

Clinical study comparing the nifurtimox-eflornithine combination with the standard eflornithine regimen for the treatment of Trypanosoma brucei gambiense human African trypanosomiasis in the meningo-encephalitic phase

Submission date 12/09/2005	Recruitment status No longer recruiting	<input type="checkbox"/> Prospectively registered
Registration date 18/04/2008	Overall study status Completed	<input type="checkbox"/> Protocol
Last Edited 28/11/2018	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

Contact name
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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers

WHO ref: A50402 and A60444; NFE0105; NFE0206

Study information

Scientific Title

Clinical study comparing the nifurtimox-eflornithine combination with the standard eflornithine regimen for the treatment of Trypanosoma brucei gambiense human African trypanosomiasis in the meningo-encephalitic phase

Study objectives

Melarsoprol is the most commonly used product for the treatment of patients suffering from human African trypanosomiasis (HAT) in the meningo-encephalitic (second, late) phase. This treatment is frequently complicated by fatal reactive encephalopathy, and at the same time resistance is beginning to appear in various countries. Eflornithine is effective and better tolerated, but it is more difficult to use. Nifurtimox, registered in several South American countries for treatment of Chagas' disease but used off label since the 1970's in series of cases of meningo-encephalitic HAT, is at present the only other potential alternative for the treatment of late-stage HAT.

The very limited number of compounds available, the lack of prospects for the development of new products and the emergence of resistance are arguments for the use of therapeutic combinations. Ideally, drug combinations should allow for reductions in the dosages of the drugs used in a way that, in particular in the case of toxic drugs such as those used for second stage HAT, the toxicity of the combination does not exceed that of either monotherapy. Of the three drug combinations nowadays possible: melarsoprol-nifurtimox, melarsoprol-eflornithine and eflornithine-nifurtimox, the last one has (in two different dosing regimens) shown the least treatment-associated toxicity and mortality in the 69 patients treated in one previous and this clinical trial to date. Good tolerability was also observed in a case series of 31 patients. The efficacy data to date suggest that efficacy is comparable to that of eflornithine and that of melarsoprol (in areas without high melarsoprol failure rates).

The main objective of the study is to compare the therapeutic combination of intravenous (IV) eflornithine and oral nifurtimox to the standard IV eflornithine regimen in terms of therapeutic efficacy and clinical safety, in patients suffering from Trypanosoma brucei gambiense (Tbg) HAT in the meningo-encephalitic phase. If therapeutic non-inferiority is shown, the combination regimen will represent an alternative therapy with simpler and shorter administration regimen, shorter hospitalisation, lower cost and some level of protection against the emergence of resistance.

Ethics approval required

Old ethics approval format

Ethics approval(s)

Ethics approval received from:

1. Ethical Clearance Committee (Uganda) on the 8th May 2005 and 8th May 2006 (ref: VCD/UNCT /06)
2. World Health Organization (WHO) Ethics Review Committee (ERC) on the 30th May 2005, and was reviewed on the 26th April 2006 and 27th February 2007

Study design

Randomised, open label, clinical non-inferiority trial

Primary study design

Interventional

Secondary study design

Randomised controlled trial

Study setting(s)

Hospital

Study type(s)

Treatment

Participant information sheet**Health condition(s) or problem(s) studied**

Human African trypanosomiasis

Interventions

1. Eflornithine IV 7 days 400 mg/kg/day 12 hourly and nifurtimox orally 10 days 15 mg/kg/day 8 hourly
2. Eflornithine IV 14 days 400 mg/kg/day 6 hourly

The total duration of follow up is 18 months for both arms.

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2. Omugo site:

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Deputy Director
Coordinating Office for Control of Trypanosomiasis in Uganda (COCTU)
P.O. Box 16345
Kampala, Uganda

Intervention Type

Drug

Phase

Not Specified

Drug/device/biological/vaccine name(s)

Eflornithine, nifurtimox

Primary outcome measure

The cure rate assessed via the number of alive subjects 18 months after treatment without laboratory signs of infection, i.e. absence of trypanosome(s) in the CSF, blood or lymph node fluid and CSF leukocytes count less than 20/μL.

Secondary outcome measures

1. The duration of survival without laboratory signs of infection up to 18 months after treatment
2. Proportion of serious adverse events and of major (grade 3 and 4) adverse events related to the treatment (adverse occurring in each treatment arm)

Overall study start date

01/11/2005

Completion date

13/06/2009

Eligibility**Key inclusion criteria**

1. Confirmed second-stage Tb gambiense infection: presence of the parasite in blood, lymph node fluid or cerebrospinal fluid (CSF) and greater than 20 white blood cells/μL in CSF
2. Age 15 years or older, either sex
3. Resident in a radius of 50 km from Omugo Sleeping Sickness Treatment Centre
4. Written informed consent of the patient or of a legally acceptable representative if the patient is a minor (less than 18 years for both genders in Uganda) or unable to communicate

Participant type(s)

Patient

Age group

Adult

Lower age limit

18 Years

Sex

Both

Target number of participants

280

Key exclusion criteria

1. Pregnant woman (systematic testing (urine human chorionic gonadotropin [HCG]) of women of childbearing potential)
2. Treated for late-stage HAT during the last 36 months. Patients previously treated for first-stage (pentamidine) can be included.
3. Unlikely to have access to the treatment centre or be accessible at their place of residence for 18 months after treatment
4. Unable to take oral medication
5. Suffering from conditions other than second stage HAT that seriously limit the chances of

survival over 18 months time

6. Severe anaemia (haemoglobin [Hb] less than 5 g/dl)

7. Severe underlying diseases upon admission (e.g. active tuberculosis and/or being treated for TB; bacterial or cryptococcal meningitis; stages 3 or 4 human immunodeficiency virus [HIV] /acquired immune deficiency syndrome [AIDS] according to the WHO clinical definition) (WHO, 1986)

8. Renal failure based on clinical examination combined with biochemistry. Calculated creatinine clearance less than 20 mL/min (Cockcroft's equation).

8.1. Males: creatinine clearance (mL/min) = $(\text{Wt [kg]} \times 140 - \text{age [years]}) \div (72 \times \text{serum creatinine [mg/dL]})$

8.2. Females: 0.85 x the above value

9. Hepatic failure based on clinical examination combined with biochemistry total bilirubin greater than 50 µmol/L, alanine aminotransferase (ALAT)/glutamate pyruvate transaminase [GPT] greater than 70 UI/L

Date of first enrolment

01/11/2005

Date of final enrolment

13/06/2009

Locations

Countries of recruitment

Switzerland

Uganda

Study participating centre

World Health Organization (WHO)

Geneva-27

Switzerland

CH-1211

Sponsor information

Organisation

UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR)

Sponsor details

20 Avenue Appia

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tdr@who.int

Sponsor type

Research organisation

Website

<http://www.who.int/tdr>

ROR

<https://ror.org/01f80g185>

Funder(s)

Funder type

Research organisation

Funder Name

United Nations Children's Fund (UNICEF)/United Nations Development Programme (UNDP)
/World Bank/World Health Organization (WHO) - Special Programme for Research and Training
in Tropical Diseases (TDR)

Results and Publications

Publication and dissemination plan

Not provided at time of registration

Intention to publish date

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	22/02/2018		Yes	No