European Clinical Research Alliance on Infectious Diseases – Primary care adaptive platform trial for pandemics and epidemics (ECRAID-Prime)

Master Protocol

A double-blind, randomised, comparative trial to investigate the effect of Investigational Medicinal Products and usual care in non-hospitalised patients with COVID-19 or COVID-like-illness

European Clinical Research Alliance on Infectious Diseases – primary care adaptive platform trial for pandemics and epidemics

Protocol ID	**EU-EcraidPC-1**
Short title	**ECRAID-Prime**
EU trial number	**2022-501707-27**
Protocol version	**5.0**
Protocol date	**22 March 2024**
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Funding party	**Horizon Europe (no: 101046109)**
Laboratory sites	**Microbiology Laboratory University of Antwerp Campus Drie Eiken – S6.20 Universiteitsplein 1 – B-2610 Antwerp, Belgium**
Pharmacy	**Per country network, a pharmacy will be available to accept, store and distribute the investigational products**

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DOCUMENT HISTORY

Document	Date of version	Summary of Changes
Master protocol	**30 JAN 2023 V1.0**	**NA**
Master protocol	**27 JUL 2023 V2.0**	**Incorporation of comments EMA and pre-evaluation member states**
Master protocol	**16 OCT 2023 V3.0**	**Revisions following comments member states in procedure 2022-501707-27-00**
UK specific master protocol	**29 NOV 2023 UK V1.0**	**Revisions following comments MHRA in procedure CTA 30913/0009/001-0001**
Master protocol	**19 JAN 2024 V4.0**	**Revisions following comments member states in procedure 2022-501707-27-00 and following comments MHRA in procedure CTA 30913/0009/001-0001**
Master protocol	**22 MAR 2024 V5.0**	**Revisions following comments member states in procedure 2022-501707-27-01, as well as minor correction for alignment throughout the protocol**

CONFIDENTIALITY STATEMENT

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the investigative team, regulatory authorities, and members of the Research Ethics Committee.

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ADR	Adaptive Design Report
AE	Adverse Event
APT	Adaptive Platform Trial
ASR	Annual Safety Report
CA	Competent Authority
CRF	Case Report Form
CTA	Clinical Trial Agreement
CTIS	Clinical Trials Information System
CTR	EU Clinical Trial Regulation 536/2014
DMP	Data Management Plan
DPIA	Data Protection Impact Assessment
DSMB	Data Safety Monitoring Board
(e)CRF	(electronic) Case Report Form
ECTR	Clinical Trial Regulation 536/2014/EU
EID	Emerging Infectious Diseases
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
FMP	File Management Plan
GCP	Good Clinical Practice
GDP	Good Documentation Practices
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
GxP	Collectively, cGCP, cGLP, cGDP, cGMP and other applicable, generally accepted industry best practice standards for the pharmaceutical or biotech industry.
IB	Investigator's Brochure
ECRAID-Prime	European Clinical Research Alliance on Infectious Diseases – Primary care adaptive platform trial for pandemics and epidemics
ICH-GCP	International Conference on Harmonisation guidelines for Good Clinical Practice
ID	Infectious Diseases
IEC	Independent Ethics Committee
IMD	Investigational Medical Device
IMP	Investigational Medicinal Product
IP	Investigational Product
ISA	Intervention Specific Appendix
M-SAP	Master Statistical Analysis Plan
OTC	Over-the-counter
PCR	Polymerase Chain Reaction
PIS	Patient Information Sheet
RdRp	RNA-dependent RNA polymerase
RSI	Reference Safety Information
RSV	Respiratory Syncytial Virus
(S)AE	(Serious) Adverse Event
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure

SUSAR	Suspected Unexpected Serious Adverse Reaction
TTR	Time to first self-report of feeling recovered
VOC	Variants of concern
WMA	World Medical Association
YR	YourResearch

SYNOPSIS

(Applicable to the Master Protocol. IP and comparator specifics are described in intervention specific appendices)

2022-501707-27

European Clinical Research Alliance on Infectious Diseases – primary care adaptive platform trial for pandemics and epidemics

Background

COVID-19 and COVID-like-illness cause significant ill-health. Given that the greatest burden of ill-health is in the community, it is in primary care and community settings where emerging antiviral and other early treatments for COVID-19 and COVID-like-illness will be of most overall benefit. Despite novel antiviral agents coming to market, it remains imperative that the search for better treatments continues, especially as many new drugs are expensive, require a diagnostic test before they are used, and may have numerous important drug interactions and exclusions. An adaptive platform trial (APT) is an efficient way to trial such potential agents as it allows for multiple interventions to be tested under a single master protocol.

Rationale

The rationale of the ECRAID-Prime trial is to test the safety and efficacy of agents for patients presenting to primary care with COVID-19 or COVID-like-illness in a phase II or III type evaluation. This helps determining whether agents should progress to a next phase of evaluation. We will additionally assess the platform trial process and procedures in order to optimize trial implementation, thereby enhancing and facilitating patient recruitment throughout the course of the trial.

Main trial

The master protocol describes a platform randomised, double-blind, multicountry, multicentre trial for the evaluation of new investigational products (IPs) for treatment of non-hospitalised patients with COVID-19 and COVID-like-illness.

Platform trial

A “platform trial” is a trial in which multiple IPs for the same illness can be tested simultaneously, and in which new interventions can be stopped or added during the course of the trial in accordance with pre-specified criteria. The master protocol will describe the overall structure and processes of the platform, while specific information regarding interventions and comparators under investigation are described in intervention specific appendices (ISAs).

Outcomes

The primary outcome will be phase dependent. For Phase IIb/III type evaluations the primary outcome will be time to first self-report of feeling recovered from symptoms of COVID-19 or COVID-like-illness. For Phase IIa type evaluations the primary outcome parameter will be viral clearance, or potentially impact on specific biomarkers.

Secondary outcomes will include: (early) sustained recovery; time to first self-report of feeling recovered from individual symptoms of COVID-19 or COVID-like-illness (for Phase IIa type evaluation); viral clearance (for Phase IIb/III type evaluation); time to first self-report of return

to usual daily activity; presence, duration and severity of individual respiratory infection symptoms; participant-reported overall wellbeing; safety evaluations of the IPs through monitoring of (serious) adverse events; use of additional antiviral medication, use of other prescribed and/or over-the-counter medication for the respiratory infection; occurrence of complications, impact on usual daily activities; impact on health care utilization; long-term (up to 6 months) consequences of COVID-19 or COVID-like-illness (including long COVID); and, the incidence of COVID-19 or COVID-like-illness in other members of the household.

Exploratory outcomes include: the emergence of mutations in causative pathogens; the experiences of researchers and network coordinators of setting up a platform trial that requires modifications throughout the execution of the trial in multiple countries; and the views and experiences of healthcare professionals and patients taking part in such a trial (qualitative interview study).

Trial design

Screening will be preferably face-to face, but can be remote dependent on the prevailing circumstances (for example a lock down), and if approved for IPs under study per country. After obtaining informed consent, eligibility for trial participation will be confirmed. Eligible participants will be randomly allocated to receive either an IP, or the specified control. Baseline information will be collected. Participants will be asked to report their symptoms each day in a daily diary (either paper or online) for 28 days following randomisation. A swab will be (self)-taken at baseline (day 0; this swab will be also used to determine disease aetiology (retrospectively)) and subsequently self-taken swabs on days 4, 7 and 14. All participants will receive an end-of-treatment telephone call assessment at day 14 (window 14-18 days) after randomisation. Participants where data capture from their daily diaries is not complete will receive a telephone call at day 28 (window 28-35 days) after randomisation. These telephone calls will elicit additional safety data, and ascertain a minimal set of outcome data for those participants where data capture from their daily diaries is not complete. Longer-term follow-up will be at 3 and 6 months by electronic questionnaire (online, app) with back-up telephone call if not completed by other means. The duration of the study for each participant is 6 months.

Nested qualitative study

A qualitative study (interviews) will be nested within the trial to understand the experiences of researchers and network coordinators in delivering the APT, the experiences of healthcare professionals and patients in taking part, and their views on and acceptance of the IPs.

Trial population

Participants who meet the following inclusion criteria may be eligible to take part in the trial:

- Aged ≥18 years on the day of inclusion.
- Presence of at least two symptoms suggestive of COVID-19 or COVID-like-illness - one respiratory (cough, sore throat, running or congested nose or sinuses, shortness of breath) and one systemic (fever, feeling feverish, sweats/chills or shivering, low energy or tiredness, headache, muscle, joint and/or body aches, loss of taste and/or smell).
- Judged by recruiting medically qualified clinician or delegate that the illness is due to a respiratory infection.
- Onset of symptoms less than 7 days (if earlier treatment is required for a particular IP, this will be specified in the ISA).
- Willing and able to give informed consent for participation in the study.

- Willing and able to comply with all trial procedures.

Any additional eligibility criteria relevant to women of child-bearing potential, including current pregnancy and/or breastfeeding will be specified in the ISAs.

Participants who meet any of the following exclusion criteria will be excluded from participation in the trial:

- Requiring admission to the hospital on the day of screening, or inclusion.
- Known allergies or hypersensitivities to any of the components used in the formulation of the IP, or the control product.
- Any disease, condition, or disorder that precludes participation in the trial, in the opinion of the person checking eligibility and taking consent.
- Any planned major surgery in the next 28 days.
- Currently participating in a trial of a pharmacological treatment.

Any additional inclusion and/or exclusion criteria for specific IPs will be detailed in the ISAs.

Interventions

Each IP will have a matching placebo and/or comparator. Usual Care alone can be an additional control arm; only this particular comparison is not double-blind. Participants will be randomised to receive either Usual Care alone, or an IP, a placebo or comparator product in addition to Usual Care. Potential participants can be included if they are eligible for at least one IP, as well as Usual Care.

SYNOPSIS additions for ISA A, ISA B and ISA C

The ECRAID-Prime trial will start with the following three arms:

A. Usual Care (control)

Participants randomised to Usual Care will receive usual clinical primary care according to standard care in the specific country, at the discretion of the responsible treating clinicians.

B. Usual Care + Nitric Oxide Nasal Spray (IP)

Nitric oxide nasal spray (NONS) is a nitric oxide donor that is expected to have an antiviral effect and to accelerate viral clearance in patients infected with SARS-CoV-2 and other respiratory viruses. NONS will be administered intranasally, six times per day [2 sprays per nostril, equivalent to 0.45 mL volume total per dose (4 sprays)], for seven days.

Additional inclusion criteria for NONS are:

- Onset of symptoms within **3 days** of randomisation.
- For women of child-bearing potential: a negative urine pregnancy test.
- For women of child-bearing potential: prepared to use a highly effective method of contraception, or abstinence for a period 30 days before and after terminating study medication intake.

C. Usual Care + Saline Nasal Spray ((comparator) IP)

Saline is a saltwater solution with possible antiviral and/or virus washing-out activity. Saline will be administered intranasally, six times per day [2 sprays per nostril, equivalent to 0.45 mL volume total per dose (4 sprays)], for seven days.

The additional inclusion criteria for Usual Care and Saline are the same as the additional inclusion criteria for NONS, as Usual Care is the comparator of Saline and Saline is the comparator of NONS.

1. INTRODUCTION, RATIONALE AND PROTOCOL STRUCTURE

1.1 Background

The World Health Organisation declared that COVID-19 (Coronavirus disease 2019) was a pandemic on 11th March 2020 [1]. Despite the successful rollout of vaccination programmes worldwide [2, 3], COVID-19 continues to rage [4] having caused over 6,000,000 deaths globally [5], and it is likely that COVID-19 will remain endemic. There is, therefore, a pressing need to identify and evaluate new therapeutics, including testing their efficacy against new variant strains of SARS-CoV-2. As lockdowns and social distancing measures have eased, there has been a resurgence of COVID-19 and COVID-like-illness, such as influenza and respiratory syncytial virus (RSV) [6], which cause significant ill-health and mortality, particularly in clinically vulnerable individuals [7, 8]. Influenza causes around 400,000 deaths globally annually [9]. Therapeutics should be evaluated in the context where they are intended to be deployed. Despite novel antiviral agents specific for SARS-CoV-2 and other viral infections such as influenza coming to market, it remains imperative that the search for better treatments continues, especially since many new drugs are expensive, require a diagnostic test before they are used, and may have many important drug interactions and exclusions. Cost-effective and safe treatments that can be used very early in in the illnesses in the community, where treatment is most likely to have maximum impact are still urgently needed. Given that the greatest burden of ill-health is in the community, with around 90% of all patient contacts take place in primary care [10], it is in primary care and community settings where emerging antiviral and other early treatments for COVID-19 and COVID-like-illness will be of most overall benefit.

Because respiratory tract infections can be caused by a variety of pathogens, a treatment that has broad-spectrum anti-viral and/or protective activity, and does not require a diagnostic test before use would be particularly attractive. Molnupiravir was originally developed as a treatment for influenza, but has been shown to have activity against coronaviruses, including SARS-CoV-2 [11], owing to its ability to induce viral error catastrophe through uptake into viral RNA by RNA-dependent RNA polymerase (RdRp) [12]. Targeting enzymes and structures that are common to many viruses, such as RdRp in RNA viruses, has the potential for broad anti-viral activity [13]. Inhaled budesonide, traditionally used as an asthma and COPD therapy, was found to speed up the time to feeling recovered by three days in community-dwelling COVID-19 patients in the UK who were older and had comorbidities, compared with those receiving usual care [14]. Antibiotics such as doxycycline and azithromycin were trialed as COVID-19 treatments due to their theoretical abilities to reduce inflammation [15, 16], which could in turn have reduced the pro-inflammatory state induced by viral infections. Treatment with antibiotics could also reduce the chance of developing a secondary bacterial infection, a potential complication that is common to respiratory tract infections, but these agents have been shown to be ineffective for this indication. There are a number of promising candidate interventions, including nose sprays that are considered to inactivate all viruses and prevent transmission into host cells. Identifying therapeutic agents with broad antiviral activity and deploying them to patients with early symptoms of COVID-19 and COVID-like-illness in the community on a syndromic basis has the potential to significantly reduce ill-health and illness duration, viral transmission, hospitalisations and deaths, and have a considerable favourable economic benefit. This is particularly important given that primary care physicians typically manage respiratory tract infection syndromic illness without knowing and/or identifying the causative pathogen. These agents should be safe and ideally inexpensive, to maximise scalability and impact.

An adaptive platform trial with nested process evaluation is an efficient way to test such potential agents as it allows for multiple interventions to be tested under a single master protocol [17]. Interventions can be added to the trial platform whilst the trial is in progress [17], negating the need to set up a new trial for each therapeutic that emerges. Through interim analyses, interventions can be dropped from the trial due to pre-specified success or futility criteria being met [17]. If appropriate, a shared control group can be used as a comparator for multiple interventions in the platform [18]. Furthermore, accumulating data can influence the course of the trial; for example, response adaptation can be used to allocate more participants to better performing interventions [19]. These features: increase trial efficiency and reduce the overall sample size; enable the trial to remain relevant to evolving circumstances, which is particularly important in the context of epidemic and pandemic illnesses; and, allow intervention findings to be disseminated in a timely fashion without having to wait for the overall conclusion of the trial.

Platform trials have been used successfully to evaluate therapeutics for COVID-19 [20-22] and influenza [23]. However, to date, there is no platform trial with Europe-wide reach to thoroughly evaluate early treatment of COVID-19 and COVID-19-like illness symptoms in patients treated in primary care. The SARS-CoV-2 pandemic has highlighted the critical importance of establishing rapid, adaptive platform trials to identify effective therapeutics for pandemic, epidemic and emerging infectious diseases. A Europe-wide, primary care adaptive trial platform would allow an evolving strategic focus on countries with higher prevalence of COVID-19 and COVID-like-illness, and would facilitate large-scale, rapid recruitment, thereby providing faster, more robust and meaningful results than would typically be possible through a single country approach. ECRAID-Prime will thus become a trial platform in perpetuity, ready to be leveraged in light of any emerging infectious disease threats.

1.2 Study rationale

The rationale of the ECRAID-Prime trial is to test safety and efficacy of treatments for patients presenting to primary care with COVID-19 and COVID-like-illness in a phase II/III type evaluation, with the aim of determining whether treatments should progress to a next phase of evaluation, and evaluate the trial process and procedures in order to optimize it and enhance recruitment. Under the master protocol, patients will be included on the basis of a syndromic clinical picture. Before medicine trial intervention is given, an initial test will be taken to establish the aetiology of the infection, to guide inclusion into appropriate trial arms guide inclusion into arms evaluating aetiology-specific treatments (as specified in the Intervention Specific Appendices (ISA) to the master protocol for such a treatment). Depending on the Investigational Product (IP) under investigation, this master protocol, therefore, allows for inclusion based on meeting syndromic inclusion criteria for some agents as well as a “test-and-treat-if-positive” approach, in case patients with a specific aetiology are expected to benefit from a specific IP only. In this way, the ECRAID-Prime trial and this master protocol retain focus on COVID-19, while also potentially giving answers to effectiveness of relevant trial interventions for any current, or future epidemic and pandemic respiratory infections. The platform will also evaluate the effect of treatments on longer-term participant outcomes captured at three and six months. It is possible that treatments given during acute illness could reduce the occurrence or severity of post-viral syndromes, such as long-COVID. Long-COVID, defined as symptoms persisting beyond four weeks after the index illness, can cause significant morbidity and economic burden through delayed return to work/usual activities [24].

1.3 Background/embedment of ECRAID-Prime in Ecraid

The European Clinical Research Alliance for Infectious Diseases (Ecraid) is an EU-funded research infrastructure with the purpose of reducing the impact of infectious diseases (ID) on individual and population health. ID pose a serious threat to European citizens and economies. Of particular concern are pathogens that have the potential to cause major epidemics or even pandemics and for which no effective treatments and/or vaccines are available. The frequency and impact of these (re-)emerging infectious diseases (EID) have been amplified by global trends such as population growth, increases in trade and travel, urbanisation, deforestation, and climate change. The COVID-19 pandemic has led to unprecedented public health measures across the globe. The vision of Ecraid is to efficiently generate rigorous evidence to improve the diagnosis, prevention and treatment of infections and to better respond to ID threats. Within Ecraid, primary care research will focus initially on COVID-19 and COVID-like-illness by implementing ECRAID-Prime and a perpetual observational study.

ECRAID-Prime will fit in this structure by recruiting patients into a therapeutic trial to treat COVID-19 and COVID-like-illness with the ultimate aim to reduce illness duration, complications, and possibly transmission of SARS-CoV-2, influenza, RSV and other respiratory pathogens.

1.4 Protocol structure

The structure of this protocol differs from a traditional study protocol. The perpetual platform nature of ECRAID-Prime allows for multiple interventions to be tested simultaneously and in series. The ECRAID-Prime master protocol will describe the overall structure and processes of the platform, while any specifics for the interventions and comparators under investigation will be fully described in separate appendices which detail all specifics to the controls, interventions and their evaluation, e.g. the IP-specific background and information, route of administration, dosage, known and potential risks and precautions, and if applicable, additional objectives, assessments and/or criteria. This will also include the stage of development of the IP and thereby the type of study evaluation that will be performed (e.g. study phase IIa, IIb, III). New interventions that enter the trial will be fully described in additional ISAs as appendix to the Master Protocol, requiring full approvals in an amendment procedure.

2. OBJECTIVES

The generic platform study objectives are listed in this section. Potential additional objectives per IP will be detailed in each ISA.

2.1 Primary study objectives

The primary objective(s) of this platform study will be phase dependent.
To assess the efficacy of the study IP versus control on:

- Time to first self-report of feeling recovered from symptoms of COVID-19 or COVID-like-illness (for Phase IIb/III type evaluation, as specified in the relevant ISA).
- Viral clearance and potentially impact on biomarkers, for example on illness severity or immunological response (for Phase IIa type evaluation as specified in the relevant ISA).

2.2 Secondary study objectives

The key secondary outcome will be early sustained recovery, which is defined recovery by day 14, sustained until day 28.
Other secondary objectives include assessment of the efficacy and safety of the study IP versus control on:

- Sustained recovery (participants' reported recovery that was maintained until 28 days)
- Time to first self-report of feeling recovered from individual symptoms of COVID-19 or COVID-like-illness (for Phase IIa type evaluation)
- Viral clearance (for Phase IIb and III type evaluation)
- Time to first self-report of return to usual daily activity
- Presence, duration and severity of individual respiratory symptoms
- Participant reported overall wellbeing
- Evaluation of overall safety of the IP by monitoring of (serious) adverse events and (serious) adverse drug reactions
- The use of additional antiviral medication
- The use of other prescribed and/or over-the-counter (OTC) medication for the RTI
- The occurrence of complications (hospitalisation, death; all-cause, non-elective hospitalisation will be assessed)
- Impact on usual daily activities
- Health care utilisation (e.g. general practitioner (GP) and hospital visits)
- Long-term (up to 6 months) consequences of COVID-19 or COVID-like-illness
- The incidence of COVID-19 and COVID-like-illness in other members of the household

2.3 Exploratory objective

Exploratory objectives include:

- The emergence of mutations in causative pathogens in participants and potentially in household members (where specified in the relevant ISA).
- To assess the experiences of researchers and network coordinators of setting up the trial in multiple countries, including views on optimising trial delivery, recruitment, and implementation (qualitative study).
- To assess healthcare professionals' views and experience of taking part in the trial (in the context of an epidemic or pandemic), the novel trial design, recruiting patients and views on the intervention(s) (qualitative study).
- To assess patient views and experiences of taking part in the trial and trial interventions, including intervention adherence (qualitative study).

3. STUDY DESIGN

3.1 Study Design

ECRAID-Prime is a randomised, double-blind, multicountry, multicentre platform trial - with early stopping for futility and superiority if prespecified criteria are met - for the evaluation of new IPs for treatment of non-hospitalised patients with COVID-19 and COVID-like-illness. When a novel IP is added to the platform, an additional ISA will be written as a substantial modification/amendment to this Master Protocol. All appropriate ethical and competent authority approvals will be gained for each ISA prior to its implementation in the platform. Evaluation of each additional IP will follow to the same core trial structure, trial processes and

data collection as described in this master protocol, and only deviate where essential, and as described in the relevant ISA. Novel IPs can be evaluated simultaneously or sequentially.

3.2 Study description

Pre-assessment by the GP or delegate (gauging interest, with general in- and exclusion criteria in mind) will preferable be done face-to face, and only remote if circumstances demand and approvals in place (see section 4.1 Population). After having fully informed the potential participant the informed consent procedure will be executed. There will be a person-to-person discussion about the trial when taking consent with all participants, and there will be an opportunity for asking questions and for full verbal explanations. This conversation may be face to face or video call (see chapter 11). After obtaining IC, eligibility for trial participation will be checked (general and specific in- and exclusion criteria). Eligible participants will be randomly allocated to receive either an IP or a control. Each IP and control will have its own appendix. The aim is for randomisation and IP initiation to occur within 7 days of symptom onset; some IPs may require a faster initiation which will be specified in its ISA. Baseline information will be collected (see section 8.3 Study Procedures). Participants will receive study instructions, including how to administer the IP/control product (if participant is allocated to a study arm with an IP or control product). IP and control treatment duration will be described in the ISAs. Use of diaries and questionnaires will be explained. These diaries and questionnaires can be online, paper-based, or completed by telephone, and the relevant and preferred approach will be explained, and access provided.

Participants will be asked to report feeling recovered, individual respiratory symptoms, overall wellbeing, AEs, use of mediation, complications, impact on usual daily activity and health care utilisation in a daily diary (either paper or online) for 28 days following randomisation.

A swab will be (self)-taken at baseline (day 0, this swab will be also used to determine disease aetiology (retrospectively)) and subsequently on day 4, 7 and 14; if additional swabs are needed then this will be specified in the ISA. Blood samples or blood spot tests (self)-taken may be taken at inclusion and later, if specified in the ISA.

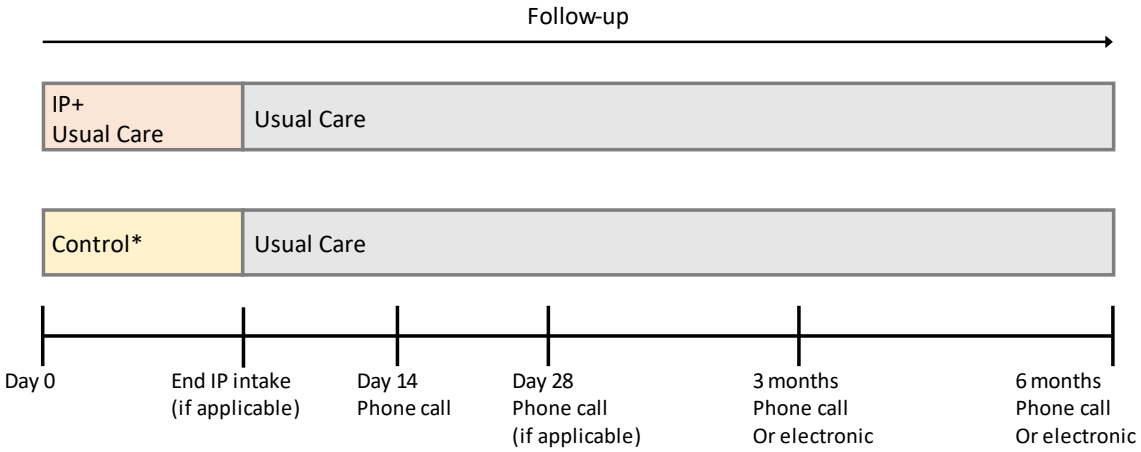
All participants will receive an end-of-treatment telephone call assessment at day 14 (window 14-18 days) after randomisation. During this call diary completion, questions related to feeling recovered and return to usual activity, IP intake, health care utilization, and (serious) adverse events ((S)AEs) not reported in the diary will be captured.

In addition, participants will receive a telephone call at day 28 (window 28-35 days) after randomisation in case their diary is incomplete to capture a minimal outcome set. Longer-term follow-up will be at 3 and 6 months by electronic questionnaire (online, app) with back-up telephone call if not completed by other means. Specifically, these calls/questionnaires will capture data on whether the participant feels recovered from their index illness, participant's reported overall wellbeing, long-term consequences of the illness, healthcare utilization related to persisting symptoms, and impact of ongoing symptoms on activities.
For more details on study procedures, see section 8.3 Study Procedures. More study specific requirements will be described in the ISA.

3.3 Schematic diagram of study design

The core schematic diagram of study design is presented below (see **Figure 1**). If the core diagram needs adaptation for a specific IP, this will be specified in the ISA.

Figure 1. Study Design



* Control = Usual Care or Usual Care + Placebo

3.4 Duration of the study per participant

The duration of the study for each participant is 6 months. Participants will be monitored daily for their acute symptoms for 28 days via a diary (paper, online). All participants will receive an end-of-treatment telephone call assessment at day 14 (window 14-18 days) after randomisation. In addition, participants will receive a telephone call at day 28 (window 28-35 days) after randomisation in case data capture is not complete, to enable capturing a minimal set of outcome data. Longer-term follow-up will be at 3 and 6 months by electronic questionnaire (online, app) with back-up telephone call if not completed by other means.

3.5 Nested qualitative study

A qualitative study will be nested within the trial to understand the experiences of researchers and network coordinators in delivering the trial, the experiences of healthcare professionals and patients in taking part in the trial, and views on and acceptance of trial interventions. The qualitative work will aim to include researchers and network coordinators from all countries and networks which take part in the trial. A sub-set of networks will be selected to undertake interviews with healthcare professionals and patients. These networks will be purposefully selected to give variation in factors such as healthcare system, geographic location in Europe and income. Interviews will be conducted with participants from these three stakeholder groups

(researchers, healthcare professionals and patients) either remotely (by telephone or online (e.g. using Microsoft Teams)) or in person as appropriate.

Interviews with researchers and network coordinators will take place throughout the period of ECRAID-Prime prior to trial set up through to completion of recruitment and follow-up of patients. We will aim to include longitudinal interviews, interviewing the same participant at multiple timepoints, where possible, to gain insights into how researchers apply learning to improve trial processes throughout the study. Interviews will ask researchers and network coordinators about how they deliver the trial and any advantages and issues of working within an existing platform to deliver trials efficiently. The number of interviews conducted will depend on the number of interventions trialled and the data collected but will be approximately 20-60 interviews.

Interviews with healthcare professionals will take place throughout the trial and will focus on key timepoints such as start of recruitment and introduction of a new intervention arm. Health care professionals will include clinicians who see patients when they first consult and who assess eligibility and/or randomise them in the trial. Network coordinators will identify eligible healthcare professionals at their sites. Interviews will ask about experiences of taking part in the trial (in the context of an endemic or pandemic situation), views of trial processes, the novel trial design and introduction of new interventions, experience of recruiting patients and views of interventions. The number of interviews will depend on data collected and the number of interventions being trialled over time but will include approximately 6 healthcare professionals per network, per trial intervention giving a total of 30-70 interviews.

Interviews with patients participating in the trial will take place at a suitable timepoint after their initial consultation (depending on their diagnosis, likely recovery time and the regimen of any trial intervention), likely around 2 weeks, to understand their experience of being recruited to the trial, trial processes, their views of the intervention and intervention adherence (where relevant). Patients in any intervention arm may be invited to take part in an interview. The number of interviews will depend on data collected and the number of interventions being trialled over time but will include approximately 10 patients per network, per trial intervention giving a total of 40-80 interviews. We will seek to obtain variation in factors such as age, symptom presentation, and intervention arm.

All individuals invited to an interview will be sent an invitation letter and participant information leaflet relevant to the stakeholder group they are in (researcher, healthcare professional, patient). We will obtain written or verbal consent prior to an interview.

4. STUDY POPULATION

4.1 Population (base)

In ECRAID-Prime there will be several options for recruitment of participants (see below for further details of each):

- Ambulatory symptomatic patients with COVID-19 or COVID-like-illness contacting the GP practice or primary health care service;

- Potentially eligible participants will receive information from their GP practice or health care service to contact them should symptoms suggestive of COVID-19 or COVID-like-illness appear;
- Central recruitment (only if the situation demands, for low-risk IPs, upon approval via an amendment/modification, and as specified in the ISA).

Participating countries can select the recruitment strategy most suitable for their situation, depending on the IP under study, and pandemic/epidemic circumstances. Where a specific IP requires a specific recruitment strategy, this will be specified in the ISA.

4.1.1 Ambulatory symptomatic patients

Potential participants for the study can be identified when they contact or present to their GP with symptoms suggestive of COVID-19 or COVID-like-illness (see section 4.2 and 4.3 for eligibility criteria).

4.1.2 Potentially eligible participants

Potentially eligible participants will receive information from the GP practice to contact the practice should symptoms suggestive of COVID-19 or COVID-like-illness appear. This information can be via personal letters (which could also be directed to specific high-risk groups, if needed for IP under investigation), via the practice website, banners, and information leaflets in the waiting room. Directly upon onset of symptoms suggestive of COVID-19 or COVID-like-illness they can contact the practice for a trial visit, or contact the local trial team to be recruited centrally (see section 4.2 and 4.3 for eligibility criteria).

4.1.3 Central recruitment

A central trial team in each country will be able to recruit and randomise participants, only if approved via an amendment/modification, and the situation in a country demands this recruitment strategy (for example during a lock-down). Potentially eligible people experiencing symptoms suggestive of COVID-19 or COVID-like-illness will be informed about the study via their GP, leaflets in pharmacies or any health and social care facility, testing centres, general advertising (e.g. radio and television), and social media. Once they expressed interest in trial participation, either face-to-face or by video, a medically qualified clinician or qualified delegate will explain the trial to the potentially eligible participant, obtain informed consent, and check and confirm eligibility. Opportunity will be given for discussion and questions prior to consent and randomisation (see chapter 11).

Once a participant has provided informed consent and has been confirmed as eligible, the study team member will collect all information for the baseline Case Report Form (CRF), contact information, randomise the patient, and arranges for a participant pack, for delivery to the participants' homes (see section 8.3 Study Procedures).

4.2 Inclusion criteria

The generic platform inclusion criteria are listed in this section. Potential additional inclusion criteria for specific IPs will be detailed in the ISA.

In order to be eligible to participate in ECRAID-Prime, a participant must (at minimum) meet all the following criteria:

1. Participant is ≥18 years of age on the day of inclusion.

If people aged <18 years are suitable for inclusion in the evaluation of an IP, then this will be described and justified in the relevant, approved ISA.

2. Presence of at least two symptoms suggestive of COVID-19 or COVID-like-illness, one respiratory (cough, sore throat, running or congested nose or sinuses, shortness of breath) and one systemic (fever, feeling feverish, sweats/chills or shivering, low energy or tiredness, headache, muscle, joint or body aches, loss of taste and/or smell).
3. Judged by recruiting medically qualified clinician or delegate that the illness is due to a respiratory infection.
4. Onset of symptoms less than 7 days (in case earlier treatment is required for a specific IP, this will be specified in the ISA).
5. Willing and able to give informed consent for participation in the study.
6. Willing and able to comply with all trial procedures (including availability of freezer at participant's home to store self-collected swabs).

Any additional eligibility criteria relevant to women of child-bearing potential, including current pregnancy or breastfeeding will be specified in the ISA. Participants of childbearing potential are defined as participants who are potentially fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy.
Highly effective contraception methods include sterilisation, combined oestrogen and progestogen containing hormonal contraception (oral, intravaginal, transdermal), progestogen-only hormonal contraception (oral, injectable, implantable), intrauterine device (IUD), intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner (provided that partner is the sole sexual partner of the WOCBP trial participant, and that the vasectomised partner has received medical assessment of the surgical success).
If women have been abstinent for the 30 days before enrolling in the trial and will agree to continue to be abstinent for a further 30 days after the end of IP intake, where this is in line with their preferred and usual lifestyle, this would also count as effective contraception.

4.3 Exclusion criteria

The generic exclusion criteria are listed in this section. Potential additional exclusion criteria for individual IPs; for example, specific comorbidities or medication use, will be detailed in the ISA.

A potential participant who meets any of the following criteria will be excluded from participation in ECRAID-Prime:

1. Requiring admission to the hospital on the day of inclusion.
2. Known allergies or hypersensitivities to any of the components used in the formulation of the IP, or the control product.
3. Any disease, condition, or disorder, or language barrier that precludes participation in the trial, in the opinion of the GP or delegate (with GP serving as supervisor) checking eligibility and taking consent.
4. Any planned major surgery in the next 28 days.
5. Currently participating in a trial of a pharmacological treatment.

4.4 Sample size calculation

Sample size requirements will be phase dependent and are detailed in the ISA.

5. STUDY TREATMENTS

The sections of this chapter e.g., name and description of the IP/control, status of development of the IP/control, description and justification of dosage and route of administration, preparation and labelling of the IP/control, will be described in the ISA.

6. OTHER TREATMENTS AND RESTRICTIONS

6.1 Concomitant therapy

6.1.1 *Permitted medication*

The ISA describes for each investigational product which co-medication will be permitted during the study. Ongoing long-term medications should be continued for the management of underlying conditions (to be recorded in the CRF).

6.1.2 Prohibited medication

The ISA describes for each IP which co-medication is not permitted during the study, which results in additional exclusion criteria.

6.1.3 Escape medication

Symptomatic therapy to manage symptoms related to COVID-19 or COVID-like-illness, such as antipyretics, analgesics, as well as other OTC medication is allowed. Use of OTC medication will be captured in the participant diary.

6.2 Lifestyle restrictions

6.2.1 Contraception measures

If there are any specific criteria for women of child-bearing potential, this will be specified in the ISA.

6.2.2 Other requirements

If there are any other requirements, then these will be described in the ISA.

7. TRACEABILITY, STORAGE, ACCOUNTABILITY AND COMPLIANCE

In ECRAID-Prime IPs will be tested, which can be Investigational Medicinal Products (IMPs) or Investigational Medical Devices (IMDs). These will be prepared and supplied by different pharmaceutical companies. Certified vendors of these pharmaceutical companies will be responsible for overall management of IPs, until arrival of the IP in a country (at a central location or directly at the site, according to country's regulation), which will include procurement, receipt, storage and stock maintenance of the IP, labelling, packaging of the IP,

and distribution of the IP. This will occur in accordance with International Conference on Harmonisation guidelines for Good Clinical Practice (ICH-GCP (R2)), good manufacturing practice (GMP), good documentation practices (GDP) and all other applicable (national) laws and regulations.

A unique IP number is printed on the study IP label. IP labels will be in the local language and comply with European and, if needed, national regulations.

IPs will be received by designated persons in each participating country (per local criteria, e.g. a central (hospital) pharmacy, or directly at recruiting sites), handled and stored safely and properly, and kept in a secured location to which only designated personnel has access. Upon receipt, all IPs must be stored according to the instructions specified in the IP handling and administration protocol. IPs are only to be dispensed in accordance with the protocol. Technical complaints are to be reported to the Sponsor's Quality Assurance.

The Site Investigator or delegate must maintain an accurate record of receipt and dispensing of the IP using an IP accountability log. Monitoring of IP accountability will be performed by monitors during site visits, remotely, and at the completion of the trial.

At the end of the study, and as appropriate during the course of the study, IP accountability will be performed, and unused IPs will be destructed in the country, by the vendor, or the Sponsor. A copy of the completed IP accountability log should be returned to the Sponsor as part of the final accountability filing.

Further detailed specification of vendor and IP handling will be described in the ISAs.

Compliance
Study product compliance will be assessed by using a study product intake diary on adherence to the prescribed dose of the study product per day:
- Days of study product intake
- Adherence to the prescribed dose per day

8. METHODS

8.1 Study parameters/ endpoints

8.1.1 Primary study endpoints (phase dependent) will be:
- Time to first self-report of feeling recovered from symptoms related to COVID-19 or COVID-like-illness (for Phase IIb/III type evaluation).
- Viral clearance and potentially impact on biomarkers of illness severity (for Phase IIa type evaluation, assessed at baseline and on days 4, 7 and 14 or specified in ISA if samples will be taken on other days).

8.1.2 Secondary study parameters/endpoints include:
Key secondary outcome: early sustained recovery (recovery by day 14 sustained until day 28).
Other secondary endpoints:
- Sustained recovery (participants' reported recovery that was maintained until 28 days)

- Time to first self-report of feeling recovered from symptoms of COVID-19 or COVID-like-illness (for Phase IIa type evaluation)
- Viral clearance (for Phase IIb/III type evaluation, assessed at baseline and on days 4, 7 and 14 or specified in ISA if samples will be taken on other days).
- Time to first self-report of return to usual daily activity.
- Presence, duration, and severity of individual respiratory symptoms (runny/congested nose, sore throat, cough, fever shortness of breath, fatigue/tiredness, sweats/chills, headache, muscle, joint and/or body aches, loss of taste/smell, diarrhoea, nausea/vomiting, other) as: absent, mild, moderate, severe.
- Participant reported overall wellbeing, reported by rating of how well participant feels (scale 0-10).
- Overall safety of the IP by reporting (serious) adverse drug reactions.
- The use of additional antiviral medication (yes/no, name of medication)
- The use of other prescribed and/or OTC medication for the respiratory infection (antibiotics, antiviral medication, ibuprofen, other pain/fever medication, inhaled medication, intranasal medication, other).
- Impact on usual daily activities (work/education, caring for (grand-) children, household activities, sports, social life), as: no, slight, moderate, severe, not applicable.
- Complications (hospitalisation, death; all-cause, non-elective hospitalisation).
- Health care utilisation for COVID-19 or COVID-like-illness (GP and hospital visits).
- Long-term consequences of COVID-19 or COVID-like-illness (e.g. cough, shortness of breath and/or difficulty breathing, fast heart rate, fatigue, tiredness and/or loss of energy, sleep alterations, loss of smell and/or taste, emotional sensitivity, depression and/or anxiety, concentration problems and/or difficulty thinking, muscle aches and or generalised body pains, diarrhoea and/or stomach pain, other).
- The incidence of COVID-19 and COVID-like-illness in other members of the household (using participants diaries and/or swabbing the symptomatic household member(s)).

8.1.3 Exploratory parameters

- Emergence of mutations in causative pathogens in index cases and potentially in household members.
- Experiences of researchers and network coordinators of setting up the trial in multiple countries, including views on optimising trial delivery, recruitment, and implementation (qualitative study).
- Healthcare professionals' views and experiences of taking part in the trial (in the context of a pandemic), the novel trial design, recruiting patients and views on the intervention(s) (qualitative study).
- Patient views and experiences of taking part in the trial and trial interventions, including how they conceptualise their illness and recovery (qualitative study).

8.1.4 Other study parameters to be recorded in the CRF

Demographics

- Age (years)
- Sex at birth (male/female/not specified)
- Ethnicity
- Household (living with others (yes/no), how many people, age of household, living situation)
- Regular paid work (yes/no)

- Healthcare worker (yes/no)

Relevant comorbidities and medication at baseline
- Relevant comorbidities ((e.g. cardiovascular disease, lung disease, asthma, diabetes, joint disease, neurological disease, severe mental illness, weakened immune system, other comorbidities) that started before inclusion in the study

Vaccination history
- COVID-19, influenza, pneumococcal and RSV vaccination status

Prior COVID-19
- Prior confirmed COVID-19
- Previous A&E/hospital overnight admission for COVID-19

Signs and symptoms at presentation
- Individual respiratory symptoms at presentation
- Overall illness severity (clinician's impression)
- Number of days with respiratory symptoms (days)

Anthropometrics
- Body weight (kg): self-reported or measured by recruiter
- Height (cm): self-reported or measured by recruiter
- Body mass index (BMI) will be calculated using the following formula: BMI = Body weight (kg)/(Height [m])^2

Lifestyle parameters
- Smoking (never, former, current, unknown)

Clinical assessments
- Body temperature (°C) measured using available device (self-reported if central/remote inclusion, self-measured using TempaDOTs, or measured by recruiter)
- Peripheral oxygen saturation level as measured non-invasively by pulse oximetry, systolic/diastolic blood pressure, respiratory rate, heart rate (if inclusion is face-to-face)

Usual care provided
- Prescribed medication
- Advice given

8.2 Randomisation, blinding and treatment allocation

8.2.1 Randomisation

With each new IP entering the platform, the randomisation ratio will be adapted. The day of randomisation will be Day 0. Treatment initiation will be as close to Day 0 as possible, using methods that may include directly dispensing IP to participants, or couriering medications to participants who are recruited centrally.

Included patients will be allocated to either an IP arm or a control arm. Each IP has a matching placebo or comparator. For specific IPs Usual Care can be a control arm (specified in ISA).
When there is more than one arm with matched placebos in the trial simultaneously, placebos will be pooled for the primary analysis. This means that allocation will be split equally between all active IP arms the participant is eligible for, and placebo. For example, if there are 2 IPs with matching placebo randomisation will be 1:1:1 (Active A):(Active B):(Placebo), and within Placebo allocation will be 1:1 (Placebo A):(Placebo B). Primary analysis for a particular IP will include all participants allocated to placebo who were eligible for the IP and randomised in the same time frame, i.e. concurrent and eligible placebo participants. Potential participants can be included if they are eligible to be randomised to at least one IP. The trial will start with three trial arm 1:1:1.

Participants will be randomised using a rapid, secure, web-based randomisation system using non-deterministic minimisation, with a random element. The minimisation factors will be age (<55/≥55 years), time since onset of symptoms (≤2/>2 days), and country (Belgium/France/Germany/Ireland/Poland/Spain/UK). The randomisation sequence will be saved electronically in a working environment with restricted access.

Participants randomised to a treatment arm will be allocated to an IP pack according to the randomisation number. This individual investigational product pack will be dispensed to participants once they are randomised.

8.2.2 Implementation

The Site Investigator will be responsible for enrolling participants into the study, randomising them, and assigning them to their given randomisation numbers.

8.2.3 Blinding

This is a patient, investigator, and sponsor-blinded study. Each IP has a matching placebo or comparator. Participants, investigators, and the Sponsor will remain blinded to the study treatment (IP, placebo or comparator) throughout the study, except for the person who is responsible for generating the randomisation sequence, and the person who needs to be unblinded in order to label the IP(s)/placebo etc. In case of a medical emergency that requires unblinding of the IP, the Site Investigator can unblind the participant in order to give optimal medical treatment.
In case there is a Usual Care only arm active, this part is not double-blind.

8.3 Study procedures

*General procedures are listed in this section (see also **Table 1**). Potential additional procedures for specific IPs will be detailed in each ISA.*

8.3.1 Baseline visit, allocation, and IP supply

Baseline visit

- Patients with symptoms suggestive of COVID-19 or COVID-like-illness will be pre-screened for eligibility, and will be fully informed about the study. Eligible patients will be requested to give informed consent prior to start of full screening and trial procedures.
- Checking inclusion and exclusion criteria
- The following information will be collected in the baseline CRF:

  - Demographics
  - Lifestyle
  - Relevant comorbidities at presentation
  - Vaccination history
  - Prior COVID-19
  - Individual signs and symptoms at presentation
  - Anthropometrics
  - Clinical assessments taken (if inclusion is face-to-face)
  - Usual Care provided
- Swab will be taken
- Participants will receive trial instructions
- Participants will be randomly allocated to IP or control group
- If allocated to IP/control product: product dispensing and instructions
- Diaries/questionnaires will be explained and in case of paper, handed over to participants. In case of serious doubt about a participant's ability to complete the online diary, a paper diary should be recommended.
- Collection of additional samples if the specific IP requires, and further specified in the ISA

Participant pack:
Participants will receive a participant pack, containing: the participant information sheet (PIS), the signed informed consent form, swab kits, instructions for the combined throat-nose self-swab and a paper diary (if applicable). If allocated to a study arm with a product, then participants will also receive an investigational product pack with the IP/control product, a participant card and instructions detailing how the study product should be administered and precautions and possible adverse drug reactions or discomforts.

Days of study product intake (if applicable):
IP intake, doses per day and for the number of days is indicated. The duration of IP/control product intake is dependent on the IP and will be described in the ISA.

8.3.2 Follow-up

<u>For 28 days</u>
- Daily diary:
  - Questions related to feeling recovered
  - Questions related to return to usual activity
  - Individual symptoms with severities
  - (Serious) adverse events
  - Participant reported overall wellbeing
  - IP intake
  - Other medication intake
  - Impact of symptoms on daily activities
  - New cases in households of participants
- Weekly diary:
  - Health care utilization
  - Complications
- Swab will be (self-)taken on day 4, 7 and 14

<u>Telephone call day 14 (+4) as end of treatment visit:</u>

- Completion of diary
- Questions related to feeling recovered and return to usual daily activity
- IP intake
- Health care utilization
- (Serious) adverse events

Telephone call day 28 (+7) in case diary data capture is not complete to capture a minimal outcome dataset

- Questions related to feeling recovered and return to usual daily activity
- IP intake
- Health care utilization
- (Serious) adverse events

Follow up 3 months

- Questions related to feeling recovered
- Questions related to return to usual activity
- Questions related to longer-term consequences of COVID-19 or COVID-like-illness
- Impact on daily activities
- Participant reported overall wellbeing
- Healthcare utilization

Follow up 6 months

- Questions related to feeling recovered
- Questions related to return to usual activity
- Questions related to longer-term consequences of COVID-19 or COVID-like-illness
- Impact on daily activities
- Participant reported overall wellbeing
- Healthcare utilization

Unscheduled call:
In case a participant discontinues the study due to the occurrence of a (S)AE, potentially related to the IP, the Site Investigator or delegate contacts the participant by telephone. In case of an SAE, a SAE form will be completed.

Contact details will be collected from the participants at baseline, including mobile and/or home telephone numbers to enable the collection of follow-up data.

8.3.3 Sample collection for laboratory measurements

Virology sampling

For the analysis of aetiology, participants will have a combined pharyngeal/nasal swab taken at baseline. The swab will be placed in 1 ml universal transport media UTM. Samples can be transported using standard transfer systems to a local laboratory, ensuring adherence to country-specific requirements for transfer of samples and according to the ECRAID-Prime laboratory sampling and storage manual. Once at the local laboratory the samples will be stored at -70°C, before transportation to the central laboratory in Antwerp, Belgium. In case the local lab does not have immediate access to a -70°C freezer, samples can be stored at -20°C. In Antwerp, samples will be stored at -70°C.

The export of all samples to Belgium will be done in accordance with country-specific regulations. The participant's date of recruitment and participant ID number will be used as identifiers for the samples. Laboratory and trial team will have access to this information for the purposes of sample identification and tracking. The participant's responsible clinician will not be informed of the results of these swabs because the results will not affect patient treatment and are only for research purposes. Analysis may be some time after swabs were taken. Each participant's swabs will be analysed to identify the causative pathogen, which will be done by a polymerase chain reaction (PCR)-based analysis with a multiplex test detecting COVID-19 or a COVID-like-illness. Upon identification of SARS-CoV-2, the sample will undergo next-gen sequencing (either short read Illumina based or long-read sequencing) to characterise the viral variants and identify variants of concern (VOCs), and also to identify viral mutations impacting the studied treatments. Following analysis, the remaining samples will be stored in a biobank being hosted by the Antwerp laboratory for Ecraid and for ECRAID-Prime. Samples will **only** be biobanked when specific consent was given for this procedure. Samples will be biobanked for further research into infectious diseases (as explained in the PIS).

Viral clearance and impact on biomarkers of illness severity

A semi-quantitative PCR will be applied in order to be able to conclude on lower test positivity. Viral clearance for a specific target (irrespective of SARS-CoV-2 or any other viral target) means that the PCR is negative on day 4, 7 or 14, or that Ct values are above a threshold of 35.

The impact on biomarkers, for example illness severity or immunological response, is dependent on the specific IP. If this will be an outcome parameter, it will be specified in the ISA.

Viral mutations

Raw sequencing reads will undergo quality assessment using FastQC, followed by quality trimming with TrimGalore v. 0.6.7 (https://github.com/FelixKrueger/TrimGalore), and reference mapping against the SARS-CoV-2 genome (GenBank: NC_045512.2) using the CLC Genomics Workbench v.9.5.3 (Qiagen). Clade and lineage assignment will be performed for all SARS-CoV-2 consensus sequences using Nextclade v.2.2.0 (https://clades.nextstrain.org) and Pangolin v1.9 (4.0.6) (https://pangolin.cog-uk.io), respectively. SARS-CoV-2 genome sequencing will be considered successful if: i) the resulting genome sequence harbored < 15% ambiguous base calls (Ns) in the consensus sequence, and ii) was successfully classified by both Pangolin and NextClade. For detection of genetic variants, trimmed reads will be mapped against the SARS-CoV-2 genome (GenBank: NC_045512.2) using the CLC Genomics Workbench v.9.5.3 (Qiagen) with a length and a similarity fraction of 0.7 and 0.99, respectively.

Other sampling

Specific biological marker levels and immunological response are dependent on the IP, and will be specified in the ISA.

Table 1. Schedule of Assessments

	Baseline and Start study	Follow-up				
	Day 0 Screening/Randomisation	Days 1-28	Telephone call 14 (+4) days	Telephone call 28(+7) days[4]	3 months	6 months
Informed consent	x					
Demographics	x					
Relevant comorbidities and medication	x					
Randomisation	x					
Anthropometrics, lifestyle parameters	x					
Clinical assessments	x[2]					
Vaccination and COVID-19 history	x					
Usual Care provided	x					
Virology sampling (swab)	x[1]	x[1]				
Dispensing study product	x					
Return to usual activity and recovered		Daily	x	x	x	x
Symptoms with severities	x	Daily				
Participant reported overall wellbeing	x	x			x	x
Impact on daily activities		Daily	x	x	x	x
Household transmission		Daily				
IP intake	x[3]	Daily[3]	x	x		
Health care utilization		Weekly	x	x		
Blood sample		If required, see ISA				
Long-term infection consequences					x	x
Interview for qualitative study (if invited)		Approximately two weeks after the initial consultation				
(S)AEs, if required see ISA	x	Daily	x	x		

[1] Virology sample will be taken on day 0, 4, 7 and 14 (if additional swabs are needed then this will be specified in the ISA)
[2] If inclusion is face-to-face
[3] The duration of study product intake is dependent on the IP requirements and can start on Day 0 or Day 1.
[4] In case data capture is not complete

8.4 Withdrawal of individual participants

Participants are free to withdraw from the study at any time for any reason if they wish to do so without any consequences to their health care.

A Site Investigator can decide to withdraw a participant from the trial at any time if the Site investigator considers it necessary for any reason including:
- Ineligibility (either arising during the trial or retrospectively)
- If participation in the study will be perceived as a major burden for the patient

The reason for withdrawal will be recorded in the CRF. Whenever feasible, the following information should be documented on the End of Study form:
- Date of last contact
- Date of last intake study product
- Date of early termination
- Primary reason for early termination

Data up to and after the time of withdrawal will be included in the analyses, if allowed by the participant if they withdraw consent.

For participants who withdraw from the study due to the occurrence of an SAE, appropriate follow-up will take place (if agreed by participant) until the SAE has abated, or until a stable situation has been reached, with findings being recorded in the SAE form. Medical care of the discontinued participant is to be arranged by and at discretion of the Site Investigator or delegate, if necessary.

8.5 Replacement of individual participants after withdrawal

Additional participants will be included to compensate for participants that withdraw (equal number); withdrawals due to adverse drug reactions or adverse events based on study procedures will not be replaced.

8.6 Discontinuation treatment of individual participants

A Site Investigator can decide to discontinue a participant from treatment at any time for safety reasons if the Site investigator considers further treatment is a health risk for the participant, at the supervising clinician’s discretion. IP specific guidance for discontinuation of treatment will be specificied in the ISA.

Cessation of study IP is not considered withdrawal from the trial (see section 8.4 for description for participants who withdraw their consent).

For participants who discontinue treatment due to the occurrence of an SAE, appropriate follow-up will take place until the SAE has abated, or until a stable situation has been reached, with findings being recorded in the SAE form. Medical care of the participant is to be arranged by the Site Investigator or delegate, if necessary.

8.7 Premature termination of the study or arm

The Sponsor has the right to terminate the trial or a specific arm prematurely if there are any relevant medical or ethical concerns, or if completing the trial is no longer feasible. Premature termination of ECRAID-Prime may occur because of a Regulatory Authority decision or a change of the opinion of the Independent Ethics Committee (IEC). If such action is taken, the reasons for terminating the trial must be documented in detail and the Sponsor must inform the IECs and the Competent Authorities (CA) (for the Member States concerned through the Clinical Trial Information System (CTIS)) within 15 days or according to local regulations. All trial participants still in the treatment period at the time of termination shall undergo a final examination which must be documented. The Sponsor must be informed without delay if any Site Investigator has ethical concerns about continuation of the trial. Premature termination of a specific IP will be considered if:

- The risk-benefit balance for the participant changes markedly
- It is no longer ethical to continue treatment with the IP
- The Sponsor considers that the trial must be discontinued for safety reasons (e.g. on the advice of the Data Safety Monitoring Board (DSMB))
- An interim analysis or results of other research show that one of the IPs is superior or inferior to another
- It is no longer feasible to complete the trial (e.g. it is unlikely that sufficient participants can be recruited in the trial within the agreed time frame etc.)

The Sponsor decides on whether to discontinue the specific IP in consultation with the trial statistician, as applicable. As directed by the Sponsor, all trial materials must be collected and all CRFs completed to the greatest extent possible. All essential documents necessary for the Trial Master File as defined in GCP will be filed.

9. SAFETY REPORTING

(S)AEs will be collected from participant's daily diaries, calls to participants, face-to-face visits with site clinicians, and medical records, and can be reported spontaneously by the participant, by the coordinating team or clinician.

ECRAID-Prime will implement a risk-assessed and proportionate approach to safety monitoring. In line with the summary of product characteristic (SmPC) or IB, we will assess the risks and the safety profile for each IP, and detail the mitigation and monitoring procedures in the ISA. All safety procedures will be according to Sponsor's Standard Operating Procedure (SOP).

9.1 Temporary halt for reasons of participant safety

The Sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise participants' health or safety. The Sponsor will submit the notification to all IECs and CAs without undue delay of a temporary halt but not later than in 15 days of the date of the temporary halt. It shall include the reasons for such action and specify follow-up measures. The study will be suspended pending a further positive decision by the accredited IECs and/or CAs, as per national regulations. The coordinating teams and investigators will take care that all participants are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

AEs will be recorded for a maximum of 28 days. AEs are defined as any undesirable experience, unrelated to the respiratory infection, occurring to a participant during the study, whether or not considered related to the IP. For each IP/control, all AEs reported by participants in a daily diary from the start of treatment for a 28-day period or during the end-of-treatment telephone call assessment at day 14 (window 14-18 days) after randomisation) will be recorded. AEs will be assessed by a registered/delegated clinician for causality and severity (definitions below).

The participant will be asked to rate the severity of symptoms related to the respiratory infection, which can also be adverse drug reactions (for example headache), in their daily diary. The severity of individual events and symptoms will be assessed over time by participants on the following scale: absent, mild, moderate, severe.
Respiratory symptoms and adverse drug reactions may overlap and can be difficult to disentangle. Trends in the prevalence in the severity of symptoms between control and IP arms will be compared, for evidence of increased severity of measured symptoms in those randomised to receive IPs.

Participants will be free to withdraw from taking the IP/control if they perceive an intolerable AE, unrelated to the respiratory infection. Participants will be provided with a participant card with a telephone number of the coordinating team, enabling them to report issues that are experienced whilst taking the drug. This card will also alert hospital clinicians about trial participation, should a participant be admitted to hospital. In the event of a medical emergency, trial participants will be instructed to show this card to the clinician they see. Based on clinical judgement, the medical monitor/study team may contact the participant to advise the participant on the appropriate clinical care.

9.2.2 Adverse drug reactions (ADRs)

All adverse events judged by either the investigator/delegate or the Sponsor as having a reasonable suspected causal relationship to an IMP qualify as adverse drug reactions (ADR). An unexpected ADR is an ADR of which the nature or severity, outcome or frequency is not consistent with the applicable reference safety information for the IP.

9.2.3 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that:

- results in death
- is life threatening (at the time of the event)
- requires hospitalisation or prolongation of existing inpatients' hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the Site Investigator.

An elective hospital admission will not be considered as an SAE.

The Site Investigator or delegate will report all SAEs to the Sponsor without undue delay after obtaining knowledge of the events. Hospitalisations will be defined as at least one overnight stay. Hospitalisation for a pre-existing condition, including elective procedures planned prior to study entry, which has not worsened, does not constitute an SAE.
SAEs must be reported to the Sponsor by the person or nominated delegate who has discovered the SAE within 24 hours of becoming aware of the event. Some SAEs occurring within the 28-day follow-up period, may be identified retrospectively from diaries which will be received after 28 days. These will be reported within 24 hours of becoming aware of the event.
The Sponsor or delegate will ensure SAEs being reviewed by the medical monitor for relatedness and expectedness as soon as possible, taking into account the reporting time for a potential suspected unexpected serious adverse reaction (SUSAR).

Procedure for immediate reporting of Serious Adverse Events

- The Study Site or national coordinating team will report all SAEs via the SAE form in the online data capture system 'Castor'. The study team at the Sponsor and the medical monitor will receive a notification about the SAE. GP, Study Site, national coordinating team will provide additional, missing or follow-up information in a timely fashion.
- If necessary, the participant may be contacted by GP practice to provide additional, missing or follow-up information as required.

A medical monitor will review the SAE once reported, collect information and report to the Sponsor within the SOP's timeframe. The Sponsor will submit an Annual Safety Report (ASR) including a list table of SAEs to all IECs and CAs of the participating countries (to all Member States concerned) through the CTIS once a year.

Expectedness

For SAEs that require reporting, expectedness of SAEs will be assessed and determined by the medical monitor, according to the relevant Reference Safety Information (RSI) section of the SmPC/IB. The RSI will be the current Sponsor and IEC/CTA approved version at the time of the event occurrence.

Assessment of Causality

The Site Investigator or delegate will report a first assessment of causality. For participants recruited centrally, an investigator, independent of the Sponsor, will make the first assessment of causality. The relationship of each SAE to the IP/control must be determined by a medically qualified individual according to the following definitions:

- **Unrelated** – where an event is not considered to be related to the IP
- **Possibly** – although a relationship to the IP cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible
- **Probably** – the temporal relationship and absence of a more likely explanation suggest the event could be related to the IP
- **Definitely** – the known effects of the IP, its therapeutic class or based on challenge testing suggest that the IP is the most likely cause

AEs/SAEs judged possibly, probably or definitely related will be considered as related to the IP.

9.2.4 Suspected unexpected serious adverse reactions (SUSARs)

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. The event must be serious (see chapter 9.2.2)
2. There must be a certain degree of probability that the event is a harmful and an undesirable reaction to the IP under investigation, regardless of the administered dose
3. The event must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
    - SmPC for an authorised medicinal product
    - IB for an unauthorised medicinal product

All SUSARs will be reported by the Sponsor or delegate to the relevant CAs and/or IECs as per national regulations.

The period for the reporting of SUSARs by the Sponsor, taking into account the seriousness of the reaction, will be as follows:

- In the case of fatal or life-threatening SUSARs, as soon as possible and in any event not later than **7 days** after the Sponsor became aware of the reaction
- In the case of non-fatal or non-life-threatening SUSARs, not later than **15 days** after the Sponsor became aware of the reaction
- In the case of a SUSARs which was initially considered to be non-fatal or nonlife-threatening but which turns out to be fatal or life-threatening, as soon as possible and in any event not later than **7 days** after the Sponsor became aware of the reaction being fatal or life-threatening

Where necessary to ensure timely reporting, the Sponsor may submit an initial incomplete report followed up by a complete report.

9.3 Unblinding procedures for safety reporting

The Site Investigator will only unblind the treatment allocation of a participant during the trial if unblinding is relevant to the safety of the participant and if knowledge of the treatment allocation could influence the immediate medical management of a participant. Emergency unblinding will be performed by the Site Investigator by either 1) opening the emergency unblinding envelope for that participant stored at the site; or 2) digitally using the randomisation tool; or 3) using a central phone number. Sites will be trained on which method for emergency unblinding to follow.

When reporting a SUSAR to the CAs as per national regulations, the Sponsor will only unblind the treatment allocation of the affected participant to whom the SUSAR relates.

Unblinded information will be accessible only to persons who need to be involved in the safety reporting to the CAs, to the DSMB, or to persons performing ongoing safety evaluations during the trial.

9.4 Annual safety report

In addition to SUSAR reporting, the Sponsor will submit a safety report to the accredited IEC and CAs of the participating countries (for the Member States concerned through CTIS), once a year.
This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported SAEs, ordered by organ system, per arm.
- a report concerning the safety of the participants, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the IP under investigation.

9.5 Follow-up of SAEs

All SAEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow-up may require additional tests or medical procedures as indicated, and/or referral to the GP or a medical specialist.
All SAEs that have not resolved by the end of the study, those that are identified retrospectively, or that have not resolved upon trial discontinuation of the participant, must be followed until any of the following occurs:

- The event resolves
- The event stabilises
- The event returns to “baseline”, if a “baseline” value/status is available
- The event can be attributed to agents other than the study intervention, or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or GP refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

9.6 Urgent safety measures and other relevant safety reporting

Where an unexpected event is likely to seriously affect the benefit-risk balance, the Sponsor and the Site Investigator(s) will take appropriate urgent safety measures to protect the participants. In addition, the Sponsor will notify the IECs and CAs of the participating countries of the event and the measures taken (for Member States concerned via CTIS). That notification will be made without undue delay but no later than **7 days** from the date the measures have been taken.
In case of data security breaches, the breach will be reported to the appropriate authority (e.g. Authoriteit Persoonsgegevens) as soon as possible, but at least within 72 hours after discovering the breach. If necessary, those affected by the breach will be informed. It will be agreed upon with participating NCTs and sites in the MSA/CTA that NCTs or sites will report data breaches concerning participant data to the Sponsor and inform applicable regulatory authorities.

9.7 Data Safety Monitoring Board

Given the adaptive nature of ECRAID-Prime, a DSMB will be set up that will review new ISAs and safety data. The DSMB is an independent committee; the chair will be selected based on clinical trial methodology, and experience with adaptive clinical trial design. Additional medical,

statistical, and other experts will be selected to ensure all necessary expertise. Members have no conflict of interest with the Sponsor of the study and IPs tested in the study.
The charter document describes the roles and responsibilities of the DSMB, including the timing of meetings, methods of providing information to and from the DSMB, frequency and format of meetings, statistical issues, and relationships with other committees. The DSMB will be unblinded to ensure the highest quality oversight of the trial, in accordance with current recommendations of regulatory authorities.

Possible recommendations of the DSMB could include:

- No action needed, trial continues as planned
- Early stopping due to, for example, clear benefit, futility, harm of an IP, or external evidence
- Stopping recruitment within a specific subgroup
- Extending recruitment (based on actual control arm outcomes being different to predicted rather than on emerging differences) or extending follow-up
- Stopping a single arm of a multi-arm trial
- Sanctioning and/or proposing protocol changes

The advice(s) of the DSMB will only be sent to the Sponsor of the study. Should the Sponsor decide not to fully implement the advice of the DSMB, the Sponsor will send the advice to the reviewing IECs, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

10. STATISTICAL ANALYSIS

Full details of the statistical analysis will be described in the Master Statistical Analysis Plan (M-SAP). An appendix to the M-SAP titled “Simulation Report” provides simulation results that justify the sample size and design of the study. In addition, the M-SAP will be accompanied by arm-specific appendices to describe any planned deviations from the M-SAP. A broad overview of the design and primary analysis is provided below.

ECRAID-Prime is an adaptive platform trial with early stopping rules for futility or superiority. Comparisons will be based on concurrent and eligible controls only, where control is either a (matched) placebo or comparator, or, if deemed necessary, Usual Care. If there are 2 matched placebos with concurrent randomisation, the primary analysis will pool controls unless it is decided otherwise and specified in the ISA. We may carry out sensitivity analyses with matched controls only included. Early stopping rules will be based on posterior probabilities with thresholds defined using simulations to ensure good trial performance with respect to power and type 1 error.

Each treatment will be analysed separately.

Baseline characteristics will be summarised by IP arm. Continuous variables will be presented as means and standard deviations (or medians and inter-quartile ranges for skewed data). Categorical and binary data will be presented as frequencies and percentages. AEs and SAEs will be summarised by treatment arm.

10.1 Primary study estimand and parameter(s)

10.1.1 Definition of the primary estimand

Participants aged ≥18 years with at least 2 symptoms suggestive of COVID-19 or COVID-like-illness (one respiratory and one systemic) and meeting the IP eligibility criteria, what is the between group difference, estimated by a hazards ratio, in time to first self-report of feeling recovered (TTR) after treatment with an IP compared with placebo or comparator, regardless of treatment discontinuation for any reason or feeling better before starting the medication, and in conjunction with concomitant medication (including anti-viral medication) as necessary? Participants who die within 28 days from randomisation will be censored at 28 days. TTR is measured by response to the daily diary question “do you feel recovered today from your respiratory infection?”, and censored at 28 days after randomisation.

Attributes of estimand:

Population – people in the community aged ≥18 years with at least 2 symptoms suggestive of COVID-19 or COVID-like-illness (one respiratory and one systemic) and meeting the IP eligibility criteria.

Treatment conditions – IP compared with placebo or comparator, regardless of treatment discontinuation for any reason or feeling better before starting the medication, and in conjunction with concomitant medication (including anti-viral medication) as necessary. Participants who die will be given a worst-case value and censored at 28 days.

Outcome variable – time to first self-report of feeling recovered, as measured by response to the daily diary question “do you feel recovered today from your respiratory infection?”, censored at 28 days after randomisation.

Handling of intercurrent events – treatment policy strategy applied to study treatment discontinuation, feeling better before starting the medication and use of concomitant medication (including anti-viral medication). Composite strategy applied to death within 28 days of randomisation.

Population level summary measure – hazard ratio.

10.1.2 Estimator

Analysis will include all eligible randomised participants with at least one follow-up time point (any diary data or information from the 28-day follow-up call) in the group to which they were randomised, regardless of subsequent treatment received. A Bayesian piecewise exponential model with weakly informative priors will be used to estimate the hazard ratio for the time to first self-report of feeling recovered within 28 days of randomisation, adjusting for stratification variables and using all observed data (including data observed after treatment discontinuation and irrespective of use of concomitant medication or feeling better before starting the medication, except for participants who die within 28 days of randomisation who will be censored at day 28.

The primary endpoint is time to recovery, as defined by the first instance that a participant reports this. The primary analysis will be a Bayesian piecewise exponential model with weakly informative priors (specified in the M-SAP), with endpoints regressed on treatment and

stratification covariates. Let θ_j denote the log hazards ratio comparing the hazards of recovery for participants in treatment group *j* versus participants in the comparator arm. We will test the hypothesis that:

H_0: $\theta_j \leq 0$

H_1: $\theta_j > 0$

If the Bayesian posterior probability of superiority (a log hazards ratio greater than 0 corresponding to quicker return/recovery) for a treatment versus control is sufficiently large (e.g. >= 0.99), the null hypothesis will be rejected and the intervention will be deemed superior to control. The exact threshold of the superiority decision criterion will be determined a priori via simulation to control the one-sided type 1 error of the study at approximately 0.025, and will be specified in the M-SAP.

We will carry out sensitivity analyses to explore the robustness of inferences from the main estimator to deviations from its underlying modelling assumptions and limitations in the data. This may include fitting an adjusted Cox proportional hazards model. A supplementary analysis using an unadjusted log-rank test may also be performed. All sensitivity and supplementary analyses will be specified in the M-SAP.

The pattern of missingness will be reported, for instance if there is a difference by group in the proportion of participants lost to follow-up, with no post-baseline data, and withdrawals. We will also check for a pattern of missingness related to intercurrent events. If the pattern of missingness differs between groups, relevant imputation methods will be used to take account of this and an additional sensitivity analysis carried out using imputation.

If an IP is evaluated in a phase IIa-type evaluation, the first interim analysis will use viral clearance and possibly impact on biomarkers as the primary outcome, and will only progress to the next stage of the trial if the IP is looking promising enough. Precise definitions and rules will be specified in the M-SAP.

10.2 Secondary study parameter(s)

Details of secondary analyses will be given in the M-SAP.

10.3 Exploratory parameters

Qualitative data collection and analysis will be done concurrently. Interview data from the three stakeholder groups (researchers, healthcare professionals and patients) will initially be analysed separately from one another, using thematic and framework analysis taking an inductive approach. Nvivo software will be used to assist with the organisation of data. A thematic framework will be used to chart data across all interviews within stakeholder groups and will aid comparisons between participants. Later stages of analysis will compare data across stakeholder groups.

10.4 Interim analysis (if applicable)

The pre-specified design allows adaptations to the trial based on the observed primary endpoint data. These adaptations include the declaration of success or futility of an intervention at an interim analysis and the dropping of treatment arms based on pre-specified decision criteria. The adaptive algorithm will be documented in the M-SAP, including pre-specified criteria for decisions regarding futility or effectiveness of interventions and/or replacing

interventions in the trial. The Simulation Report in the M-SAP will contain extensive simulations to explore the performance of the adaptive design, including power and type 1 error.

The timing of the first interim analysis and frequency of subsequent interim analyses will be pre-specified in in the M-SAP and DSMB charter and will be based on both simulations and logistical considerations.

10.5 Subgroup analysis

We will look at the effect of aetiology on treatment effect by fitting the primary outcome model with an interaction term between aetiology and treatment, where aetiology is split for the most prevalent circulating viruses (2 or 3, and rest) at the time of inclusion.
Additionally, subgroup analyses will be performed by age, comorbidity status and vaccination status.

10.6 Definition of population for analysis

For each intervention, the primary analysis population is defined as participants who were randomised to that intervention or the usual care arm and eligible for randomisation to that intervention, during the same time frame when the intervention was actively randomising (i.e. Concurrent Randomised and Eligible Analysis Population) and have at least one post-baseline measurement.

Primary Analysis Set:
For each IP, all participants randomised to either the IP or its comparator (placebo or usual care and eligible for the IP). Participants later found to be ineligible (randomised in error) will be excluded. Non-concurrent comparators will not be included.
Safety Analysis Set:
All participants who took at least one dose of IP.
Symptomatic Analysis Set:
Primary Analysis Set restricted to those participants who report having the symptom at baseline.
Symptom Free Analysis Set:
Primary Analysis Set restricted to those participants who report not having the symptom at baseline.
Virology Analysis Set:
To be defined

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be performed in accordance with all applicable laws and regulations including the ICH-GCP (R2), the ethical principles that have their origin in the ‘World Medical Association Declaration of Helsinki’ (64th WMA General Assembly, Fortaleza, Brazil, October 2013), the

Clinical Trial Regulation 536/2014/EU (ECTR), the updated version of the European General Data Protection Regulation (GDPR), (EU) 2016/679, and other locally applicable laws.

11.2 Recruitment and informed consent

Participants can be approached for the study by various routes, such as the GP, practice personnel, testing centres, flyers, social media. Research staff will be trained in consent procedures that protect the rights of the participant and adhere to the ethical principles described above. For each study participant, informed consent will be obtained before any protocol-related activities. As part of this procedure, the Study Sites' or central teams' Investigator or delegate will explain verbally and in writing (incorporated in the PIS) the nature of the study, its purpose, procedures, expected duration, and the benefits and risks involved in study participation. The PIS will clearly state that participation in this study is completely voluntary and that withdrawal is possible at any time and without any consequences. The potential participants must be given as much time as needed to read and understand the PIS and to ask questions face-to-face or by video conference. If potential participants are willing to participate, they will be asked to sign and date the approved ICF. The Site Investigator or suitable delegate (according to national regulation) carrying out the informed consent procedure will co-sign and date the ICF after the participant has signed. The participants must receive a copy of the signed ICF. The original signed ICF will be retained at the Study Site. The protocol and ICF, PIS and any proposed advertising material will be submitted to the appropriate IEC and CAs (and other institutions or authorities, if applicable according to local regulation) for written approval. The Sponsor will be responsible to submit and, where necessary, obtain approval from the above parties for all substantial modifications to the original approved documents. Relevant sections in the public trial register will be updated accordingly.

The consenting party will be asked to sign and date an informed consent form. Obtaining a participant's consent to participate in medical research may be complicated by COVID-19 measures (lockdown) and/or due to short timelines and the process being remote. Deviations in consent procedures might occur per participating country, following national law and locally accepted procedures with regards to challenging COVID-measures and/or inclusion timelines and strategies.

Any potential participant approached to take part in the qualitative study will be provided with an additional PIS specific to their role (researcher, healthcare professional or patient). Written informed consent will be taken prior to the start of an interview.

11.3 Benefits and risks assessment, group relatedness

Participation in this trial poses a minimal risk of inconvenience through sample collection, follow-up (calls) and potential side-effects of the IP.

Discomfort of respiratory swabs
(Self-)collecting combined pharyngeal/nasal swabs may cause transient discomfort. Discomfort and risk will be minimized by using experienced clinical staff and proper guidance for self-swabbing. Since the pandemic, self-swabbing has become a routine procedure for most in the community.
Custody of data and samples is specified in section 12.

Blood sampling
Blood sampling will only be performed when required for a specific IP. If blood sampling will be required for an IP, then the procedures and risks will be specified in the ISA.

Adverse drug reactions of the IP
Potential adverse drug reactions and risks of the IP will be specified per IP in the ISA and PIS.

Overall benefit for participants in the intervention group are related to the expected treatment effects of the IP on their respiratory infection.

11.4 Compensation for injury

The participants taking part in the trial will be covered by the insurance taken out by the Sponsor for this study in accordance with national regulatory requirements. This insurance covers damage to research participants through injury or death caused by study participation.

The Sponsor certifies that it has taken out a liability insurance policy in accordance with national regulatory requirements. The liability insurance of the recruiting physician/ GP practice and their team is arranged according to their national requirements regarding liability insurance.

11.5 Incentives (if applicable)

Reimbursement of travel and parking costs to the participant will be considered if allowed by local regulations and by the accredited IECs. A small gift or gift card for time dedicated to study participation (diary completion) may be offered to the participants who participated in the trial and to any individuals who participated in an interview, if allowed by local regulations and approved by the applicable accredited IECs.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

eCRF
All data required by the protocol will be recorded in a secured electronic case report form (eCRF) specifically designed for this study. This data capturing software, Castor, meets all requirements according to ICH-GCP standards, applicable data protection laws and complies with provisions set forth by the General Data Protection Regulation (EU) 2016/679. The eCRF will be web-based and accessible by investigator site staff, national coordinating teams, Sponsor study team members and monitors and will be specific password protected. Persons will not be given access to the eCRF system until they have been trained on the eCRF, and will be granted access only to those participants and/or sections of the eCRF relevant to their task.

An eCRF will be completed for each study participant. All data generated during the study will be reported in the eCRF by the Investigator, the national coordinating team, or designated person. The Site Investigator or central team will ensure that all data are entered promptly,

legibly, completely, accurately and conform to participants reports or source documents, in accordance with specific instructions accompanying the eCRF. Data not requiring a separate written record can be recorded directly in the eCRF. All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification. Should a correction be necessary, the corrected information will be recorded in the eCRF by the authorized person. All (corrected) data will be tracked through an audit trail. The Site Investigator will oversee and coordinate data collection and protection. The Site Investigator must certify that the data entered are complete and accurate by signing-off the data in the eCRF at completion of the trial, or completion of a specific intervention.

Source documents
Source data are all the information in original records and certified copies of original records of clinical findings, observations, or other activities in the study, which are necessary for the reconstruction and evaluation of the study. Source documents are printed or electronic documents containing source data. Sponsor provides an Investigator Site File to store study documents. Source documents include but are not limited to: ICFs; laboratory results; lists of adverse events; lists of concomitant medication; documentation of existing conditions. All source documents will be kept in a locked facility at the Study Site.

YourResearch
In ECRAID-Prime, participants will be recruited in/via GP practices whereas the follow-up of participants can be performed by NCT members. Therefore, contact details of participants (name, phone number and email address) need to be shared between GP practices and the NCT. In order to do this in a GDPR compliant way, the Your Research system (YR) will be used. YR is a cloud-based, secure, GDPR compliant, ISO 27001 certified system. Users will get role-based access and only have access to the contact details of participants that they are allowed to. No other data will be captured and stored in the YR system. Two factor authentication is compulsory for all users.

GPs will enter contact details in YR during, or after the inclusion of a participant. GPs will only have access to participants of their own GP practice, whereas the NCT member(s) will have access to contact details of participants of all GP practices in their Network (country). Data entered in YR will never be exported or linked to collected clinical data in the CASTOR EDC system. After the end of the studytrial, data will be deleted from the YR database. System administrators will not have access to any contact details of participants.

Data confidentiality
All source documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed ICF, the participant will be referred to by a unique trial-specific number in any database, not by name. The unique trial-specific number will not contain any identifiers that allow to identify the subject. Information linking the participant to trial-related and database materials will be maintained in a secure location at the Study Site. The key to code and recode participant identifiers will only be accessible to Study Site staff and national coordinating team (covered in ICF). Coded (pseudonymized) participant data and records will be held in strictest confidence by the Site Investigator, their healthcare staff, and by all central research staff, as permitted by law.

Besides the monitor, members of IECs/Review Boards, the Sponsor's clinical quality assurance group or any other Sponsor's representative may carry out source data checks and/or on-site audits or inspections. In compliance with GCP, direct access to source data will be required for these monitoring, audit and inspection visits. The Site Investigator will assure the monitor, Health authorities and the Sponsor or its representative of all necessary support at all times, providing direct access to source data and documents, according to all regulation. The confidentiality of the verified data, the identity and personal medical information of the participants should be respected during these monitoring visits, audits and inspections, being understood that monitors/auditors/inspectors are bound by professional secrecy.
The Sponsor will make sure that each participant gave a written consent about the collection of its private data, being strictly required for study quality control.

Retention of records and archiving
All data, collected in the eCRF, source documents and all other essential documents will be saved securely for at least 25 years. The Sponsor will be responsible for the retention of data in the eCRF. The Sponsor will setup a local data warehouse (DWH) that will be populated with collected data from the Castor eCRF. All data residing in the DWH will be directly accessible for reporting purposes. Data required for further analysis can directly be exported from the Castor database or can be exported from the DWH. The DWH resides within the UMCU. Role based authorization prevents unauthorized data access.
At the end of the study and after the database has been locked, all essential documents and study data will be archived for 25 years in accordance with the CTR and UMCU Archiving Standard Operating Procedures. The Study Site and central team will be responsible for the storage of source documents for 25 years according to article 58 of the EU Clinical Trial Regulation 536/2014.

Further details on handling and storage of data and will be provided in the Data Management Plans (DMP), the Data Protection Impact Assessment (DPIA) and the File Management Plan (FMP).

12.2 Monitoring and Quality Assurance

The trial will be conducted in accordance with the most recently approved protocol, the approved ISAs, Good Clinical Practice, relevant regulations and SOPs. The objective of the monitoring procedures is to ensure that the trial participant's safety and rights are respected, that accurate, valid and complete data is collected, and that the trial is conducted in accordance with the trial protocol and the ISAs.

To ensure the accuracy and reliability of study results qualified Site Investigators and Study Sites will be participating. Appropriate guidance, review and training of study procedures with the Site Investigator and site personnel will be offered by the Sponsor and the national coordinating team.
A teleconference or network initiation visit will be conducted before activation of the national network. The national team will cascade training down to their Study Sites. All study activities mentioned in the protocol such as, IP handling, sampling, processing, responsibilities and data capture requirements with the Site Investigator and site staff will be reviewed during execution of the study.

During the study, the national networks and Study Sites will be regularly monitored to ensure the quality and completeness of the data and samples collected. The monitor regularly visits the NCT and/or Study Sites to assure that the Site Investigator will receive appropriate support in his/her activities. The Site Investigator will secure access for the monitor to all necessary documentation for trial-related monitoring. Visits will be performed as frequent as necessary depending on the recruitment frequency and on the risk assessment of each IP. A monitoring plan will define the monitoring frequency and procedures, where IP specific items might be added if deemed necessary.

The on-site visits will for example consist of checking consent procedures, access/storage of patient identifiers, trial supply and sample storage/handling, IP access/storage/accountability and handling, data entry, source document verification, etc. Remote and/or centralized monitoring will for instance consist of automatic validation checks for data discrepancies in the eCRF, electronic rules in the eCRF to check for missing data, data queries, identifying unusual data patterns and following up on recruitment rates.

Any discrepancies will be resolved with the NCT, Site Investigator or designee, as appropriate.

Intervention-specific monitoring items issues are addressed in each ISA. In addition, further details of monitoring procedures are described in a separate monitoring plan.

12.3 Substantial modifications

A ‘substantial modification’ is defined in the CTR as any change to any aspect of the clinical trial which is made after notification of a decision referred to in Articles 8, 14, 19, 20 or 23 and which is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial.

All substantial modifications to the original approved documents and the addition of new interventions will be submitted for approval to all participating concerned Member States via CTIS or via local submission (for the United Kingdom). Approval is required prior to initiation except for changes necessary to eliminate an immediate hazard to participants. Where stopping of any intervention is needed, this is an operational issue and randomisation to that intervention will no longer be available. This will be reported to all IECs and CAs of the participating countries (for the Member States concerned via CTIS).

Non-substantial modifications (amendments) will be recorded and filed by the Sponsor and notified to the applicable review bodies at the time of next substantial modification (amendment) notification in accordance with the national regulatory requirements.

12.4 Annual progress report

The Sponsor will submit a summary of the progress of the trial to the accredited IECs once a year. Information will be provided based on applicable recruitment, e.g. on the date of inclusion of the first participant, numbers of participants included and numbers of participants that have completed the trial, SAEs, serious adverse reactions, and substantial modifications.
The Chief Investigator must ensure that a status report is submitted at least annually to the IECs and CAs that approved the protocol.

12.5 Temporary halt and (prematurely) end of study report

ECRAID-Prime is designed as a platform trial, allowing for continued research in participants with COVID-19 or COVID-like-illness in primary care. The platform allows for the study to be perpetual.
It is anticipated that after inclusion of the initially planned sample size, the study could continue to include additional participants and test additional interventions until one of the following occurs:

- The effectiveness and/or cost-effectiveness of all interventions are known and there are no new plausible interventions to test
- All the interventions have been tested

Should the trial be stopped, the end of trial is the date of the last scheduled follow-up for any participant. The Sponsor will notify the IECs and CAs of the end of the study within a period of 90 days (for the participating Member States concerned via CTIS).

Within one year after ending a specific intervention, the Sponsor/Site Investigator will submit an intervention-specific study report with the results of that IP, including any publications regarding that IP, to the accredited IEC/CAs (for Member States concerned via CTIS).

In accordance with article 38 of the CTR, the Sponsor will suspend the study, or specific trial arms if there is sufficient ground that continuation of the study will jeopardise participant health or safety. The temporary halt or early termination of a clinical trial (arm) for reasons of a change of the benefit-risk balance will be notified to the Member States concerned via CTIS or to the IEC and CA of non-EEA country without undue delay but not later than in 15 days of the date of the temporary halt or early termination. It shall include the reasons for such action and specify follow-up measures. The restart of the clinical trial following a temporary halt shall be deemed to be a substantial modification subject to the authorisation procedure laid down in Chapter III of the CTR.

12.6 Public disclosure and publication policy

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in European drug regulatory affairs Clinical Trials (EudraCT). In addition, after finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Sponsor's clinical trial results website and all required Health Authority websites (e.g., Clinicaltrials.gov, EudraCT).

Study results will be disseminated in compliance with Ecraid's publication policy, via manuscripts in peer-reviewed open-access scientific journals, conference abstracts, posters and/or oral presentations, ensuring an accurate and balanced presentation of these data. Before submission, manuscripts or conference abstracts shall be reviewed by the ECRAID-Prime trial management board and Network PIs. All parties are committed to review within a period of 2 weeks and shall not unduly delay the submission of the study results. Proposed publications shall not include either the Sponsor confidential information other than the study results or personal data on any participants, such as name or initials.
Results will also be published in the European database: https://euclinicaltrials.eu, when the summaries become available. In addition, lay terms summary of study results will be published on the Ecraid website.

13. STRUCTURED RISK ANALYSIS

All elements of this chapter, potential issues of concern and/or synthesis will be described in the ISA.

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15. APPENDIX I STUDY FLOW CHART