# Fexinidazole as a new oral treatment for human African trypanosomiasis due to *Trypanosoma brucei rhodesiense*: a prospective, open-label, single-arm, phase 2–3, non-randomised study

*Enock Matovu, Westain Nyirenda, Anthony Eriatu, Deolinda Alves, Christelle Perdrieu, Marshal Lemerani, Charles Wamboga, Veerle Lejon, Jorge Seixas, Aita Signorell, Anne Reymondier, Elisabeth Baudin, Bruno Scherrer, Olaf Valverde Mordt*

## Summary

**Background** ***Rhodesiense*** **human African trypanosomiasis is a neglected disease with epidemic potential that can rapidly become lethal if left untreated. The aim of this study was to show that fexinidazole could offer an alternative to existing treatments (melarsoprol for stage 2 and suramin for stage 1** ***rhodesiense*** **human African trypanosomiasis), using a benchmark study design.**

**Methods** **This was a prospective, open-label, single-arm, phase 2–3, non-randomised study done in two centres (Lwala, Uganda and Rumphi, Malawi). Participants were enrolled if they were aged 6 years or older, weighed 20 kg or more, had parasitologically confirmed** ***rhodesiense*** **human African trypanosomiasis, were able to swallow fexinidazole tablets with a meal, and had a Karnofsky score of 40 or more. Pregnant or breastfeeding women were eligible after the first trimester of pregnancy. While admitted to hospital, participants received oral fexinidazole for 10 days at the recommended dosage according to bodyweight and were followed up for 12 months. The fatality and non-response to treatment rates observed with fexinidazole were compared with predefined rates based on literature. The primary endpoint was the fatality rate at end of hospital admission (EoH) in participants with stage 2** ***rhodesiense*** **human African trypanosomiasis (considering only deaths possibly related to the disease or fexinidazole), to be compared with 8·5%, an approximation of the fatality rate obtained with melarsoprol. This study is registered with ClinicalTrials.gov, NCT03974178.**

**Findings** **Between Sept 29, 2019, and Oct 12, 2022, 46 participants with** ***rhodesiense*** **human African trypanosomiasis were screened, of whom 45 were included and treated (35 with stage 2 and ten with stage 1 disease). One death occurred during treatment but was considered unrelated to** ***rhodesiense*** **human African trypanosomiasis or fexinidazole and excluded from the efficacy analysis. No other deaths had occurred by EoH in participants with stage 2** ***rhodesiense*** **human African trypanosomiasis, giving a fatality rate of 0 (0%) of 34 (90% CI 0–8·43), which was lower than the predefined 8·5% rate (p=0·0488). One participant with stage 2** ***rhodesiense*** **human African trypanosomiasis had a relapse at week 9. No failures were reported in participants with stage 1** ***rhodesiense*** **human African trypanosomiasis. No unexpected safety signals were identified on the basis of standard assessments and electrocardiograms.**

**Interpretation** **Fexinidazole is a safe and easy-to-use treatment, and is a better-accepted alternative to existing treatments for** ***rhodesiense*** **human African trypanosomiasis, such as melarsoprol or suramin.**

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## Introduction

Human African trypanosomiasis caused by *Trypanosoma brucei rhodesiense* is the zoonotic, acute form of sleeping sickness in Eastern Africa.[1,2] *Rhodesiense* human African trypanosomiasis has caused large epidemics in the past century,[1–3] and can kill within weeks to months if left untreated.[4] Despite a large reduction in the number of annual cases since 2000 (from 709 cases to 38 cases globally between 2000 and 2022),[5] the risk of disease outbreaks remains,[6,7] given its zoonotic reservoir and potentially unpredictable transmission to humans.

Suramin is the treatment of choice for early-stage (haemolymphatic stage 1) *rhodesiense* human African trypanosomiasis; however, the treatment is long (over a month) and associated with reversible nephropathy due to the high drug concentration in the kidneys.[8,9] Given that suramin does not penetrate the cerebrospinal fluid, late-stage (meningoencephalitic stage 2) *rhodesiense* human African trypanosomiasis is treated with injectable melarsoprol. This arsenic derivative is used despite causing 5–18% of patients to develop encephalopathic syndromes that are fatal in 10–70% of cases.[9]

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**College of Veterinary Medicine, Animal Resources and Biosecurity, Makerere University, Kampala, Uganda** (E Matovu PhD); **Rumphi District Hospital, Rumphi, Malawi** (W Nyirenda MD); **Lwala Hospital, Acet, Otuboi, Kaberamaido, Uganda** (A Eriatu MD); **Department of Research and Development, Drugs for Neglected Diseases Initiative, Geneva, Switzerland** (D Alves Dipl, C Perdrieu PharmD, A Reymondier PharmD, O Valverde Mordt MSc); **Ministry of Health, Lilongwe, Malawi** (M Lemerani MSc); **Ministry of Health, Vector Control Division, Kampala, Uganda** (C Wamboga MD); **Intertryp, IRD, CIRAD, University of Montpellier, Montpellier, France** (V Lejon PhD); **Instituto de Higiene e Medicina Tropical, Universidade Nova de Lisboa, Lisboa, Portugal** (J Seixas MD PhD); **Swiss Tropical and Public Health Institute, Allschwil, Switzerland** (A Signorell PhD); **University of Basel, Basel, Switzerland** (A Signorell); **Epicentre, Paris, France** (E Baudin MSc); **Bruno Scherrer Conseil, Saint-Arnoult-en-Yvelines, France** (B Scherrer PhD)

Correspondence to:
Dr Olaf Valverde Mordt, Department of Research and Development, Drugs for Neglected Diseases Initiative, Geneva 1202, Switzerland
**ovalverde@extern.dndi.org**

## Research in context

### Evidence before this study

The present study is part of a wider development programme started by Drugs for Neglected Diseases initiative (DNDi) in 2005; therefore, most publications on fexinidazole clinical research for human African trypanosomiasis have been written within or around the DNDi programme. To identify other relevant publications, we searched PubMed and Google using the terms "human African trypanosomiasis" and "fexinidazole", from Jan 1, 2020 until July 31, 2024. Publications in English and French were considered, including the references cited in those publications (and in the publications related to the DNDi programme), and we retained those covering efficacy and safety of available treatments. Based on three previous clinical trials of the DNDi programme, fexinidazole was registered in 2018 as the first all-oral treatment for all stages of *gambiense* human African trypanosomiasis (the chronic form of sleeping sickness). Melarsoprol, an injectable arsenic derivative that causes a toxic encephalopathy in 5–18% of patients, of whom 10–70% die, is still used to treat late-stage *rhodesiense* human African trypanosomiasis (the acute form of sleeping sickness). For stage 1 *rhodesiense* human African trypanosomiasis, suramin, also an injectable drug, is administered for more than 1 month.

### Added value of this study

In-vitro and in-vivo studies showed that fexinidazole could also be effective against *Trypanosoma brucei rhodesiense,* thus constituting a valuable alternative for the treatment of *rhodesiense* human African trypanosomiasis. The key innovative feature of this open-label study was to investigate the effectiveness and safety of fexinidazole for treating *rhodesiense* human African trypanosomiasis. Given the low incidence of *rhodesiense* human African trypanosomiasis cases, a comparative trial would have been logistically impossible to accomplish within a reasonable timespan. Despite the limitations of the benchmark study design, this study indicates that fexinidazole is efficacious and safe in both stages of *rhodesiense* human African trypanosomiasis.

### Implications of all the available evidence

*Rhodesiense* human African trypanosomiasis can rapidly become lethal if left untreated, and yet is neglected, despite its epidemic potential. Fexinidazole is a safe, easy-to-use, and effective alternative to existing treatments for *rhodesiense* human African trypanosomiasis. Having a suitable treatment for both stages of *rhodesiense* human African trypanosomiasis overcomes the need for disease staging, saving most patients from a painful lumbar puncture and reducing the costs of equipment, infrastructure, and trained personnel.

Fexinidazole was first registered by the National Drug Authority in the Democratic Republic of the Congo in 2018 as the first all-oral drug to treat *gambiense* Human African trypanosomiasis, the chronic form of sleeping sickness. This 2-substituted 5-nitroimidazole shows in-vitro and in-vivo activity against both *T b rhodesiense* and *gambiense* parasites,[10] with an expected similar susceptibility. Fexinidazole acts primarily as a biologically active prodrug, with the sulfoxide and sulfone metabolites providing most of the trypanocidal activity.[11] The aim of our study was to show that fexinidazole could offer an alternative to existing treatments for *rhodesiense* human African trypanosomiasis.

## Methods

### Study design and participants

This was a prospective, open-label, single-arm, phase 2–3, non-randomised study done in two centres (Lwala, Uganda and Rumphi, Malawi), with a large geographical area for case searching (up to 300 km from the study centres) to optimise participant detection, because of the rarity of *rhodesiense* human African trypanosomiasis.

In this single-arm benchmark study, participants were treated with fexinidazole only. The justification for the benchmark study design is provided in appendix 1 (p 1).

See Online for appendix 1

Participants were identified through passive or active screening. Parasite detection and disease staging were done in blood, lymph, and cerebrospinal fluid (appendix 1 p 3). Eligible participants were adults and children aged six years or older and weighing 20 kg or more, with parasitologically confirmed *rhodesiense* human African trypanosomiasis by microscopy, able to swallow fexinidazole tablets with a solid meal, and with a Karnofsky score of 40 or more.[12] Pregnant or breastfeeding women could be included in the study after the first trimester of pregnancy.[13]

Participants who had a severely deteriorated general condition, severe hepatic impairment, known hypersensitivity to fexinidazole (or other nitroimidazole drugs, or any of the excipients), or any relevant clinically active medical condition other than *rhodesiense* human African trypanosomiasis were excluded. Participants were pretreated for soil-transmitted helminths with albendazole and tested and, if necessary, treated for malaria with artemisinin derivatives (mainly artemether lumefantrine).

The study protocol was approved by the National Health Science Research Committee in Malawi, and the Vector Control Division-Research and Ethics Committee in Uganda, and is available online.[14] The protocol also received a positive opinion from the Commission Cantonale d'Ethique de la Recherche (Geneva, Switzerland). The study was done in accordance with the Declaration of Helsinki and the International Council for

Harmonisation E6 Good Clinical Practice Guidelines. Written informed consent was obtained from the participants (for adults) or the parent or guardian (for children, who were also required to assent). An independent data safety monitoring board (DSMB) regularly reviewed the study data and met when a death occurred to discuss its cause or causes.

### Procedures

General health was qualified as good, altered, or bad by the investigators according to their overview of interrogation, physical and neurological exam, vital signs and laboratory results. Fexinidazole was administered orally as 600 mg tablets in a dose regimen dependent on bodyweight to participants who were admitted to hospital during treatment. Participants weighing 35 kg or more were given the full dose—1800 mg once per day for 4 days, followed by 1200 mg once per day for 6 days. Participants weighing at least 20 kg but less than 35 kg received a reduced dose—1200 mg once per day for 4 days, followed by 600 mg once per day for 6 days. Given that food increases fexinidazole absorption,[15] the daily dose was taken within 30 min of the main meal. Temporary interruption of treatment was permitted for up to 1 day, with reintroduction at the discretion of the investigator (the clinician in charge of the patient) and one additional treatment day to compensate.[14] The dosing regimens of fexinidazole used in the study are those approved for the treatment of *gambiense* human African trypanosomiasis. The 10-day regimen is well tolerated,[13,16–18] and achieves cerebrospinal fluid concentrations of the pharmacologically active metabolites that are expected to be effective in stage 2 *gambiense* human African trypanosomiasis.[15]

Participants were observed for approximately 12 months (appendix 1 p 4). In case of relapse, melarsoprol was used as rescue treatment for participants with stage 2 *rhodesiense* human African trypanosomiasis while suramin was used for participants with stage 1 *rhodesiense* human African trypanosomiasis. The schedule of procedures is available in appendix 1 (pp 5–6).

### Outcomes

The rationale for the various study objectives is provided in appendix 1 (p 7). The major issue with existing treatments for *rhodesiense* human African trypanosomiasis is the neurological and systemic toxicity of melarsoprol. The primary objective was, therefore, to show that the fatality rate (due to *rhodesiense* human African trypanosomiasis or treatment-related death, as described in the literature) at the end of hospital admission (EoH) in participants with stage 2 *rhodesiense* human African trypanosomiasis treated with fexinidazole was less than 8·5%, an approximation of the fatality rate obtained with melarsoprol (8·4%).[19] All deaths were to be reviewed by the DSMB; if a participant died but the DSMB determined that the death was not related to *rhodesiense* human African trypanosomiasis or fexinidazole, the participant was considered non-evaluable for efficacy purposes.

The secondary efficacy objectives were based on treatment outcome, defined as non-response to treatment or success depending on the presence or absence of trypanosomes in body fluids (blood, lymph node aspirate, and cerebrospinal fluid),[20] white-blood-cell count in the cerebrospinal fluid, clinical signs of relapse (including death), and use of rescue medication. Parasitological and white-blood-cell counting techniques were done according to WHO recommendations.[21] The mini-anion exchange centrifugation technique (mAECT) on blood or buffy coat (mAECT-BC) was introduced specifically for this study as it is the most sensitive field test for detecting parasites.[22,23] The criteria for success were adapted from WHO guidelines (appendix 1 pp 8–9).[21,24]

The definition of endpoints and benchmarks for comparison are provided in table 1. The unacceptable rates for the various endpoints were proposed while designing the study, on the basis of discussions of the WHO network for human African trypanosomiasis elimination at the sixth meeting of the subgroup, integration of new tools into national and global policies, held in 2016 (appendix 1 pp 10–11).

Safety was assessed by recording adverse events, standard haematology and biochemistry laboratory parameters, and electrocardiograms (appendix 1 pp 5–6). After EoH (between day 12 and day 18 after treatment start), only adverse events considered as related to fexinidazole and serious adverse events (SAEs) were reported.

Adverse events of special interest were defined as neuropsychiatric signs and symptoms (excluding headaches and insomnia, which were reported as adverse events) requiring specialised therapeutic intervention.

For the first time in a study on fexinidazole, the pharmacokinetic profile of fexinidazole and its metabolites, M1 (fexinidazole sulfoxide) and M2 (fexinidazole sulfone),[25] was investigated at the beginning and end of the loading phase (the first 4 days of treatment with a higher dose of fexinidazole than in the last 6 days; appendix 1 pp 5, 21–22).

### Statistical analysis

The study planned to enrol 34 evaluable participants with stage 2 *rhodesiense* human African trypanosomiasis, as evidenced by the presence of *T b rhodesiense* in the cerebrospinal fluid, or parasite present in another body fluid and a cerebrospinal fluid white-blood-cell count higher than 5 cells/μL. This sample size was the minimal sample size to allow comparison with the 8·4% mortality rate found with melarsoprol as documented in the literature (appendix 1 p 2). Additionally, participants with confirmed stage 1 *rhodesiense* human African trypanosomiasis were recruited in parallel, without any predefined targeted sample size.

| | Evaluation criteria* | Target† | Benchmark |
|---|---|---|---|
| **Primary endpoint** | | | |
| *rhodesiense* human African trypanosomiasis or treatment-related fatality rate at EoH in evaluable participants with stage 2 *rhodesiense* human African trypanosomiasis treated with fexinidazole | Death possibly related to *rhodesiense* human African trypanosomiasis or treatment, according to DSMB‡ | <8·5% | Melarsoprol |
| **Secondary short-term efficacy endpoint** | | | |
| Treatment non-response rate at EoH in evaluable participants with stage 2 *rhodesiense* human African trypanosomiasis treated with fexinidazole | Any of the following criteria: presence of trypanosomes in any body fluid at EoT; death related to *rhodesiense* human African trypanosomiasis or fexinidazole at EoH, according to DSMB; and absence of clinical improvement leading to the use of rescue medication | <9% | Melarsoprol |
| **Secondary long-term efficacy endpoint** | | | |
| Proven treatment non-response rate at test of cure (12 months) in evaluable participants with stage 2 *rhodesiense* human African trypanosomiasis treated with fexinidazole | Any of the following criteria at 12 months (or before): presence of trypanosomes in any body fluid; death related to *rhodesiense* human African trypanosomiasis or fexinidazole, according to DSMB; absence of clinical improvement leading to the use of rescue medication; white-blood-cell count in the cerebrospinal fluid >20 cells/μL, which was unlikely to be due to causes other than *rhodesiense* human African trypanosomiasis | <12% | Melarsoprol |
| **Other secondary efficacy endpoints** | | | |
| Treatment non-response rate at EoH in participants with stage 1 *rhodesiense* human African trypanosomiasis treated with fexinidazole | NA | NA§ | Suramin |
| Treatment non-response rate at 12 months in participants with stage 1 *rhodesiense* human African trypanosomiasis treated with fexinidazole | NA | NA§ | Suramin |
| Treatment non-response rate at EoH in evaluable participants treated with fexinidazole, regardless of *rhodesiense* human African trypanosomiasis stage | NA | <8·5% | |
| Treatment non-response rate at 12 months in evaluable participants treated with fexinidazole, regardless of *rhodesiense* human African trypanosomiasis stage | NA | <12% | Melarsoprol |
| **Secondary safety endpoints** | | | |
| Occurrence of all treatment-emergent adverse events until EoH and occurrence of treatment-emergent adverse events considered as serious or possibly related to fexinidazole until month 12 | Clinically significant abnormalities in laboratory parameters or electrocardiogram were to be recorded as adverse events | NA | Melarsoprol and suramin, as reported in the literature[19]¶ |

DSMB=Data Safety Monitoring Board. EoH=end of hospital admission. EoT=end of treatment. NA=not applicable. *Treatment outcome (success or treatmen non-response) was determined as per modified WHO recommendations.[21,24] †The comparison to the predefined unacceptable rate was done using a one-sided exact test at the 0·05 significance level. ‡The final adjudication of causality was done by independent experts from the DSMB committee. If a death was unrelated to *rhodesiense* human African trypanosomiasis or the treatment during hospital admission, the participant was considered non-evaluable for efficacy purposes. §Because of the small number of participants with stage 1 *rhodesiense* human African trypanosomiasis, the comparison with unacceptable rate was not separately performed. ¶For more information on the toxicity of melarsoprol and suramin, see WHO guidelines.[8,9]

***Table 1:*** **Definition of study endpoints and benchmarks for comparison**

The fatality rate (due to *rhodesiense* human African trypanosomiasis or treatment-related death) at EoH was provided with two-sided 90% CIs estimated with the Clopper Pearson exact method, using SAS software version 9.4. A two-sided 90% CI was preferred to a two-sided 95% CI because of the paucity of patients and consequently the feasibility of the study, and it is equivalent to a one-sided 95% CI.

The minimal sample size to be able to obtain a statistically significant result was 34 evaluable participants with stage-2 disease, considering an (alpha) error of 0·05, calculated with a one-sided exact test for proportions, to be compared to the threshold of 8·5% (appendix 1 pp 1–2).

Evaluable participants were those who took at least one dose of fexinidazole and were eligible for efficacy purposes. Participants were considered non-evaluable for efficacy if they died for reasons unrelated to *rhodesiense* human African trypanosomiasis or treatment, or if they left the hospital voluntarily with unknown primary endpoint (appendix 1 pp 8–9).

The same analysis was repeated on participants who took at least one dose of fexinidazole and on participants who completed the 10-day fexinidazole treatment (both as sensitivity analyses). The primary endpoint was also analysed in evaluable participants with stage 1 *rhodesiense* human African trypanosomiasis (descriptively) and in evaluable participants regardless of *rhodesiense* human African trypanosomiasis stage (comparison with the 8·5% rate), as a secondary analysis.

Comparison of the treatment non-response rates to the predefined thresholds was done using the same approach.

The safety endpoints were descriptively analysed in participants who took at least one dose of fexinidazole. The pharmacokinetic endpoints were descriptively summarised and compared between adults and children.

### Role of the funding sources

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

## Results

Between Sep 29, 2019 and Oct 12, 2022, 46 participants were screened, of whom 45 (98%) were enrolled and treated (43 in Malawi and two in Uganda).

The study population included nine (20%) participants younger than 12 years and a higher proportion of males than females (table 2). One female participant was seven months pregnant. Four (9%) participants had previously been treated for *rhodesiense* human African trypanosomiasis, 215–379 days before entering this study.

All 45 participants presented with trypanosomes in the blood, except one who only had trypanosomes detected in the cerebrospinal fluid (table 2). Lymph node aspirate was not done in any participant. 35 (78%) participants had

| | Total (n=45) |
|---|---|
| **Demographics** | |
| Age (years) | 27·0 (16·1) |
| Male | 31 (69%) |
| <12 years | 5 (11%) |
| ≥12 years | 26 (58%) |
| Female | 14 (31%) |
| <12 years | 4 (9%) |
| ≥12 years and not gone through the menopause | 9 (20%) |
| ≥12 years and gone through the menopause | 1 (2%) |
| Weight (kg) | 48·1 (15·0) |
| BMI (kg/m²) | 19·0 (3·6) |
| **Diagnostic and parasitological findings** | |
| Blood tests | |
| Positive mAECT* | 44/45 (98%)* |
| Positive mAECT with >50 trypanosomes observed[b] | 29/43 (67%)† |
| Positive mAECT-BC‡ | 5/6 (83%)‡ |
| Lymph examination | |
| Not done | 45 (100%) |
| Cerebrospinal fluid examination | |
| Positive for trypanosomes | 34 (76%) |
| Cerebrospinal fluid white-blood-cell count (cells /µL) | 62·1 (96·4) |
| Trypanosomes in any body fluid | 45 (100%) |
| Disease stage | |
| Stage 1 | 10 (22%) |
| Stage 2 | 35 (78%) |
| **Vital signs and general health** | |
| Systolic blood pressure (mm Hg) | 102·8 (16·9) |
| Diastolic blood pressure (mm Hg) | 61·4 (11·4) |
| Temperature (°C) | 37·5 (1·1) |
| Heart rate (beats/min) | 106·2 (16·4) |
| Respiratory rate (cycles/min) | 22·8 (3·8) |
| Karnofsky score | 71·8 (11·1) |
| Altered or bad general health | 42 (93%) |

Data are n (%), n/N (%), or mean (SD). BMI=body-mass index. mAECT=mini-anion exchange centrifugation technique. mAECTBC=mini-anion exchange centrifugation technique on buffy coat. *The participant who was negative for mAECT was also negative for mAECT-BC and thick or thin blood smear, but had trypanosomes in the cerebrospinal fluid. †The semiquantification of trypanosomes in the blood was assessed by mAECT. The semiquantification could not be done in one of the 44 participants with positive mAECT blood test. ‡mAECT-BC was done in six participants.

***Table 2:*** **Baseline characteristics of the participants with *rhodesiense* human African trypanosomiasis treated with fexinidazole**

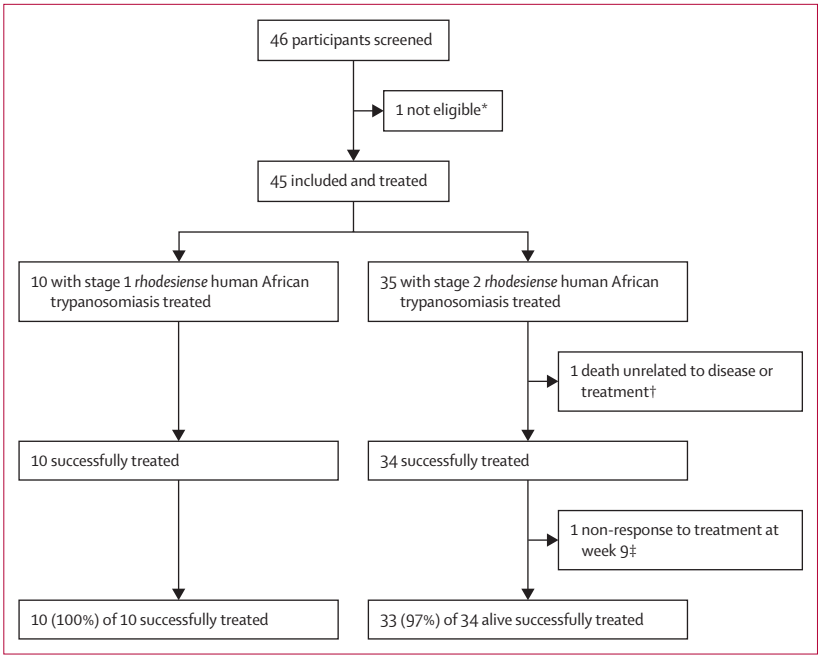


***Figure:*** **Study flow chart with treatment outcome**
*The screen failure was caused by an inability to ingest at least one complete meal per day and compromised general health and severely deteriorated general condition. †The participant died during hospital admission from causes considered unrelated to *rhodesiense* human African trypanosomiasis and fexinidazole. For more information, see appendix 1 (p 13). ‡The participant had a relapse (confirmed by the presence of trypanosomes in the cerebrospinal fluid) and was successfully treated with melarsoprol. For more information, see appendix 1 (p 13).

stage 2 *rhodesiense* human African trypanosomiasis, 34 (76%) participants had trypanosomes in the cerebrospinal fluid, and one (2%) participant was trypanosome-negative in the cerebrospinal fluid but had a cerebrospinal fluid white-blood-cell count higher than 5 cells/µL. The remaining ten (22%) participants were diagnosed with stage 1 *rhodesiense* human African trypanosomiasis.

At baseline, 42 (93%) participants were in altered or bad general health. 11 (24%) participants had a Karnofsky score of 50 or 60 (ie, needing frequent or occasional assistance for daily activities). Tachycardia was frequently observed, with 34 (75%) of participants with a baseline heart rate of 98 beats per min or higher (first quartile; appendix 1 p 12). Median values for baseline laboratory parameters were lower than normal for haemoglobin, basophils, platelets, and albumin.

All 45 participants completed the full course of treatment, except one participant with stage 2 *rhodesiense* human African trypanosomiasis who died during hospital admission on day 8, after 7 days of fexinidazole, following an SAE of acute kidney injury which started at day 4. This participant was non-evaluable for efficacy because the investigator and the DSMB considered the death to be unrelated to *rhodesiense* human African trypanosomiasis and fexinidazole (which was accepted by DNDi; figure; appendix 1 p 13).

The primary objective was reached, because no deaths related to fexinidazole or *rhodesiense* human African trypanosomiasis were observed by EoH in the 34 evaluable participants with stage 2 *rhodesiense* human African trypanosomiasis, giving an attributable fatality rate of 0 of 34 (90% CI 0–8·43), with an upper limit of the CI that was smaller than the predefined unacceptable rate of 8·5% (p=0·0488; table 3). Sensitivity analyses showed consistent results (appendix 1 p 14).

Regarding the secondary short-term efficacy endpoint, no participant with stage 2 *rhodesiense* human African

| | Stage 1 *rhodesiense* human African trypanosomiasis | Stage 2 *rhodesiense* human African trypanosomiasis | Total |
|---|---|---|---|
| **Number of participants** | | | |
| Evaluable participants | 10 | 34 | 44 |
| Non-evaluable participants* | 0 | 1* | 1* |
| **Fatality rate at EoH†** | | | |
| n/N (%) | 0/10 (0%) | 0/34 (0%) | 0/44 (0%) |
| 90% CI | .. | 0–8·43 | 0–6·58 |
| Comparison with the unacceptable fatality rate at EoH (8·5%)‡ | Not applicable§ | p=0·0488 (primary endpoint) | p=0·0201 |
| **Failure rate at EoH** | | | |
| n/N (%) | 0/10 (0%) | 0/34 (0%) | 0/44 (0%) |
| 90% CI | .. | 0–8·43 | 0–6·58 |
| Comparison with the unacceptable failure rate at EoH (9%)‡ | Not applicable§ | p=0·0405 | p=0·0158 |
| **Failure rate at 12 months** | | | |
| n/N (%) | 0/10 (0%) | 1/34 (3%) | 1/44 (2%) |
| 90% CI | .. | 0·15–13·21 | 0·12–10·34 |
| Comparison with the unacceptable failure rate at 12 months (12%)‡ | Not applicable§ | p=0·0730 | p=0·0253 |

Data are provided as the fatality or treatment non-response rate (number of deaths or failures/number of participants analysed), with Clopper–Pearson 90% CI of the fatality or failure rate (a two-sided 90% CI was preferred to a two-sided 95% CI because of the paucity of patients and consequently the feasibility of the study). EoH=end of hospitalisation. n=number of participants with the event. N=number of participants analysed. *One participant died during hospital admission from causes considered unrelated to *rhodesiense* human African trypanosomiasis and fexinidazole. The participant was considered non-evaluable for efficacy purposes. †Only considering deaths possibly related to *rhodesiense* human African trypanosomiasis and to fexinidazole at EoH. ‡The comparison to the predefined threshold was done using a one-sided exact test at the 0·05 significance level. §The comparison with unacceptable rate using a one-sided exact test at the 0·05 significance level was to be done if the sample size was 34 or more (minimal sample size to get a rejectable null hypothesis). Because of the small number of participants with stage 1 *rhodesiense* human African trypanosomiasis, the comparison was not done and the CI was not calculated.

***Table 3:*** **Treatment outcome in the participants with *rhodesiense* human African trypanosomiasis treated with fexinidazole**

trypanosomiasis showed any trypanosome in blood or cerebrospinal fluid, and no participant had needed rescue medication by EoH, giving a treatment non-response rate of 0 of 34 (90% CI 0–8·43), which was smaller than the unacceptable rate of 9% (p=0·0405; table 3).

One relapse was reported at the week 9 visit in a participant with stage 2 *rhodesiense* human African trypanosomiasis who had trypanosomes in the cerebrospinal fluid (figure; appendix 1 p 13), indicating a probable relapse which was also identified by the exploratory analysis finding the same microsatellite DNA.

| | Any adverse event | Any treatment-related adverse event |
|---|---|---|
| Any adverse event during hospital admission | 22 (49%) [40] | 5 (11%) [7] |
| Gastrointestinal disorders | 10 (22%) [10] | 2 (4%) [2] |
| Vomiting | 6 (13%) [6] | 1 (2%) [1] |
| Nausea | 2 (4%) [2] | 0 |
| Dysphagia | 1 (2%) [1] | 0 |
| Gastritis | 1 (2%) [1] | 1 (2%) [1] |
| Investigations | 9 (20%) [10] | 4 (9%) [5] |
| Electrocardiogram U-wave abnormality* | 3 (7%) [4] | 1 (2%) [2] |
| Electrocardiogram QT prolonged* | 2 (4%) [2] | 2 (4%) [2] |
| Blood pressure increased | 1 (2%) [1] | 1 (2%) [1] |
| Haemoglobin decreased | 1 (2%) [1] | 0 |
| Electrocardiogram T wave abnormal* | 1 (2%) [1] | 0 |
| Electrocardiogram T wave inversion* | 1 (2%) [1] | 0 |
| Metabolism and nutrition disorders | 4 (9%) [4] | 0 |
| Hypoalbuminaemia† | 3 (7%) [3] | 0 |
| Dehydration | 1 (2%) [1] | 0 |
| Vascular disorders | 3 (7%) [3] | 0 |
| Hypertension | 3 (7%) [3] | 0 |
| Infections and infestations | 3 (7%) [3] | 0 |
| Malaria | 2 (4%) [2] | 0 |
| Bacteraemia | 1 (2%) [1] | 0 |
| Blood and lymphatic system disorders | 2 (4%) [2] | 0 |
| Anaemia | 1 (2%) [1] | 0 |
| Thrombocytopenia | 1 (2%) [1] | 0 |
| Nervous system disorders | 2 (4%) [2] | 0 |
| Epilepsy | 1 (2%) [1] | 0 |
| Extrapyramidal disorder | 1 (2%) [1] | 0 |
| Renal and urinary disorders | 2 (4%) [2] | 0 |
| Acute kidney injury†‡ | 1 (2%) [1] | 0 |
| Chromaturia | 1 (2%) [1] | 0 |
| General disorders and administration site conditions | 2 (4%) [2] | 0 |
| Hypothermia | 1 (2%) [1] | 0 |
| Inflammation† | 1 (2%) [1] | 0 |
| Musculoskeletal and connective tissue disorders | 1 (2%) [1] | 0 |
| Neck pain | 1 (2%) [1] | 0 |
| Cardiac disorders | 1 (2%) [1] | 0 |
| Sinus tachycardia*† | 1 (2%) [1] | 0 |
| Any adverse event during follow-up | 2 (4%) [2] | 0 (0%) [0] |
| Infections and infestations | 2 (4%) [2] | 0 |
| Pneumonia†‡ | 1 (2%) [1] | 0 |
| Urinary tract infection‡ | 1 (2%) [1] | 0 |

Data are n (%) [number of events]. The dictionary used was the Medical Dictionary for Regulatory Activities version 22·0 or higher. *Non-serious electrocardiogram abnormalities, which were reported as adverse events. †Reported as severe in intensity. ‡Reported as serious. §During the follow-up period (from month 1), only serious adverse events and treatment-related adverse events were to be reported.

***Table 4:*** **Incidence of treatment-emergent adverse events in the total (n=45) participants with *rhodesiense* human African trypanosomiasis treated with fexinidazole, by period (hospital admission and follow-up)**

Regarding the secondary long-term efficacy endpoint, although the treatment non-response rate was low 12 months after treatment initiation (one [3%] of 34; 90% CI 0·15–13·21), the upper limit of the CI was higher than the unacceptable rate of 12%, meaning that statistical significance was not reached (p=0·0730; table 3).

No deaths or treatment non-responses were reported in the ten participants with stage 1 *rhodesiense* human African trypanosomiasis (figure).

The four participants who had been treated for *rhodesiense* human African trypanosomiasis before the study (three with melarsoprol and one with suramin) but were enrolled because of a relapse or a reinfection, were all cured at 12 months.

The most frequently reported adverse events were vomiting, hypertension, electrocardiogram U-wave abnormality, and hypoalbuminaemia, as well as nausea, QT prolonged on electrocardiogram, and malaria (table 4). There were no adverse events of special interest (appendix 1 p 15). Three SAEs were reported (all unrelated to fexinidazole and all in participants with stage 2 *rhodesiense* human African trypanosomiasis); one fatal SAE during hospital admission (described above) and two SAEs during follow-up period, from which the participants fully recovered (table 4; appendix 1 p 16).

There were no adverse events suggesting hepatic toxicity and no adverse events of neutropenia. Two participants had SAEs associated with serious infections (pneumonia and urinary tract infection), without associated neutropenia. Both cases were considered unrelated to fexinidazole.

Hypoalbuminaemia was reported in three (7%) participants on day 5; one event was severe and all events resolved within 6–61 days. Haematological abnormalities (haemoglobin decreased, anaemia, and thrombocytopenia) were reported in three (7%) participants; all events were mild to moderate in intensity and resolved within 5–6 days. None of these laboratory abnormalities were considered related to fexinidazole. Almost all abnormal liver function tests normalised by the end of treatment.

Nine electrocardiogram abnormalities were reported as adverse events in eight (18%) participants, with four adverse events considered related to fexinidazole in three participants (table 4). All electrocardiogram events were mild to moderate in intensity and resolved within 7–65 days (except sinus tachycardia, which was severe and did not resolve until the participant's death). QT interval corrected according to Fridericia's formula increased on average by 20 ms and heart rate by 10 beats per minute.

One pregnant woman was exposed to treatment during the third trimester of pregnancy, with a baby born 72 days after the last dose of fexinidazole. At the most recent follow-up, 14 months after the mother's treatment, both the mother and the baby, aged 1 year, were in good health.

A gradual decrease in heart rate and rapid improvement in general health status and Karnofsky score were seen by EoH (appendix 1 p 12). There were no participants with a score of 60 (ie, needing occasional assistance) or lower, and all but one were in good health. Participants had a median increase in weight of 3·6 kg (IQR 0·9–7·0) at the 12 month visit.

A rapid improvement in signs and symptoms of *rhodesiense* human African trypanosomiasis was observed from day 5 and confirmed at EoH (appendix 1 p 17). The percentage of participants with completely normal physical examination increased markedly from baseline (15 [33%] of 45) to end of treatment (33 [75%] of 44) and EoH (37 [84%] of 44). The same was observed for normal neurological examination (18 [40%] of 45 at baseline increasing to 36 [82%] of 44 at end of treatment and EoH). From month 1 visit after treatment start, physical and neurological abnormalities were very rare (appendix 1 pp 18–20).

Fexinidazole exposure was within the expected range, correlating with anti-parasitic activity, and there was no overexposure resulting in adverse effects (appendix 1 pp 21–22).

At screening, only ten participants had white-blood-cell count higher than 100/µL in the cerebrospinal fluid (table 5). All ten participants but one had a strong reduction in cerebrospinal fluid white-blood-cell count, already detected at end of treatment. One participant showed a strong increase at month 6 (169 cells/µL) and did not receive rescue treatment. This participant had HIV infection and was not under anti-retroviral treatment during follow-up. After discussing with the investigator, anti-retroviral treatment was restarted and the cerebrospinal fluid white-blood-cell count returned to acceptable levels at end of study (14 cells/µL). Another

| | Screening | EoT | Week 9 | Month 6 | Month 12 |
|---|---|---|---|---|---|
| **Cerebrospinal fluid white-blood-cell count (cells/µL)** | | | | | |
| N* | 45 | 44 | 44 | 44 | 43 |
| Mean (SD) | 62·1 (96·4) | 19·6 (25·7) | 3·6 (6·1) | 6·4 (25·8) | 2·0 (3·0) |
| Median (IQR) | 8·0 (3·0–61·0) | 7·5 (3·0–28·5) | 1·0 (0–4·5) | 0 (0–2·0) | 1·0 (0–3·0) |
| Minimum; maximum | 0; 363·0 | 0; 88·0 | 0; 25·0 | 0; 169·0 | 0; 14·0 |
| **Cerebrospinal fluid white-blood-cell count by category** | | | | | |
| ≤5 cells/µL | 18 (40%) | 20 (45%) | 35 (80%) | 38 (86%) | 38 (88%) |
| 6–20 cells/µL | 10 (22%) | 10 (23%) | 8 (18%) | 3 (7%) | 5 (12%) |
| 21–50 cells/µL | 3 (7%) | 7 (16%) | 1 (2%) | 2 (5%) | 0 |
| 51–99 cells/µL | 4 (9%) | 7 (16%) | 0 | 0 | 0 |
| ≥100 cells/µL | 10 (22%)† | 0 | 0 | 1 (2%)‡ | 0 |

EoT=end of treatment. N=number of participants analysed. *Missing data are due to one participant who died before EoT and another participant who refused to have a lumbar puncture at month 12 (but who was in good clinical condition). †The number of ten patients with cerebrospinal fluid white-blood-cell count of 100 cells/µL or higher at screening remains valid when excluding the value of 100 cells/µL from the category (ie, cerebrospinal fluid white-blood-cell count >100 cells/µL at screening). ‡One participant had a cerebrospinal fluid white-blood-cell count of 169 cells/µL at month 6. The participant did not receive rescue treatment. This participant had an HIV infection and was not under antiretroviral treatment during follow-up. After discussing with the investigator, antiretroviral treatment was restarted and the number of white blood cells in the cerebrospinal fluid returned to acceptable levels at end of study (14 cells/µL).

***Table 5:*** **White-blood-cell count in the cerebrospinal fluid in participants *rhodesiense* human African trypanosomiasis treated with fexinidazole**

participant had a medical history of AIDS, but such a condition did not affect the outcome of HAT treatment and the patient was cured at end of study.

## Discussion

The primary objective of this study was met, no *rhodesiense* human African trypanosomiasis or treatment-related deaths were observed in participants with stage 2 *rhodesiense* human African trypanosomiasis treated with fexinidazole by hospital discharge, resulting in a 0% (0 of 34; 90% CI 0·00–8·43) fatality rate, which was lower than the unacceptable rate of 8·5%. Although the treatment non-response rate 12 months after treatment initiation was low (2·94%; 90% CI 0·15–13·21, due to one treatment non-response at 9 weeks), the secondary long-term objective was not met because the upper limit of the CI slightly exceeded the predefined unacceptable rate of 12%.

For the short-term fatality and treatment non-response rates to be lower than those observed with melarsoprol (the only reference treatment for advanced stage *rhodesiense* human African trypanosomiasis), no deaths related to *rhodesiense* human African trypanosomiasis or fexinidazole and no treatment non-response could occur by hospital discharge with such limited sample size (34 evaluable participants in stage 2 disease). The benchmark rates, which were compatible with the IMPAMEL III results on melarsoprol obtained in Uganda and Tanzania,[19] were very conservative for a study that mostly included participants from Malawi, given that the fatality rate is known to depend upon the site, country, and year. In 2014, the observed fatality rate was 23·3% at the Rumphi site in Malawi versus only 6·7% at the Lwala site in Uganda (information obtained from the hospital archives and Ministry of Health in each country). Such difference between both countries persisted across years.

Even if it was the only available reference drug, a direct comparison with melarsoprol was considered unreasonable because of the treatment toxicity and the rarity of *rhodesiense* human African trypanosomiasis cases.[26] Melarsoprol treatment is associated with severe adverse drug reactions, most importantly encephalopathy.[9] The fatality rate (safety) was selected as the primary endpoint rather than the overall treatment non-response rate (efficacy) because of the high mortality rate associated with melarsoprol treatment.

When the study was designed, the reported incidence of *rhodesiense* human African trypanosomiasis was very low. Between 2012 to 2017, the annual number of cases in all *rhodesiense* human African trypanosomiasis-endemic countries decreased from 110 patients to 27 patients.[5] The study was done in the two countries that reported most cases over this period.[5] Only two of the participants were enrolled in Uganda despite a wide search. In Malawi, the case search was extended to a second focus of *rhodesiense* human African trypanosomiasis (Nkhotakota), 300 km away from the trial site.

At the end of 2018, fexinidazole was registered for the treatment of *gambiense* human African trypanosomiasis, the most common form of sleeping sickness. There was a strong demand to extend the indication of fexinidazole to *rhodesiense* human African trypanosomiasis given the unacceptable toxicity of the standard of care.[27]

No new safety signals were detected and the safety profile of fexinidazole in participants with *rhodesiense* human African trypanosomiasis remains similar to that in patients with *gambiense* human African trypanosomiasis.[13,16–18]

In general, the participants were admitted in poor health; however, most participants showed rapid improvement in their clinical condition, which could explain the relatively low incidence of participants reporting adverse events during hospital admission (22 [49%] patients reporting 40 adverse events) compared with previous clinical trials in *gambiense* human African trypanosomiasis (>90%).[16–18] Vomiting was reported in six (13%) participants, which is 30% less than the pooled incidence of vomiting in previous fexinidazole studies in *gambiense* human African trypanosomiasis (42%, unpublished). Low haemoglobin levels normalised within 5–6 days without any specific interventions other than treatment with fexinidazole. This aspect could facilitate rural treatment by avoiding blood transfusions. Despite the potential proarrhythmic effect of fexinidazole, only non-serious electrocardiogram abnormalities (including one severe) were reported, even among participants who had been treated for malaria with artemether lumefantrine, which are known proarrhythmic drugs. No signs of hepatotoxicity or cases of neutropenia were observed. As for the identified risk of psychiatric events, none was detected. These findings are also supported by the successful off-label treatment of a Danish patient who contracted stage 2 *rhodesiense* human African trypanosomiasis during a trip to Zambia, showing no sign of relapse over 6 months and no side-effects.[28]

In December, 2023, the European Medicines Agency gave a positive scientific opinion for the extended use of fexinidazole against *rhodesiense* human African trypanosomiasis,[29] and in June, 2024, the WHO treatment guidelines listed fexinidazole as the first-line treatment of *rhodesiense* human African trypanosomiasis for patients aged at least 6 years and weighing 20 kg or more.[9] Fexinidazole has not been studied in younger or lighter children and in pregnant women in their first trimester; its use in these populations may only be considered in exceptional cases.[9,30]

Limitations of this small (ie, 45 participants) study include its benchmark design, a choice dictated by the scarcity of *rhodesiense* human African trypanosomiasis cases, which precluded a comparative trial, and the fact that the primary endpoint included a subjective component, given that the causality of death with regards to *rhodesiense* human African trypanosomiasis or fexinidazole had to be assessed. Despite high parasitaemia at diagnosis (two thirds of participants with >50

trypanosomes in the mAECT in blood), only ten participants had cerebrospinal fluid white-blood-cell counts higher than 100 cells/μL, a concentration that was associated with a higher risk of treatment non-response among patients with *gambiense* human African trypanosomiasis treated with fexinidazole.[9] This characteristic also limits the generalisability of the study findings.

Fexinidazole might contribute to reducing the mortality due to *rhodesiense* human African trypanosomiasis or its treatment in areas that are typically remote and have scarce resources, given that this all-oral treatment is easier to administer and safer than existing drugs. Efficacy of fexinidazole against *rhodesiense* human African trypanosomiasis in both stages can reduce the need for painful lumbar punctures, reduce the costs for patients, and allow simpler patient management.

#### Contributors

BS, OVM, CP, and DA conceived and designed the study. CP and DA managed the study. EM was the Principal Investigator and responsible for the general oversight of the study. ML and CW were the National Coordinating Investigators (in Malawi and Uganda, respectively) and responsible for the study coordination in each country. WN and AE were the Site Principal Investigators and oversaw the study at their site in Malawi and Uganda, respectively. EM had the overall responsibility for the two clinical study sites. EB managed the study data and prepared the final tables, figures, and listings. No authors were prohibited from accessing the data. VL, JS, and AS participated in training the research teams. OVM did a medical review of safety data. AR supported the safety evaluation of the trial. All authors commented on a draft and approved the final version. OVM, BS, DA, EM, EB, and AR had full access to all the data in the study; OVM, BS, EB, and DA verified the data. OVM had final responsibility for the decision to submit for publication.

#### Equitable partnership declaration

The authors of this paper have submitted an equitable partnership declaration (appendix 2). This statement allows researchers to describe how their work engages with researchers, communities, and environments in the countries of study. This statement is part of *The Lancet Global Health*'s broader goal to decolonise global health.

#### Declaration of interests

BS reports personal fees from Drugs for Neglected Diseases initiative (DNDi) during the conduct of the study and personal fees from DNDi outside the submitted work. OVM, CP, DA, and AR report employment at DNDi. All other authors declare no competing interests.

#### Data sharing

The data underlying the results of this study are available upon request because they contain potentially sensitive personal information, which must be de-identified at the individual level. Interested researchers can request access to de-identified participant data from Vivli, the data-sharing partner of the DNDi, commissioner of this study, at https://vivli.org/ourmember/dndi/.

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See **Online** for appendix 2

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