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A trial to understand how a new formulation of flucytosine works in the body among people with early cryptococcal disease

Submission date
31/01/2024

Recruitment status
Recruiting

Registration date
07/02/2024

Overall study status
Ongoing

Last Edited
13/11/2024

Condition category
Infections and Infestations

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

Plain English summary of protocol

Background and study aims

Cryptococcal disease is caused by a fungus called Cryptococcus which is breathed into the lungs and can then spread into the bloodstream. The standard initial treatment for early cryptococcal disease is 2 weeks of a medicine called fluconazole usually taken as a pill/tablet by mouth. If not picked up in time or if not properly treated, cryptococcal disease can spread from the bloodstream and develop into a more serious brain infection called cryptococcal meningitis. Cryptococcal meningitis is a common and severe form of meningitis. The aim of this study is to develop improved treatments for cryptococcal disease in people who do not show any symptoms of the more serious brain infection.

Another study called EFFECT is testing whether combined treatment with fluconazole for 2 weeks plus another medicine called flucytosine is effective at treating early cryptococcal disease. There is already good evidence that combining these two drugs is an effective treatment for patients diagnosed with cryptococcal meningitis (brain infection). The study is investigating whether the combination also prevents meningitis from developing in people who have cryptococcal disease (in the blood only) but do not yet have meningitis (brain infection). Both drugs are taken by mouth. However, flucytosine must be taken 4 times per day (every 6 hours), which is a challenge.

This study called 5FC PROTECT is investigating a new flucytosine formulation, using the same active ingredient at a higher concentration, for the treatment of early cryptococcal disease. The researchers are doing this study to see whether cryptococcal disease can be effectively treated with this new sustained release (SR) flucytosine formulation which stays in the body longer and permits the medicine (in the form of a sachet of dissolvable pellets) to be taken twice a day, instead of four times a day. They have already shown that a single dose of this new formulation is acceptably safe in healthy volunteers. They are now testing whether this new formulation of flucytosine in combination with fluconazole, is effective and safe in patients with early cryptococcal disease. At the end of the study, data will be used to inform cryptococcal treatment guidelines and help make the best and most practical treatments for cryptococcal disease available to patients in Africa.

Who can participate?
All adult patients aged 18 years or older living with advanced HIV who have early cryptococcal disease diagnosed for the first time at Khayelitsha and Mitchell's Plain Hospital, Cape Town, South Africa, or at affiliated local clinics, and who are referred to the trial site at the University of Cape Town to participate in this study.

What does the study involve?
Eligible participants will be treated with fluconazole (1200 mg once daily) plus sustained-release flucytosine (6 g twice daily) for 14 days. Fluconazole (800 mg daily) will be given to all participants for a further 8 weeks and fluconazole 200 mg daily thereafter as per national guidelines. Participants will be admitted overnight on day 1/2 and 7/8 for blood tests, contacted on working days of the first week by telephone for adherence counselling, seen at an outpatient clinic on day 15 and contacted by telephone at 1 month to determine survival status.

Where is the study run from?
The University of Cape Town (South Africa)

When is the study starting and how long is it expected to run for?
December 2023 to July 2026

Who is funding the study?
National Institute for Health and Care Research (UK)

Who is the main contact?
Prof. Nelesh Govender, neleshg@nicd.ac.za

Contact information

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
NIHR134342

Study information

Scientific Title
Population-pharmacokinetics, safety and tolerability of sustained-release flucytosine pellets for the treatment of asymptomatic cryptococcal antigen-positive individuals: a single-arm trial

Acronym
5FC PROTECT

Study objectives
The new formulation of flucytosine will reach effective drug levels in the blood of patients with cryptococcal antigenaemia but without signs and symptoms of meningitis, and that it will be safe, acceptable and well tolerated.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 18/07/2024, University of Cape Town Human Research Ethics Committee (E 53, Room 46, Old Main Building, Groote Schuur Hospital, Observatory, Cape Town, 7925, South Africa; +27 (0)21 406 6492; hrec-enquiries@uct.ac.za), ref: 136/2024

Study design
Single-centre interventional open-label single-arm population pharmacokinetics trial

Primary study design
Interventional

Study type(s)

Treatment

Health condition(s) or problem(s) studied
Individuals with advanced HIV disease, without symptoms of meningitis, who are blood-cryptococcal antigen-positive (CrAg) and cerebrospinal fluid (CSF) CrAg-negative or who decline lumbar puncture (LP)

Interventions
All participants will receive flucytosine (sustained-release, Viatris, 6 g twice per day, orally, in fasting conditions) plus fluconazole (1200 mg/day, orally) for 14 days. All participants will then receive fluconazole 800 mg daily to 10 weeks, and fluconazole 200 mg daily thereafter for a minimum of 12 months as per national guidelines. Antiretroviral treatment will be commenced on day 15 as per current guidelines.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Flucytosine, fluconazole

Primary outcome(s)
Area under the plasma concentration versus time curve for 5FC, and possibly 5FU, from dose administration until 24 h, AUC(0-24h))

Pharmacokinetics:
Plasma level concentrations of 5FC and metabolite 5FU

Population PK parameters for SR 5FC:
Depending on the final structural and stochastic population PK model, but e.g. for a two-compartment model the following primary PK parameters: apparent oral clearance (CL/F); absorption rate constant (ka); intercompartmental clearance (Q/F); central and peripheral volume of distribution (Vc/F and Vp/F, respectively). Identifiable between-subject variabilities and between-occasion variabilities on any of the primary PK parameters.

Exposure and target attainment:
1. Area-under-curve plasma concentration versus time for 5FC and 5FU, from the start of treatment to t, where t is the time of the last quantifiable concentration (AUC(0-t))
2. Area under the plasma concentration versus time curve for 5FC and 5FU, with extrapolation to infinity (AUC(0 ∞))
3. Maximum observed plasma concentration (Cmax) and Cmax at steady-state (Cmax,ss)
4. Time to maximum observed plasma concentration (tmax)
5. Minimum observed plasma concentration (Cmin) and Cmin at steady-state (Cmin,ss)
6. Average for 5FC and 5FU concentration during a dosing interval (AUC(0- t) / t)(Cav)
7. Fluctuation ([(Cmax-Cmin)/Cav])
8. Apparent initial and terminal elimination half-life (t½)
9. Time within a predefined therapeutic window for individually predicted 5FC plasma

concentrations (therapeutic monitoring boundaries of ≥20 mg/L and ≤100 mg/L) and time above the published MIC90 value of 8 mg/L Note: if quantifiable, all parameters will be estimated for both 5FC and 5FU

Key secondary outcome(s))
Tolerability and safety:
Proportions of participants developing clinical and laboratory-defined grade III/IV/V adverse events and treatment discontinuation due to AEs, measured using clinical assessments, laboratory tests, interviews and patient medical records up to day 30

Additional exploratory outcomes:
1. All-cause mortality at 2 and 4 weeks, measured using patient medical records and interviews
2. Development of symptomatic cryptococcal meningitis within the first 4 weeks, measured using patient medical records and interviews
3. Change in blood fungal antigen concentration measured using CrAg titre/CrAg semi-quantitative (SQ) assay score from baseline to 2 weeks post-treatmentinitiation
4. Acceptability and palatability of SR 5FC (taste, texture, flavour), measured using a participant questionnaire (visual analogue scale) on days 2, 8 and 15

Completion date
31/07/2026

Eligibility

Key inclusion criteria
1. Consecutive patients aged >=18 years
2. HIV-seropositive
3. CD4 count of <200 cells/µl
4. Serum/plasma CrAg test positive within the last 21 days
5. CSF CrAg test negative or LP not done (declined)
6. Willing to participate in the study

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
100 years

Sex
All

Key exclusion criteria
1. Prior episode of CM or cryptococcal antigenaemia
2. Pregnancy (confirmed by urine or serum pregnancy test) or breastfeeding
3. Women of childbearing potential who do not agree to use contraception during the study period.
4. Male participants (or their female partners of childbearing potential) who do not agree to use effective contraception during the study period.
5. Already taking high-dose fluconazole treatment (800-1200 mg/day) for ≥10 days
6. Known dihydropyridine dehydrogenase (DPD) deficiency
7. Previous serious reaction to flucytosine or fluconazole
8. Contraindicated concomitant medications including: cisapride and the class of antihistamines including terfenadine
9. HIV-seronegative
10. Clinical symptoms/ signs of symptomatic meningitis at any time since CrAg screening, i.e. a progressively severe headache OR a headache and marked nuchal rigidity OR a headache and vomiting OR seizures OR a Glasgow Coma Scale (GCS) score of <15
11. CSF positive for CM (i.e. positive microscopy with India Ink, culture, or CrAg test) at any time between the CrAg test and screening for eligibility
12. Jaundice
13. Participants <40 kg or BMI<16 (with severe signs of malnutrition)
14. History of radiotherapy
15. Additional serious or life-threatening disease or HIV-related complications or co-morbidities (notably, diseases affecting gastrointestinal tract and participants likely to die within 14 days from conditions other than cryptococcal disease) based on the opinion of the investigator
16. Absolute neutrophil count of <500 x 106/L on baseline blood testing
17. Platelets <50,000x106/L on baseline blood testing
18. Creatinine clearance; eGFR < 60 ml/min on baseline blood testing (calculation method Cockroft/Gault)
19. Hepatic impairment (transaminases >3x upper limit of normal) on baseline blood testing
20. Participants should be excluded in case of any severe medical or psychiatric condition that may increase the risk associated with trial participation or may interfere with the interpretation of trial results.
21. Late exclusion criteria: Microbiological evidence of CM on CSF if full CSF results are not available at randomisation (e.g. screening CSF CrAg negative but culture on the same sample later returns positive for CM)

Date of first enrolment
15/01/2024

Date of final enrolment
31/01/2026

Locations

Countries of recruitment
South Africa

Study participating centre

UCT Clinical Research Centre, Groote Schuur Hospital
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Sponsor information

Organisation
Wits Health Consortium (Pty) Ltd

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date.

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

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes