ISRCTN10248064 https://doi.org/10.1186/ISRCTN10248064

AMBITION-cm: AMBIsome Therapy Induction OptimizatioN - Intermittent high dose AmBisome® on a high dose fluconazole backbone for cryptococcal meningitis induction therapy in sub-Saharan Africa

Submission date
25/11/2013

Recruitment status
No longer recruiting

Registration date
22/01/2014

Overall study status
Completed

Last Edited
05/03/2021

Condition category
Infections and Infestations

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
Cryptococcal meningitis is a leading cause of death in HIV-infected individuals in Africa. The current standard for initial treatment in developed countries is 2 weeks of amphotericin B-based therapy. The combination of the costs associated with prolonged hospital admissions, the difficulties in administration and the need for laboratory monitoring make amphotericin B deoxycholate treatment difficult in much of Africa. A modified form of amphotericin B is available called liposomal amphotericin B (AmBisome®). This is considerably less toxic than standard amphotericin B, and is known to be effective in the treatment of cryptococcal meningitis. Its use has been limited by the high cost of therapy, but recent data suggest that due to its lower toxicity, higher doses of AmBisome® can be given safely and much shorter courses may be effective in the treatment of cryptococcal meningitis. A large reduction in the number of doses and duration of hospitalisation, together with reduced pricing of AmBisome®, may result in cryptococcal meningitis treatment costs that are not more than the costs of 2 weeks of conventional amphotericin B, and provide a convenient, safe and effective alternative to conventional amphotericin B therapy. This study aims to define the most effective and most cost-effective schedules for AmBisome® use in the treatment of cryptococcal meningitis.

Who can participate?
The study population will be HIV-positive patients, over 18 years of age, with cryptococcal meningitis, at participating centres in Tanzania, Botswana and South Africa.

What does the study involve?
The study consists of two steps. The first step will test the safety and effectiveness of one-, two- or three-dose AmBisome® treatment regimens compared to the standard 14-day course. Patients will be randomly allocated to one of these four treatment strategies. The shortest of these AmBisome®regimens that is found to be safe and effective in step 1 will then be

continued in the larger step 2 trial, along with the standard 14-day course, to determine whether or not it is as effective as the standard treatment in terms of preventing deaths from cryptococcal meningitis. All patients will also receive fluconazole, and antiretroviral therapy for HIV will be started 4-6 weeks after initiation of antifungal therapy.

What are the possible benefits and risks of participating?
Patients enrolled in the study will benefit from access to essential antifungal drugs that may otherwise not be available to them, and expert medical care from clinicians experienced in the management of cryptococcal meningitis. Patients will undergo lumbar punctures (in which a needle is inserted into the lower part of the spine) at study days 1, 3, 7 and 14. Any potential discomfort will be eased by experienced clinicians performing the procedure and, of course, adequate pain relief. There is potential risk of toxicity due to the high dose AmBisome®; however, a high dose has been used extensively in patients in other studies. Toxicity will be very closely monitored. It is more likely that study participants will benefit from the reduced toxicity profile of the shorter course AmBisome® regimens, and may also be able to benefit from shorter hospital stays and avoid the complications associated with multiple intravenous infusions.

Where is the study run from?
The study will be sponsored by St George's University of London. One Chief Investigator will be based at Princess Marina Hospital, Gaborone, Botswana and the second at St George's University of London. Patients will be recruited at sites in Tanzania, Botswana and South Africa.

When is the study starting and how long is it expected to run for?
The study will begin in June 2014 with Step 1 and run for 2 years. Step 2 will recruit for a further 2 years based on the results of step 1.

Who is funding the study?
Step 1 is funded by Gilead (UK).
Step 2 is funded by EDCTP. Step 2 has now been registered separately, please see ISRCTN72509687.

Who is the main contact?
Dr Joe Jarvis
joejarvis@doctors.org.uk

Contact information

Type(s)
Scientific

Contact name
Prof Thomas Harrison

Contact details
St George's, University of London
Cranmer Terrace
London
United Kingdom
SW17 0RE

Additional identifiers

Protocol serial number
13.0204 (Sponsor number)

Study information

Scientific Title
Intermittent high dose AmBisome® on a high dose fluconazole backbone for cryptococcal meningitis induction therapy in sub-Saharan Africa: An adaptive randomized controlled non-inferiority trial

Acronym
AMBITION-cm

Study objectives
Short-course high-dose AmBisome® given with high dose fluconazole will be non-inferior to 2 weeks daily-dosed AmBisome® based induction therapy for the treatment of HIV-associated cryptococcal meningitis.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. UK: London School of Hygiene and Tropical Medicine Research Ethics Committee, approval granted 10/02/2014
2. Botswana: Princess Marina Hospital REC, Health Research Development Committee, Ministry of Health, approval granted 29/06/2014; Health Research Development Committee (HRDC), approval granted 29/07/2014
3. Tanzania: Bugando Medical Centre/Catholic University of Health and Allied Sciences (BMC /CUHAS) Research Ethics Committee, approval granted 08/03/2014; National Institute for Medical Research, 29/12/2014

Primary study design
Interventional

Study design
Adaptive open-label phase II/III randomised non-inferiority trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
HIV-associated cryptococcal meningitis

Interventions
Current interventions as of 24/10/2017:
A trial to compare alternative short course AmBisome® (amphotericin) regimens for the treatment of HIV-associated cryptococcal meningitis.

STEP 1 (EFA endpoint, phase II):
Patients will be randomised into one of four alternative treatment strategies for the initial treatment of HIV-associated cryptococcal meningitis.
1. AmBisome® 10 mg/kg day 1 (single dose)
2. AmBisome® 10 mg/kg day 1, AmBisome® 5 mg/kg day 3 (two doses)
3. AmBisome® 10 mg/kg day 1, AmBisome® 5 mg/kg days 3, and 7 (three doses)
4. AmBisome® 3 mg/kg/d for 14 days (standard dose, 'control arm')

STEP 2 (clinical endpoint, Phase III):

1. L-AmB 10 mg/kg day 1 (“single dose”) given with fluconazole 1200mg/day plus flucytosine 100mg/kg/d for 14-days.
2. Amphotericin B deoxycholate 1 mg/kg/d for 7-days given with flucytosine 100mg/kg/d (standard dose, “control arm”) followed by fluconazole 1200mg/day for 7-days.
All patients also receive fluconazole 1200 mg/d for first 2 weeks, then 800 mg/d until 10 weeks, and 200 mg/d thereafter. ART will be commenced 4-6 weeks after initiation of antifungal therapy.

Previous interventions:
A trial to compare alternative short course AmBisome® (amphotericin) regimens for the treatment of HIV-associated cryptococcal meningitis.

STEP 1 (EFA endpoint, phase II):
Patients will be randomised into one of four alternative treatment strategies for the initial treatment of HIV-associated cryptococcal meningitis.
1. AmBisome® 10 mg/kg day 1 (single dose)
2. AmBisome® 10 mg/kg day 1, AmBisome® 5 mg/kg day 3 (two doses)
3. AmBisome® 10 mg/kg day 1, AmBisome® 5 mg/kg days 3, and 7 (three doses)
4. AmBisome® 3 mg/kg/d for 14 days (standard dose, 'control arm')

STEP 2 (clinical endpoint, Phase III):
1. The shortest course AmBisome® regimen tested in STEP 1 (either regimen 1, 2 or 3 above) meeting pre-defined safety and efficacy criteria and selected by the Trial Steering Committee for further study ('short course')
2. AmBisome® 3 mg/kg/d for 14 days (standard dose, 'control arm')

All patients also receive fluconazole 1200 mg/d for first 2 weeks, then 800 mg/d until antiretroviral therapy (ART) started, then 400 mg/d until 10 weeks, and 200 mg/d thereafter. ART will be commenced 34 weeks after initiation of antifungal therapy.

Intervention Type
Drug

Phase
Phase II/III

Drug/device/biological/vaccine name(s)
AmBisome® (amphotericin)

Primary outcome(s)

Current primary outcome measures as of 24/10/2017:
STEP 1: Early Fungicidal Activity (EFA) in the first 2 weeks of treatment
STEP 2: all-cause mortality within the first 10 weeks after randomization (non-inferiority)

Previous primary outcome measures:
STEP 1: Early Fungicidal Activity (EFA) in the first 2 weeks of treatment
STEP 2: All-cause mortality in the first 14 and 70 days after randomization

Key secondary outcome(s)
Current secondary outcome meaures as of 24/10/2017:
Step 1:
1. Pharmacokinetic (PK) parameters and Pharmacokinetic/Pharmacodynamic (PK/PD) associations of alternative schedules of intermittent high dose Ambisome.
2. Proportion of patients in each arm suffering clinical and laboratory-defined grade iii/iv adverse events; median % change from baseline in laboratory-defined parameters by treatment arm.
3. Health service costs by treatment arm.

Step2:
1. Early Fungicidal Activity
2. Proportions of patients developing clinical and laboratory-defined grade III/IV adverse events; median % change from baseline in laboratory defined parameters
3. PK parameters and PK/PD associations
4. Health service costs by treatment arm
5. All-cause mortality within the first 2 and 4 weeks
6. All-cause mortality within the first 10 weeks (superiority)
7. Rates of cryptococcal relapse / IRIS within the first 10 weeks
8. Disability at 10 weeks

Previous secondary outcome measures:
1. Pharmacokinetic (PK) parameters and Pharmacokinetic/Pharmacodynamic (PK/PD) associations of alternative schedules of intermittent high dose Ambisome.
2. Proportion of patients in each arm suffering clinical and laboratory-defined grade iii/iv adverse events; median % change from baseline in laboratory-defined parameters by treatment arm.
3. Health service costs by treatment arm.

Completion date
30/11/2017

Eligibility

Key inclusion criteria
1. Consecutive patients (male and female) aged > 18 years with a first episode of cryptococcal meningitis (CSF India ink or CrAg test)
2. Known to be HIV positive or willing to undertake an HIV test
3. Willing to agree to participate in the study

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
80

Key exclusion criteria
1. Pregnancy or lactation
2. Previous serious reaction to study drugs
3. Already taking antifungals for >48 hours
4. Concomitant medication that is contraindicated with study drugs

Date of first enrolment
01/11/2014

Date of final enrolment
22/08/2017

Locations

Countries of recruitment
United Kingdom

England

Botswana

South Africa

Tanzania

Zimbabwe

Study participating centre
St George's University of London
London
United Kingdom
SW17 0RE

Sponsor information

Organisation
St George's University of London (UK)

ROR
https://ror.org/040f08y74

Funder(s)

Funder type
Industry

Funder Name
Gilead (UK) - Investigator Initiated Award (Step 1)

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	18/01/2019	10/03/2020	Yes	No
Protocol article	protocol	17/06/2015		Yes	No