

High dose fluconazole with or without flucytosine in the treatment of human immunodeficiency virus (HIV)-associated cryptococcal meningitis

Submission date 11/02/2008	Recruitment status No longer recruiting	<input type="checkbox"/> Prospectively registered
Registration date 20/03/2008	Overall study status Completed	<input type="checkbox"/> Protocol
Last Edited 05/01/2010	Condition category Infections and Infestations	<input type="checkbox"/> Statistical analysis plan
		<input checked="" type="checkbox"/> Results
		<input type="checkbox"/> Individual participant data

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
MRC (UK) ref: 76201; 1.0

Study information

Scientific Title

A randomised controlled clinical trial to evaluate high dose fluconazole with or without flucytosine in the treatment of human immunodeficiency virus (HIV)-associated cryptococcal meningitis

Study objectives

As of 27/02/2009 this record was updated to include the second phase Step 2 within this record. Ethics approval was extended to include this phase. All additions to this record regarding Step 2 can be found in the relevant field under the title Step 2. The titles for Step 2 are as follows:
Step 2 public title: High dose fluconazole with short course amphotericin B, with or without flucytosine in the treatment of human immunodeficiency virus (HIV)-associated cryptococcal meningitis

Step 2 scientific title: A randomised controlled clinical trial to evaluate high dose fluconazole with short course amphotericin B, with or without flucytosine in the treatment of human immunodeficiency virus (HIV)-associated cryptococcal meningitis

Please also note that the anticipated start and end dates for Step 2 are as follows:

Step 2 anticipated start date: 01/03/2009

Step 2 anticipated end date: 01/01/2010

At the time of registration, the initial trial dates reflected Step 1 of this trial, and therefore these have been amended to include the Step 2 dates as above; the initial end date (for Step 1) was 18/02/2009.

Step 1 hypothesis:

Addition of flucytosine to fluconazole will lead to more rapid sterilisation of cerebrospinal fluid (CSF) in cryptococcal meningitis.

Step 2 hypotheses:

1. In the presence of a short course of amphotericin B, the addition of flucytosine to fluconazole (1200 mg/d) will lead to more rapid sterilisation of cerebrospinal fluid (CSF) in cryptococcal meningitis
2. A short course of amphotericin B will avoid toxicity observed in longer courses of amphotericin B.

Ethics approval required

Old ethics approval format

Ethics approval(s)

1. Malawi National Health Sciences Research Committee approved on the 8th November 2007 (Step 2 amendment: 17th February 2009)
2. Wandsworth LREC (covering St Georges University of London UK) approved on the 8th January 2008 (Step 2 amendment: 13th February 2009)
3. Institutional review board (IRB) University of North Carolina at Chapel Hill approved on the 29th November 2007 (Step 2 amendment pending as of 26/02/2009)

Study design

Randomised open-labelled controlled trial

Primary study design

Interventional

Study type(s)

Treatment

Health condition(s) or problem(s) studied

Cryptococcal meningitis/ HIV

Interventions

Step 1:

1. Fluconazole 1,200 mg/d for two weeks
 2. Fluconazole 1,200 mg/d plus flucytosine 100 mg/kg/d for two weeks
- After two weeks all patients receive fluconazole 800 mg/d.

Step 2:

1. Amphotericin B 1 mg/kg daily for 7 days plus fluconazole 1200 mg/d (started concurrently) for 2 weeks
 2. Amphotericin B 1 mg/kg daily for 7 days, plus fluconazole 1200 mg/d, plus flucytosine 100 mg/kg/day (started concurrently) for 2 weeks
- After two weeks all patients receive fluconazole 800 mg/d.

Intervention Type

Drug

Phase

Not Applicable

Drug/device/biological/vaccine name(s)

Fluconazole, flucytosine

Primary outcome(s)

Early fungicidal activity (rate of clearance of infection) of alternative regimens over the first two weeks of therapy.

Key secondary outcome(s)

1. Clinical and laboratory side effects
2. Mortality at 2 and 10 weeks

Completion date

01/01/2010

Eligibility**Key inclusion criteria**

1. Patients greater than 18 years, either sex
2. A first episode of cryptococcal meningitis

Participant type(s)

Patient

Healthy volunteers allowed

No

Age group

Adult

Lower age limit

18 years

Sex

All

Key exclusion criteria

1. Alanine aminotransferase (ALT) greater than five times the upper limit of normal
2. Pregnancy or lactation
3. Previous serious reaction to study drugs
4. Taking systemic anti-fungals
5. Polymorphonuclear leukocytes (PMNs) less than $500 \times 10^6/L$
6. Platelets less than $50,000 \times 10^6/L$
7. Concomitant medication that is contraindicated with any study drugs
8. Already on antiretroviral therapy (ART)

STEP 2 additional criteria:

9. Initial creatinine greater than 2.5 mg/dl

Date of first enrolment

18/02/2008

Date of final enrolment

01/01/2010

Locations**Countries of recruitment**

United Kingdom

Malawi

Study participating centre

Cranmer Terrace

London

United Kingdom

SW17 ORE

Sponsor information**Organisation**

St George's University of London (UK)

ROR

<https://ror.org/040f08y74>

Funder(s)

Funder type

Research council

Funder Name

Medical Research Council (UK) (grant ID: 76201)

Alternative Name(s)

Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

Funding Body Type

Government organisation

Funding Body Subtype

National government

Location

United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/02/2010		Yes	No