

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	<input type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
Registration date 07/02/2024	Overall study status Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
Last Edited 13/11/2024	Condition category Infections and Infestations	<input type="checkbox"/> Individual participant data <input checked="" type="checkbox"/> 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

Study website

<https://witsmycology.co.za/projects/projects.html>

Contact information

Type(s)

Principal Investigator

Contact name

Prof Nelesh Govender

ORCID ID

<https://orcid.org/0000-0001-7869-9462>

Contact details

1 Modderfontein Road
Sandringham
Johannesburg
South Africa
2131
+27 (0)11 555 0353
nelesh.govender@wits.ac.za

Type(s)

Principal Investigator

Contact name

Dr Sile Molloy

ORCID ID

<https://orcid.org/0000-0001-8847-2325>

Contact details

St George's University of London
London
United Kingdom
SW17 0RE
+44 (0)208 728 5613
smolloy@sgul.ac.uk

Type(s)

Scientific

Contact name

Dr Kyla Comins

ORCID ID

<https://orcid.org/0000-0002-3338-5862>

Contact details

Room 41, Floor F, Neuroscience Institute, Groote Schuur Hospital, Observatory
Cape Town
South Africa
7925
+27 (0)76 080 5005
kyla.comins@uct.ac.za

Type(s)

Public

Contact name

Mr Jack Adams

Contact details

St George's University of London
London
United Kingdom
SW17 0RE
+44 (0)208 725 5613
jadams@sgul.ac.uk

Type(s)

Principal Investigator

Contact name

Prof Nelesh Govender

ORCID ID

<http://orcid.org/0000-0001-7869-9462>

Contact details

1 Modderfontein Road
Sandringham
Johannesburg
South Africa
2131
+27 (0)11 555 0353
neleshg@nicd.ac.za

Additional identifiers**EudraCT/CTIS number**

Nil known

IRAS number**ClinicalTrials.gov number**

Nil known

Secondary identifying numbers

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

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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

Secondary study design

Non randomised study

Study setting(s)

University/medical school/dental school

Study type(s)

Treatment

Participant information sheet

Not available in web format. Please use contact details to request a participant information sheet

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, Viartis, 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

Pharmaceutical study type(s)

Pharmacokinetic

Phase

Phase II

Drug/device/biological/vaccine name(s)

Flucytosine, fluconazole

Primary outcome measure

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 (k_a); intercompartmental clearance (Q/F); central and peripheral volume of distribution (V_c/F and V_p/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 ($AUC(0-\infty)$)
3. Maximum observed plasma concentration (C_{max}) and C_{max} at steady-state ($C_{max,ss}$)
4. Time to maximum observed plasma concentration (t_{max})
5. Minimum observed plasma concentration (C_{min}) and C_{min} at steady-state ($C_{min,ss}$)
6. Average for 5FC and 5FU concentration during a dosing interval ($AUC(0-t) / t$) (C_{av})
7. Fluctuation ($[(C_{max}-C_{min})/C_{av}]$)
8. Apparent initial and terminal elimination half-life ($t_{1/2}$)
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

Secondary outcome measures

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-treatment initiation
4. Acceptability and palatability of SR 5FC (taste, texture, flavour), measured using a participant questionnaire (visual analogue scale) on days 2, 8 and 15

Overall study start date

01/12/2023

Completion date

31/07/2026

Eligibility

Key inclusion criteria

1. Consecutive patients aged ≥ 18 years
2. HIV-seropositive
3. CD4 count of < 200 cells/ μ l
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

Age group

Adult

Lower age limit

18 Years

Upper age limit

100 Years

Sex

Both

Target number of participants

36

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 $< 500 \times 10^6/L$ on baseline blood testing
17. Platelets $< 50,000 \times 10^6/L$ on baseline blood testing
18. Creatinine clearance; eGFR < 60 ml/min on baseline blood testing (calculation method Cockcroft/Gault)
19. Hepatic impairment (transaminases $> 3 \times$ 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

Room L51, Old Main Building, Observatory

Cape Town

South Africa

7925

Sponsor information

Organisation

Wits Health Consortium (Pty) Ltd

Sponsor details

31 Princess of Wales Terrace

Parktown

Johannesburg

South Africa

2193

+27 (0)11 274 9200

ceo@witshealth.co.za

Sponsor type

Research organisation

Website

<https://www.witshealth.co.za/>

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

Publication and dissemination plan

The results will be analysed and published as soon as possible after trial close. The Trial Management Group will form the basis of the Writing Committee and will advise on the nature of the publication. The names of all investigators who have contributed will be included in the authorship of any publication. The authorship policy will be agreed upon before any publication and will be inclusive and decided in a fair transparent manner. The members of the TSC and DMC will be listed with their affiliations in the Acknowledgements/Appendix of the main publication. The funders will have no role in the decision to publish or the content of the publication.

Intention to publish date

31/07/2027

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