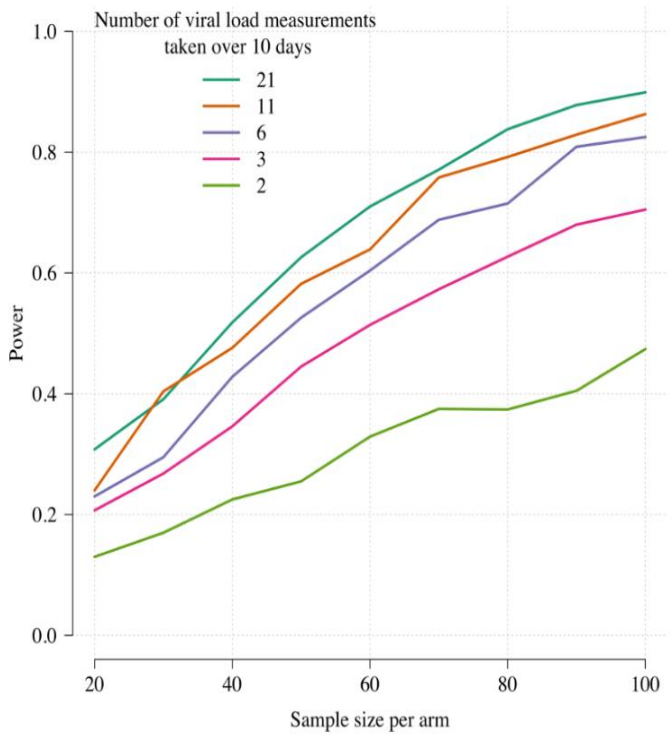

Figure 4. The relationship between the number of qPCR viral load measurements taken over 10 days and the power (1-type 2 error) to detect an effect size of 10% increase in viral clearance rate relative to control. This assumes that patients are recruited at peak viral load (4).

4. OBJECTIVES AND ENDPOINTS

	Objectives	Endpoint	Timepoint(s) of evaluation of this endpoint (if applicable)
Primary	<u>For all interventions trialled, there are two primary objectives:</u> 1) To evaluate SARS-CoV-2 antiviral efficacy in-vivo (accelerated viral clearance relative to the no study drug arm). This is a superiority comparison. 2) To compare SARS-CoV-2 antiviral efficacy with current best antiviral treatment option (accelerated viral clearance relative to the positive control arm). This is a non-inferiority or superiority comparison.	Rate of viral clearance (estimated from the $\log_{10}$ viral density derived from qPCR of standardised duplicate oropharyngeal swabs/ saliva taken daily from baseline (day 0) to day 5 for each therapeutic arm compared with the contemporaneous no antiviral treatment control/ positive control)	Days 0-5
Secondary	To characterise the determinants of viral kinetics in early COVID-19 disease.	Rate of viral clearance (as for primary endpoint)	Days 0-5
	To determine optimal dosing regimens through pharmacometric assessment for antiviral drugs with evidence of efficacy (e.g. Nirmatrelvir/ritonavir, Ensitrelvir etc)		Days 0-5
	Characterise viral rebound of studied treatment arms in comparison to contemporaneous controls (e.g. no study drug arm, positive control)	After stopping treatment for at least 24 hours (or 5 days if no drug is given or a single dose monoclonal antibody is given) rebound is defined as a oropharyngeal eluate viral density estimate >1000 genomes per ml for at least 1 timepoint (average 2 swabs), after <u>≥</u>2 consecutive days of average daily viral density estimate less than 100 genomes per ml	Days 0-14*
	To compare rates of fever clearance and rates of symptom resolution with respect to no treatment	The following comparisons will be made: • Time to resolution of fever	Days 0-28

		• Area Under the Curve of recorded temperature • Time to resolution of symptoms	
Tertiary	Characterise the relationship between viral clearance and hospitalisation (hospitalisation for clinical reasons)	Hospitalisation for clinical reasons up to day 28	Days 0-28
	Characterise the relationship between viral clearance, randomisation arm and other measures (covariates) and development of post-acute COVID-19 (i.e. long COVID)	Score on post-acute COVID-19 (i.e. long COVID) questionnaire at day 120 – modified COVID-19 Yorkshire Rehabilitation Scale (*C19 YRSm*)	Day 120

*If a patient develops symptoms outside the planned swabbing schedule of D0-D5, D7 and D14, an extra swab can be performed up until D28.

5. STUDY DESIGN

The study is a randomised, open label, controlled adaptive platform trial that will be conducted in low-risk patients with COVID-19, recruited from outpatient COVID-19/ Acute Respiratory Infection (ARI) clinics or through other approved facilities, or from inpatient isolation facilities, or by patient self-referral to the study site, that is previously healthy patients 18 to 60 years old with early symptomatic COVID-19 and without co-morbidities (see appendix 4). The study is being performed in Thailand, Brazil, Nepal and Laos.

After obtaining fully informed consent, we will recruit adult patients with early symptomatic COVID-19 (less than 4 days (96 hours) since the reported onset of symptoms), who are positive by a SARS-CoV-2 lateral flow antigen test (identifying those with higher starting viral densities (20-22)) OR a positive PCR test for SARS-CoV-2 within the last 24hrs with a Ct value of less than 25 (all viral targets). Patients will be included who can be followed up reliably for 120 days.It is expected that vaccination coverage will continue to increase during the study period as well as the cumulative number of natural infections.

The primary pharmacodynamic measure in this study is the rate of viral clearance (expressed as the slope of a fitted regression to the linear segment of the serial standardized oropharyngeal sample qPCR densities from day 0 to day 5) following treatment (5). Each site will include a no antiviral treatment control arm consisting of patients not receiving any antiviral treatment, although local hospital supportive treatment will remain unchanged for the patients including antipyretics, anti-tussives, antihistamines, vitamins etc and other required medications, in the clinical judgement of the treating Physician.

5.1. Interventions

Intervention arms will be of three types:

A) Small molecule drugs: The list of intervention drugs is Nitazoxanide, , Nirmatrelvir/Ritonavir (the positive control), and Hydroxychloroquine . We are adding in Metformin and Atilotrelvir/Ritonavir. The interventions will be chosen in order of priority, as well as local feasibility at sites (availability of drugs, local EC and regulatory approvals). Additional repurposed and newly available drugs can be added to the list. A number of drugs have been assessed and removed from this platform study. These include Ivermectin, Remdesivir, Favipiravir, Molnupiravir, Ensitrelvir, Fluoxetine, and a combination of Molnupiravir and Nirmatrelvir/Ritonavir.

B) Monoclonal antibodies such as sotrovimab, other monoclonal antibodies may become available and included later. Evusheld and Regeneron have been assessed and removed from the platform study.

C) Dose finding study of Nirmatrelvir/Ritonavir, the following combinations of doses will be used (either from PAXLOVID or a high quality generic version)

1. Nirmatrelvir 300mg + Ritonavir 100mg twice daily for 5 days (standard dose and positive (+ve) control)
2. Nirmatrelvir 300mg + Ritonavir 50mg twice daily for 5 days
3. Nirmatrelvir 150mg + Ritonavir 50mg twice daily for 5 days
4. Nirmatrelvir 300mg alone twice daily for 5 days

At any given time in the study, it is possible that not all intervention arms are available. Randomisation is explained further below. Ratios will be uniform across each stage of randomisation and will be at least 20% in the control arm in each stage.

Randomisation will be continuously monitored by MORU. A positive SARS-CoV-2 lateral flow antigen test will be used as the main inclusion criteria. A positive lateral flow test result implies a relatively high viral load at the start of the study intervention (20-22). In order to assess viral clearance dynamics accurately over time initial high viral densities are required. In non-vaccinated patients, seronegativity implies there will be limited host control of the infection initially and was previously strongly correlated with higher viral loads (17), although this also depends on the variant.

We aim to identify interventions that accelerate viral clearance by a minimum of 20% (corresponding approximately to a reduction of 2 days in the mean time to viral clearance). Any intervention drug that shows an acceleration of viral clearance, defined as a greater than 90% probability of accelerating viral clearance by more than 20%, or if there is evidence of accelerated viral clearance from other studies (e.g. Molnupiravir, Nirmatrelvir/ritonavir), will be selected for inclusion in a nested pharmacokinetic-pharmacodynamic study. In this nested study, frequent blood sampling will allow assessment of the relationships between plasma drug concentrations and viral clearance. The design of the pharmacokinetic study depends on the known pharmacokinetic properties of each drug. In each case no more than 10 blood samples (20mL) will be taken. For interventions not selected for the intense pharmacokinetic-pharmacodynamic study above, drug level samples at D3, D7 or D14 may be tested to determine a dose-response relationship. Any intervention arm that meets the futility endpoint (less than 10% probability of accelerating viral clearance by more than 20%) will be dropped from the study. New arms can be added at any time during the trial. Decisions concerning success and futility will be made sequentially at the pre-specified interim analysis to be conducted after 50 patients are enrolled, and thereafter after every 25 patients to ensure control of type 1 and type 2 error (Figure 5). The nested intensive PK-PD substudy will be performed on all arms of the dose finding sub study and in the other arms will be triggered if the probability that viral clearance is accelerated by more than 20% goes above 90%, or if there is evidence of accelerated viral clearance from other studies (e.g. Molnupiravir, Nirmatrelvir/ritonavir). A non-intensive PK-PD analysis can be conducted where determination of a dose-response relationship is required (e.g. heterogeneity in the effect).

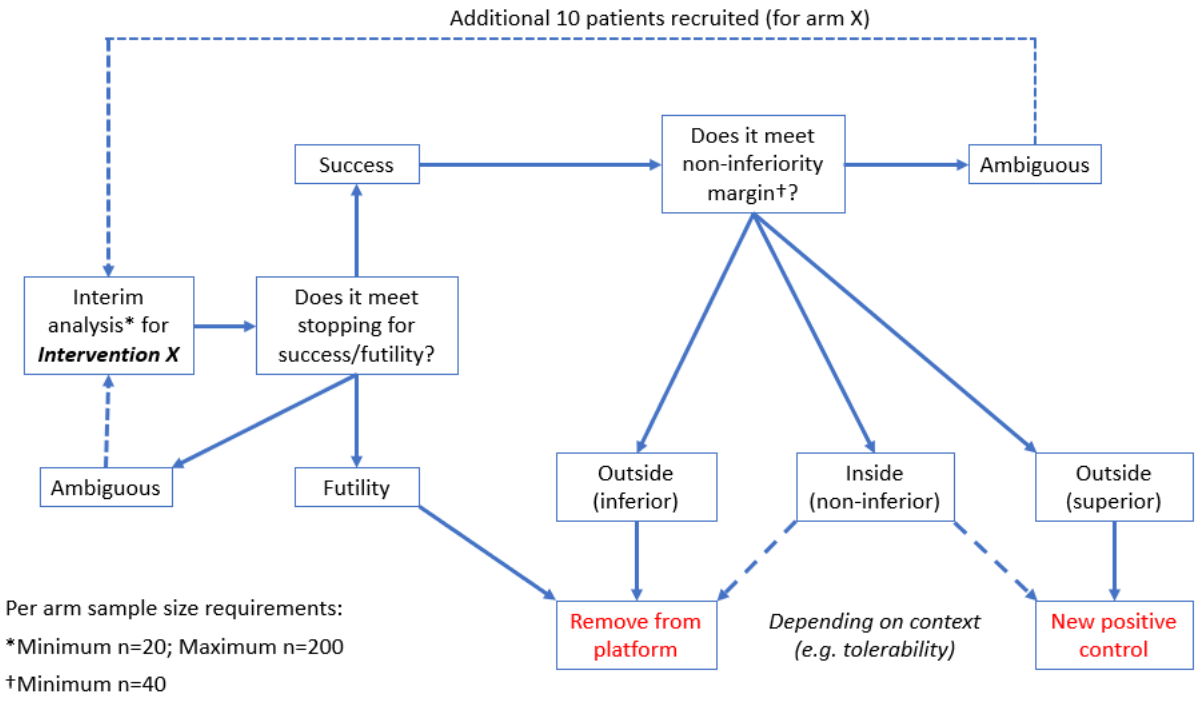

Figure 5. Schematic representation of the stopping rules as of January 2023

5.2. Randomisation

There are two ways in which participants can be randomised (depending on availability of interventions). Simple randomisation involves randomising the participants once. All drugs currently available in the study may be included in this, including the dose finding doses. Factorial randomisation, if interventions are available and this is currently active, will involve randomising the participant to randomisation part A AND THEN part B, thus they may receive 2 separate interventions.

- **Randomisation part A**

Enrolled patients are randomised to (i) a small molecule drug (see list below, not all options will be available at any given time), (ii) no study drug, or (iii) the positive control (e.g. currently standard dose Nirmatrelvir/ritonavir).

The list of studied small molecule drugs includes: Nitazoxanide, , Nirmatrelvir/ritonavir (standard dose (300/100mg twice daily for 5 days) – positive control), Hydroxychloroquine, Metformin and Atilotrelvir/Ritonavir

The list of additional doses for Nirmatrelvir/Ritonavir

- Nirmatrelvir 300mg + Ritonavir 50mg twice daily for 5 days
- Nirmatrelvir 150mg + Ritonavir 50mg twice daily for 5 days
- Nirmatrelvir 300mg alone twice daily for 5 days.

- **Randomisation part B (as a factorial design)**

If monoclonal antibodies are available at the site, enrolled patients are additionally randomised to (i) a monoclonal antibody (see list below) or (ii) no study drug.

The list of studied monoclonal antibodies includes: Sotrovimab and other monoclonal antibodies that become available.

6. PATIENT IDENTIFICATION AND RECRUITMENT

6.1. Study Patients

Previously healthy adult patients with early symptomatic COVID-19.

6.2. Inclusion Criteria

- Patient understands the procedures and requirements and is willing and able to give informed consent for full participation in the study.
- Previously healthy adults, male or female, aged 18 to 60 years at time of consent with early symptomatic COVID-19.
- SARS-CoV-2 positive by lateral flow antigen test OR a positive PCR test for SARS-CoV-2 within the last 24hrs with a Ct value of less than 25 (all viral targets).
- Symptoms of COVID-19 (including fever, or history of fever) for less than 4 days (96 hours).
- Oxygen saturation ≥96% measured by pulse-oximetry at time of screening.
- Able to walk unaided and unimpeded in ADLs.
- Agrees and is able to adhere to all study procedures, including availability and contact information for follow-up visits.

6.3. Exclusion Criteria

The patient may not enter the study if ANY of the following apply:

- Taking any concomitant medications or drugs (see appendix 4)†
- Presence of any chronic illness/ condition requiring long term treatment, or other significant comorbidity (see appendix 4 for the full list)
- Laboratory abnormalities discovered at screening (see appendix 4)
- For females: pregnancy, actively trying to become pregnant, or lactation
- Contraindication to taking, or known hypersensitivity reaction to any of the proposed therapeutics (see appendix 4)
- Currently participating in another COVID-19 therapeutic or vaccine trial
- Evidence of pneumonia (although imaging is NOT required)

† healthy women on the oral contraceptive pill are eligible to join the study.

7. STUDY SET-UP AND PROCEDURES

Recruitment of patients will be from outpatient COVID-19/ ARI clinics or through other approved facilities, or from inpatient isolation facilities, or by patient self-referral to the study site. Patients with a positive SARS-CoV-2 rapid lateral flow antigen test OR a positive PCR test for SARS-CoV-2 within the last 24hrs with a Ct value of less than 25 (all targets) will be enrolled in the study after providing fully informed written consent. In each study site there will be a designated research ward for study procedures. In accordance with local and national infection control guidelines the initial assessments will be conducted in a designated research ward set-up to manage COVID-19 patients. Patients will receive care in either an inpatient or outpatient setting, in accordance with local and national guidelines. All recruited patients will be visited at their home or place of residence, or be seen in the designated clinical trials unit or hospital ward. All personnel will wear appropriate personal protective equipment (PPE). For home visits a trained member of personnel will perform the swabbing or ask the patient to self-swab (and may ask the patient to give a saliva sample).

The rapid lateral flow antigen test will be performed by trained study personnel. Patients will be eligible for the trial if the test is positive within a specified period of time (detailed in a separate SOP based upon manufacturer's guidelines). A positive band appearing rapidly is correlated with a higher viral load in the swab sample (personal communication, Prof. Tim Peto). A digital photograph of the test result may be taken to allow for future analysis. The exact details of this will be detailed in the separate work instruction.

Participants will be asked if they have been in the study before and whether any relatives have been in the study. After enrolment into the study, the patient will be randomised once for simple randomisation or twice for factorial design randomisation (randomisation part A and part B; if interventions are available). Further details of the randomisation procedures are given below (see section 7.6.1). An oropharyngeal swab will be obtained in duplicate by the study team using a standard operating procedure (SOP) after a full explanation is provided to the patient. Swabs will be taken in duplicate again prior to receiving the study drug. The patient may have further swabs between 6 – 18 hours after the initial swabs post dose, either by study personnel or by self-swabbing. To minimise patient discomfort, all SARS-CoV-2 qPCRs will be performed on eluates from standard oropharyngeal swabs, taken in duplicate (22-26). In addition, patients may be asked to have an extra set of daily swabs done by study peronnel or self-swabbing or by giving a sample of saliva during the first 5 days of the trial (see section 7.1). The patient will undergo a physical examination and blood sampling for routine haematology and biochemistry and other baseline investigations (see Section 7.5). For oral study drugs, the first dose will be administered and observed at the research ward/ hospital. Subsequent doses will be administered by the ward personnel in hospital if the patient is an inpatient, at the patient's home, or current residence, supervised by study personnel (if multiple doses, then one of the doses per day will be observed). In case a study drug requires parenteral administration, this will be provided under supervision by the study personnel in the research ward, or hospital, or the patient's home.

7.1. Virological sampling

Serial oropharyngeal swabs will be taken in duplicate (one swab each tonsil) at least once per day, and up to twice per day (4 swabs total) by the study team or by self-swabbing (25) according to the sample schedule. Patients need to consent to at least once a day swabbing. One set of swabs will be taken from the back of the throat (oropharynx; tonsillar fossa) by trained study personnel according to the SOP abiding by strict PPE measures. Patients may also be asked to have an extra second set of daily swabs done by self-swab according to a set of given instructions.,or by study personnel over the first 5 days. They will be informed of the details by the study personnel. Each swab will be placed in 3mL of viral transport medium (VTM) (Thermofisher M4RT®), snapped off and sealed. In addition, some patients may be asked to give a sample of saliva, detailed in a set of separate instructions. The volume of saliva will be standardised. The purpose of self-swabbing/ saliva collection is to assess and validate methods of determining the viral density in the oropharynx in a less intrusive manner, or supplement the results from the oropharyngeal swabs to improve the characterisation of the viral clearance. As discussed later, the faster clearance of the virus over time means the later swabs (day 7) are less useful in terms of determining clearance than earlier in the study. Swab 6 and 10 will have been removed but swab 7 and 14 will remain to better characterise any viral rebound. As such the study will determine rate until day 5, and not day 7 as previous, and better characterisation of the earlier slope, with extra samples should be beneficial. If these results are informative, they may subsequently be included in the SAP for endpoint analysis. At least once daily sampling will be performed by the study personnel who will place the swabs in the transport medium, and document the time. The samples will be kept cool, and subsequently stored at -80°C as detailed in the SOP. Transport times will be recorded, as well as the time at which the swab is frozen at -80°C. Viral genomes from the throat swabs will be quantitated by RT-qPCR, according to published methods (28). Each observed value will be recorded along with the RNAseP $\log_{10}$ density (representing human cell numbers). The exact details of the analysis are given in the SAP (29, 30). The measurements for the patient over time will be used to estimate the rate of viral clearance under a Bayesian hierarchical linear mixed effects model. The concentration of urea in the VTM will also be measured and compared with the serum urea concentration in the baseline biochemistry sample. This comparison enables determination of the

extracellular fluid content in the eluate volume of the oropharyngeal samples. The urea concentration in throat fluid is the same as in serum, so that the dilution factor of the throat sample in the VTM fluid can be easily calculated (31). Blood will also be taken for quantitative virology and other baseline assessments (see Section 7.5). All samples positive for SARS-CoV-2 on qPCR will be sequenced using Next Generation Sequencing (NGS), or canonical variant mutation analysis will be used to determine the virus genotype, in order to determine the effect of viral genetics on viral load and response to treatment.

7.2. Recruitment

Potential patients with a positive SARS-CoV-2 test obtained during routine screening, or those with symptoms in keeping with COVID-19, even if they do not have the results of their SARS-CoV-2 test, or have not been tested yet, may be contacted by the research group. Alternatively, they may contact the research group for participation in the study. Each will be provided with a written participant information sheet.

7.3. Screening and Eligibility Assessment

Eligibility assessment will occur at the point of screening. If, based on the inclusion and exclusion criteria, the patient is eligible and willing to complete the full study, they will be included provided informed consent is obtained.

7.4. Informed Consent

Written and verbal versions of the Participant Information and Informed Consent will be presented to the patients detailing the exact nature of the study; what it will involve for the patient; the implications and constraints of the protocol; and the known side effects of the medicines under evaluation and any risks involved in taking part. It will be stated clearly that the patient is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The patient will be allowed as much time as required to consider the information as long as they remain eligible and within the time-frame for recruitment into the study, and the opportunity to question the Investigator or other independent parties to decide whether they will participate. Written Informed Consent will then be documented by a patient dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced and have been authorised to do so by the site PI. A copy of the signed Informed Consent will be given to the patient. The original signed form will be retained at the study site.

7.5. Baseline Assessments

A physical exam, vital signs, symptom review and basic demographics will be recorded. Temperature will be recorded 12 hours later either by the patient or study personel. Oropharyngeal viral swabs will be taken by the study personnel in duplicate (swabs will be taken at two timepoints prior to study drug being administered) (and possibly a saliva sample see section 7.1). A total of 20 ml of venous blood for study testing will be taken at this point. Administration of the therapeutic may be delayed until the results of the FBC and Biochemistry will be available (although these will ideally be available within 1 hour of sample collection i.e. before randomisation), to determine if there is any contraindication. If these bloods are not available in this timeframe, then the patient can be safely enrolled, randomised, and given their first dose, and can be excluded prior to their next dose if laboratory abnormalities resulting in a contraindication are present. If an FBC and Biochemistry has been taken in the previous 24hrs, the results of these can be used to determine whether there is a contraindication.

Laboratory tests at baseline

- Blood sample for
    - Full blood count (FBC) and differential count

    - Biochemistry (including U&Es, creatinine, LFTs and LDH)
    - Fibrinogen, Ferritin, TNF/IL-6/IL-1
    - Serology (antibody responses)
    - Stored sample
    - Drug level
    - Host genotyping to assess determinants of the therapeutic response
- Oropharyngeal swab in duplicate (and possibly a saliva sample see section 7.1)
- ECG (this is not a requirement)

7.6 Days of study

7.6.1 Randomisation D0

After enrolment, the patient may be randomised once for simple randomisation or twice for factorial design randomisation using an online randomisation application. The number of arms at a site can be limited by the approval and availability of the study drug at that site. Randomisation to the no antiviral treatment control arm (no intervention) will be fixed at a minimum of 20% throughout the study. The randomisation ratios will be uniform for all available interventions in each stage of randomisation. The drug allocations are not blinded for the patient for practical reasons. For patients randomised to an active drug, the first treatment dose (hour 0) will be supervised by study team after a viral swab (and possibly a saliva sample see section 7.1) is taken again for qPCR (taken in duplicate) (see appendix 1 for schedule of activities). The patient will then be observed for a minimum of 1 hour in the ward. Further swabs (taken either by the study personnel or self-swabbing) may be taken at hours 6-18 after initial swabs post dose. A second temperature will be recorded by the patient or the study personnel.

For the therapeutic arms for which intensive PK has been triggered, and for the dose finding arms, patients will stay for extra blood tests for drug monitoring levels, according to the schedule in the drug-specific appendix. For further details of the intensive PK schedules for the individual therapeutics please see the appendix 2.

7.6.2 Day 1- day 5

The following variables will be assessed daily:

- Eligibility check, and assessment of treatment (taking of medications taken will be observed by the study personnel and the time recorded. In participants who are outpatients, for medications taken more than once daily, the patient will record the time non-observed doses are taken).
- Oropharyngeal swabs for qPCR will be taken in duplicate (and possibly a saliva sample see section 7.1) by the study personnel at least once by the study personnel (time taken recorded by the study personnel), with the option of further swabs being taken by the study personnel or by the participant (self-swabbing).
- Temperature recorded at least twice daily by study personnel or participant (information collected in a diary and reviewed by the study personnel daily). This is important to determine if the treatments affect how febrile the patient is, or the overall effect on their temperature.
- Study personnel/ patient completes a brief symptom questionnaire each day.
- Vital signs will be measured by the study personnel.
- Blood samples will be taken (ideally day 3) for antibody levels and for later pharmacokinetic analyses (pre- or post-dose depending on the therapeutic in question) and FBC and biochemistry, to assess potential drug adverse effects.

7.6.3 Day 6, 7 and 14

- Eligibility check, and assessment of treatment (taking of medications taken will be observed by the study personnel and the time recorded. In participants who are outpatients, for medications taken more than once daily, the patient will record the time non-observed doses are taken).
- Temperature recorded twice daily by study personnel or participant (information collected in a diary card and reviewed by the study personnel daily). This is important to determine if the treatments affect how febrile the patient is, or the overall effect on their temperature.
- Patient/study personnel will complete a brief symptom questionnaire. This is important to determine how treatments effect the patient's symptoms.
- All patients will have oropharyngeal swabs taken in duplicate (and possibly a saliva sample see section 7.1) either at home (if feasible) or at the research ward EXCEPT on D6 when they will not be swabbed. These extra swabs are to better capture viral rebound should this occur, as has been described with certain antivirals. D7 swabs, although no-longer used for determining the rate of clearance, are useful for characterising rebound (which according to certain definitions can occur within 2 days of stopping a medication), or detecting mutants. The patient will be reviewed in person on this day anyway for bloods, and the swabs can be done without inconvenience.
- Blood samples will be taken (at D7 and D14) for antibody levels and for later pharmacokinetic analyses (pre- or post-dose depending on the therapeutic in question) and FBC and biochemistry, to assess potential drug adverse effects.
- The exact timepoints of swabs used to characterise viral rebound will be defined in the SAP. The current definition is: After stopping treatment for at least 24 hours (or 5 days if no drug is given or a single dose monoclonal antibody is given) rebound is defined as a oropharyngeal eluate viral density estimate >1000 genomes per ml for at least 1 timepoint (average 2 swabs), after $\geq$2 consecutive days of average daily viral density estimate less than 100 genomes per ml.
- Study personnel/patient will also complete a brief symptom questionnaire, vital signs (EXCEPT on day 6) and follow up temperature will be measured by the patient or study personnel.

7.6.4 Day 28 assessment

The day 28 follow-up assessment will be through a telephone call or a visit to check whether the patient recovered uneventfully for whether there was progression to more severe illness or need for hospitalisation for clinical reasons. A brief symptom questionnaire will also be completed. This final assessment will have an allowed window -2/ +7 days based upon calculation from Day 0.

7.6.5 Day 120 assessment

The day 120 follow-up assessment will be through a telephone call or visit to determine if the patient has any ongoing symptoms i.e. post-acute COVID-19. This final assessment is performed using the C19 YRSm, and will have an allowed window -10/ +30 days based upon calculation from Day 0. The severity of symptoms will be assessed following the standard C19 YRSm.

Patients will either complete the assessment over the phone, or be given the questionnaire in advance to read the answers out to one of the study team over the phone.

7.7 Intensive pharmacokinetic sampling

For those study drugs in the dose finding sub study, or that are shown to be effective antivirals in other studies or meet the success criteria of the study (defined as a greater than 90% probability of accelerating viral clearance by more than 20%), we will then conduct intensive pharmacokinetic (PK) sampling for further patients who are enrolled into that arm. The exact sampling schedule will depend on the study drug characteristics (see appendix 2), but in general the patient will stay at the ward for the remainder of the day to have further blood tests performed. A cannula will be inserted so that blood can be drawn without the need

for repeated venepuncture. A further blood test will be performed the next day, either at the ward or at their home if feasible. The volume of blood from this will not exceed 20 mls.

For any intervention not selected for the intense pharmacokinetic-pharmacodynamic study above, drug level samples at D3, D7 or D14 may be tested to determine a dose-response relationship. PK-PD analysis at D3, D7 or D14 can be conducted where determination of a dose-response relationship is required (e.g. heterogeneity in the effect or unusual clearance characteristics).

7.8 Management of patients who become ill

During the study, although this is unlikely, the patient may deteriorate clinically from their COVID-19 or may develop a new intercurrent illness or potentially a side-effect related to the study medication.

All patients who develop difficulty with activities of daily living or complain of shortness of breath will be assessed initially by the study personnel and their oxygen saturation measured and, if necessary, brought to the clinic research physician for further assessment. Based on this assessment, they may be referred to hospital, re-examined the next day, or asked to update the research team by mobile phone frequently on their well-being. The physician may decide to repeat study oropharyngeal swabs in duplicate if symptoms of COVID-19 recur, for the duration of the illness, to characterise symptomatic viral rebound.

If a patient is referred to hospital, a clinical assessment will be made by the hospital physician and a diagnosis made. The decision to stop study drug will depend on that diagnosis and be made between the hospital team and the study PI.

The hospital physicians will have the responsibility for patient care but the research team will continue to follow the progress of the patients in hospital. Treatment for COVID-19 severe enough to warrant hospitalisation will follow national guidelines. For those patients where treatment is changed (i.e. a new treatment is started for clinical reasons) an extra set of swabs in duplicate (and possibly a saliva sample see section 7.1) should be collected prior to the initiation of the new treatment (i.e. 2 sets of swabs will be taken in duplicate). This will only occur if the patient is within the first 7 days of the study.

The D0, D3, D7 and D14 blood samples will be tested for FBC and biochemistry (e.g. U&Es, LFTs) to assess for drug-related adverse effects or abnormalities which require a potential dose adjustment or stopping the therapeutic or clinical intervention. The responsibility for evaluating and acting upon the results of blood tests will belong to the study team at the local site. They will use their clinical judgement in the assessment of the patient, further tests and onwards referral. At any point of the study, extra laboratory tests may be conducted on the patient if felt to be clinically indicated by the research team, based on symptoms or previous laboratory abnormalities.

7.9 Sample Handling and Retention

Samples will be transferred to designated testing facilities, where they will undergo testing in accordance with best practice laboratory measures and safety procedures.

Oropharyngeal swabs (and possibly a saliva sample see section 7.1) will be processed using validated quantitative Real-Time quantitative Polymerase Chain Reaction (qPCR) to detect SARS-CoV-2, according to the study SOP. A urea measurement will be measured on each and compared to the baseline blood concentration. Swabs will be tested in duplicate.

The samples will be retained as per University of Oxford and local site regulations. Consenting patients may rescind their consent up until the completion of the study. Unless requested the samples collected prior to date of withdrawal will be retained for study analysis.

Samples, including those for PK, may be transferred to MORU or other designated testing facilities outside the site country, with appropriate material transfer agreements (MTA) and associated approvals prior to shipment.

8 DISCONTINUATION/WITHDRAWAL OF PATIENTS FROM STUDY

Patients may choose to stop treatment and/or study assessments but may remain on study follow-up. Patients may also withdraw their consent, meaning that they wish to withdraw from the study completely. In the case of withdrawal from both treatment and active follow up the following options for a tiered withdrawal from the study would apply a) Patients withdraw from the study but permit data and samples obtained up until the point of withdrawal to be retained for use in the study analysis. No further data or samples would be collected after withdrawal, b) Patients withdraw from active follow-up and further communication but allow the trial team to continue to access their medical records and any relevant hospital data that is recorded as part of routine standard of care; i.e., CT-Scans, blood results and disease progression data etc.

In addition, the Investigator may discontinue a patient from the trial treatment at any time if the Investigator considers it necessary for any reason including, but not limited to:

- Pregnancy
- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or trial requirements
- An adverse event which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures
- Disease progression which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures

The reason for discontinuation and/or withdrawal will be recorded in the Case Report Form. qPCR data from patients withdrawn from the study will still be analysed if at least three distinct timepoints are available for the estimation of a clearance slope. The sample size is adaptive so there is no need to replace withdrawn patients.

Consenting patients may rescind their consent up until the completion of the study. Unless requested, data and samples collected prior to the date of withdrawal will be retained in the study database and analysis.

8.1 Definition of End of Study

The end of study is the date of the 120 day follow up visit of the last enrolled patient.

9 SAFETY REPORTING

9.1 Definitions

Adverse Event (AE)	Any untoward medical occurrence in a patient to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a patient to an investigational medicinal product which is related to any dose administered to that patient.

	The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation[§] • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect. Other "important medical events" may also be considered serious if they jeopardise the patient or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. Hospitalisation is defined as an unplanned, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. The patient must be admitted overnight, a short stay of several hours to receive treatment is not considered hospitalisation. If a patient is admitted overnight or longer for social/economic or isolation reasons and is otherwise medically stable, this does not constitute a SAE. Other examples of visits to a hospital facility that are not considered hospitalisation are: Emergency room visits, outpatient surgery, pre-planned or elective procedures for a pre-existing condition (as long as that condition has not deteriorated while on trial treatment or brought forward because of worsening symptoms) and for the purpose of this study, being hospitalised for COVID-19 isolation.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.

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.

Any pregnancy occurring during the clinical trial and the outcome of the pregnancy should be recorded and followed up for congenital abnormality or birth defect, at which point it would fall within the definition of "serious".

9.2 Causality

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

Definitely related: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Probably related: There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

Possibly related: There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).

Unlikely to be related: There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication), or there is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).

Not related: There is no evidence of any causal relationship.

9.3 Procedures for Recording Adverse Events

A symptom questionnaire will be performed daily until D5 with a final follow-up assessment on D28 to aid in the identification of adverse events. The participant will be assessed on day 120 for post-acute COVID-19 but after day 28 study adverse events will not be recorded. The severity of adverse events will be assessed following the Common Terminology Criteria for Adverse Events (CTCAE) v5.0:

1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening, 5 = fatal.

AEs occurring in patients from enrolment and during trial participation that are observed by the Investigator or reported by the patient with severity **grade of 3 (severe) or higher** will be recorded on the CRF, whether or not attributed to trial medication.

When drug combinations are assessed, the team will separately record all clinical AEs (**grade of 1 or higher**) for those given the combination (e.g. molnupiravir **and** nirmatrelvir/ritonavir), as well as those being given the same drugs individually (e.g. molnupiravir **or** nirmatrelvir/ritonavir). This will be important to monitor the safety and tolerability of combinations in direct comparison to the individual drugs.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to trial medication, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

AEs considered related to the trial medication as judged by a medically qualified investigator or the Sponsor will be followed either until resolution, or the event is considered stable.

It will be left to the Investigator's clinical judgment to decide whether or not an AE is of sufficient severity to require the patient's removal from treatment. A patient may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the patient must undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.

9.4 Grading of laboratory abnormalities

Abnormal laboratory findings detected during the study or are present at baseline and worsen following the taking of study medication will be reported as AEs or SAEs. If found to be abnormal the values will be graded according to the CTCAE v5.0. AEs and SAEs of severity grade 3 or higher will be recorded in the CRF and will be followed up until grade 2 or below, returned to baseline, or deemed to be permanent. For laboratory results

that are not available in the CTCAE v5.0, the site investigator should make a determination as to whether or not the laboratory abnormality is clinically significant. If the site investigator believes a laboratory abnormality is clinically significant, it should be reported as an adverse event and a grade should be identified to the best of their ability.

9.5 Reporting Procedures for Serious Adverse Events

All SAEs detected by the site investigator must be reported to the PLATCOV safety team within 24 hours of site awareness. The Serious Adverse Event CRF documenting the SAE should be emailed to PLATCOVsafetyteam@tropmedres.ac. The PLATCOV safety team will inform the DSMB within 10 days of initial notification of the SAE and keep the DSMB updated as needed.

Further reports should be submitted, if required, until the SAE is resolved, is deemed stable/ permanent or results in death. A final status should be determined for any SAEs ongoing at the study end date.

The site PI must also report the SAEs to the local ethics committee and the regulatory authority in accordance with local requirements.

9.5.1 Expectedness

Expectedness will be determined according to the Investigators' Brochure/Summary of Product Characteristics.

9.5.2 SUSAR Reporting

All SUSARs occurring within the study will be reported by the site PI to the relevant Competent Authority and to the local Ethics Committee and other parties as applicable. For fatal and life-threatening SUSARs, this will be done no later than 7 calendar days after MORU is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

Site PIs will be informed of all SUSARs for the relevant IMP that occur at any of the PLATCOV study sites.

9.6 Data Safety Monitoring Board (DSMB)

An independent Data Safety and Monitoring Board (DSMB) will be set up consisting of qualified volunteers with the necessary knowledge of clinical trials. The DSMB will receive summary reports from MORU as defined per charter or per ad-hoc request, prior to each meeting. All data reviewed by the DSMB will be in the strictest confidence. A DSMB charter will outline its responsibilities and how it will operate.

An interim report will be prepared by the Trial Statistician for the pre-specified interim analysis. In case of safety concerns, additional information or formal interim analyses can be requested by the DSMB.

The DSMB will meet formally at the following timepoints:

- before the study starts
- after the first 50 patients have been accrued into the study (10 per arm)
- At additional time-points as indicated by the DSMB after their review, if deemed necessary

All DSMB recommendations will be communicated to site PIs. The site PI will be responsible for submitting the written DSMB summary reports with recommendations as applicable to local/ national ethics committees and other applicable groups.

10 STATISTICS AND ANALYSIS

10.1 Overview of adaptive study design and overall approach

This is a platform trial that will evaluate multiple antiviral treatments for COVID-19. The sample size is adaptive with multiple planned interim analyses. By specifying an adaptive sample size, we can more rapidly identify treatments that work and possibly remove treatments that do not work. Clinical trials with adaptive designs are increasingly being used in research, including in such successful and prominent COVID-19 studies as the RECOVERY study. In addition, the FDA and EMA supply guidance on studies with these designs[1]. They do not have fixed sample sizes, as do conventional RCTs. The number of patients recruited depends on the results (i.e. they are adaptive). The benefits of an adaptive sample size are increased efficiency and ethical considerations (i.e. they can stop ineffective arms earlier, identify effective arms earlier, and limit numbers in ineffective arms compared to fixed sample number studies). Because of these advantages this type of study is likely to become more prevalent, but it is important that the study is well-designed in advance, that the adaptive design is appropriate for the overall study design,and has mechanisms in place to control type I error.

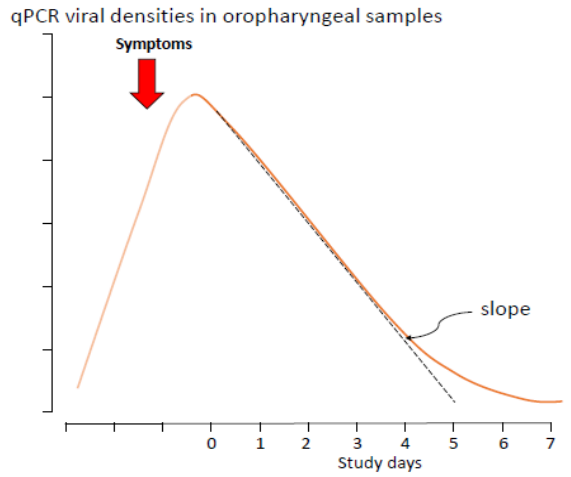

Figure 6 qPCR viral densities in oropharyngeal samples over time, showing time of likely symptom onset relative to viral densities and study days

The main pharmacodynamic endpoint is the rate of viral clearance, estimated from serial qPCR measurements in each patient (4). There is considerable inter-individual variability in clearance rates which are first order and predominantly monoexponential, although there is some evidence of a biexponential component. The measured end point is the slope of the the initial log linear decline in qPCR estimated viral densities (Figure 6). The clearance rate is correlated with both disease progression and the presence of symptoms. As this is a multi-centre trial, populations may differ between sites with respect to key covariates. Therefore, the main analytic approach will be to fit a hierarchical Bayesian model to the serial qPCR measurements (using default weakly informative Bayesian priors to aid model fitting), whereby the baseline viral loads (intercept) and the first-order clearance rates (slope of initial decline) can vary between sites and between individuals. The viral clearance slope is also dependent on the randomised study arm. Stopping an intervention arm for futility or success, triggering an intensive PK-PD nested sub-study, may be decided using the posterior probabilities that the arm results in an increased slope (increase set as 20%, following the results of the first interim analysis). The PK-PD nested sub-study may be also triggered if there is evidence of accelerated viral clearance from other studies (e.g. Molnupiravir, Nirmatrelvir/ritonavir).

10.2 Results of the first interim analysis

As pre-specified in the SAP, the first interim analysis, triggered once data from the first 50 patients were available, was presented to the Trial Steering Committee and the DSMB. This analysis showed that the positive control arm (REGN-CoV-2) had a substantially larger effect on viral clearance than anticipated, with over 50% increase in viral clearance relative to the negative control arm (Figure 7). In addition, the intra-individual variation in viral load estimation was greater than anticipated, resulting in larger uncertainty around effect sizes. For these reasons, we changed the threshold effect size defining futility and success from 5% increase

[1] https://www.fda.gov/media/78495/download
https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-methodological-issues-confirmatory-clinical-trials-planned-adaptive-design_en.pdf

in viral clearance to 12.5% increase in the viral clearance and subsequently to 20%. Under this threshold, we would need an average of 50 patients randomised to an intervention that has no effect on viral clearance to demonstrate futility. For therapeutics which may potentially be used in prophylaxis, where a lesser antiviral effect may be required to be clinically useful, a different success threshold, and maximum number of patients, may be described in the SAP for the analysis.

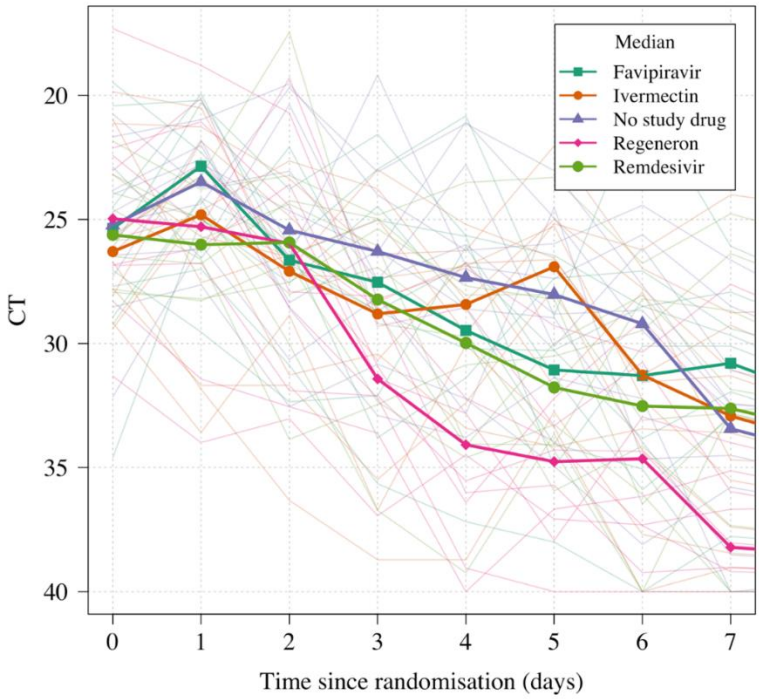

Figure 7 Data from the first interim analysis (first 50 patients recruited into the study).

10.3 Bayesian hierarchical model of viral clearance

At each interim analysis we will fit a series of Bayesian hierarchical (mixed effects) model to the serial viral load measurements (modelled directly on the Ct scale). The main linear model will take the following form:

$$y_{k,i,t} \sim \text{Student}(\alpha_0 + \alpha_k + \alpha_i + (\beta_0 + \beta_i + \beta_k + \beta_{T(i)})t\ ,\ \text{sigma}^2,\ \text{dof})$$

where $y_{k,i,t}$ is the observed $\log_{10}$ viral load for individual i at time t from site k (two values per timepoint), and T(i) is the randomised arm assigned to individual i. Sigma^2 is the measurement error (residual error). The error model is a t-distribution with degrees of freedom inferred from the data (dof). The slope of viral clearance decomposes into 4 terms: the population mean slope β_0; the site random effect β_k; the individual random effect β_i; and the treatment effect (fixed across sites and individuals) $\beta_{T(i)}$. The intercept term (baseline viral load) decomposes into 3 terms: the population intercept α_0; the site random effect α_k; and the individual random effect α_i. All comparisons are made relative to the no antiviral treatment control arm, so we set $\beta_{control} = 0$. Adjustment will be made for human RNaseP concentration. The model will treat viral load corresponding to CT values of 40 as left censored. An equivalent non-linear model (allowing for an initial increase in viral load, followed by a linear decrease) will also be fitted to the data as a sensitivity analysis.

The SAP has further details of the analysis.

10.4 Time varying effects

Characterising and identifying time varying effects not specified in the main model is important for two reasons:

- Monoclonal antibodies (type B- see study design section) - where the efficacy can be reduced in infections with spike protein mutant SARS-CoV-2 strains. Therefore, it is possible that a waning effect is observed over time justifying early stopping.
- New interventions which are added later on during the trial cannot be compared directly to all data from the control arm without accounting for possible differences in population over time (as an epidemic evolves, included populations may differ in a single site over time).

We will use descriptive approaches to detect time-varying effects (residual plots over time, mean slopes in control individuals over time). If substantial time-varying effects are observed, we will add a smooth time varying spline component to the linear model. The base model will not include this for simplicity.

10.5 Sample size estimation, randomisation and statistical considerations for the Bayesian group sequential design

The platform study has two main objectives:

- Identify interventions that are unlikely to be of clinical benefit (i.e. demonstrate futility)
- Identify interventions that could have clinical benefit and determine optimal dosing (from PK-PD studies) for phase 3 evaluations.

The required sample size depends on how stringent the thresholds are that define futility or success. Before the trial started we used simulation to determine the probability thresholds that result in control of the type 1 error at 10% and control of the type 2 error at 20% using as a minimum effect size a 5% increase in viral clearance. Following the first interim analysis at 50 patients, the minimum threshold was changed to 12.5%. It was subsequently increased to 20%.

For the following interim analyses, the decisions made for a treatment arm *T* are as follows:

- Stopping for futility: if Probability($\beta_T > 0.20 * \beta_0$) < 0.1
- Stopping for success/Triggering intensive PK-PD nested sub-study: if Probability($\beta_T > 0.20 * \beta_0$) > 0.9

The first interim analysis was carried out after 50 patients were enrolled. We will then carry out interim analyses every 25 patients. The initial thresholds for futility and success were chosen after simulating 6000 trials with all combinations of futility thresholds in the set {0.05, 0.1, 0.2} and success thresholds in the set {0.8, 0.9, 0.95, 0.99} (12 combinations in total, 500 simulations per combination). The maximum sample size was set at 400 patients in total with 6 arms (5 intervention arms and 1 control arm). Out of the 5 interventions, 1 was effective with an effect size of 10% and the other 4 were ineffective (no increase in slope). Type 1 error for a particular combination of futility and success thresholds was calculated as the average number of times any of the ineffective arms were declared effective divided by the number of decisions (note this the per decision type 1 error not the family wide error rate which is dependent on the number of arms). The type 2 error was calculated as the number of times the effective arm was declared ineffective or no decision was reached by 400 patients. Appendix 3 shows how type 1 and type 2 error varies across choices of thresholds. The thresholds we have chosen allow us to control type 1 errors at 10% and type 2 errors at 20%.

For these futility and success thresholds, the simulations demonstrate the number of patients randomised per arm in order to reach a decision is:

- 50 patients (average; median is 30) for each efficacious intervention (effect size of 10% increase in viral clearance) means approximately 60 patients for an effect size of 20% increase in viral clearance, as per the current futility/ success threshold. However, a maximum number of 200 patients per arm

may be required, although further recruitment can occur after consultation with the DSMB or TSC, if it is felt that more precision of the result is beneficial. In the case that a stopping rule is not met before this number we will stop recruitment to an arm at 200 patients (excluding comparator arms e.g. negative and positive controls. This means more than 200 patients may be enrolled into the positive control at the time- i.e. more than 200 patients may be enrolled to the positive control at the time e.g nirmatrelvir/ritonavir (current positive control at the time of writing).

- 40 patients (average; median is 25) for each inactive intervention (effect size of 0).

Therefore, supposing there were 5 interventions of type A in the platform, and assuming that only 1 of the 5 were in fact effective, we would need on average a total of 50 + 4*40 = 210 patients randomised to interventions of type A (approximately 66% of the total sample size: a minimum of 20% of samples are randomised to the negative control and thus ~13% of patients are randomised to each intervention arm and the positive control arm). This implies a total of ~320 patients for the first set of interventions identified (this does not include any intensive PK sub-studies).

This study is open-label and so a centralised server-based randomisation system will be used. Only designated study personnel will be authorised to access the webapp for patient allocation. The webapp will be password protected. All randomisation activities will be traced within the webapp and attributed to a timestamp along with the anonymised patient study code, age and sex.

10.6 Sample size for the intensive PK-PD sub-study

All drugs in the dose finding sub study and any drugs with evidence of accelerated viral clearance from other studies (e.g. Molnupiravir, Nirmatrelvir/ritonavir) or which meet the success endpoint (>90% probability that clearance is accelerated by more than 20% relative to control) will be included in an intensive PK-PD study. The sample size calculation for each sub-study will be drug dependent and will use the information regarding the variability in clearance in the intervention arm versus the variability in clearance in the control arm (i.e. it will be determined by the results). Larger observed variability in the intervention arm would be expected if an active intervention had variation in exposures that corresponded to variation around the near maximal effect concentration (eg EC_{95}).

We will use a PK simulation-based approach where we will simulate predicted drug AUC values for patients given the characteristics of the patients in each site (weight and sex) and use the observed variability in viral clearance rates to estimate the necessary sample size to infer a dose-response relationship whereby a 10% increase in AUC resulted in a 10% increase in the slope of viral clearance with 80% power and 5% type 1 error.

10.7 Change to sampling schedule

The initial sample schedule was based on simulations of data from untreated individuals in 2020. Since then there have been a number of new variants, new treatments and the greater knowledge of viral dynamics from patients randomised into the study. These results demonstrate that over time, the rate of viral clearance has increased and viral half-life has decreased (see Figure 8 below (32)). The result of faster clearance over time has been more undetectable viral loads at later timepoints between D0 and D7 i.e. D6 and D7. In addition, there appears to be a second slower phase to clearance, which is less affected by effective therapeutics (thus later timepoints can even dilute the observed antiviral effect). Updated simulations have shown that the ideal duration of sampling is until day 4 or 5 and we have conservatively changed the endpoint to be clearance up to day 5.

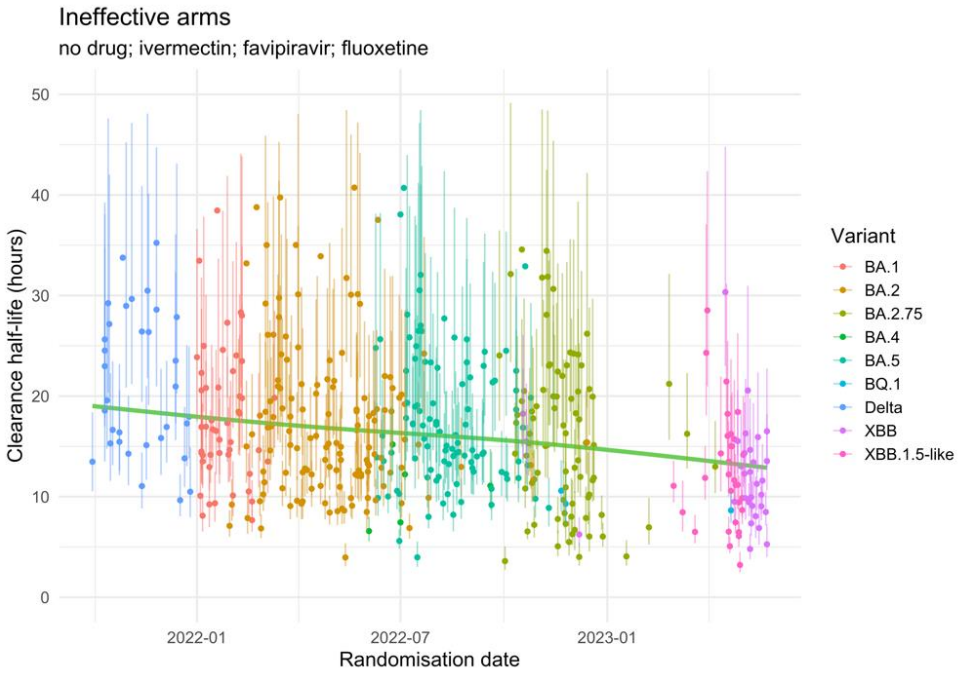

Figure 8 Clearance half-lives over time for the ineffective arms in PLATCOV showing an increased rate of clearance.

10.8 Final analysis of primary outcome

The final analysis will fit a series Bayesian hierarchical linear and non-linear models to the serial $\log_{10}$ viral load measurements (copies per mL). The primary estimates of interest are the relative changes in the rate of viral clearance for the intervention arms (including the positive control arm) compared to the no study drug arm. These will be reported as their mean posterior estimates along with credible intervals. All analyses will be done using *R* using the package *rstan* along with bespoke software. All analysis code is openly available via a GitHub repository: https://github.com/jwatowatson/PLATCOV-SAP. Anonymised viral load data and key meta data (e.g. site, strata, randomised allocation) will be made available at publication of results.

11 DATA MANAGEMENT

11.1 Access to Data

Direct access will be granted to authorised representatives from the University of Oxford and any host institution for monitoring and/or audit of the study to ensure compliance with regulations. Outcome data and treatment assignment data will be made available for analysis in real time.

11.2 Data Handling and Record Keeping

Clinical study data will be recorded on CRFs and entered on to a password-protected database by the local study PI, research nurse or designee. The study database will be built in MACRO EDC, a clinical data management system that is compliant with ICH GCP and FDA 21 CFR Part 11 and will be hosted in a secure, access-restricted server in MORU. The study database will include internal quality checks to identify data that appear inconsistent, incomplete, or inaccurate.

Measures will be taken to ensure non-disclosure of information that is potentially harmful to patients. Paper records (for example, patient identifiable information for the purposes of follow-up, the screening logs and signed ICFs) will be kept in locked cabinets; electronic data will only be accessible to personnel with user accounts and passwords. The database contains an audit trail that keeps record of changes to data and user

activity within the database. All electronic data will be stored on secure servers that are backed up daily, with weekly off-site storage.

Patient records at site will, taking into account the ability of the sites, be stored in binders in the secured access-limited room or scanned and stored electronically. The records will be retained for at least five years following completion of the study, or according to local site regulation. The study database will be retained indefinitely.

With patient's consent, clinical data and results from blood analyses stored in the database may be shared according to the terms defined in the MORU data sharing policy with other researchers to use in the future.

Data generated from this study will adhere to the 2016 "Statement on data sharing in public health emergencies"(https://wellcome.ac.uk/press-release/statement-data-sharing-public-health-emergencies).

12 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with relevant regulations and standard operating procedures.

The study will be conducted in compliance with this protocol, International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP) and any applicable regulatory requirement(s). Monitoring will be overseen by the MORU Clinical Trials Support Group (CTSG) according to a prespecified risk-based monitoring plan to ensure compliance to the study protocol and applicable guidelines and regulations. Biological specimens will be processed, stored and shipped in accordance with MORU SOPs.

Data validation will be performed to identify errors or discrepancies and thus ensure completeness, validity and accuracy of data.

13 ETHICAL AND REGULATORY CONSIDERATIONS

This study will be conducted in patients who would be unlikely to progress to severe illness. The investigated medications may benefit the patient; i.e. shorten the duration of symptoms or decrease their severity, but are unlikely to have a significant adverse effect on the patient's illness and subsequent health, including when drugs are used in combination where there may potentially be more side effects (this is not expected) but also greater benefit in terms of shortening illness and decreasing severity. Assessing drug combinations may be important in preventing the development of drug resistance, and may be beneficial to those with a greater likelihood of severe illness (i.e. the wider population). No drug intervention has been shown to be unequivocally beneficial at this point in the illness, in this population, and clinical equipoise exists between the interventions and the no antiviral treatment (although local supportive treatment will be fully provided including antipyretics (e.g. paracetamol), anti-tussives, antihistamines, vitamins etc and any treatments clinically indicated by the Physician looking after the patient. Funds will be set aside to cover hospital costs in the unlikely event of a drug adverse reaction.

Women who are pregnant, actively trying to become pregnant, or breast feeding will be excluded from this study as it is not known if any of the treatments being tested will have additional benefits that would outweigh any risks associated with pregnancy/breast feeding.

13.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the current revision of the Declaration of Helsinki.

13.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

13.3 Approvals

The protocol, informed consent form and participant information sheet will be submitted to OxTREC and local ethics committees for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all amendments to the original approved documents.

13.4 Patient Confidentiality

The study personnel will ensure that the patients' anonymity is maintained. The patients will be identified only by a patient ID number on all study documents and any electronic database, with the exception of the CRF, where patient initials may be added. The name and any other identifying detail will NOT be included in any study data electronic file. All documents will be stored securely and only accessible by study personnel and authorised personnel. The study will comply with the Data Protection Act 2018, which requires that personal data must not be kept as identifiable data for longer than necessary for the purposes concerned.

13.5 Expenses

Patients will be financially compensated for their time in the study, in accordance with local EC guidance and approval.

13.6 Risk

All of the treatments being tested *initially (see Appendix 2 for study drugs)* are generally well tolerated with the main adverse effects related to gastrointestinal symptoms (abdominal pain, diarrhoea, nausea and vomiting). In the case of intravenously/subcutaneously administered treatments there may be discomfort, bleeding or bruising of the skin at the site of needle puncture. Further information regarding specific side effects for each of the drugs used in the study can be found in Appendix 2. These are usually mild and settle without the need for medical intervention.

The risks associated with blood withdrawal during the study include discomfort, occasional bleeding or bruising at the site of needle puncture, and very rarely infection. The risks associated with nose and throat swabbing are limited to some slight discomfort.

The risks associated with the interaction of two study drugs during randomisation or with the combination of molnupiravir and nirmaterlvir/ritonavir are low. The drugs are not known to interact and participants will be monitored for adverse events.

13.7 Benefits

It is not yet known if any of the treatments being tested will have additional benefits for the patient in the management of COVID-19. Although an individual patient may not personally benefit, this study should help future COVID-19 patients by discovering treatments that work in early disease and ruling out those do not. Remuneration will be provided to the patients for the period they are enrolled in the study. Patients will be reimbursed for costs associated with traveling to the study site and loss of work time. The amount will be determined per local allowed guidelines and ethics committee policies .

13.8 Reporting

The PI shall submit an Annual Progress Report to OxTREC on the anniversary of the date of approval of the study. In addition, the PI shall submit an End of Study Report to OxTREC within 12 months of completion of the study.

13.9 Finance and insurance

13.9.1 Funding: ACT- Accelerator

This trial is funded by the COVID-19 Therapeutics Accelerator (CTA), managed with MORU through the Wellcome Trust. CTA is a philanthropic collaboration supporting efforts to research, develop and bring effective treatments against COVID-19 to market quickly and accessibly. CTA and Wellcome Trust have had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit the results.

13.9.2 Insurance:

The University has a specialist insurance policy in place which would operate in the event of any patient suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London).

13.10 Data ownership

The data generated in this study belongs to the study group as a whole. The final database will be shared amongst the site PI and key members of the research team.

The database may be shared with researchers not directly involved in this study but only after the main paper has been published and in accordance with MORU guidelines on data sharing. The database will only be shared if future publications are not compromised. The criteria for authorship will be consistent with the international guidelines (http://www.icmje.org/#author).

13.11 Publication policy

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by by the COVID-19 Therapeutics Accelerator (CTA). Authorship will be determined in accordance with the International Committee of Medical Journal Editors (ICMJE) guidelines and other contributors will be acknowledged.

The results of the study will be summarised in lay language, in both English and the language(s) commonly spoken at the study sites, and disseminated to key stakeholders, user communities and patients.

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Appendices

15 Appendix 1: Schedule of activities

Procedures	D0				D1	D2	D3	D4	D5	D6	D7	D14	D28 (-2/ +7)	D120 (-10/+30)	If new Tx/ symptoms
	Pre-1st dose	H0	H1	H6-18											
Screening incl. Lateral Flow Ag test and urine pregnancy test	X														
Eligibility assessment	X														
Informed consent	X														
Randomisation	X														
Baseline information captured (inc symptoms, physical exam, ECG (optional))	X														
Vital signs	X				X	X	X	X	X		X	X			
Symptom checklist			X[1]		X	X	X	X	X	X	X	X	X		
Observed dose		X[1]			X[1]	X[1]	X[1]	X[1]	X[1]	X[1]					
Observation post dose			X[1]												
*Temperature**			X		X	X	X	X	X	X	X	X			
C19 YRSm														X	
Virology															
*Oropharyngeal swabs***	X	X		X***	X	X	X	X	X		X	X			X
Possible extra swabs					X	X	X	X	X						
Bloods															
FBC+diff	X[2]						X				X	X			

Biochemistry (including U&Es, LFTs LDH)	X[2]						X				X	X			
Fibrinogen/ FDP	X						X				X	X			
Ferritin	X						X				X	X			
TNF/IL-6/IL-1	X						X				X	X			
Serology and stored sample	X						X				X	X			
Drug level	X						X				X	X			
Host genotyping	X						X				X	X			

* Performed at least twice a day. For those taking drugs which are more than once per day, the patient will also record the time the dose was taken for any non-observed doses.

** Taken in duplicate at least once a day, up to twice per day, either by the study team or as a self-swab. Time swab done recorded. Some patients may be asked to give a saliva sample as well (see section 7.1)

***May be taken by the study personnel or self-swabbing, 6-18 hours after H0.

X[1]Depends on dosing schedule of the drug (see appendix 2). The first dose will be given at the designated trial facility. For drugs where further doses are required, at least one dose per day will be observed by the study team. The time the drug is taken will be recorded by the study team.

X[2] Results will be used to detect laboratory abnormalities included in the exclusion criteria (see appendix 4 exclusion criteria)

The final column, If new Tx/symptoms, refers to if the treatment is changed while the patient is within the 1st 7 days of the study, or if new symptoms develop between day 7 and day 28 (see section 7.8 Management of patients who become ill).

Note: PK sampling schedules for determination of antiviral drug level are mentioned in Appendix 2.

16 Appendix 2: Study drugs

The maximum duration of treatment is 7 days so many of the toxicity concerns related to chronic dosing are not relevant to this short course treatment

16.1 Nitazoxanide

Rationale

Nitazoxanide is a broad-spectrum antiprotozoal and antiviral drug first discovered in the 1980s. It has an excellent safety profile, the only contraindication to nitazoxanide being a hypersensitivity reaction to nitazoxanide. Nitazoxanide has demonstrated broad-spectrum *in vitro* antiviral activity including against SARS-CoV-2. There are also reports from trials suggesting benefit and given the low cost, safety, tolerability and availability of this drug, it would be an attractive candidate in the prevention and treatment of COVID-19, if shown to have benefit in this illness. Nitazoxanide has *in vitro* activity against the novel coronavirus SARS-CoV-2, which causes coronavirus disease (COVID-19). The EC50 on Vero E6 cells (the concentration to decrease the cytopathic effect of the virus by 50%) was reportedly 2.12µM (1). Nitazoxanide has a molar mass of 307.283g/mmol, and as such 2.12µM corresponds to a concentration of 0.65mg/L.

Although the above study on SARS-CoV-2 used nitazoxanide, the active metabolite tizoxanide inhibits influenza, respiratory syncytial virus, parainfluenza, coronavirus, rotavirus, norovirus, hepatitis B, hepatitis C, dengue, yellow fever, Japanese encephalitis virus and human immunodeficiency virus *in vitro* (2). Nitazoxanide was able to protect 90% of mice from death in a lethal challenge model of Japanese Encephalitis (3). The exact mechanism by which nitazoxanide exhibits its antiviral effects are uncertain, but augmented host responses as opposed to direct antiviral effects are postulated. Nitazoxanide is able to increase interferon responses in HCV/HIV coinfected individuals (4).

A double-blind randomised placebo-controlled trial of nitazoxanide in acute uncomplicated influenza found a significant reduction in duration of symptoms in the 600mg BD nitazoxanide group, but not the 300mg BD one (5). Additionally, viral titres were significantly decreased in the 600mg BD nitazoxanide group. Another study using the same doses in cases of severe respiratory infection caused by all respiratory viruses, did not show an effect (6). Nitazoxanide is being assessed in clinical trials in COVID-19, and published results suggest an increased time to viral clearance, although this result may be confounded by differences in initial viral loads (7).

Composition & dose

One tablet of nitazoxanide as ALINIA® tablets contain 500 mg of nitazoxanide (https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021497s001,021498s004lbl.pdf).

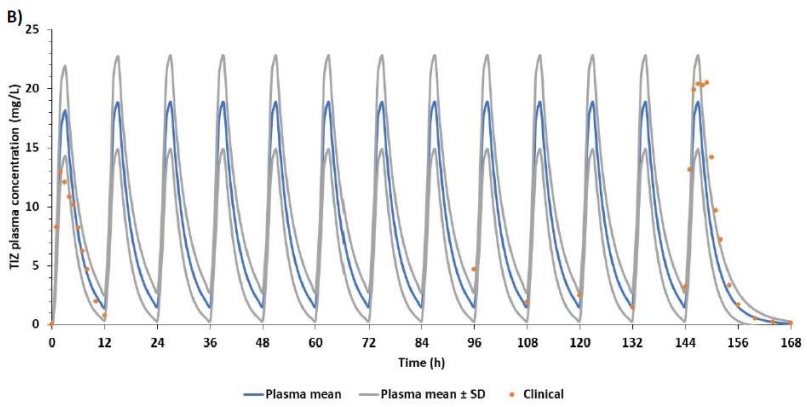
Nitazoxanide will either be obtained by the sponsor or the local teams from a reliable manufacturer.

High dose nitazoxanide is given as 1.5 g bd.

The dose in this trial is: **1.5g PO twice daily for 7 days** (taken with food).

Pharmacokinetic characteristics

Following oral administration of nitazoxanide, the drug is rapidly hydrolysed to its active constituent, tizoxanide, and then conjugated to produce active tizoxanide glucuronide; nitazoxanide is not detected in plasma and > 99% of tizoxanide is bound to proteins. The bioavailabilities of tizoxanide and tizoxanide glucuronide are increased 2-fold with food. The mean Tmax of tizoxanide, is 2.5h with a half-life of 1 to 2h (8). The mean Tmax of the tizoxanide glucuronide is 4 to 6h. A dose of 1g PO BD of nitazoxanide produces a Cmax of 24mg/ml of tizoxanide and 26.4mg/ml



tizoxanide glucuronide and the half-lives increase to 6.4 and 3.5 hours, respectively. Tizoxanide is excreted in the urine, bile and faeces, and tizoxanide glucuronide is excreted in urine and bile (its concentration is x10 that of plasma).

Pharmacokinetic sampling schedule: (only if there is evidence of accelerated viral clearance)

All patients will need to be admitted for 12 hours for intense sampling. The timings may be the following but the number and timing are subject to change:

Pre-dose D0H0, then
1, 2, 3, 4, 6, 9, 12 and 24h

Note that blood will be taken on D3 and D7 for routine haematology and biochemistry. The EDTA sample will be used to measure the drug concentrations.

Toxicity

Nitazoxanide is a safe and well-tolerated drug. Reported toxicities include:

Gastrointestinal disorders: diarrhoea, gastroesophageal reflux disease

Nervous System disorders: dizziness

Respiratory, thoracic and mediastinal disorders: dyspnoea

Skin and subcutaneous tissue disorders: rash, urticaria

Risks related to nitazoxanide are very low. This is a very safe and generally well tolerated medication but adverse reactions relating to the central nervous system (headache and rare reports of dizziness), the gastrointestinal system (abdominal pain and nausea and rare reports of diarrhoea and gastro-oesophageal reflux), and genitourinary system (urine discolouration) have been described as well as post-marketing cases of dyspnoea, skin rash and urticaria. In one study, side effects of nitazoxanide did not differ from those of the placebo when used for the treatment of giardiasis, and does not cause side effects when used in healthy adults (9). This lack of significant side-effects is seen in doses up to 4g in humans. The LD50 of various animals is 10g/Kg. A study of 365 patients with AIDS receiving nitazoxanide 500-1500mg twice daily for a median duration of 62 days (1-1528 days) concluded that “No safety issues were identified at doses up to 3000 mg/day or for long durations of treatment” (10). These risks will be mitigated by excluding participation if people have had a previous serious adverse reaction to nitazoxanide.

Nitazoxanide may be used after the first trimester of pregnancy with severe symptoms of cryptosporidiosis. Adverse events have not been observed in animal reproduction studies although human data are not available. It is not known whether nitazoxanide enters into breast milk, and the manufacturer suggests balancing risk of exposure to the infant and benefit to the mother. We will exclude pregnant women and women breastfeeding from this study and ask female patients of child-bearing age to undergo a pregnancy test and take precautions not to become pregnant (contraception). Those who do become pregnant will be followed up. However, given the lack of evidence of harmful effects and its use later in pregnancy, the risk to a foetus seems low. The mitigating factors of a pregnancy test and advising contraception will make the likelihood of pregnancy within the trial and potential risk, even lower.

Contraindications and cautions

Known hypersensitivity. The Pharmacokinetics of nitazoxanide in patients with compromised renal or hepatic function have not been studied.

Relevant Drug interactions

None

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16.2 Nirmatrelvir/ritonavir (e.g. PAXLOVID™)

Rationale

PAXLOVID™ is a therapeutic combination of 2 compounds, Nirmatrelvir and ritonavir, taken at the same time as separate pills. Nirmatrelvir (PF-07321332) is an oral covalent 3CL protease inhibitor of SARS-CoV-2 and ritonavir is an inhibitor of HIV-1 and HIV-2 protease. Ritonavir inhibits cytochrome P450A and CYP2D6 which inhibits the metabolism of nirmatrelvir.

Coronoviruses contain two proteases, main protease – Mpro (also known as 3CL protease – 3CLpro) and papain-like protease. Pfizer developed a SARS-CoV Mpro inhibitor in 2002 (PF-00835231) which demonstrated in vitro and in vivo activity against SARS-CoV-2 (1). Other studies also found successful in vitro inhibition of SARS-CoV-2 replication in derived alveolar basal epithelial cells expressing ACE2 (2) and human bronchial epithelial cells (3). This compound had insufficient bioavailability so the oral version PF-07321332 was developed (4).

A Phase 2/3 EPIC-HR randomised double blind control trial from Pfizer looked at non-hospitalised patients at risk of progressing to severe illness. Intervention was ritonavir and nirmatrelvir started within three or five days of symptom onset. Primary endpoint was COVID-19-related hospitalisation or all cause death up to day 28. For those receiving PAXLOVID™ within 3 days, 3/389 (0.7%) were hospitalised with zero deaths., compared to the placebo 27/385 hospitalised with 7 deaths, p<0.0001. For treatment within 5 days, 6/607 (6.7%) were hospitalised with no deaths, compared to 41/612 (with 10 deaths) in the placebo group (p<0.0001) (5).

Composition & dose

Administered as 300MG of nirmatrelvir (two 150MG tablets) with one 100 MG tablet of ritonavir given twice daily for 5 days.

Nirmatrelvir/ritonavir will either be obtained by the sponsor or the local teams from a reliable manufacturer (including high-quality generics manufacturers).

Pharmacokinetic characteristics

Ritonavir is administered with nirmatrelvir as a pharmacokinetic enhancer resulting in higher systemic concentrations and longer half-life of nirmatrelvir. This supports a twice daily administration. Nirmatrelvir (when given with ritonavir) is eliminated renally, with a half-life of 6.05 hours, peak concentration is at 3 hours. Ritonavir is metabolised in the liver, with a half-life of 6.15 hours, peak concentration is at 3.98 hours.

Pharmacokinetic sampling schedule:

The timings may be the following but the number and timing are subject to change:

Pre-dose D0H0, then
1, 2, 3, 4, 6, 9, 12 and 24h post dose

Note that blood will be taken on D3 and D7 for routine haematology and biochemistry. The EDTA sample will be used to measure the drug concentrations.

Toxicity

Repeat-dose toxicity studies up to 1 month duration of nirmatrelvir in rats and monkeys resulted in

no adverse findings. Ritonavir can cause retinal toxicity with long term use (6), although this is not relevant for the short-term use in the study. Ritonavir alone does not cause any issues related to HIV drug-resistance.

Contraindications

In our study, nirmatrelvir/ritonavir is contraindicated in:

hypersensitivity to nirmatrelvir/ritonavir or any of its ingredients, including ritonavir.

co-administration with drugs highly dependent on CYP4503 A.

co-administration with potent CYP450 3A inducers

More details regarding concomitant medication can be found at:

https://www.covid19-druginteractions.org/checker

https://crediblemeds.org/

https://compendium.ch/fr/Patient - this is a Swiss website dealing with drug interactions

https://www.bnf.org/products/bnf-online/ - available only in the UK

Cautions

Caution should be given in patients with pre-existing liver disease/hepatitis or live enzyme abnormalities. Dose reduction for renal impairment (eGFR ≥ 30 to <60 mL/min) is 150MG nirmatrelvir and 100 MG ritonavir.

Drug Interactions

Contraindicated with drugs that are highly dependent on CYP3A for clearance or are potent CYP3A inducers (see above). There are no theoretical drug interactions in combination molnupiravir.

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16.3 Nirmatrelvir/ritonavir (e.g. PAXLOVID™) dose finding

Rationale

Finding the optimal dose of Ritonavir to boost Nirmatrelvir to the levels required for a significant clinically beneficial effect, while balancing the side-effects of Ritonavir-induced dysgeusia and drug-drug interactions, could increase the number of patients able to access Nirmaltrelvir.

Nirmatrelvir/Ritonavir (e.g. PAXLOVID™) is one of the two main licensed treatments for COVID-19. The other is molnupiravir. PAXLOVID™ is licensed in numerous countries across the world. Despite clinical efficacy demonstrated in the pre-registration phase III studies (1), and it being widely considered the most effective COVID-19 medication, several important drawbacks prevent its widespread use. Amongst these are drug-drug interactions from the Ritonavir component, which prevents many of the highest risk individuals most at need from accessing the medication (2). Additionally, a bad taste, or dysgeusia, from Ritonavir affects patient uptake and reduces adherence.

Other important limitations include the high cost (c.$500/ course) and concern regarding viral rebound. More recently, in a vaccinated population of normal and high-risk patients, PAXLOVID™ did not demonstrate clinical efficacy over placebo, reflecting most likely the overall reduction of severe outcomes in COVID-19 in an increasingly immune population. Despite this, recent modelling suggests that increased use of PAXLOVID in the USA could avert large numbers of hospitalisations and save $57billion USD even in low COVID-19 transmission scenarios. Thus, addressing barriers to uptake of antivirals against COVID-19 has health and economic benefits to societies as a whole (3).

In the urgent context of the pandemic, the dose of Ritonavir chosen to boost the Nirmatrelvir was the upper end of the range used to boost other protease inhibitors (e.g. HIV)- 100mg BD. This made sense- guaranteeing maximal boosting and Nirmatrelvir levels, but dose-finding studies with lower dose Ritonavir were not conducted. We do not know if the maximal boosting effect could have been achieved with less, or whether the antiviral benefit could be achieved without Ritonavir. Many protease inhibitors are boosted equally well at lower doses of Ritonavir than 100mg BD e.g., saquinavir, fosamprenivir and darunavir are boosted equally well with a dose as little as 50mg/day (4). A phase I study in healthy volunteers did show rapid elimination, and low peak levels of Nirmatrelvir given without Ritonavir, although without a pharmacodynamic measure of efficacy. At a dose of 150mg (half the current dose of Nirmatrelvir used in PAXLOVID, the drug levels surpass the EC90 for several hours, which suggests that the drug will have some efficacy (see below figure) (5). Additionally, the well-established down-regulation of CYP3A enzymes with inflammation and infection (thus potentially meaning higher levels) means healthy volunteer studies may underestimate drug levels of CYP3A excreted drugs (6).

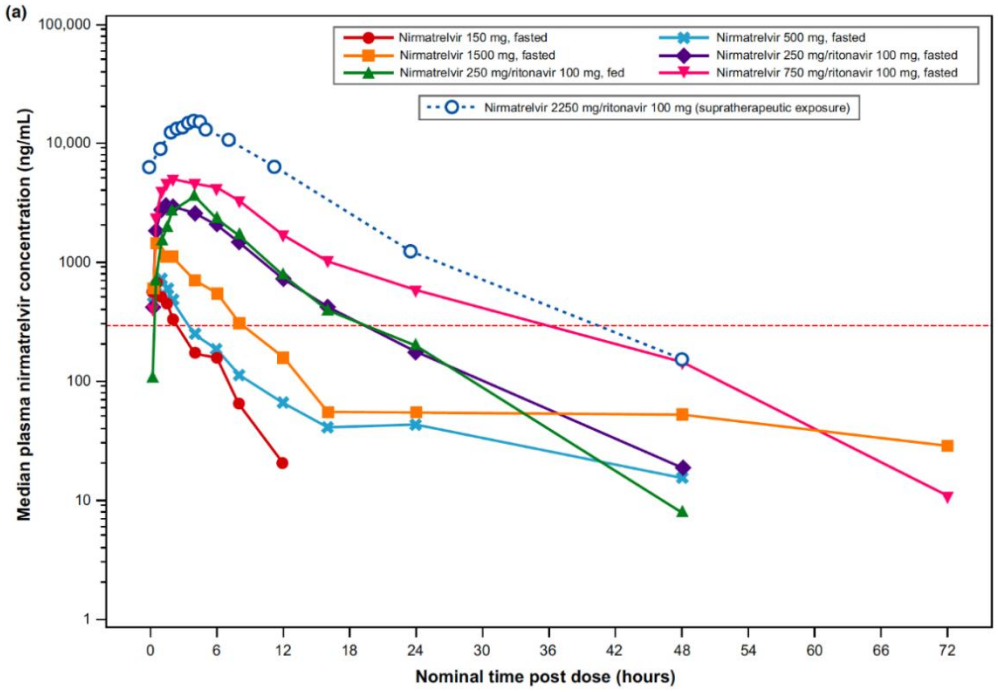

Figure 2 *Median plasma Nirmatrelvir concentration-time profiles (semi-logscales) for single-ascending dose and supratherapeutic exposure cohorts*

By determining the dose-response relationship of the Nirmatrelvir, regimens could be suggested which additionally reduce the dose of Nirmatrelvir, thereby decreasing the cost and allowing better access in poorer nations, or longer courses which may prevent rebound. The arrival of generic PAXLOVID through the Medicines Patents Pool (MPP) could hasten this reduction in cost.

Composition & dose

Patients will be randomised to PAXLOVID or a high-quality generic version in the following doses:

- Nirmatrelvir 300mg + Ritonavir 100mg twice daily for 5 days
- Nirmatrelvir 300mg + Ritonavir 50mg twice daily for 5 days
- Nirmatrelvir 150mg + Ritonavir 50mg twice daily for 5 days
- Nirmatrelvir 300mg alone twice daily for 5 days

Nirmatrelvir/Ritonavir will either be obtained by the sponsor or the local teams from a reliable manufacturer (including high-quality generics manufacturers).

Pharmacokinetic characteristics

Ritonavir is administered with Nirmatrelvir as a pharmacokinetic enhancer resulting in higher systemic concentrations and longer half-life of Nirmatrelvir. This supports a twice daily administration. Nirmatrelvir (when given with Ritonavir) is eliminated renally, with a half-life of 6.05 hours, peak concentration is at 3 hours. Ritonavir is metabolised in the liver, with a half-life of 6.15 hours, peak concentration is at 3.98 hours.

Pharmacokinetic sampling schedule

The timings may be the following but the number and timing are subject to change:

Pre-dose D0H0
1, 2, 3, 4, 6, 9, 12 and 24h post dose.

Note that blood will be taken on D3 and D7 for routine haematology and biochemistry. The EDTA sample will be used to measure the drug concentrations.

Safety and toxicity

PAXLOVID at a dose of 300mg Nirmatrelvir and 100mg Ritonavir BD has a well-established safety profile and has been given to more than 500 patients in PLATCOV alone. Reductions in the Nirmatrelvir or Ritonavir would be unlikely to worsen the existing safety profile. We are not using any doses higher than those currently licensed. Repeat-dose toxicity studies up to 1 month duration of Nirmatrelvir in rats and monkeys resulted in no adverse findings. Ritonavir can cause retinal toxicity with long term use, although this is not relevant for the short-term use in the study. Ritonavir alone does not cause any issues related to HIV drug-resistance.

Contraindications

In our study, Nirmatrelvir/Ritonavir is contraindicated in:

hypersensitivity to Nirmatrelvir/Ritonavir or any of its ingredients, including Ritonavir.

co-administration with drugs highly dependent on CYP4503 A.

co-administration with potent CYP450 3A inducers

More details regarding concomitant medication can be found at:

https://www.covid19-druginteractions.org/checker

https://crediblemeds.org/

https://compendium.ch/fr/Patient - this is a Swiss website dealing with drug interactions

https://www.bnf.org/products/bnf-online/ - available only in the UK

Cautions

Caution should be given in patients with pre-existing liver disease/hepatitis or live enzyme abnormalities. Dose reduction for renal impairment (eGFR ≥ 30 to <60 mL/min) is 150MG Nirmatrelvir and 100 MG Ritonavir.

Drug Interactions

Contraindicated with drugs that are highly dependent on CYP3A for clearance or are potent CYP3A inducers (see above). There are no theoretical drug interactions in combination molnupiravir.

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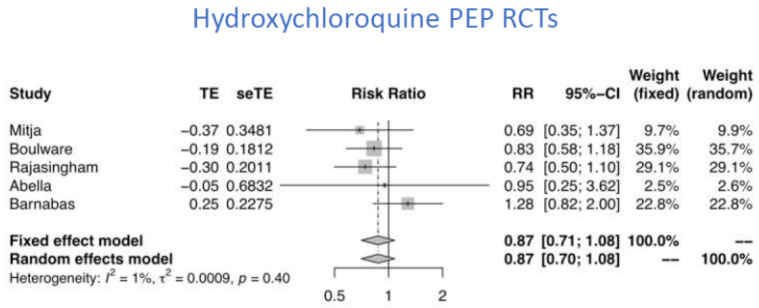
16.4 Hydroxychloroquine

Rationale

Although hydroxychloroquine and chloroquine have shown anti-SARS-CoV-2 activity *in vitro* (1-4), hydroxychloroquine in hospitalised patients did not result in clinical benefit in two large randomised controlled trials (5,6). Although this is strong evidence that it is ineffective in late stage disease, the evidence earlier in the disease process is equivocal including in early treatment. Meta-analysis of RCTs in pre-exposure prophylaxis is in the direction of benefit. There is therefore substantial uncertainty whether hydroxychloroquine has significant antiviral activity against SARS-CoV-2 in humans, and importantly for new pandemics, when vaccines and treatments may not be available.



Composition and dose

The reference form of hydroxychloroquine is the Sanofi product, Plaquenil® (https://www.medicines.org.uk/emc/product/1764/smpc).

Hydroxychloroquine will either be obtained by the sponsor or the local teams from a reliable manufacturer. One tablet of hydroxychloroquine sulphate contains 200 mg of hydroxychloroquine sulphate which is equivalent to 155 mg hydroxychloroquine base. Hydroxychloroquine will be given for 7 days.

The dosing schedule of hydroxychloroquine is:

Day 0

2 tablets at time 0
2 tablets 12 hours later, then

Days 1 – 6

2 tablets per day

That is a total of 800 mg of hydroxychloroquine sulphate (salt) on the first day of treatment and 400 mg of hydroxychloroquine sulphate as a maintenance dose. The doses will be given with food to reduce gastric upset.

Pharmacokinetic characteristics

Hydroxychloroquine is generally well-absorbed, reaches a Cmax at a mean of ~2-3 hours, and following distribution and a multiexponential disposition profile, has a long terminal elimination half-life of ~54 days (5). The disposition of hydroxychloroquine in healthy volunteers is shown in Figure 3 (6).

Pharmacokinetic sampling schedule: (only if there is evidence of accelerated viral clearance)

All patients will need to be admitted for 12 hours for intense venous blood sampling around the **loading dose**.

The timings may be the following but the number and timing are subject to change:

Pre-dose D0H0, then
1, 2, 3, 4, 6, 9, 12 and 24h post dose

Note that blood will be taken on D3 and D7 for routine haematology and biochemistry. The EDTA sample will be used to measure the drug concentrations.

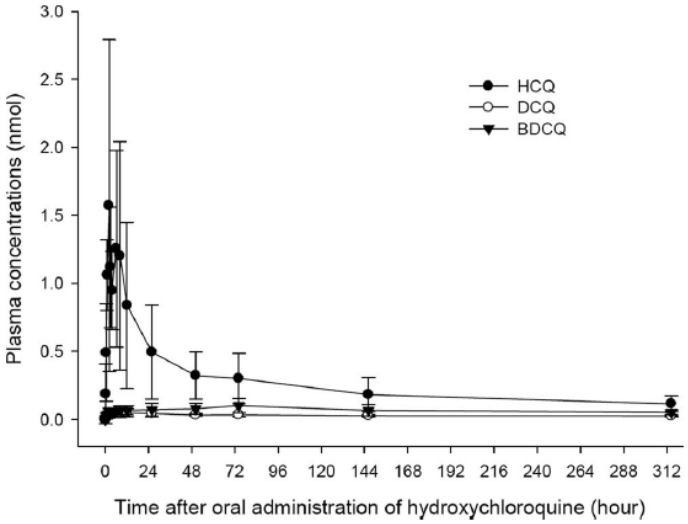


FIG. 3. Plasma concentrations (mean and standard deviation) of HCQ and its metabolites in the six healthy subjects in study Ia before and after the administration of a single oral dose of HCQ sulfate at 400 mg.

Toxicity

Studies recruiting 2,795 participants using hydroxychloroquine in COVID-19 have confirmed the safety of this drug (7). Hydroxychloroquine is well-tolerated and has been used for many years to treat patients with rheumatological diseases. The toxicity associated with long term use e.g. retinal disease, myopathy is not seen with short term use.

The most common side effects include dyspepsia, nausea, vomiting, headache and blurred vision; the latter is dose related and usually transient but patients should be warned about driving and operating machinery. Postural hypotension may occur in patients with a fever.

Cardiac toxicity

Hydroxychloroquine (and chloroquine) cause dose related QRS and QT prolongation but these are only clinically important in:

Overdose (4)
those with pre-existing QT prolongation
patients with QT prolonging diseases e.g. myxoedema, ischaemic heart disease, hypokalaemia
patients on QT prolonging drugs.

The large randomised controlled trials in COVID-19 (RECOVERY and SOLIDARITY) did not find an excess of arrhythmias in patients receiving high dose hydroxychloroquine.

More details regarding concomitant medication can be found at:

https://www.bnf.org/products/bnf-online/ - available in the UK
https://www.uptodate.com/drug-interactions/?source=responsive_home#di-druglist – this requires a subscription

https://compendium.ch/fr/Patient - A Swiss website which deals with drug interactions
https://crediblemeds.org/

Skin
These include:

exacerbation of psoriasis (case reports)

acute generalised exanthematous pustulosis (AGEP) that may be associated with fever and neutrophilia and resolves with discontinuation of the offending drug

itching / prickly sensation that is more common in dark skinned individuals

Contraindications

In our study, hydroxychloroquine is contraindicated in:

those with known hypersensitivity to hydroxychloroquine or other 4-aminoquinolines (e.g. amodiaquine)

patients with pre-existing retinopathy of the eye

severe liver disease, severe renal disease, epilepsy, porphyria and myasthenia gravis are relative contraindications but such patients would not be enrolled in this trial

Cautions

Long term use of hydroxychloroquine has caused hypoglycaemia in type II diabetes. Diabetic individuals will not be recruited.

Patients with a history of unexplained syncope and/ or family history of sudden unexplained cardiac death, should have an ECG is performed and should be enrolled only if the Bazett QTc <430 ms in males and <450 ms in females.

We will conduct ECGs in all patients randomised into the hydroxychloroquine arm and exclude those if the Bazett QTc <430 ms in males and <450 ms in females. Relevant drug interactions

Antacids may reduce absorption of hydroxychloroquine so it is advised that a 4-hour interval be observed between hydroxychloroquine sulphate and antacid dosing

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Infectious Diseases, Volume 7, Issue 11, November 2020, ofaa500, https://doi.org/10.1093/ofid/ofaa500

16.5 Atilotrelvir/ritonavir

Rationale

Atilotrelvir (GST-HG171) is an oral covalent 3CL protease inhibitor of SARS-CoV-2. It is taken with Ritonavir, a protease inhibitor that inhibits cytochrome P450A and CYP2D6. This in turn inhibits the metabolism of atilotrelvir allowing a longer half-life.

Atilotrelvir has broad-spectrum activity against the variants of SARS-CoV-2, including Beta, Delta, Omicron B.1.1.529, Omicron BA.4, BA.5 variants. For wild type the IC_{50} was 3.0. In an invitro head-to-head comparison with Nirmatrelvir, atilotrelvir was found to have 5-10 fold higher potency in a cytopathic effect assay (1).

H11-k18-hACE2 mice were challenged intra-nasally with wildtype SARS-CoV-2 virus, and treated with atilotrelvir, Nirmatrelvir or a control. Atilotrelvir reduced the viral copies of the three genes (ORF1ab, N gene and S gene) for 1.7, 2.1, and 1.3 log more than Nirmatrelvir (1).

A phase 1 study was performed in 78 enrolled subjects. The drug was well tolerated, with no reports of serious adverse events (SAEs) or AEs that led to withdrawal after dosing. There were 5 drug related grade 2 AEs (consisting of hypertriglyceridemia, low white blood cell count and hypoglycaemia). A dose of 150MG atilotrelvir and 100MG Ritonavir BD was chosen based on the population PK modelling (2).

A randomised, double-blind, placebo-controlled phase 2/3 trial was carried out in China. The trial included adult patients with mild-to-moderate COVID-19 with symptoms onset ≤72 h. Participants were randomised 1:1 to receive atilotrelvir (150 mg) plus Ritonavir (100 mg) or corresponding placebo tablets twice daily for 5 days. Primary efficacy endpoint was time to sustained recovery of clinical symptoms within 28 days. Clinical recovery was defined as a score of 0 out of 11 COVID-19 related symptoms for at least 2 consecutive days. Patients who received atilotrelvir showed shortened median time to sustained recovery of clinical symptoms compared to the placebo group (13 days vs 15 days P = 0.031). There was a significant difference in LS mean change in SARS-CoV-2 viral load from baseline to day 4. Adverse event incidence was similar in both groups, there was one SAE in the atilotrelvir arm and two in the placebo arm (3).

Composition & dose

The dose is – 150mg atilotrelvir plus 100mg Ritonavir – both taken twice a day for 5 days.

Pharmacokinetic sampling schedule

The timings may be the following but the number and timing are subject to change:

Pre-dose D0H0
1, 2, 3, 4, 6, 9, 12 and 24h post dose.

Note that blood will be taken on D3 and D7 for routine haematology and biochemistry. The EDTA sample will be used to measure the drug concentrations.

Pharmacokinetic characteristics

Half-life of atilotrelvir 150mg when given with Ritonavir 100mg is 3.84 hours. The concentration at 12-h post-administration is 816.1 ng/mL.

Common adverse effects

In the phase 2/3 placebo controlled clinical trial, The incidence of adverse events was similar in the atilotrelvir (320/617, 51.9%) and placebo (298/610, 48.9%) group. The most common AE in both arms was hypertriglyceridemia. Drug-related adverse events were reported for 222 (36.0%) of 617 patients in the

atilotrelvir plus Ritonavir group and 182 (29.8%) of 610 patients in the placebo group. All of them were non-serious, most of grade 1/2, and more than half resolved by the end of the study (3).

Contraindications

Hypersensitivity. Contraindicated with drugs that are highly dependent on CYP3A for clearance or are potent CYP3A inducers (see below)

Drug Interactions

Contraindicated with drugs that are highly dependent on CYP3A for clearance, such as -

- Alpha1-adrenoreceptor antagonist: alfuzosin
- Antianginal: ranolazine
- Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
- Anti-gout: colchicine
- Antipsychotics: lurasidone, pimozide, clozapine
- HMG-CoA reductase inhibitors: lovastatin, simvastatin
- PDE5 inhibitor: sildenafil when used for pulmonary arterial hypertension (PAH)
- Sedative/hypnotics: triazolam, oral midazolam

Contraindicated in drugs that are potent CYP3A inducers such as

- Anticancer drugs: apalutamide
- Anticonvulsant: carbamazepine, phenobarbital, phenytoin
- Antimycobacterials: rifampin
- Herbal products: St. John's Wort (hypericum perforatum)

References

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16.6 Sotrovimab

Rationale

Sotrovimab (VIR-7831) is an Fc-engineered IgG1 human monoclonal antibody developed from a parental antibody isolated from a survivor of the SARS outbreak in 2003 (1). Sotrovimab targets a highly conserved epitope in the SARS-CoV-2 spike protein at a region that does not compete with angiotensin-converting enzyme 2 binding.

In-vitro testing has shown that sotrovimab is able to retain activity against alpha, beta, gamma, delta and kappa variants, and even omicron pseudotyped virus encoding the then most prevalent haplotype of the Omicron spike. The same study showed that Syrian Golden hamsters infected with wildtype SARS-CoV-2 had significantly decreased total viral load and infectious virus levels with sotrovimab (2).

A multicentre randomized, double-blind, multicentre, placebo-controlled, phase 3 study tested sotrovimab on non-hospitalised patients with symptomatic, mild to moderate COVID-19 and at least 1 risk factor for disease progression. Symptom onset was within 5 days, median age was 53. Primary efficacy outcome was all-cause hospitalization longer than 24 hours for acute illness management or death through day 29. Primary outcome was significantly reduced with sotrovimab (6/528 – 1%) compared to placebo (30/529 – 6%) by 79% (95% CI, 50% – 91%; P<.001) (3).

N.B. – REGN-COV2 (the initial positive control monoclonal antibody) was shown in vitro studies to fail to neutralise omicron (4), although the in-vivo significance of this is yet to be determined.

Composition & dose

Recommended dose is 500MG sotrovimab administered as a single intravenous infusion over 60 minutes. Patients should be monitored for at least 1 hour after administration.

0.9% Sodium Chloride of 5% dextrose for injection, one vial of sotrovimab is 500MG/8ML.

Pharmacokinetic characteristics

The mean systemic clearance is 125 mL/day, and the median terminal half-life is approximately 49 days. The geometric mean maximum plasma concentration (Cmax) after a 1-hour sotrovimab intravenous infusion to be 117.6 mcg/mL, and the geometric mean Day 29 concentration to be 24.5 mcg/mL.

Toxicity

Serious hypersensitivity reactions, including anaphylaxis, have been reported with administration of

sotrovimab. If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur during infusion, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Contraindications

Hypersensitivity

Cautions

Renal impairment is not expected to impact the pharmacokinetics of sotrovimab since monoclonal antibodies with molecular weight >69 kDa do not undergo renal elimination. The effect of hepatic insufficiency is unknown. The effect of other covariates (e.g., sex, race, body weight, disease of severity on the pharmacokinetics is also unknown.

Pharmacokinetic schedule: only if there is evidence of accelerated viral clearance

As a type B intervention (positive control), intensive pharmacokinetic sampling will not be conducted on those receiving sotrovimab.

Drug Interactions

No formal drug interaction studies have been performed with sotrovimab. Sotrovimab is not renally

excreted or metabolized by cytochrome P450 (CYP) enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely.

References

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16.7 Metformin

Rationale

Metformin is one of the most widely used drugs to treat type 2 diabetes mellitus since being approved in the UK in 1958 and the USA in 1995. It is a biguanide and works by decreasing intestinal glucose absorption, improving peripheral glucose uptake, lowering fasting plasma insulin levels and increasing insulin sensitivity. This results in a reduction of blood glucose concentrations without causing overt hypoglycaemia (1).

More recently it has been suggested as a treatment for COVID-19. It acts through several mechanism – it causes AMP-activated protein kinase (AMPK) activation, inhibition of mTOR pathway preventing immune hyperactivation and increases cellular pH to interference with viral endocytic cycle (2).

There has been In vitro evidence of metformin significantly inhibiting SARS-CoV-2 growth in cell culture models. IC50 values from dose-variation studies in infected cells were found to be 0.4 in Calu3 cells and 1.43 mM in Caco2 cells (3).

There have been several clinical trials assessing the effectiveness of metformin against COVID-19. All of the following clinical trials had populations that were overweight or obese. A small trial by Ventura-López et al. in Mexico compared 10 patients taking placebo with 10 taking a dose of 620MG of metformin glycinateBD for 14 days. The patients were hospitalized with severe COVID-19 (median BMI = 28.54). There was no difference in number of days hospitalized, however metformin decreased number of days until undetectable viral load (4).

The COVID-OUT trial gave 1500MG of immediate release metformin OD for 14 days to non-hospitalised patients. The metformin was given as an increasing dose over 6 days. 663 received metformin and 660 received the control (median BMI = 30). Metformin did not prevent the composite endpoint of hypoxemia, ED visit, hospitalization, or death. However, benefit was seen when hypoxaemia was removed aOR = 0.58 (95% CI, 0.35 to 0.94) (5).

Another aspect of the COVID-OUT trial looked at long COVID (post-COVID condition). Long COVID was defined as a formal diagnosis being given by a medical provider (median BMI 29.8). There were 562 in the placebo arm and 564 in the metformin arm. Metformin reduced long COVID incidence by 41% (6).

The TOGETHER trial gave at risk patients 750 MG of metformin BD for 10 days (94% had a BMI of >30). 215 were randomised to the metformin arm and 203 to placebo. In the metformin arm there was no reduction in hospitalisations due to COVID-19 and no difference in viral clearance at day 7 (7).

Composition & dose

The metformin dose will be 500MG metformin modified release, three times per day for 5 days.

Pharmacokinetic characteristics

Metformin is not metabolised, it is excreted unchanged in the urine. It has a half life of approximately 6.5 hours and a T_{max} of 7 hours for the modified release formulation (8).

Common adverse effects

Nausea, vomiting, diarrhoea, abdominal pain, loss of appetite, metallic taste in mouth

Contraindications

Severe renal impairment, hypersensitivity to metformin, acute or chronic metabolic acidosis (including diabetic ketoacidosis).

Drug Interactions

Insulin, sulfonylureas, meglitinides, corticosteroids, carbonic anhydrase inhibitors

References

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17 Appendix 3: Sample size simulations

Sample size projections were done via simulation. Each simulation used a pharmacodynamic model of viral clearance (4) that was fitted to prospectively collected viral load data in 46 individuals. For simplicity, we assumed there was no site dependent effects.

Interim analyses were performed after 50 patients were enrolled and then for every subsequent 25 patients. In the simulation, out of the 5 interventions 4 were ineffective (no increase in viral clearance) and 1 was effective (10% increase in viral clearance). Figures 9 & 10 show the type 1 and 1-type 2 errors for different choices of stopping rule thresholds, respectively.

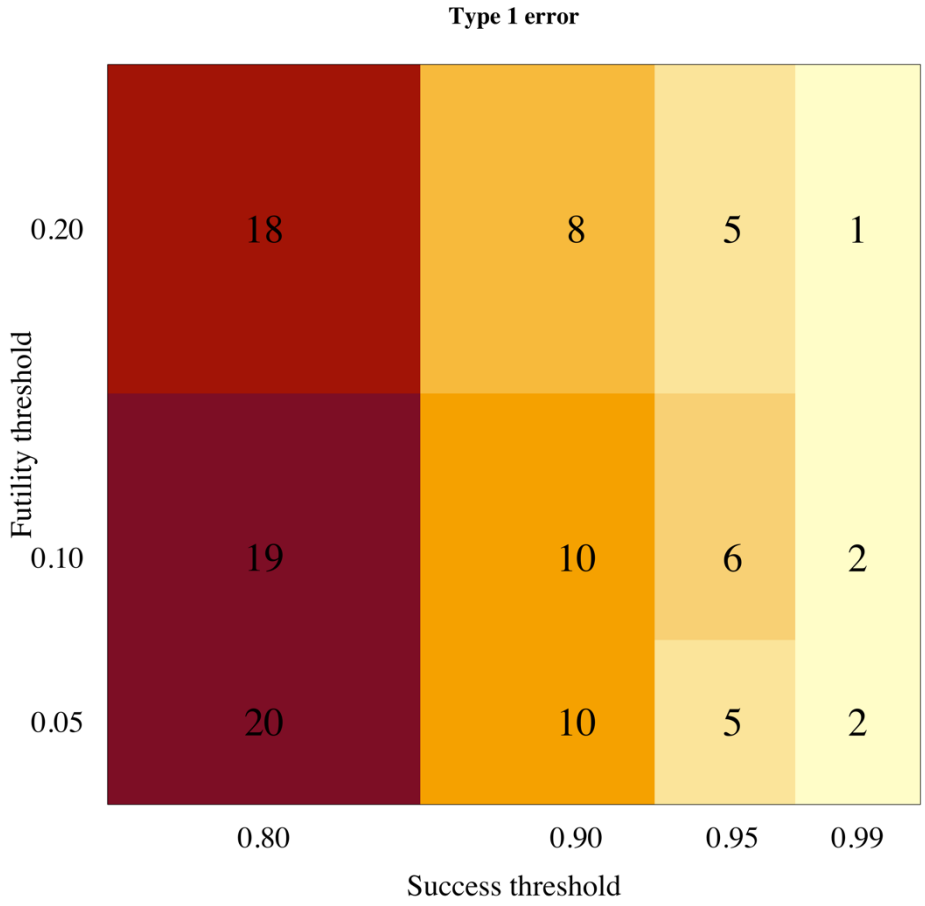

Figure 9 Estimated type 1 error

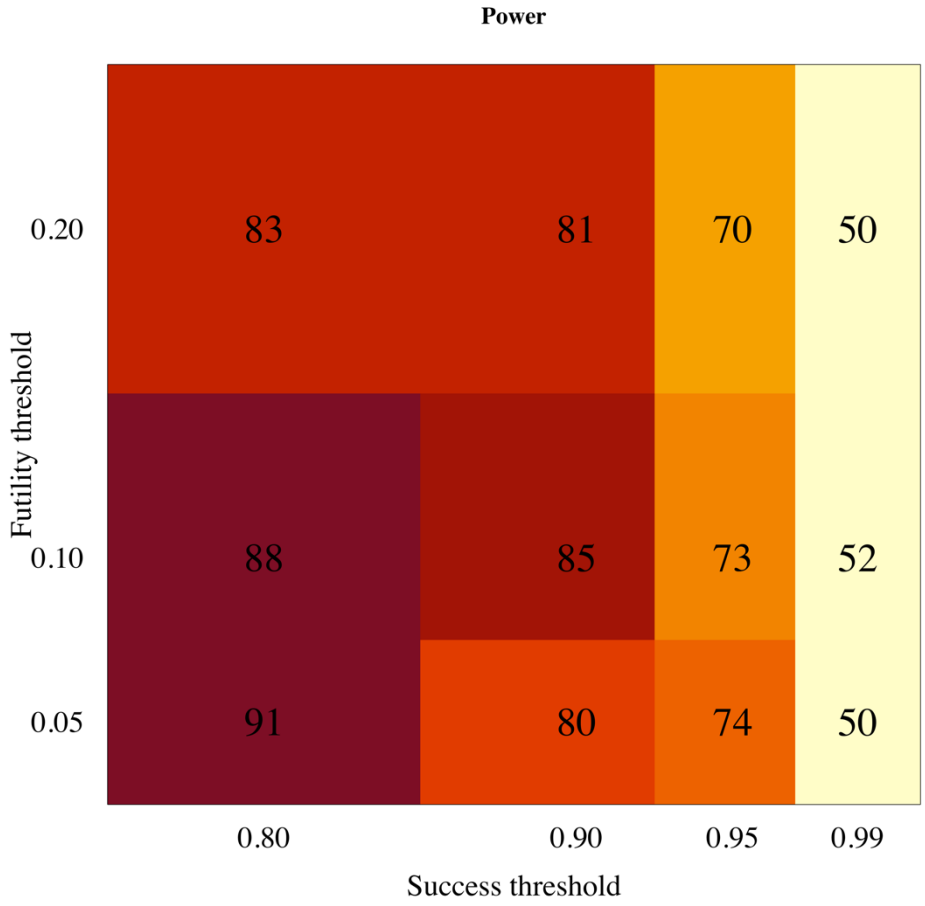

Figure 10 Estimated power (1-type 2 error)

18 Appendix 4: Exclusion criteria

The exclusion criteria in the Master Protocol are expanded upon here. The exclusion criteria in **bold** below have a corresponding section in this appendix where more details are given. The patient may not enter the study if ANY of the following apply:

- **Taking any concomitant medications or drugs†**
- **Presence of any chronic illness/ condition requiring long term treatment, or other significant comorbidity**
- **Laboratory abnormalities discovered at screening**
- For females: pregnancy, actively trying to become pregnant, or lactation
- **Contraindication to taking, or known hypersensitivity reaction to any of the proposed therapeutics**
- Currently participating in another COVID-19 therapeutic or vaccine trial
- Evidence of pneumonia (although imaging is NOT required)

† healthy women on the oral contraceptive pill are eligible to join the study.

1. Taking any concomitant medications or drugs

The study will exclude all patients taking **regular drugs** including herbal drugs for the treatment of COVID-19, but some patients may take over the counter drugs or other vitamin and herbal supplements if considered safe in the judgement of the site investigator upon screening assessment. Patients should be counseled to end and avoid all non-essential medications during study participation. In certain circumstances where a patient is on a regular medication, which does not reflect an excluded underlying illness, and in the decision of the study PI is not likely to interfere with the study outcomes, or predispose the patient to any increased risk, a decision can be made to enrol. In all cases, the risks/ benefits of this decision should be documented, as well as the person(s) making the decision.

Drug interactions change rapidly as new data become available. If in any doubt, please refer to some of the web sites below:

https://www.covid19-druginteractions.org/checker

https://crediblemeds.org/

https://compendium.ch/fr/Patient - this is a Swiss website dealing with drug interactions

https://www.bnf.org/products/bnf-online/ - available only in the UK

https://www.uptodate.com/drug-interactions/?source=responsive_home#di-druglist – this requires a subscription

2. Presence of any chronic illness/ condition requiring long term treatment, or other significant comorbidity

The protocol excludes almost all individuals with a chronic illness of any severity and those with an illness that requires long term treatment.

BMI ≥ 35 kg/m^2

Diet controlled diabetes mellitus

Reduced kidney function – eGFR < 70 mls/min/1.73m^2*

Any known underlying liver disease, HIV infection and other immunocompromised condition.

Asplenia

Any underlying bleeding disorder e.g. haemophilia, von Willibrand's disease

Suffering with any other disease which in the opinion of the investigator poses undue risk to the potential patient

*eGFR for males is calculated based on the Chronic Kidney Disease Epidemiology Collaboration (Andrew S Levey, Lesley A Stevens et al. 2009)

https://qxmd.com/calculate/calculator_251/egfr-using-ckd-epi

3. Laboratory abnormalities discovered at screening

These are:

haemoglobin < 8 g/dL

platelet count < 50,000/uL

ALT > x 2 ULN

total bilirubin > 1.5 x ULN

eGFR < 70 mls/min/1.73m^2

4. Contraindication to taking, or known hypersensitivity reaction to any of the proposed therapeutics:

Where a contraindication is mentioned in the above sections, or an above contraindication incorporates drug-specific contraindications below, it is not repeated again in this section, unless further information is given which warrants some repetition. For a complete list of drug-specific contraindications please see the section for that drug in Appendix 2.

To repeat, a known hypersensitivity reaction to ANY of the proposed therapeutics below (even if the patient were to be randomised to a different treatment arm or control) is an exclusion criterion from entering into the study.

The following are relevant contraindications (i.e. in potentially eligible patients):

Nitazoxanide

No additional contraindications

Sotrovimab

No additional contraindications

Atilotrelvir/Ritonavir

No additional contraindications

Metformin

No additional contraindications

Nirmatrelvir/Ritonavir

No additional contraindications

Nirmatrelvir/Ritonavir dose finding

No additional contraindications

Hydroxychloroquine

No additional contraindications

References for exclusion criteria

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19 Appendix 5: Amendment History

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	3.0	11 July 2022	Professor Sir Nicholas J White and Dr William Schilling	1. Co-investigators changed 2. Sponsor address changed. 3. Synopsis: removed "Study Patient" row 4. Selection criteria changed throughout 5. Synopsis: Clarified in "Planned Sample Size" that no fixed sample size 6. Synopsis: Changed "Planned Study Period" from "2 years" to "3 years" 7. Synopsis: Updated "interventions" information of type A and B throughout 8. Synopsis: Updated "Control" throughout 9. Synopsis: Updated "Rational" throughout 10. Objectives and/or endpoint wording changed throughout 11. Section "3 Background and rationale": Updated information of small molecule medications and updated to reflect current global vaccine and COVID-19 situation including omicron variant. 12. Section "3.1 Proposal": Emphasis of why this type of trial is most suited and clarification of the expected outcome of the interim analysis. 13. Section "5 Study design": Updated information about the places to recruit the participants, site and current study design. 14. Section "5.1 Interventions": Pick the winner no longer applies, language changed to reflect addition of small molecule drugs and updated Figure 4 15. Section "7 Study set-up and procedures": Updated study procedures. Swabs will be done in duplicate before receiving the first dose of the intervention (or if on no intervention arm). 16. Section "7.1 Virological sampling": Clarification that duplicate means one swab on each tonsil, increased viral transport medium (VTM), updated the laboratory procedures and added saliva collection process in some participants

				17. Section "7.5 Baseline assessments": if the results haven't returned the participant can be given the first dose then excluded later if there are laboratory abnormalities. The procedures are also updated. 18. Section "7.6.1 Randomisation D0": Updated the ratio of randomisation as no antiviral treatment will be fixed at "at least 20%" throughout the study and the randomisation ratios will be uniform for all available interventions. 19. Section "7.6.2 Day 1 - day 7": Updated the procedures during day 1- day 7 20. Section "7.7 Intensive pharmacokinetic sampling": Explained more details about the study drugs for intensive PK sampling. 21. Section "7.8 Management of patients who become ill": If treatment arm is changed, duplicate swabs will be taken again prior to any new treatment. 22. Section "9.1 Definition/Serious Adverse Event (SAE)": Removed "and not otherwise receiving medical treatment" 23. Section "10.1 Overview of adaptive study design and overall approach": Added new information. 24. Section "10.2 Results of the first interim analysis": This new section and Figure 6 have been added. 25. Section "10.3 Bayesian hierarchical model of viral clearance": Statistical explanation has been updated. 26. Section "Estimating the optimal structural model for clearance rate": Deleted. No-longer required as the methodology has been validated. 27. Section "10.5 Sample size estimation, randomisation and statistical considerations for the Bayesian group sequential design": Information have been updated. 28. Section "10.7 Final analysis of primary outcome": Linear and non-linear models are being used, package *rstan* is being used instead

				of *rstanarm*. Analysis code available from github, link was given. 29. Section "13 Ethical and regulatory considerations": Clarification of what treatment will be given to no antiviral treatment arm. 30. Section "13.7 Benefits": Maximum amount per patient (£400 GBP) has been removed. 31. Section "14 References": References have been updated. 32. Section "15 Appendix 1 Schedule of activities": "If new treatment" column and explanation below the table have been added/updated. 33. Section "16 Appendix 2 Study drugs": • Hydroxychloroquine, lopinavir/ritonavir, miglustat, nitazoxanide and nebulized unfractionated heparin (UFH): Reference order updated. • Remdesivir: Changed for more up to date information with more references. • Ivermectin: Dosing table changed for higher mg of tablets and reference order updated. • REGN-COV2: Dose changed from 1,200 mg to 600 mg of casirivimab and 1,200 mg to 600 mg of imdevimab and reference order updated. • Favipiravir: Introduction changed for more up to date information including references. • Molnupiravir, nirmatrelvir/ritonavir (PAXLOVID™), sotrovimab, fluoxetine, fluvoxamine and AZD7442 (evusheld): Monograph added (Section 16.10 – 16.15). 34. Section "18 Appendix 4 Exclusion criteria": • Update information to comply with the exclusion criteria • Added line to include herbal drugs in regular drugs • Added line of the decision of the study PI whether to enrol participants taking regular medications. • Add in the list of the most severe comorbidities, and include HIV and other immunocompromised condition.

				• Changed the BMI from ≥ 30 to ≥ 35 kg/m^2. • Changed the eGFR limit of exclusion from <80 to <70 mls/min/1.73m^2 • Added contraindications for hydroxychloroquine (prolong QTc), molnupiravir, nirmatrelvir/ritonavir (PAXLOVID™), sotrovimab, fluoxetine, fluvoxamine and AZD7442 (evusheld). • Added that study may be done as an inpatient or an outpatient throughout. 35. Administrative changes
2	4.0	17 August 2022	Professor Sir Nicholas J White and Dr William Schilling	1. Funder: Update funder name including grant reference number 2. Section "1: Synopsis": Updated "Planned Sample Size" by adding expected total participant and study countries 3. Section "1: Synopsis": Updated "interventions" information of type A 4. Section "3 Background and rationale": Added information about 'viral rebound' and clarify more about assessment 5. Section "5.1 Interventions": Added "Ensitrelvir and a combination of Molnupiravir and Nirmatrelvir/Ritonavir" in type A and "Evusheld" in type B 6. Section "7.6 Days of Study": Added Day 10 activities to capture asymptomatic viral rebound and safety concern for viral rebound 7. Section "7.8 Management of patients who become ill": Added new procedure to determine the viral rebound which is important with certain antivirals (e.g. Paxlovid) and may impact effectiveness of these against onward viral transmission. 8. Section "9.3 Procedures for recording adverse events": Added safety evaluation for combination drugs 9. Section "10.5 Sample size estimation, randomisation and statistical considerations for the Bayesian group sequential design": Added tentative sample size (60 patients) in each arm for an effect size of 12.5% increase in viral clearance 10. Section "11.2 Data handling and record keeping": Extended the

				retention of the records to “at least five years” 11. Section “15 Appendix 1 Schedule of activities”: • Added column “D10” • Changed column title from “If new treatment” to “if new treatment/symptoms” • Clarified the definition of “if new treatment/symptoms” 12. Section “16 Appendix 2 Study drugs”: • Molnupiravir: Updated section “drug interaction” • Nirmatrelvir/ritonavir (e.g. PAXLOVID™): Updated section “drug interaction” • Ensitrelvir: Added monograph (Section 16.16). 13. Section “18 Appendix 4 Exclusion criteria”: Added contraindications for ensitrelvir and molnupiravir and nirmatrelvir/ritonavir combination 14. Administrative changes
3	5.0	23 May 23	Professor Sir Nicholas J White and Dr William Schilling	1. Updated investigators 2. Changed designation of investigators 3. Changed age cut off to 60 from 50 4. Added maximum sample size per intervention arm to 120 (excluding controls) 5. Increased total enrolment number from 1,500 to 3,000. 6. Increased duration of study from 3 to 6 years 7. Increased participant enrollment to 120 days 8. Added assessment at day 120 using modified COVID-19 Yorkshire Rehabilitation Scale (C19 YRSm) to measure for symptoms of post-acute COVID-19 (long COVID) and added day 120 C19 YRSm to schedule of activities 9. AEs will only be assessed up until day 28, not day 120. 10. SARS-CoV-2 antibody RDT has been removed. 11. Medications no longer in the trial have been removed (included all information given in the appendices regarding them). 12. Categories of interventions relabelled 13. Viral clearance cut-off increased from 12.5 to 20% 14. Added schematic to explain stopping rules as of January 2023. 15. Added factorial randomisation 16. ECG now listed as optional

				17. Virological rebound characterisation will be defined in SAP. 18. Included justification for drug combination. 19. Removed drugs that are not being used in trial at present 20. Statement that risk of combination drugs interacting is low 21. Added name of funder 22. Updated references 23. Administrative changes e.g. grammar errors corrected, updated spelling from American English to English English (randomisation)
4	6.0	04 Oct 23	Professor Sir Nicholas J White and Dr William Schilling	1. Explained can increase number in intervention past 120 if DSMB or TSC agree 2. Added in new interventions and removed old ones (Evusheld removed, Hydroxychloroquine and Fluoxetine added) 3. Wording of the primary endpoint clarified. 4. Two secondary endpoints added: viral rebound and symptom/ fever resolution. 5. Changes made to sample schedule, now swabbing day 0 to day 5 once or twice per day to characterise viral clearance, and on day 6, 7, 10 and 14 to characterize viral rebound. This is based on data simulations 6. Minor changes made to make rationale and proposal more up-to-date and clearer 7. Added ensitrelvir to list of drugs with evidence of antiviral effects from other studies 8. Clarified that interventions not selected for intense PK-PD may have blood tests on days 3, 7 and 14 for determination of dose-response relationship 9. Added possibility of patient self-swabbing 10. Re-described viral clearance curve as biexponential 11. Explained that success threshold and maximum number of patients may be changed for therapeutics which may potentially be used in prophylaxis

				12. Description added of the sample size calculation for intensive PK-PD sub-study 13. Diagram included showing half-life decrease over time 14. New drugs added to appendices 15. Significant comorbidities causing exclusion removed 16. Contraindications added to new interventions 17. Window of follow-up for D120 assessment increased from -/+ 5 days to -10/+30 days.
5	7.0	07 Aug 24	Professor Sir Nicholas J White, Dr William Schilling and Dr. Simon Boyd	1. Added new investigators, Dr. Ellen and Dr. Seers. 2. Set limit of maximum participants per arm at 200. 3. Increased number of participants to be enrolled in total across sites to 3800 and updated the maximum number in Figure 5. 4. Atilotrelvir/Ritonavir and Metformin added. 5. Dose finding for ritonavir boosted nirmatrelvir added. 6. Interventions no longer in use removed (Ensitrelvir, Molnupiravir, Combination of Molnupiravir and Nirmatrelvir/ritonavir (Paxlovid), Fluoxetine). 7. Added two new abbreviations 8. Background and rationale have been updated with more recent references and new Figure. 9. Removed mention of comparative study between Molnupiravir and Nirmatrelvir/ritonavir (Paxlovid) as already done. 10. Clarification of study sites. 11. Allowed temperature to be measured multiples times per day. 12. Additional swab added at 6-18 hours post baseline swabs. 13. Added vital signs measurement to day 1–5. 14. Removed oropharyngeal swabs and vital signs measurement on day 6. 15. Added possibility of extra swabs days 1-5 and removed all activities on day 10 to schedule of activities (section 7.6.2). 16. New drugs including dose finding added to the Appendix and old drugs removed.

				17. Allowed other time points to be added/taken away in the intense pharmacokinetic study. 18. Contraindications added to new interventions. 19.Changed “staff” to “personnel” for continuity. 20. Minor grammar changes.