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A pilot, randomized, open-label, non-active comparator controlled clinical trial to evaluate the effects of letermovir prophylaxis on T-cell immune activation in participants with treated HIV-1 Infection

Submission date
10/08/2023

Registration date
15/12/2023

Last Edited
07/10/2026

Recruitment status
Recruiting

Overall study status
Ongoing

Condition category
Infections and Infestations

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

Plain English summary of protocol
Background and study aims
People living with HIV (PLWH), even with an undetectable viral load (VL) on antiretroviral treatment (ART), develop health conditions, such as heart disease, diabetes, various cancers, and conditions that can affect the brain, more commonly than the general population. These conditions occur earlier in PLWH compared to HIV negative individuals with similar lifestyles. Ongoing inflammation in the body despite antiretroviral therapy is thought to be contributing to the development of these conditions that can affect healthy ageing in PLWH.
Cytomegalovirus (CMV) is a very common infection in PLWH and is an important driver of inflammation in the body that can affect the function of the immune immune cells in the body (defense system) causing unwanted activation and damage of the gut making it more leaky. A drug with potent activity against CMV called valganciclovir has previously shown to reduce this potentially damaging inflammation in the body.
In this study, we want to investigate if a new drug called Letermovir, in combination with HIV treatment, will prevent CMV from replicating (multiplying), and thereby reduce inflammation in the body. Letermovir has received approval to prevent CMV from multiplying in patients receiving bone marrow transplants. It has been shown to have a more favourable side-effect profile compared to other available drugs and is predicted to interact little with anti-HIV drugs. The aim of this study is to find out if the letermovir is safe and effective in reducing CMV related immune activation and inflammation PLWH. These findings will be used to help us design larger studies to identify individuals who would benefit most from this treatment to prevent the development of health conditions that can affect their quality of life.

Who can participate?
Patients aged 50 years or older, HIV-1 antibody positive for over 12 months.

What does the study involve?
Not provided at time of registration

What are the possible benefits and risks of participating?
Benefits:
Not provided at time of registration
Risks:
ADVERSE REACTIONS:
As with all clinical studies of drugs in development, participants may experience adverse reactions to Letermovir. Individual drug specific precautions with regards to participant eligibility, dose modifications and stopping rules have been implemented in the protocol to minimise potential risks to participants. Participants will be carefully monitored for adverse events at each visit. Monitoring will include patient reported symptoms, and changes in examination or laboratory findings. Participants will be informed of the known side effects (see participant information leaflet) prior to agreeing to take part in the study, and this will be updated as and when new information becomes available. All participants who discontinue or withdraw from the study will be followed up for a period of 14 days after cessation of study drug for any new or continuing serious clinical adverse experiences.

Blood Sample and IV (Venepuncture)
For biomedical research, risks to the participant have been minimized. Risks include those associated with venepuncture to obtain the whole blood specimen. These specimens will be obtained at the time of routine blood specimens drawn in the main trial. Phlebotomy is routinely carried out by appropriately trained staff and is associated with minimal discomfort. Participants will be informed of the possibility of discomfort, bruising or haematoma at the site of needle entry.

Biopsy:
Colorectal biopsy is a routinely performed procedure undertaken by appropriately trained medical staff and commonly performed as a day case. Like any invasive procedure potential risks include, bleeding, perforation (1 in 5000) and difficulty with urination. However, these risks are very rare, and participants will be informed of these risks prior to the procedure and provide written informed consent.

Contraception:
It is not known if the study drug may affect an unborn or nursing baby. Participants who are pregnant, trying to become pregnant or breast-feeding, may not participate in the study. The study doctor will perform a blood or urine pregnancy test before the start of and during the study, for females who are able to have a baby. Female participants will need to practice appropriate contraception methods. Male participants must agree not to donate sperm during this time. If a female participant becomes pregnant or a male participant impregnates his female partner during the study, the pregnancy must be immediately reported to the Sponsor and followed to outcome.

Where is the study run from?
University College London (UK)

When is the study starting and how long is it expected to run for?
August 2026 to February 2029

Who is funding the study?
Merck Sharp & Dohme (UK)

Who is the main contact?
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Contact information

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Scientific

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Clinical Trials Information System (CTIS)
2020-000288-22

Integrated Research Application System (IRAS)
1006176

Central Portfolio Management System (CPMS)
60394

Protocol serial number
125096

Study information

Scientific Title
A pilot, randomized, open-label, non-active comparator controlled clinical trial to evaluate the effects of letermovir prophylaxis on T-cell immune activation in participants with treated HIV-1 Infection

Acronym
PROACTIV TRIAL

Study objectives
Primary objective:
To compare changes in peripheral CD8 T-cell activation in the letermovir treated versus comparator group from baseline to week 12

Secondary objectives:
1. To assess the durability of CD8 T-cell activation changes in the off- trial drug follow-up period
2. To assess changes in intestinal epithelium integrity, CMV DNA and HIV-1 replication in the gut at weeks 0, 12 and 24 in the letermovir versus comparator group.
3. To assess and compare changes in CD8 T cell activation and other components of adaptive and innate immunity i.e. CD4 T cells and Natural Killer (NK) cells, in blood at weeks 0, 4, 8, 12, 16 and 24 and in the gut from available colorectal biopsies at weeks 0, 12 and 24 in the letermovir treated versus comparator group
4. To assess changes in the levels of systemic inflammatory biomarkers at weeks 0, 4, 8, 12, 16, and 24 between the two groups
5. To assess changes in CMV DNA levels in blood and saliva at weeks 0, 4, 8, 12, 16
6. To assess the tolerability of letermovir in treated HIV-1 infection

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 14/12/2023, West of Scotland REC 1 (West of Scotland Research Ethics Service, Paisley, PA2 7DE, United Kingdom; +44 141 314 0212; WosRec1@ggc.scot.nhs.uk), ref: 23/WS/0137

Primary study design
Interventional

Study design
Interventional randomized controlled trial

Study type(s)
Safety

Health condition(s) or problem(s) studied
Human immunodeficiency virus 1

Interventions
This is a randomized, parallel, and controlled, open-label clinical trial. A 1:1 randomisation procedure will assign the participant to receive either letermovir 480mg PO OD (letermovir oral formulation of 240mg), or no additional intervention, as per standard care for 12 weeks with a further 12 weeks of follow-up, off trial drug. Biopsies will be taken at Day 1, Week 12 and Week 24. Blood sampling at each visit.

All participants will remain on their baseline ART regimen (standard treatment) throughout the trial. Randomized participants will receive a 4-week supply of trial medication on Day 1 (Visit 2). Participants will be instructed to take their first dose of all trial medication at least within 24 hours of the Day 0 trial visit. Participants on the letermovir arm will be instructed to take letermovir 480 mg once a day orally, with or without food, at approximately the same time each day for 12 weeks with a further 12 weeks of follow-up, off trial drug.

Sealed EnvelopeTM web-based randomisation system will be used. Block randomisation will be used. Investigators randomise patients by completing an on-screen form with patient details, stratification factors, inclusion and exclusion criteria. Investigators are immediately shown the treatment allocation.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Prevymis [Letermovir]

Primary outcome(s)
Percentage of activated CD8 T cells (CD38+HLADR+) measured in PBMC in response to letermovir at baseline, weeks 4, 8, 12, 16 and 24

Key secondary outcome(s)
1. The change in the off-study drug period between week 12 and week 24 in the percentage of activated CD8 T cells (CD38+HLADR+) measured in PBMC.
2. The number and percentage of activated CD4 and CD8 T cells (CD38+HLADR+) measured in PBMCs at weeks 0, 4, 8, 12, 16 and 24
3. The number and percentage of activated CD4 and CD8 T cells (CD38+HLADR+) measured in colorectal biopsies at weeks 0, 12 and 24

4. Markers of immune activation, in CD8 and CD4 T cell subsets and NK cells, measured in PBMC at weeks 0, 4, 8, 12, 16 and 24
5. Markers of immune activation, as above measured in colorectal biopsies at weeks 0, 12 and 24
6. Markers of soluble inflammatory markers, namely IL-1, IL-6, IP-10, TNF-α, sTNFRII, LPS, sCD14, CRP, iFABP, sICAM-1, sVCAM-1, measured in plasma at weeks 0, 4, 8, 12, 16 and 24.
7. Quantification of CMV DNA levels in blood and saliva measured at weeks 0, 4, 8, 12, 16 and 24.
8. Levels of CMV DNA, HIV-1 RNA and intestinal tight junction integrity measured in colorectal biopsies at weeks 0, 12 and 24.
9. Safety defined as Adverse Events and Serious Adverse Events by group

Completion date
01/02/2029

Eligibility

Key inclusion criteria
1. Is HIV-1 antibody positive with a plasma HIV-1 RNA ≤50 copies/mL for greater than 12 months
2. ≥50 years of age of any gender
3. Females of childbearing potential who agree to avoid pregnancy for the duration of the trial and follow methods of contraception as detailed in section 7.1
4. Has a nadir CD4 of ≤200 cells/mm3 prior to screening
5. Has been on antiretroviral therapy for ≥ 6 months
6. Has documented CMV IgG seropositivity within one year of trial screening
7. Has an undetectable (≤168 international units/mL) CMV Deoxyribonucleic acid (DNA) within 14 days prior to randomisation
8. Laboratory parameters are not clinically significant as determined by the investigator
9. The participant (or legally acceptable representative, if applicable) has provided written informed consent for the trial and Future Biomedical Research

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
50 Years

Upper age limit
100 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Has a history of ulcerative colitis or Crohn’s disease or active colitis within 6 months prior to randomisation
2. Has a history of CMV end-organ disease within 6 months prior to randomisation
3. Has significant hypersensitivity or other contraindication to any of the components of the trial drug as described in the SmPC
4. Has a detectable HCV RNA or hepatitis B surface antigen (HBsAg) within 90 days prior to randomisation
5. Has a history of malignancy ≤5 years prior to signing informed consent
6. Is pregnant or expecting to conceive, is breastfeeding, or plans to breastfeed from the time of consent through 90 days after the last dose of trial therapy
7. Has received within 7 days prior to screening any of the following: ganciclovir; valganciclovir; foscarnet; acyclovir (≥ 3200 mg PO per day or ≥25 mg/kg IV per day); valaciclovir (≥3000 mg PO per day) or famciclovir (≥1500 mg PO per day).
8. Has used systemic immunosuppressive therapy or immune modulators within 30 days prior to treatment in this trial or is anticipated to need them during the trial

Date of first enrolment
07/10/2026

Date of final enrolment
01/07/2028

Locations

Countries of recruitment
United Kingdom

Study participating centre
-
-
-
England
-

Sponsor information

Organisation
University College London

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Industry

Funder Name
Merck Sharp and Dohme

Alternative Name(s)
MSD United Kingdom, Merck Sharp & Dohme, Merck Sharp & Dohme Corp., MSD

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Data sharing statement to be made available at a later date