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Clinical trial for the treatment of COVID-19 and COVID-like illness in primary care

Submission date
03/11/2022

Recruitment status
Recruiting

Registration date
21/11/2022

Overall study status
Ongoing

Last Edited
13/01/2026

Condition category
Infections and Infestations

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Most people with COVID-19 and COVID-like illness do not become seriously ill. Some people, however, do go on to have more serious symptoms and may even need to be admitted to hospital. The aim of this study is to investigate the effectiveness and safety of medicinal products to treat COVID-19 and COVID-like illness in adult patients across Europe. This study will investigate whether the medicinal products help patients to recover patients faster, reduce the severity of the symptoms, reduce complications that require treatment in hospital, and prevent spread to family members/housemates.

Who can participate?
Patients aged 18 years or over and experiencing symptoms of a COVID-19 or COVID-like illness, presenting to primary care with COVID-19 and COVID-like-illness in Belgium, France, Germany, Ireland, Poland, Spain and the UK

What does the study involve?
Participants will be randomly allocated to receive either usual care alone or an investigational product, a placebo or a comparator product in addition to usual care.
Participants allocated to the usual care group will receive usual clinical care. Participants allocated to usual care + nitric oxide nasal spray will receive nitric oxide nasal spray (NONS) administered intranasally (into the nose) in addition to usual care, six times per day [two sprays per nostril, equivalent to 0.45 ml volume total per dose (four sprays)], for 7 days.
Participants allocated to usual care + saline nasal spray will receive a saltwater solution administered intranasally in addition to usual care, six times per day [two sprays per nostril, equivalent to 0.45 ml volume total per dose (four sprays)], for 7 days. Participants allocated to the usual care + LTX-109 will receive LTX-109 0.5% weight/weight administered intranasally, three times per day [1 spray per nostril, equivalent to 280uL volume total per dose (2 sprays)] for 3days.
Participants allocated to the usual care + LTX-109-placebo will receive LTX-109 0.0% weight /weight administered intranasally, three times per day [1 spray per nostril, equivalent to 280uL volume total per dose (2 sprays)] for 3days.
The duration of the study for each participant is 3 months. Participants will be monitored daily for their acute symptoms for 28 days with a diary. They will receive a phone call between 28 days

and 35 days in case data capture is not complete. Longer-term follow-up will be at 3 months by a phone call or electronic questionnaire. A combined throat/nose swab will be taken at the start of the study and on day 4 for NONS and Saline, and at the start of the study and on days 1, 3 and 5 for LTX-109 and LTX-109-placebo.

What are the possible benefits and risks of participating?
The overall benefits for participants in the intervention group are related to the prevention or treatment effects of the study drug on their COVID-19 or COVID-like illness. Taking part in the study can have possible disadvantages. Participants may experience side effects from the medicinal product. There may be a brief period of discomfort from (self-)taking the combined throat/nose swabs. Taking part in the study will take up some of the time of the participant.

Where is the study run from?
This study is being led by the University Medical Center Utrecht (UMCU) and managed by Ecraid (European Clinical Research Alliance on Infectious Diseases) in the Netherlands. It is a collaboration between the UMCU, the University of Oxford (UK), the University of Antwerp (Belgium), ECRIN (European Clinical Research Infrastructure Network, France) and Ecraid.

When is the study starting and how long is it expected to run for?
December 2021 to December 2025

Who is funding the study?
European Union

Who is the main contact?
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Contact information

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Additional identifiers

Clinical Trials Information System (CTIS)
2022-501707-27-01

Integrated Research Application System (IRAS)
1008573

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
EU-EcraidPC-1

Study information

Scientific Title
European Clinical Research Alliance on Infectious Diseases – PRIMary care adaptive platform trial for pandemics and Epidemics

Acronym
ECRAID-Prime

Study objectives
Current study objectives as of 13/01/2026:
To assess the efficacy of the study IP versus control (Usual Care) or versus a comparator (placebo, or comparator IP) on:
1. 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 intervention-specific appendix).
2. Viral clearance, and potentially viral load and/or impact on biomarkers, for example on illness severity or immunological response (for Phase IIa type evaluation as specified in the relevant intervention-specific appendix).

Previous study hypothesis as of 23/07/2024:
The primary objective(s) of this platform study will be phase-dependent.
To assess the efficacy of the study IP versus control on:
1. 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 intervention-specific appendix).
2. Viral clearance and potential impact on biomarkers, for example on illness severity or immunological response (for Phase IIa type evaluation as specified in the relevant intervention-specific appendix).

Previous study hypothesis:
To test the 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 the next phase of evaluation, and evaluate the trial process and procedures to in order to optimize it and enhance recruitment.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 25/05/2024, Federal Agency for Medicines and Health Products (avenue Galilee 5/03, Brussels, 1210, Belgium; +32 (0)25284000; ct.rd@fagg-afmps.be), ref: 2022-501707-27-01

Study design
Adaptive platform randomized double-blind multicentre trial

Primary study design
Interventional

Study type(s)

Treatment

Health condition(s) or problem(s) studied
Reducing illness duration, complications, and possibly transmission of COVID-19 (SARS-CoV-2 infection) and other respiratory pathogens

Interventions
Current interventions as of 13/01/2026:
Eligible participants will be randomly allocated to receive either an investigational product (IP) or the specified control. Each investigational product has a matching placebo or comparator. Besides this matching placebo or comparator IP, usual care alone can be an additional control arm, this comparison is not double-blind. Participants will be randomised to receive either usual care alone or an investigational product, a placebo or a comparator product in addition to usual care.

The ECRAID-Prime trial is a platform trial which means that multiple investigational products for the same illness can be tested simultaneously, and new interventions can be added during the course of the trial in accordance with pre-specified criteria. The names of all treatments of actions, including the control and details of the interventions (dose, duration, how it is administered) are intervention specific and will be described in intervention-specific appendices that will be added to the master protocol. Up to this point three investigational products have been selected.

Participants will be randomized to receive either usual care alone or an investigational product, a placebo or a comparator product in addition to usual care. Potential participants can be included if they are eligible to be randomized to at least one investigational product, as well as the usual care arm.

A. Usual care arm
Participants randomized to the usual care arm will receive usual clinical care according to standard care in the specific country, at the discretion of responsible treating clinicians and according to the participant's own decisions about self-care for the specific respiratory tract infection.

B. Usual care + nitric oxide nasal spray
Nitric oxide nasal spray (NONS) is a nitric oxide donor. NONS will be administered intranasally in addition to usual care, six times per day [two sprays per nostril, equivalent to 0.45 ml volume total per dose (four sprays)], for 7 days.

C. Usual care + saline nasal spray
Saline is a saltwater solution and will be administered intranasally in addition to usual care, six times per day [two sprays per nostril, equivalent to 0.45 ml volume total per dose (four sprays)], for 7 days.

D. Usual care + LTX-109
LTX-109 is a broad acting antiviral and antibacterial agent and will be administered intranasally in addition to usual care, three times per day [1 spray per nostril, equivalent to 280uL volume per dose (2 sprays)], for three days.

Previous interventions:
Eligible participants will be randomly allocated to receive either an investigational product (IP) or the specified control. Each investigational product has a matching placebo or comparator.

Besides this matching placebo or comparator IP, usual care alone can be an additional control arm, this comparison is not double-blind. Participants will be randomised to receive either usual care alone or an investigational product, a placebo or a comparator product in addition to usual care.

The ECRAID-Prime trial is a platform trial which means that multiple investigational products for the same illness can be tested simultaneously, and new interventions can be added during the course of the trial in accordance with pre-specified criteria. The names of all treatments of actions, including the control and details of the interventions (dose, duration, how it is administered) are intervention specific and will be described in intervention-specific appendices that will be added to the master protocol. Up to this point two investigational products have been selected.

Participants will be randomized to receive either usual care alone or an investigational product, a placebo or a comparator product in addition to usual care. Potential participants can be included if they are eligible to be randomized to at least one investigational product, as well as the usual care arm.

A. Usual care arm
Participants randomized to the usual care arm will receive usual clinical care according to standard care in the specific country, at the discretion of responsible treating clinicians and according to the participant's own decisions about self-care for the specific respiratory tract infection.

B. Usual care + nitric oxide nasal spray
Nitric oxide nasal spray (NONS) is a nitric oxide donor. NONS will be administered intranasally in addition to usual care, six times per day [two sprays per nostril, equivalent to 0.45 ml volume total per dose (four sprays)], for 7 days.

C. Usual care + saline nasal spray
Saline is a saltwater solution and will be administered intranasally in addition to usual care, six times per day [two sprays per nostril, equivalent to 0.45 ml volume total per dose (four sprays)], for 7 days.

Intervention Type
Other

Primary outcome(s)
Current primary outcome measure as of 13/01/2026:
The primary outcome will be Phase dependent. For Phase IIb/III type evaluations, the primary outcome will be:
1. Time to first self-report of feeling fully recovered from symptoms related to COVID-19 or COVID-like illness (days), measured using self-report for 28 days (or month 3 if not recovered).

For Phase IIa type evaluations the primary outcome parameter will be:
2. Viral clearance measured using semi-quantitative PCR at baseline and on day 4, and impact on biomarkers of illness severity (if this will be an outcome parameter, then this will be specified in the intervention-specific appendix). The impact on biomarkers, for example on illness severity or immunological response is dependent on the specific investigational product (also the method and timepoints are dependent on the investigational product). If this will be an outcome parameter, then this will be specified in the intervention-specific appendix of that investigational product.

Previous primary outcome measure as of 23/07/2024:
The primary outcome will be Phase dependent. For Phase IIb/III type evaluations the primary outcome will be:
1. Time to first self-report of feeling fully recovered from symptoms related to COVID-19 or COVID-like illness (days), measured using self-report for 28 days (or months 3 and 6 if not recovered).

For Phase IIa type evaluations the primary outcome parameter will be:
2. Viral clearance assessed using semi-quantitive PCR at baseline and on days 4, 7 and 14, and impact on biomarkers of illness severity (if this will be an outcome parameter, then this will be specified in the intervention-specific appendix). The impact on biomarkers, for example on illness severity or immunological response is dependent on the specific investigational product (also the method and timepoints are dependent on the investigational product). If this will be an outcome parameter, then this will be specified in the intervention-specific appendix of that investigational product. So far, there are no compounds selected for which this will be an outcome parameter.

Previous primary outcome measure from 03/02/2023 to 23/07/2024:
Primary study endpoints are dependent on the study phase and can be:
1. Time to first self-report of feeling fully recovered from symptoms related to COVID-19 or COVID-like illness (days), measured using self-report for 28 days (or months 3 and 6 if not recovered).
2. Viral clearance assessed using semi-quantitive PCR at baseline and on days 4, 7 and 14, and impact on biomarkers of illness severity (if this will be an outcome parameter, then this will be specified in the intervention-specific appendix). The impact on biomarkers, for example on illness severity or immunological response is dependent on the specific investigational product (also the method and timepoints are dependent on the investigational product). If this will be an outcome parameter, then this will be specified in the intervention-specific appendix of that investigational product. So far, there are no compounds selected for which this will be an outcome parameter.

Previous primary outcome measure as of 04/01/2023 to 03/02/2023:
Primary study endpoints are dependent on the study phase and can be:
1. Time to first self-report of feeling recovered from symptoms related to COVID-19 or COVID-like illness (days), measured using self-report until the end of the study.
2. Viral clearance assessed using semi-quantitive PCR at baseline and on days 4, 7 and 14, and impact on biomarkers of illness severity (if this will be an outcome parameter, then this will be specified in the intervention-specific appendix). The impact on biomarkers, for example on illness severity or immunological response is dependent on the specific investigational product (also the method and timepoints are dependent on the investigational product). If this will be an outcome parameter, then this will be specified in the intervention-specific appendix of that investigational product. So far, there are no compounds selected for which this will be an outcome parameter.

Previous primary outcome measure:
Primary study endpoints are dependent on the study phase and can be:
1. Time to first self-report of feeling fully recovered from symptoms related to COVID-19 or COVID-like illness (days), measured using self-report until the end of the study
2. Viral clearance assessed using semi-quantitive PCR at baseline and on days 4, 7 and 14, and impact on biomarkers of illness severity (if this will be an outcome parameter, then this will be specified in the intervention-specific appendix). The impact on biomarkers, for example on

illness severity or immunological response is dependent on the specific investigational product (also the method and timepoints are dependent on the investigational product). If this will be an outcome parameter, then this will be specified in the intervention-specific appendix of that investigational product. So far, there are no compounds selected for which this will be an outcome parameter.

Key secondary outcome(s))

Current key secondary outcomes as of 13/01/2026:
1. Sustained recovery, measured using self-report for 28 days
2. Time to first self-report of feeling fully recovered from individual symptoms of COVID-19 or COVID-like illness (days) (for Phase IIa type evaluation), measured using self-report for 28 days (or months 3 and 6 if not recovered).
3. Reduction in viral load
4. Tolerability of the IP
5. IP intake adherence
6. Time to first self-report of return to usual daily activity (days), measured using self-report until the end of the study
7. 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, other) as: absent, mild, moderate, severe, measured using a daily diary at day 0-28.
8. Participant-reported overall wellbeing, reported by rating of how well the participant feels (scale 0-10) at day 0-28, and after 3 months
9. Evaluation of the overall safety of the IP by monitoring of AEs for the duration of IP administration and a defined period after the IP administration finishes. The duration of investigational product administration is dependent on the investigational product and will be specified in the intervention-specific appendix, for the selected IPs only side effects will be measured, as safety data are already available.
10. The use of additional antiviral medication (yes/no, name of medication), using a daily diary on days 0-28
11. The use of other prescribed and/or OTC medication for the respiratory tract infection, yes /no, using a daily diary at days 0-28
12. Occurrence of complications (i.e. hospitalisation, death; all-cause, non-elective hospitalisation) measured using weekly diary on days 7, 14, 21 and 28 or Serious Adverse Event reporting during the entire duration of study participation.
13. Impact on usual daily activities (work/education, caring for (grand-) children, household activities, sports, social life), as: no, slight, moderate, severe, not applicable, measured at day 1-28, after 3
14. Healthcare utilisation for COVID-19 or COVID-like-illness (GP and hospital visits) measured using participant diary on days 1-28, months 3
15. 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) measured using a follow-up call or electronic questionnaire after 3 and 6 months
16. The incidence of COVID-19 and COVID-like-illness in other members of the household, measured using participants' diaries and/or swabbing the symptomatic household member(s) at daily day 0 - 28, if this will be measured using swabs in household members then timepoint(s) will be specified in the intervention-specific appendix

Exploratory parameters:
1. Emergence of mutations in causative pathogens in index cases and potentially in household members measured using combined pharyngeal/nasal swabs for participants swabs that are taken at Day 0 and 4 can be used, if this will be measured in household members then timepoint (s) will be specified in the intervention-specific appendix
2. 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) measured using interviews either remotely (by telephone or online 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 the 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
3. Healthcare professionals' views and experience 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) measured using interviews either remotely (by telephone or online or in person as appropriate). Interviews with healthcare professionals will take place throughout the trial and will focus on key timepoints such as the start of recruitment and the introduction of a new intervention arm.
4. Patient views and experiences of taking part in the trial and trial interventions, including how they conceptualise their illness and recovery (qualitative study) measured using interviews either remotely (by telephone or online or in person as appropriate). 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).

Previous secondary outcome measures as of 23/07/2024:
1. Sustained recovery, measured using self-report for 28 days
2. Time to first self-report of feeling fully recovered from individual symptoms of COVID-19 or COVID-like illness (days) (for Phase IIa type evaluation), measured using self-report for 28 days (or months 3 and 6 if not recovered).
3. Viral clearance (for Phase IIb and III type evaluation) assessed using semi-quantitive PCR at baseline and on days 4, 7 and 14, and impact on biomarkers of illness severity (if this will be an outcome parameter, then this will be specified in the intervention-specific appendix). The impact on biomarkers, for example on illness severity or immunological response is dependent on the specific investigational product (also the method and timepoints are dependent on the investigational product). If this will be an outcome parameter, then this will be specified in the intervention-specific appendix of that investigational product. So far, there are no compounds selected for which this will be an outcome parameter.
4. Time to first self-report of return to usual daily activity (days), measured using self-report until the end of the study
5. 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, other) as: absent, mild, moderate, severe, measured using a daily diary at day 0-28.
6. Participant-reported overall wellbeing, reported by rating of how well participant feels (scale 0-10) at day 0-28, and after 3 months and 6 months
7. Evaluation of overall safety of the IP by monitoring of AEs for the duration of IP administration and a defined period after the IP administration finishes. The duration of investigational product administration is dependent on the investigational product and will be specified in the intervention-specific appendix, for the selected IPs only side effects will be

measured, as safety data are already available.
8. The use of additional antiviral medication (yes/no, name of medication), using a daily diary on days 0-28
9. The use of other prescribed and/or OTC medication for the respiratory tract infection, yes/no, using a daily diary at days 0-28
10. Occurrence of complications (i.e. hospitalisation, death; all-cause, non-elective hospitalisation) measured using weekly diary on days 7, 14, 21 and 28 or Serious Adverse Event reporting during the entire duration of study participation.
11. Impact on usual daily activities (work/education, caring for (grand-) children, household activities, sports, social life), as: no, slight, moderate, severe, not applicable, measured at day 1-28, after 3 and 6 months
12. Healthcare utilisation for COVID-19 or COVID-like-illness (GP and hospital visits) measured using participant diary on days 1-28, months 3 and 6
13. 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) measured using a follow-up call or electronic questionnaire after 3 and 6 months
14. The incidence of COVID-19 and COVID-like-illness in other members of the household, measured using participants' diaries and/or swabbing the symptomatic household member(s) at daily day 0 - 28, if this will be measured using swabs in household members then timepoint(s) will be specified in the intervention specific appendix

Exploratory parameters:
1. Emergence of mutations in causative pathogens in index cases and potentially in household members measured using combined pharyngeal/nasal swabs for participants swabs that are taken at Day 0, 4, 7 and 14 can be used, if this will be measured in household members then timepoint(s) will be specified in the intervention specific appendix
2. 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) measured using interviews either remotely (by telephone or online 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 the 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
3. Healthcare professionals' views and experience 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) measured using interviews either remotely (by telephone or online or in person as appropriate). Interviews with healthcare professionals will take place throughout the trial and will focus on key timepoints such as the start of recruitment and the introduction of a new intervention arm.
4. Patient views and experiences of taking part in the trial and trial interventions, including how they conceptualise their illness and recovery (qualitative study) measured using interviews either remotely (by telephone or online or in person as appropriate). 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).

Previous secondary outcome measures from 03/02/2023 to 23/07/2024:
Secondary study parameters/endpoints include:
1. Time to first self-report of feeling fully recovered from symptoms related to COVID-19 or COVID-like illness (days) (for Phase IIa type evaluation), measured using self-report for 28 days (or month 3 and 6 if not recovered).
2. Viral clearance (for Phase IIb and III type evaluation) assessed using semi-quantitive PCR at baseline and on days 4, 7 and 14, and impact on biomarkers of illness severity (if this will be an outcome parameter, then this will be specified in the intervention-specific appendix). The impact on biomarkers, for example on illness severity or immunological response is dependent on the specific investigational product (also the method and timepoints are dependent on the investigational product). If this will be an outcome parameter, then this will be specified in the intervention specific appendix of that investigational product. So far, there are no compounds selected for which this will be an outcome parameter.
3. Time to first self-report of return to usual daily activity (days), measured using self-report until the end of the study
4. Presence and severity of COVID-19 or COVID-like-illness 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, other) as: absent, mild, moderate, severe, measured using a daily diary at day 0-28.
5. Participant-reported overall wellbeing, reported by rating of how well participant feels (scale 0-10) at day 0-28, and after 3 months and 6 months
6. Possible side effects of the IP measured using a daily diary at day 1-28
7. Evaluation of overall safety of the IP by monitoring of AEs for the duration of IP administration and a defined period after the IP administration finishes. The duration of investigational product administration is dependent on the investigational product and will be specified in the intervention specific appendix, for the selected IPs only side effects will be measured, as safety data are already available.
8. The use of additional antiviral medication (yes/no, name of medication), using a daily diary at day 0-28
9. 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), yes/no, using a daily diary at day 0-28
10. Impact on usual daily activities (work/education, caring for (grand-) children, household activities, sports, social life), as: no, slight, moderate, severe, not applicable, measured at day 1-28, after 3 and 6 months
11. Complications (i.e. hospitalisation, death) measured using weekly diary at day 7, 14, 21 and 28 or Serious Adverse Event reporting during the entire duration of study participation
12. Healthcare utilisation for COVID-19 or COVID-like-illness (GP and hospital visits) measured using participant diary at day 1-28, months 3 and 6
13. 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) measured using a follow-up call or electronic questionnaire after 3 and 6 months
14. The incidence of COVID-19 and COVID-like-illness in other members of the household, measured using participants' diaries and/or swabbing the symptomatic household member(s) at daily day 0 - 28, if this will be measured using swabs in household members then timepoint(s) will be specified in the intervention specific appendix

Exploratory parameters:
1. Emergence of mutations in causative pathogens in index cases and potentially in household

members measured using combined pharyngeal/nasal swabs for participants swabs that are taken at Day 0, 4, 7 and 14 can be used, if this will be measured in household members then timepoint(s) will be specified in the intervention specific appendix
2. 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) measured using interviews either remotely (by telephone or online 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
3. Healthcare professionals' views and experience 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) measured using interviews either remotely (by telephone or online or in person as appropriate). 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.
4. Patient views and experiences of taking part in the trial and trial interventions, including how they conceptualise their illness and recovery (qualitative study) measured using interviews either remotely (by telephone or online or in person as appropriate). 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).

Previous secondary outcome measures as of 04/01/2023 to 03/02/2023:
Secondary study parameters/endpoints include:
1. Viral clearance (for Phase IIb and III type evaluation)
2. Time to first self-report of return to usual daily activity (days), measured using self-report until the end of the study
3. Presence and severity of COVID-19 or COVID-like-illness 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, other) as: absent, mild, moderate, severe, measured using a daily diary at day 0-28.
4. Participant-reported overall wellbeing, reported by rating of how well participant feels (scale 0-10) at day 0-28, and after 3 months and 6 months
5. Possible side effects of the IP measured using a daily diary at day 1-28
6. Evaluation of overall safety of the IP by monitoring of AEs for the duration of IP administration and a defined period after the IP administration finishes. The duration of investigational product administration is dependent on the investigational product and will be specified in the intervention specific appendix, for the selected IPs only side effects will be measured, as safety data are already available.
7. Impact on usual daily activities (work/education, caring for (grand-) children, household activities, sports, social life), as: no, slight, moderate, severe, not applicable, measured at day 1-28, after 3 and 6 months
8. Complications (i.e. hospitalisation, death) measured using weekly diary at day 7, 14, 21 and 28 or Serious Adverse Event reporting during the entire duration of study participation
9. Healthcare utilisation for COVID-19 or COVID-like-illness (GP and hospital visits) measured using participant diary at day 1-28, months 3 and 6
10. 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) measured using a follow-up call or electronic questionnaire after 3 and 6 months
11. The incidence of COVID-19 and COVID-like-illness in other members of the household, measured using participants' diaries and/or swabbing the symptomatic household member(s) at daily day 0 - 28, if this will be measured using swabs in household members then timepoint(s) will be specified in the intervention specific appendix

Exploratory parameters:
1. Emergence of mutations in causative pathogens in index cases and potentially in household members measured using combined pharyngeal/nasal swabs for participants swabs that are taken at Day 0, 4, 7 and 14 can be used, if this will be measured in household members then timepoint(s) will be specified in the intervention specific appendix
2. 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) measured using interviews either remotely (by telephone or online 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
3. Healthcare professionals' views and experience 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) measured using interviews either remotely (by telephone or online or in person as appropriate). 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.
4. Patient views and experiences of taking part in the trial and trial interventions, including how they conceptualise their illness and recovery (qualitative study) measured using interviews either remotely (by telephone or online or in person as appropriate). 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).

Previous secondary outcome measures:
Secondary study parameters/endpoints include:
1. Time to first self-report of return to usual daily activity (days), measured using self-report until the end of the study
2. Presence and severity of COVID-19 or COVID-like-illness 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, other) as: absent, mild, moderate, severe, measured using a daily diary at day 0-28.
3. Participant-reported overall wellbeing, reported by rating of how well participant feels (scale 0-10) at day 0-28, and after 3 months and 6 months
4. Possible side effects of the IP measured using a daily diary at day 1-28
5. Evaluation of overall safety of the IP by monitoring of AEs for the duration of IP administration and a defined period after the IP administration finishes. The duration of investigational product administration is dependent on the investigational product and will be specified in the intervention specific appendix, for the selected IPs only side effects will be measured, as safety data are already available.
6. Impact on usual daily activities (work/education, caring for (grand-) children, household

activities, sports, social life), as: no, slight, moderate, severe, not applicable, measured at day 1-28, after 3 and 6 months
7. Complications (i.e. hospitalisation, death) measured using weekly diary at day 7, 14, 21 and 28 or Serious Adverse Event reporting during the entire duration of study participation
8. Healthcare utilisation for COVID-19 or COVID-like-illness (GP and hospital visits) measured using participant diary at day 1-28, months 3 and 6
9. 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) measured using a follow-up call or electronic questionnaire after 3 and 6 months
10. The incidence of COVID-19 and COVID-like-illness in other members of the household, measured using participants' diaries and/or swabbing the symptomatic household member(s) at daily day 0 - 28, if this will be measured using swabs in household members then timepoint(s) will be specified in the intervention specific appendix

Exploratory parameters:
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3. Healthcare professionals’ views and experience 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) measured using interviews either remotely (by telephone or online or in person as appropriate). 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.
4. Patient views and experiences of taking part in the trial and trial interventions, including how they conceptualise their illness and recovery (qualitative study) measured using interviews either remotely (by telephone or online or in person as appropriate). 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).

Completion date
30/11/2026

Eligibility

Key inclusion criteria

Current key inclusion criteria as of 13/01/2026:
In order to be eligible to participate in ECRAID-Prime, a participant must (at least) meet all the following criteria (there can be additional intervention-specific inclusion 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 investigational product, then this will be described and justified in the relevant, approved intervention-specific appendix
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 a medically qualified clinician or research nurse that the illness is due to COVID-19 or COVID-like illness
4. Onset of symptoms less than x days (x will be specified in the intervention-specific appendix)
5. Willing and able to give informed consent for participation in the study
6. Willing and able to comply with all trial procedures
7. Any additional eligibility criteria relevant to women of child-bearing potential including current pregnancy or breastfeeding will be specified in the intervention-specific appendix

Previous key inclusion criteria:
In order to be eligible to participate in ECRAID-Prime, a participant must (at least) meet all the following criteria (there can be additional intervention-specific inclusion 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 investigational product, then this will be described and justified in the relevant, approved intervention-specific appendix
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 a medically qualified clinician or research nurse that the illness is due to COVID-19 or COVID-like illness
4. Onset of symptoms less than 7 days (in case earlier treatment is required for a specific investigational product, this will be specified in the intervention-specific appendix)
5. Willing and able to give informed consent for participation in the study
6. Willing and able to comply with all trial procedures
7. Any additional eligibility criteria relevant to women of child-bearing potential including current pregnancy or breastfeeding will be specified in the intervention-specific appendix

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
150 years

Sex
All

Total final enrolment
0

Key exclusion criteria
Current key exclusion criteria as of 13/01/2026:
A potential participant who meets any of the following criteria will be excluded from participation in ECRAID-Prime (there can be additional intervention-specific exclusion criteria).
1. Requiring admission to the hospital on the day of screening, or inclusion
2. Known allergies or hypersensitivities to any of the components used in the formulation of the investigational product, placebo or the comparator product
3. Any disease, condition, or disorder that precludes participation in the trial, in the opinion of the person checking eligibility and taking consent
4. Any planned major surgery in the next 28 days
5. Currently participating in a trial of an investigational product
6. Any personnel involved in the study

Previous key exclusion criteria:
A potential participant who meets any of the following criteria will be excluded from participation in ECRAID-Prime (there can be additional intervention-specific exclusion criteria).
1. Requiring admission to the hospital on the day of screening, or inclusion
2. Known allergies or hypersensitivities to any of the components used in the formulation of the investigational product, or the control product
3. Any disease, condition, or disorder that precludes participation in the trial, in the opinion of the person checking eligibility and taking consent
4. Any planned major surgery in the next 28 days
5. Currently participating in a trial of an investigational product

Date of first enrolment
03/10/2024

Date of final enrolment
31/03/2026

Locations

Countries of recruitment
United Kingdom

Belgium

France

Georgia

Germany

Ireland

Netherlands

Poland

Spain

Study participating centre
Nuffield Department of Primary Care Health Sciences, University of Oxford
Gibson Building 1st floor
Radcliffe Observatory Quarter
Woodstock Road
Oxford
England
OX2 6GG

Study participating centre
Honiton Surgery
Marlpits Lane
Honiton
England
EX14 2NY

Study participating centre
Melrose Surgery
73 London Road
Reading
England
RG1 5BS

Study participating centre
Bovey Tracey and Chudleigh Medical Practice
Riverside Surgery, Le Molay, Littry Way
Bovey Tracey
England
TQ13 9QP

Study participating centre
Banbury Cross Health Centre
South Bar House
6 Oxford Road
Banbury

England
OX16 9AD

Study participating centre
St. Bartholemews Medical Centre
Manzil Way
Oxford
England
OX4 1XB

Study participating centre
Bicester Health Centre
The Health Centre
Coker Close
Bicester
England
OX26 6AT

Study participating centre
Gosford Hill Medical Centre
167 Oxford Road
Kidlington
England
OX5 2NS

Study participating centre
The White Horse Medical Practice
The Faringdon Medical Centre
Volunteer Way
Faringdon
England
SN7 7YU

Study participating centre
Hedena Health
207 London Road
Headington
Oxford
England
OX3 9JA

Study participating centre
Huisartsenpraktijk Pairon Muyldermans
-
Schilde
Belgium
2970

Study participating centre
Artsenpraktijk Waarloos
Grote Steenweg 47
Kontich
Belgium
2550

Study participating centre
Medisch Huis Ter Linden
Strijdersstraat 20
Edegem
Belgium
2650

Study participating centre
Hausärztliche Gemeinschaftspraxis Jung/Marold/Beetz
Hauptstraße 12
Gössenheim
Germany
97780

Study participating centre
CAP Mas Font
Passeig de la Marina, 2
Viladecans, Barcelona
Spain
08840

Study participating centre
CAP Alhambra
C/ de l'Alhambra, 20
L'Hospitalet de Llobregat, Barcelona

Spain
08902

Study participating centre
CAP Vila Vella
Carretera de Sant Boi, 0
Sant Vicenç dels Horts, Barcelona
Spain
08620

Study participating centre
GPs at Tallaght Cross
3rd Floor, Russell Centre, Tallaght Cross West
Tallaght, Dublin 24
Ireland
D24DH74

Sponsor information

Organisation
University Medical Center Utrecht

ROR
https://ror.org/0575yy874

Funder(s)

Funder type
Government

Funder Name
European Union

Results and Publications

Individual participant data (IPD) sharing plan
Descriptive metadata will be made fully open through a cohort browser. Controlled access, participant-level data will be made available through a controlled access data platform.

Restricted access, participant-level data will be made available to internal partners (e.g., statisticians at participating institutions) within the ECRAID-Prime internal network through the UMCU data warehouse infrastructure. Restricted access participant-level data that includes individual identifiers (e.g., birth date) will not be made openly accessible in line with national, European and international legal, ethical and privacy concerns and to ensure that data sharing complies with the GDPR.

IPD sharing plan summary

Stored in non-publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 5.0	22/03/2024	09/10/2024	No	No
Protocol file	ISA A version 4.0	22/03/2024	09/10/2024	No	No
Protocol file	ISA B version 4.0	22/03/2024	09/10/2024	No	No
Protocol file	ISA C version 4.0	22/03/2024	09/10/2024	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes