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Combination antifungal therapy for candida bloodstream infections

Submission date
11/12/2025

Recruitment status
Not yet recruiting

Registration date
19/12/2025

Overall study status
Ongoing

Last Edited
25/11/2026

Condition category
Infections and Infestations

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

Plain English summary of protocol
Background and study aims
The COMBAT Candida trial will investigate whether combination therapy with two licensed drugs (micafungin and flucytosine) is better than micafungin alone for the treatment of patients with Candida Bloodstream Infections (BSI) at 5 hospitals in Johannesburg, South Africa. These drugs have been chosen because micafungin is internationally recommended as the first-line treatment of this infection, and the addition of flucytosine has been shown to improve fungal killing in laboratory experiments. Flucytosine is also used in combination therapy for another severe fungal infection, HIV-associated cryptococcal meningitis, where it has been shown to be safe and effective through randomised trials.

Who can participate?
Patients who have Candida BSI at the trial sites will be invited to participate. If they do not have the capacity to make a decision about participation at the time of enrolment, informed consent will be obtained retrospectively from them at the earliest opportunity when they regain capacity and following provision of proxy consent. Proxy consent will be requested from their next of kin, a family member, or an independent clinician. If consent is provided, the participant will be randomly assigned to receive either micafungin alone (standard care) or micafungin plus flucytosine (the trial intervention) for two weeks after their blood is clear of Candida.

What does the study involve?
During the first phase of the trial, participants will be assessed for eligibility using specified inclusion and exclusion criteria. Participants will then be randomised to a control or one or two intervention arms. Those in the intervention arms will be randomised to receive either a standard dose of flucytosine (100 mg/kg daily) or a half measure of this dose (50 mg/kg daily). The levels of flucytosine in the blood will then be measured and the lower dose will be selected to be used in the next phase of the trial providing that the first phase shows that sufficient blood levels are achieved with this dose to kill the Candida.

During the second phase of the trial, there will be two arms of the trial: micafungin alone (the internationally recommended treatment), or micafungin plus flucytosine at the selected dose from phase 1. Success of each treatment arm of the trial will be measured by assessing survival of participants during the 30 days after enrolment into the study, how effectively the blood is

cleared of Candida, whether the Candida infection persists on treatment or relapses following treatment, and whether antifungal resistance emerges in any Candida identified growing on the body (by using swabs of nose, mouth, hands, armpits, groins, and skin between the buttocks).

What are the possible benefits and risks of participating?
Benefits not provided at registration.

The independent Data Monitoring Committee (DMC) will closely monitor the trial. Risks associated with the combination of micafungin and flucytosine are expected to be low, and this combination is already recommended in international guidelines for complex invasive candidiasis and for the treatment of cryptococcal meningitis. Both drugs are included in the South African and WHO Essential Medicine List (EML).

There are very few drug-drug interactions reported for either trial drug. For micafungin, co-administration of certain drugs may increase the risk of hepatotoxicity, and for flucytosine, co-administration may increase the risk of haemotological toxicity - both of which will be monitored closely. Patients will be excluded from participation if they are already taking cytarabine, which is the only contraindicated medication with flucytosine.

Where is the study run from?
Wits Health Consortium, South Africa.

When is the study starting and how long is it expected to run for?
January 2027 to January 2031.

Who is funding the study?
Wellcome Trust, UK.

Who is the main contact?
Nelesh Govender, Nelesh.Govender@wits.ac.za

Contact information

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Scientific, Public

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Study information

Scientific Title
Combination antifungal therapy with micafungin plus flucytosine vs. micafungin alone for adults with candida bloodstream infections: an open-label phase III randomised controlled trial

Acronym
COMBAT Candida

Study objectives
Current study objectives 16/06/2026:
Primary Objective

To determine whether combination treatment of micafungin plus flucytosine for 2 weeks following blood sterility is superior to standard treatment of micafungin monotherapy in improving clinical, mycological and resistance outcomes.

Secondary Objectives
To determine the following:
1. All-cause mortality at day 30 and 90;
2. Time to all-cause mortality within 30 and 90 days;
3. Proportion of participants who have a breakthrough of Candida BSI during treatment;
4. Proportion of participants who have a relapse of Candida BSI at day 14, EOT +5 days, day 30 and EOT +30days;
5. Time to blood culture sterility;
6. Time to micafungin resistance in colonising or invasive Candida spp;
7. Proportion of participants who have any micafungin resistance detected in any colonising or invasive Candida spp up until day 14, EOT+5 days, day 30;
8. Duration of ICU admission and hospitalisation;
9. Rate of change in fungal biomarkers (serum beta-D-glucan (BDG), blood Candida qPCR) up until day 30;
10. Proportion who develop grade 3 cytopaenias, other grade 4 adverse events and other serious adverse events (SAEs) up until EOT +5 days.

Exploratory outcomes
- Estimate of flucytosine % time > MIC and micafungin AUC/MIC of the infecting Candida spp to assess for any relationship between drug exposure and clinical / mycological outcomes.
- Flucytosine resistance % in infecting/colonising Candida species isolated from participants on combination therapy vs. monotherapy. Incidence of ocular complications of candidaemia through opthalmic assessment during the second week of treatment.

Previous study objectives:
Primary Objective
To determine whether combination treatment of micafungin plus flucytosine for 2 weeks following blood sterility is superior to standard treatment of micafungin monotherapy in improving clinical, mycological and resistance outcomes.

Secondary Objectives
To determine the following:
1. All-cause mortality at day 30 and 90;
2. Time to all-cause mortality within 30 and 90 days;
3. Proportion of participants who have a breakthrough of Candida BSI during treatment;
4. Proportion of participants who have a relapse of Candida BSI at day 14, EOT +5 days, day 30 and EOT +30days;
5. Time to blood culture sterility;
6. Time to micafungin resistance in colonising or invasive Candida spp;
7. Proportion of participants who have any micafungin resistance detected in any colonising or invasive Candida spp up until day 14, EOT+5 days, day 30;
8. Duration of ICU admission and hospitalisation;
9. Rate of change in fungal biomarkers (serum beta-D-glucan (BDG), blood Candida qPCR) up until day 30;
10. Proportion who develop grade 3 cytopaenias, other grade 4 adverse events and other serious adverse events (SAEs) up until EOT +5 days.

Ethics approval required

Ethics approval required

Ethics approval(s)
1. Approved 05/08/2026, South African Health Products Regulatory Authority (Head Office Building A, Loftus Park, 402 Kirkness Street, Arcadia, Pretoria, 0007, South Africa; +27 (0)12 501 0417; ayanda.sam@sahpra.org.za), ref: 20260522

2. Approved 01/09/2026, University of the Witwatersrand Human Research Ethics Commitee (Medical) (Faculty of Health Sciences, Phillip Tobias Building Offices 301-304, 3rd Floor, Corner York Road and 29 Princess of Wales Terrace, Parktown, Johannesburg, 2193, South Africa; +27 (0) 11 274 9200; jpalmer@witsethics.co.za), ref: 260506

Primary study design
Interventional

Allocation
Randomized controlled trial

Masking
Open (masking not used)

Control
Active

Assignment
Parallel

Purpose
Treatment

Study type(s)

Health condition(s) or problem(s) studied
Candida spp. Bloodstream Infections

Interventions
Current interventions as of 16/06/2026:
Step 1 – Dose-selection

Micafungin 100 mg/d IV plus flucytosine 50 mg/kg PO/NG (split QDS)
Micafungin 100 mg/d IV plus flucytosine 100 mg/kg PO/NG (split QDS)
Micafungin 100 mg/d IV – INTERNATIONAL FIRST-LINE STANDARD

Step 2 – Optimal dose

Micafungin 100 mg/d IV plus flucytosine either 50 mg/kg or 100 mg/kg PO/NG (split QDS) - INTERVENTION
Micafungin 100 mg/d IV – INTERNATIONAL FIRST-LINE STANDARD

For each arm:

- Oral switch to fluconazole 800 mg (or fluconazole plus flucytosine if in a combination arm) can be made if clinical improvement, bloodstream clearance of Candida and fluconazole susceptibility are confirmed after 7 days of treatment.
- Antifungals to be continued for 2 weeks following blood culture sterility

The intervention will be given for 14 days following the first of all subsequent blood cultures, which are negative for Candida spp taken during treatment (clearance of the initial +/- any breakthrough Candida BSI).

During Step 1 (dose-selection phase), plasma will be taken at 12 time points during the first week: 0.25, 0.5, 1, 2, 6, 24, 48, 72, 96, 120, 144, 168 hours, for the analysis of flucytosine and micafungin PK in participants of the intervention arms.

During both steps, blood will be drawn at baseline to check full blood count and differential (FBC), serum creatinine and alanine transaminase (ALT) and aspartate aminotransferase (AST) levels, then every 3-4 days for FBC and ALT/AST up until EOT +5 days. Blood cultures will be taken at baseline (0h), 12h, 24h, 36h, 48h (each timepoint within a window of +/- 6 hours, but at least 6 hours apart) after treatment is started and 12 hourly as per this schedule until 2 consecutive blood cultures are negative (for any bacterial or fungal growth) following >48 hours incubation (usually takes 1-2 days). Blood cultures will then be taken every day until day 7 and then every 3-4 days until 5 days after the end of treatment (EOT), to check for breakthrough (during treatment) or relapse (after treatment) of infection. Composite superficial swabs will be taken from commonly colonised body sites (i.e. nares/ oral, hands/ axillae/ groins and perianal skin) twice weekly until discharge from hospital, and during a study visit at day 30 (or within the following 7 days) after start of treatment for Candida culture and resistance testing. Participants will be followed up at least every 3 days during treatment until EOT + 5 days to record survival, any newly identified complications, grade 3 cytopenias, other grade 4 AEs and SAEs, and at 30 days (or within the following 7 days) and 90 days (or within the following 30 days), by phone call, to determine hospitalisation and survival status. A further pre-dose plasma level of micafungin and flucytosine will be taken along with safety bloods on day 1 and day 7.

Previous interventions:
A randomisation sequence was generated using a computer algorithm with permuted blocks stratified by site only.

Step 1 – Dose-selection

Micafungin 100 mg/d IV plus flucytosine 50 mg/kg PO/NG (split QDS)
Micafungin 100 mg/d IV plus flucytosine 100 mg/kg PO/NG (split QDS)
Micafungin 100 mg/d IV – INTERNATIONAL FIRST-LINE STANDARD

Step 2 – Optimal dose

Micafungin 100 mg/d IV plus flucytosine either 50 mg/kg or 100 mg/kg PO/NG (split QDS) - INTERVENTION
Micafungin 100 mg/d IV – INTERNATIONAL FIRST-LINE STANDARD

For each arm:

- Oral switch to fluconazole 800 mg (or fluconazole plus flucytosine if in a combination arm) can be made if clinical improvement, bloodstream clearance of Candida and fluconazole susceptibility is confirmed after 7 days of treatment.

- Antifungals to be continued for 2 weeks following blood culture sterility (a single blood culture negative for Candida is referred to as sterility throughout)

The intervention will be given for 14 days following the first blood culture which is negative for Candida spp taken during treatment (initial +/- any breakthrough Candida BSI).

During Step 1 (dose-selection phase), plasma will be taken at 12 time points during the first week: 0.25, 0.5, 1, 2, 6, 24, 48, 72, 96, 120, 148, 168 hours, for the analysis of flucytosine and micafungin PK in participants of the intervention arms.

During both steps, blood will be drawn at baseline to check full blood count and differential (FBC), serum creatinine and alanine transaminase (ALT) and aspartate aminotransferase (AST) levels, then every 3-4 days for FBC and ALT/AST up until EOT +5 days. Blood cultures will be taken at baseline (0h), 12h (+/-6h), 24h (+/-6h), 36h (+/- 6h), 48h (+/-6h) after treatment is started and 12 hourly as per this schedule until blood cultures are negative for >48 hours (usually takes 1-2 days), and then every 3-4 days until 5 days after end of treatment (EOT), to check for breakthrough (or relapse) of infection. Composite superficial swabs will be taken from commonly colonised body sites (i.e. nares/ oral, hands/ axillae/ groins and perianal skin) twice weekly until discharge from hospital, and during a study visit at day 30 after start of treatment for Candida culture and resistance testing. Participants will be followed at least every 3 days during treatment until EOT + 5days to record any grade 3 cytopenias, other grade 4 AEs and SAEs, and at 30 days and 90 days (by phone call, or visit if discharged from hospital) to determine hospitalisation and survival status. A further pre-dose plasma level of micafungin and flucytosine will be taken along with safety bloods on day 1 and day 7.

Intervention Type
Drug

Phase
Phase III

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

Primary outcome(s)
1. STEP 1 – Dose-selection: A target flucytosine exposure of >45% time/MIC derived from prior work will be used. A population pharmacokinetic model of flucytosine plasma concentrations will be developed. This model will be used to simulate the probability of target attainment. The lowest dose achieving the PKPD target in >90% of patients will be taken forward to step 2. This is measured using PK blood sampling at day 1 and day 7.

2. STEP 2 – Primary efficacy outcome (hierarchical composite at 30 days): 1) time to death (all-cause mortality, measured in ordinal blocks of 5 days); 2) breakthrough during treatment (binary – whether or not any blood cultures taken after blood culture sterility, become positive with Candida spp); 3) relapse within 30 days after end of treatment (binary - whether or not a blood culture taken following the end of treatment is positive with the same Candida spp as grown from the initial blood culture); 4) time-to-blood culture-sterility (measured in ordinal blocks of 12 hour periods); 5) time to emergence of micafungin resistance (MIC > EUCAST breakpoint) in any commensal Candida species. This is measured using the Win Ratio (Hierarchical Composite) at day 30

Previous primary outcomes as of 16/06/2026:
1. STEP 1 – Dose-selection: population pharmacokinetic modelling of flucytosine plasma concentrations to assess for achievement of target drug exposure of flucytosine in plasma measured using PK blood sampling at day 1 and day 7
2. STEP 2 – Primary efficacy outcome (hierarchical composite at 30 days): 1) time to death (all-cause mortality, measured in ordinal blocks of 5 days); 2) breakthrough Candida BSI during treatment (binary – whether or not any blood cultures taken subsequent to blood culture sterility for ≥48 hours, become positive with Candida spp); 3) Candida BSI relapse within 30 days after end of treatment (binary - whether or not a blood culture taken following the end of treatment is positive with the same Candida spp as grown from the initial blood culture, measured until EOT +30); 4) time-to-blood culture-sterility (measured in ordinal blocks of 12 hour periods from first blood culture positive, to first blood culture negative, when blood cultures remain negative during twice daily testing); 5) time to emergence of micafungin resistance (MIC > EUCAST breakpoint) in any commensal Candida species (measured as an ordinal variable using twice weekly swabbing episode) measured using Win Ratio (Hierarchical Composite) at day 30

Key secondary outcome(s)
1. All-cause mortality measured using number of deaths (site records) at day 30 and day 90

2. Time to all-cause mortality measured using time-to-event at day 30 and day 90

3. Candida BSI breakthrough during treatment measured using proportion of patients with a positive blood culture indicating a new Candida bloodstream infection at scheduled timepoints until EOT+5

4. Relapse of Candida BSI after treatment measured using proportion of participants with a positive blood culture from the same Candida spp at day 14, EOT +5, day 30 and EOT +30

5. Time to blood culture sterility measured using time to negative blood culture with no subsequent positive within 48 hours at scheduled timepoints until EOT +5

6. Time to micafungin resistance in colonising or invasive Candida spp measured using time to detection of micafungin resistance (MIC above EUCAST breakpoint) in a colonising or invasive Candida spp at every 3/4 days until day 30

7. Proportion of participants who have micafungin resistance detected measured using resitance (MIC above EUCAST breakpoint) detected in any colonising or invasive Candida spp at day 14, EOT+5 & day 30

8. Duration of ICU admission and hospitalisation measured using time spent in ICU/hospital from site records at up until day 90

9. Rate of change in fungal biomarkers measured using serum beta-D-glucan & blood Candida qPCR at until day 30

10. Serious adverse events (SAEs) measured using proportion with grade 3 cytopaenias, other grade 4 adverse events and other SAEs at up until EOT +5

Completion date
15/01/2031

Eligibility

Key inclusion criteria
Current key inclusion criteria:
1. Age ≥18 years
2. Evidence of microscopy-confirmed yeast bloodstream infection
3. ≥1 Systemic signs of infection during a 24-hour period before or after blood culture draw

Previous key inclusion criteria:
1. Age ≥18 years
2. Evidence of microscopy-confirmed yeast bloodstream infection
3. ≥1 Systemic signs of infection during a 24 hour period before and after blood culture draw

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
110 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
Current key exclusion criteria:
1. Yeast growing in blood culture is confirmed not to be a Candida spp (late exclusion criterion - may take up to 3 days to identify the organism)
2. Invasive candidiasis with complex organ or prosthetic involvement (e.g. infection involving material that cannot be removed within 5 days of randomisation, osteomyelitis, endocarditis or myocarditis, endophthalmitis, chorioretinitis or any central nervous system involvement) identified as likely to present within 5 days of Candida BSI (late exclusion criterion)
3. Pregnancy or breastfeeding
4. Receipt of a systemic antifungal, at treatment-dose, to which the Candida spp causing bloodstream infection is susceptible (> 3 doses of a once daily or >5 doses of a twice daily drug within 4 days of randomisation). This will be a late exclusion criteria once antifungal susceptibility testing results are available.
5. Micafungin or flucytosine resistant Candida spp (by EUCAST breakpoint) in initial bloodstream isolate (late exclusion criteria)
6. A known hypersensitivity to trial drugs
7. Co-administration of cytarabine
8. Known complete dihydropyrimidine dehydrogenase deficiency
9. Alanine transferase or aspartate aminotransferase level >10-fold upper limit of normal, or

history of chronic cirrhosis (Child-Pugh score >9)
10. Neutrophil count <500 x10^6/L or platelet count <50,000 x 10^6/L
11. Previous participation in this trial or in another trial for the same indication
12. The site principal investigator (PI) is of the opinion that the individual is not suitable for participation in the study due to any other factors
13. For Step 1 only, haemoglobin <8g/dL, or participants without adequate intravenous access for regular blood draws during the first 24 hours of treatment.

Previous key exclusion criteria:
1. Complicated invasive candidiasis (e.g. septic arthritis in a prosthetic joint, osteomyelitis, endocarditis or myocarditis, endopthalmitis, chorioretinitis or any central nervous system involvement)
2. Pregnancy or breastfeeding
3. Receipt of a systemic antifungal, at treatment-dose, to which the Candida spp causing bloodstream infection is susceptible (> 3 doses of a once daily or >5 doses of a twice daily drug within 4 days of randomisation). This will be a late exclusion criteria once antifungal susceptibility testing results are available.
4. Micafungin or flucytosine resistant Candida spp (by EUCAST breakpoint) in initial bloodstream isolate (late exclusion criteria)
5. A known hypersensitivity to trial drugs
6. Co-administration of cytarabine
7. Known complete dihydropyrimidine dehydrogenase deficiency
8. Alanine transferase or aspartate aminotransferase level >10-fold upper limit of normal, or history of chronic cirrhosis (Child-Pugh score >9)
9. Neutrophil count <500 x10^6/L or platelet count <50,000 x 10^6/L
10. Previous participation in this trial or in another trial for the same indication
11. The principal investigator (PI) is of the opinion that the individual is not suitable for participation in the study due to any other medical factors
12. For Step 1 only, an estimated Glomerular Filtration Rate (eGFR) of <50mL/min/1.73 m^2, haemoglobin <8g/dL, or participants without adequate intravenous access for regular blood draws during the first 24 hours of treatment.

Late Exclusion Criteria:
1. Yeast growing in blood culture is confirmed not to be a Candida spp (may take up to 3 days to identify the organism)
2. Evidence of Candida eye infection (retinopathy or endophthalmitis) on baseline fundoscopic examination (up to day 5 of treatment), or any other complication diagnosed after enrolment but up to day 5.
3. Participant enrolled but later found to be ineligible by any other trial inclusion and exclusion criteria.

Date of first enrolment
15/01/2027

Date of final enrolment
15/11/2030

Locations

Countries of recruitment
South Africa

Study participating centre
Charlotte Maxeke Johannesburg Academic Hospital (CMJAH)
Johannesburg
South Africa
2193

Study participating centre
Chris Hani Baragwanath Academic Hospital (CHBAH)
Johannesburg
South Africa
1864

Study participating centre
Helen Joseph Hospital (HJH)
Johannesburg
South Africa
2092

Study participating centre
Netcare Milpark Hospital (NM)
Johannesburg
South Africa
2193

Study participating centre
Wits Donald Gordon Medical Centre (WDGMC)
Johannesburg
South Africa
2193

Sponsor information

Organisation
Wits Health Consortium

Funder(s)

Funder type

Funder Name
Wellcome Trust

Alternative Name(s)
Wellcome, WT

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

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

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 1.4	06/08/2026	08/09/2026	No	No