Oral fexinidazole for late-stage African *Trypanosoma brucei gambiense* trypanosomiasis: a pivotal multicentre, randomised, non-inferiority trial

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Summary

Background Few therapeutic options are available to treat the late-stage of human African trypanosomiasis, a neglected tropical disease, caused by *Trypanosoma brucei gambiense* (g-HAT). The firstline treatment is a combination therapy of oral nifurtimox and intravenous eflornithine that needs to be administered in a hospital setting by trained personnel, which is not optimal given that patients often live in remote areas with few health resources. Therefore, we aimed to assess the safety and efficacy of an oral regimen of fexinidazole (a 2-substituted 5-nitroimidazole with proven trypanocidal activity) versus nifurtimox eflornithine combination therapy in patients with late-stage g-HAT.

Methods In this randomised, phase 2/3, open-label, non-inferiority trial, we recruited patients aged 15 years and older with late-stage g-HAT from g-HAT treatment centres in the Democratic Republic of the Congo (n=9) and the Central African Republic (n=1). Patients were randomly assigned (2:1) to receive either fexinidazole or nifurtimox eflornithine combination therapy according to a predefined randomisation list (block size six). The funder, data management personnel, and study statisticians were masked to treatment. Oral fexinidazole was given once a day (days 1–4: 1800 mg, days 5–10: 1200 mg). Oral nifurtimox was given three times a day (days 1–10: 15 mg/kg per day) with eflornithine twice a day as 2 h infusions (days 1–7: 400 mg/kg per day). The primary endpoint was success at 18 months (ie, deemed as patients being alive, having no evidence of trypanosomes in any body fluid, not requiring rescue medication, and having a cerebrospinal fluid white blood cell count ≤20 cells per µL). Safety was assessed through routine monitoring. Primary efficacy analysis was done in the modified intention-to-treat population and safety analyses in the intention-to-treat population. The acceptable margin for the difference in success rates was defined as 13%. This study has been completed and is registered with ClinicalTrials.gov, numberNCT01685827.

Findings Between October, 2012, and November, 2016, 419 patients were pre-screened. Of the 409 eligible patients, 14 were not included because they did not meet all inclusion criteria (n=12) or for another reason (n=2). Therefore, 394 patients were randomly assigned, 264 to receive fexinidazole and 130 to receive nifurtimox eflornithine combination therapy. Success at 18 months was recorded in 239 (91%) patients given fexinidazole and 124 (98%) patients given nifurtimox eflornithine combination therapy, within the margin of acceptable difference of –6·4% (97·06% CI –11·2 to –1·6; p=0·0029). We noted no difference in the proportion of patients who experienced treatment-related adverse events (215 [81%] in the fexinidazole group *vs* 102 [79%] in the nifurtimox eflornithine combination therapy group). Treatment discontinuations were unrelated to treatment (n=2 [1%] in the fexinidazole group). Temporary nifurtimox eflornithine combination therapy interruption occurred in three (2%) patients. 11 patients died during the study (nine [3%] in the fexinidazole group *vs* two [2%] in the nifurtimox eflornithine combination therapy group).

Interpretation Our findings show that oral fexinidazole is effective and safe for the treatment of *T b gambiense* infection compared with nifurtimox eflornithine combination therapy in late-stage HAT patients. Fexinidazole could be a key asset in the elimination of this fatal neglected disease.

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Introduction

Human African trypanosomiasis (HAT; ie, sleeping sickness) is a neglected tropical disease caused by *Trypanosoma brucei gambiense* (g-HAT) transmitted by the tsetse fly. It is a fatal disease that is endemic in sub-Saharan Africa.[1] Most reported cases (>80%) are diagnosed and treated in the Democratic Republic of the Congo.[2]

g-HAT is characterised by clinically distinct stages. The early or haemolymphatic stage is associated with mild non-specific symptoms, including intermittent fever, headache, pruritus, and lymphadenopathy, with trypanosomes being present in the blood and lymphatic system. Without appropriate diagnosis and treatment, the condition progresses to late or meningoencephalitic-stage HAT, in

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Research in context

Evidence before this study

Available treatments for late-stage gambiense human African trypanosomiasis (g-HAT) include melarsoprol, which is associated with an unacceptable rate of severe adverse reactions, eflornithine monotherapy, and the more recently developed nifurtimox eflornithine combination therapy. Experts have highlighted the urgent need to develop easy to use and effective therapies for late-stage HAT by stating that currently available options are suboptimal. The nifurtimox eflornithine combination therapy regimen was shown to be non-inferior to eflornithine monotherapy (lower relapse rates at 18 months, 5·7% with eflornithine and 1·4% with nifurtimox eflornithine combination therapy) and to present safety advantages, as well as a less intensive or frequent regimen of infusions. Thus, nifurtimox eflornithine combination therapy is currently the firstline treatment for late-stage g-HAT. Whereas nifurtimox is administered orally, a major drawback of nifurtimox eflornithine combination therapy treatment is the intravenous administration of eflornithine, which is not convenient in rural hospitals of disease-endemic countries such as the Democratic Republic of the Congo, where the current trial was mainly conducted; oral eflornithine would not provide adequate therapeutic levels in plasma and cerebrospinal fluid for patients with late-stage g-HAT.

Added value of this study

Fexinidazole is a drug candidate with trypanocidal activity identified by the Drugs for Neglected Diseases *initiative* during a data-mining project. First-in-human studies with an oral formulation showed the desired exposure could be obtained with a loading dose of 1800 mg/day for 4 days followed by a 1200 mg/day regimen for 6 days administered with a normal meal, and that this regimen was well tolerated. This study shows that fexinidazole is effective and safe for the treatment of *Trypsanosome brucei gambiense* infection compared with nifurtimox eflornithine combination therapy in late-stage HAT patients, and confirms the clinical interest of fexinidazole. With treatment success rates at 18 months of 91·2% (n=239) in the fexinidazole group versus 97·6% (n=124) in the nifurtimox eflornithine combination therapy group, the difference between groups (–6·4%, 97·06% CI –11·2 to –1·6) was within the predetermined 13% margin of acceptable difference (p=0·0029).

Implications of all the available evidence

Fexinidazole is the only available oral monotherapy developed and tested so far to treat patients with late-stage g-HAT. Development of a new easier-to-use HAT treatment involving a simplified, short-course regimen that can be administered orally at a primary health-care facility fills an unmet need in the control of HAT. Oral treatment circumvents all potential complications associated with intravenous catheter use, which may also have a positive pharmacoeconomic impact. Fexinidazole may be a key asset in the elimination of this fatal neglected disease.

which parasites invade the CNS. These patients display neurological signs such as mental confusion, worsening sleep disturbances and, eventually, coma, and death.[3,4]

Few therapeutic options are available to treat late-stage g-HAT. The firstline treatment nifurtimox eflornithine combination therapy needs to be administered in a hospital setting by trained personnel,[5,6] which is not optimal, given that patients often live in remote areas with few health resources. As such, the development of an easier-to-use g-HAT treatment involving a simplified, short-course regimen that could be given orally at a primary health-care facility would fill an unmet need in this population.[7] Findings of first-in-human studies with an oral formulation of fexinidazole, a 2-substituted 5-nitroimidazole with proven trypanocidal activity that was safe and effective in preclinical studies, showed that the desired exposure could be obtained with a well tolerated 10-day treatment regimen that included a loading dose of 1800 mg per day for 4 days (D1–D4) followed by a 1200 mg per day regimen for 6 days (D5–D10) given with a simple, locally adapted meal.[8,9] In this study we aimed to assess the safety and efficacy of fexinidazole compared with nifurtimox eflornithine combination therapy in the treatment of patients with late-stage g-HAT.

Methods

Study design and participants

In this multicentre, randomised, open-label, active control, parallel-group, pivotal phase 2/3, non-inferiority trial, we recruited patients aged 15 years or older with parasitologically confirmed late-stage g-HAT infection from nine g-HAT treatment centres in the Democratic Republic of the Congo and one in the Central African Republic. Patients were randomly assigned (2:1) to receive either fexinidazole or nifurtimox eflornithine combination therapy. Other patients (ie, non-enrolled) received standard treatment. Patients with g-HAT often live in remote areas with limited resources and infrastructure, and might live in areas of armed conflict. Before starting the study, extensive training courses in good clinical practice, pharmacy management, nursing, hygiene, and waste disposal procedures were performed, involving 34 physicians, 36 laboratory technicians, and 63 nurses.

Individuals who tested positive on a card agglutination test for trypanosomiasis or who had enlarged cervical lymph nodes underwent lymph node puncture and, if negative, further investigations. The WOO test (capillary tube centrifugation) or the mini-anion exchange centrifugation technique in whole blood or

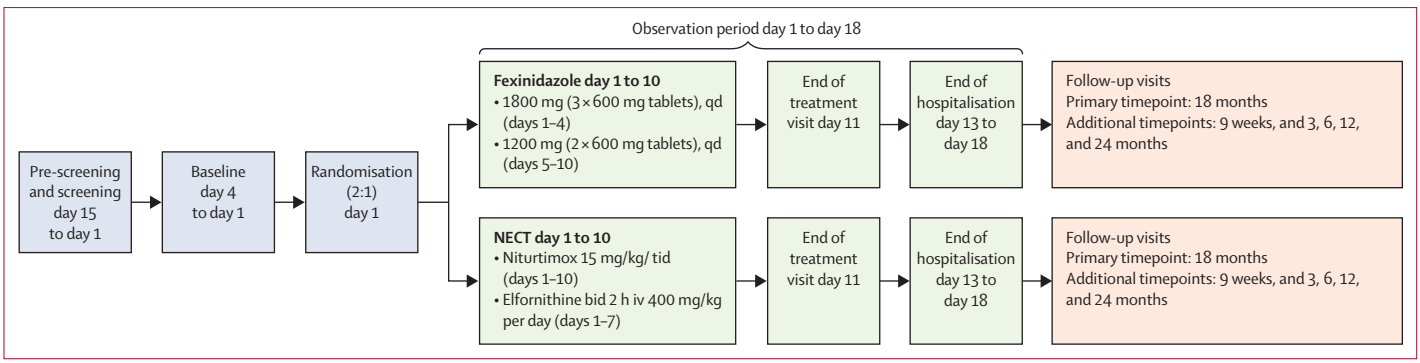

Figure 1: **Study design**
NECT=nifurtimox eflornithine combination therapy. bid=twice per day. qd=once a day. tid=three times a day. iv=intravenous. The week 9 visit was done in a subset of patients, as per protocol amendment.

buffy coat technique[10] were then used to confirm the presence of parasites in blood (appendix). Lumbar puncture was done to detect parasites and establish the white blood cell count in cerebrospinal fluid. Only patients in whom parasites were found in at least one body fluid (ie, blood or lymph node fluid), with a cerebrospinal fluid white blood cell count higher than 20 cells per µL or trypanosomes in the cerebrospinal fluid were eligible. Exclusion criteria included: clinically significant laboratory test abnormalities, pregnancy, unstable abnormalities on electrocardiogram (ECG), QT interval corrected using Fridericia's formula (QTcF) of at least 450 ms (on automatic reading on two successive ECGs in resting position, done 10–20 min apart), and patients not tested for malaria or not having received appropriate treatment for malaria or for soil-transmitted helminthiasis.

The methodology used in this trial was as closely aligned as possible to that of Priotto and colleagues[11] for nifurtimox eflornithine combination therapy so these study results could be used as a benchmark for setting our hypotheses. The study was done in compliance with Good Clinical Practice guideline ICH E6. A novel pre-review process brought together an ad-hoc committee of ethics committee representatives from African and European countries, in collaboration with the Ethics Committee of the Faculty of Medicine of the University of Paris-Descartes and scientific experts under the coordination of the WHO.[12] The committee's recommendations were advisory with final decisions made by host country regional ethics committees. Ethics committees involved in the formal ethical review were Médecins Sans Frontières International Ethical Review Board (Geneva, Switzerland), Research Ethics Committee of the Ministry of Health (Kinshasa, Democratic Republic of the Congo), and the Scientific Committee of the Faculty of Medicine, Bangui University, Central African Republic. All participants gave written informed consent. An independent data safety and monitoring board reviewed the study data regularly.

Randomisation and masking

Patients were randomly assigned (2:1) on day 1 to receive either fexinidazole or nifurtimox eflornithine combination therapy according to a predefined randomisation list stratified by site. Randomisation was centralised to avoid selection bias and occurred in blocks of six patients. The 2:1 randomisation ratio was chosen to increase the number of patients exposed to fexinidazole to strengthen the safety evaluation of this new compound. Every patient received a unique identifier that remained the same throughout the study. This was an open-label study because the route of administration and dosing regimens differed between treatment groups; a double dummy study was not feasible and would have required placebo infusions. However, the funder, data management personnel, and statisticians (except the independent statistician in charge of the interim analysis) were masked to treatment until the final analysis at 18 months.

See Online for appendix

Procedures

Oral fexinidazole was given once a day with food (1800 mg, 3×600 mg tablets) on days 1–4, followed by 1200 mg (2×600 mg tablets) once a day on days 5–10. In the nifurtimox eflornithine combination therapy group, nifurtimox tablets were given three times a day at a dose of 15 mg/kg per day for 10 days (days 1–10) with eflornithine given twice a day as a 2 h intravenous infusion at a total dose of 400 mg/kg for 7 days (days 1–7).

Patients underwent pre-screening (according to the National Sleeping Sickness control programme) and screening, randomisation after signature of informed consent, and baseline assessments were done before treatment initiation. The total duration of treatment was 10 days in both groups. Patients were assessed on day 11 at the end of treatment visit. Patients were admitted to hospital from the time of their arrival at the investigational site until the end of hospitalisation visit between days 13 and 18, when they were permitted to leave if their clinical status was deemed satisfactory by the Principal Investigator (figure 1).

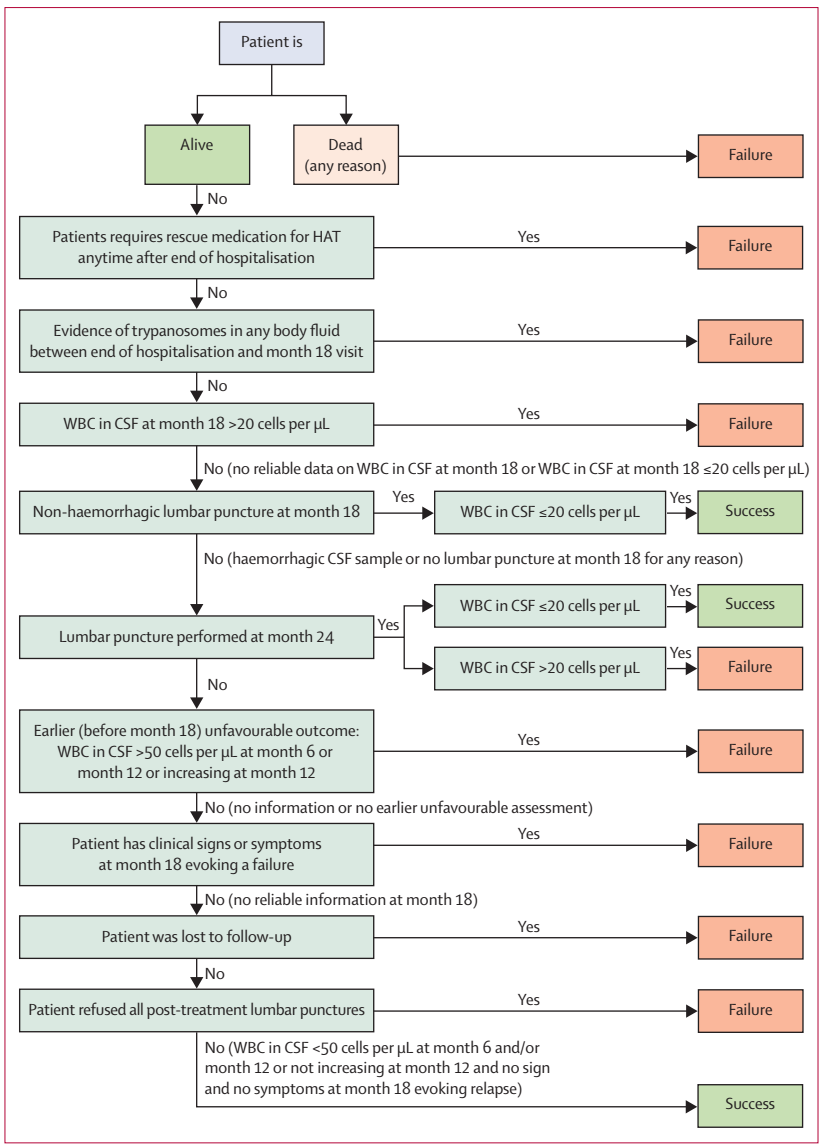

Figure 2: **Algorithm of classification to categorise treatment success**
CSF=cerebrospinal fluid. HAT=human African trypanosomiasis. WBC=white blood cell.

At screening, all patients were tested for malaria infection before being eligible. Patients who tested positive received antimalarial treatment and had a recovery period of at least 3 days before starting study treatment for g-HAT. All patients received treatment for soil-transmitted helminthiasis. Malaria and helminthiasis treatments, and any other drug or procedure required during the 24-month follow up, were provided free of charge by the funder. Unless there was a clear medical need, patients refrained from using any medication to treat concurrent conditions until after g-HAT treatment.

During the hospitalisation period, extensive explorations were done—ie, Karnofsky score, urine pregnancy test, signs and symptoms of HAT, vital signs, physical examination, neurological examination, haematology and biochemistry (baseline, D5, D8, D11), blood sampling on dry blood spot filter paper (for pharmacokinetic measurements in the fexinidazole group): D8 3·5 h, D9 3 h, D10 3 h, and 7 h after dosing, D10 24 h (ie, D11: this timepoint also in cerebrospinal fluid) and 48 h after last D10 dosing (ie, D12). In addition to baseline ECGs, digitalised ECGs for participants given fexinidazole were also recorded on D2, D3, and D4 before daily dosing and D4 4 h and 23 h, D10 2–3 h after dosing; for participants given nifurtimox eflornithine combination therapy on D7 2–3 h and D10 2–3 h. ECGs recording were sent to a central ECG lab for centralised reading. A lumbar puncture was done 1 day after the last study dose and at follow-up visits to assess cerebrospinal fluid for trypanosomes, and to obtain a leukocyte count and pharmacokinetic measurement. Follow-up assessments were done at 3, 6, 12, 18, and 24 months, and included blood and lymph sampling for detection of trypanosomes and cerebrospinal fluid sampling for detection of trypanosomes and white blood cell count (except at M3 when lumbar puncture was only done in case of suspicion of disease progression). The same physical examination as during hospitalisation was done at each follow-up visit (appendix). Of note, the week 9 visit was added as a safety precaution after a protocol amendment. Participants were followed up for 18 months for assessment of the primary endpoint[13] and further long-term follow-up continued to 24 months.

The active pharmaceutical ingredient of fexinidazole was synthesised by Sanofi-Chinoin (Chinoin Pharmaceutical and Chemical Works Private, Budapest, Hungary) and Centipharm (Grasse, France). The manufacture and quality control of fexinidazole tablets was done by Aptuit Verona (Verona, Italy). Nifurtimox eflornithine combination therapy was bought from MSF logistic Bordeaux (Mérignac, France). The labelling, packaging, and central storage (before distribution) of the investigational medicinal products and comparator were done by Bertin Pharma (Artigues, France). Fexinidazole tablets were packaged in aluminium-aluminium blister packs. Ten blister packs were packaged in an individual treatment pack, sufficient to treat one patient. Nifurtimox eflornithine combination therapy was provided in its originator primary packaging, with its original label covered by the specific study label. Nifurtimox tablets (Lampit) and eflornithine bottles (Ornidyl) were provided for each patient in a cardboard box specially designed as secondary packaging for the study. The two products were labelled for the study and packaged in an individual treatment pack, sufficient to treat one patient. The material required for the sterile infusions was packaged in separate packs.

Outcomes

The primary objective was to show the success rate with oral fexinidazole was within an acceptable margin of

difference with nifurtimox eflornithine combination therapy, as assessed at the test of cure visit, 18 months after the end of treatment (figure 1), based on adapted WHO criteria.[14] The treatment was deemed a success at 18 months if: patients were alive, had no evidence of trypanosomes in any body fluid, did not require rescue medication, and had a cerebrospinal fluid white blood cell count of 20 cells per µL or lower. Patients who refused a lumbar puncture (or who had a haemorrhagic cerebrospinal fluid sample) at month 18 were deemed a success if none of the criteria for failure were met at month 24. A specific algorithm was built to evaluate the success rate of patients if no lumbar puncture was available at any planned intervention (figure 2).

The safety and tolerability of treatment was assessed through routine monitoring of adverse events during the observation period from day 1 to day 18. Serious adverse events were reported and collected from the signature of informed consent up to the end of the follow-up period. Any clinical sign, symptom, or abnormal laboratory result was reported as an adverse event if it occurred or worsened after the start of study treatment and till the end of hospitalisation, and if the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE, version 4.03) grade was higher than 1. Patients were advised to return to the investigational site at any time during the follow-up period if they experienced any adverse events.

Statistical analysis

A sample size of 390 patients was calculated assuming a success rate of 89% for fexinidazole and 94% for nifurtimox eflornithine combination therapy and a 13% margin of acceptable difference, using a global power of 80%, with a global one-sided type I error rate of 0·025. The power refers to the probability that the 95% confidence interval (CI) of the difference in success rates between treatment groups would exclude the chosen limit of an unacceptable difference. Once adjusted for multiplicity of testing, the CI was 97·06%. The 13% difference in success rate between treatments was defined following an email survey of experienced g-HAT physicians (n=19) mainly from the most endemic countries who independently provided their thresholds of unacceptable difference in the context of advantages provided by an oral regimen. Two-thirds of the respondents considered a threshold of 13% or higher as non-acceptable.

No provision for patients lost to follow-up was planned, because the missing outcomes were imputed (failure), with the exception of the five patients (two assigned to fexinidazole and three assigned to nifurtimox eflornithine combination therapy) fleeing an area of armed conflict (in Central African Republic) after the start of the study who had no post-treatment data available. These patients were removed from the primary analysis set and replaced by four other patients, to reach the expected sample size; they were not taken into account in the primary efficacy analysis, but were included in the safety analysis.

The primary efficacy analysis was initially planned to be performed on the intention-to-treat population consisting of all patients who took at least one dose. Due to armed conflict in Central African Republic the intention-to-treat and per-protocol populations were amended to exclude all patients of this region who did not have any post-hospitalisation visit due to the war conditions. The primary analysis was done in this modified

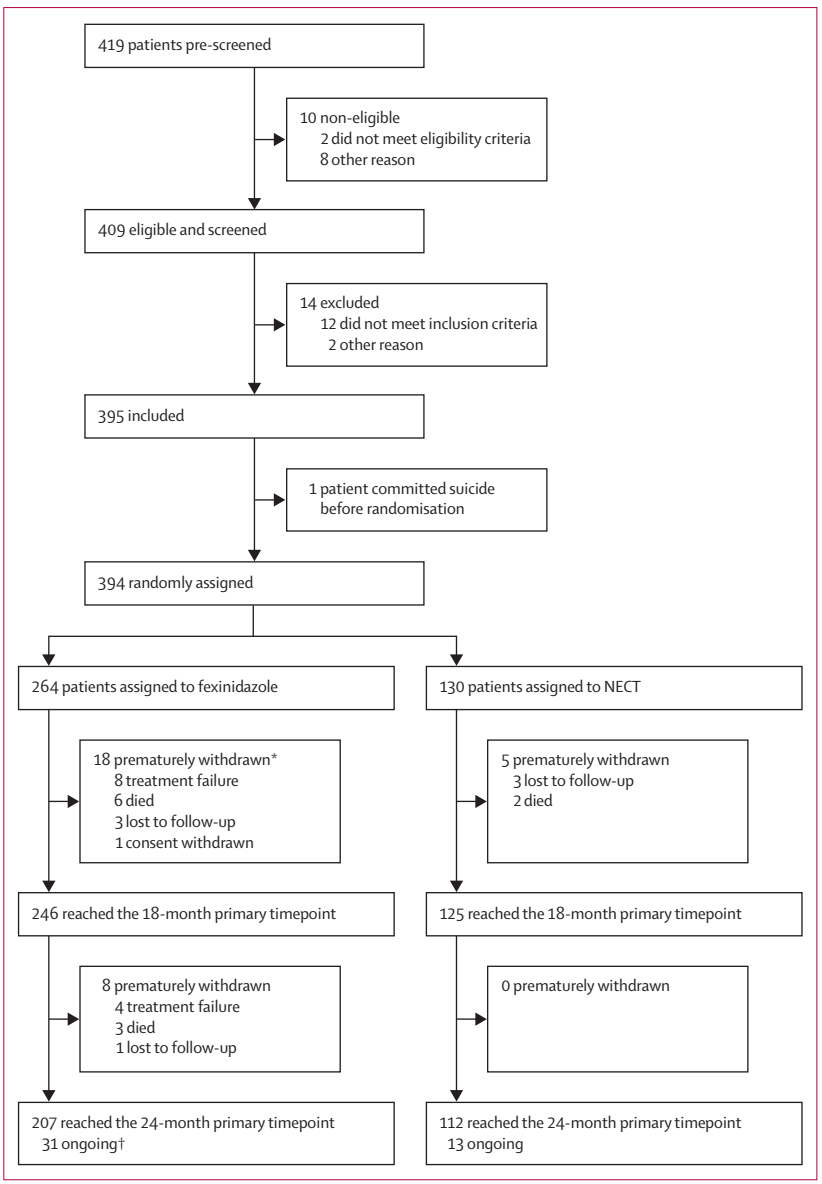

Figure 3: **Trial profile and patient disposition**
NECT=nifurtimox eflornithine combination therapy. *In the fexinidazole group, two additional patients were prematurely withdrawn. In the NECT group three additional patients were prematurely withdrawn. These five patients were excluded from the modified intention-to-treat population and are not taken into account in this flowchart. †One patient assigned to fexinidazole is considered ongoing because the end-of-study status was determined after the clinical database had been exported. However, the patient attending the 24-month visit should be considered completed.

intention-to-treat population. A sensitivity analysis was added to include the intention-to-treat population (here equal to the randomised one). Statistical analysis of the primary efficacy endpoint was done using the Blackwelder non-inferiority test.[15] The two-sided Pocock-adjusted CI for the difference was associated with the Blackwelder test. All summaries and statistical analyses were generated with SAS software (version 9.4).

This study is registered with ClinicalTrials.gov, number NCT01685827.

	Fexinidazole (n=264)	Nifurtimox eflornithine combination therapy group (n=130)
Demographics		
Men	161 (61·0%)	80 (61·5%)
Women	103 (39·0%)	50 (38·5%)
Age (years)	34·5 (12·6)	35·3 (13·2)
Weight (kg)	50·5 (8·2)	50·7 (9·6)
BMI (kg/m²)	19·2 (2·4)	19·2 (2·4)
Parasitological findings		
HAT examination performed	264 (100·0%)	130 (100·0%)
Presence of trypanosomes		
In lymph nodes	99 (37·6%)	41 (31·5%)
In blood		
CATT	260 (98·5%)	130 (100·0%)
Thin blood smear	3 (1·1%)	2 (1·5%)
Thick blood smear	1 (0·4%)	0 (0·0%)
CTC (WOO)	68 (25·9%)	31 (23·8%)
mAECT	55 (20·9%)	25 (19·2%)
mAECT- buffy coat	29 (11·0%)	24 (18·5%)
In cerebrospinal fluid	175 (66·3%)	90 (69·2%)
White blood cells in cerebrospinal fluid	378 (670·6%)	317·1 (427·6%)
Vital signs and general health		
SBP (mm Hg)	106·1 (12·7)	108·4 (13·7)
DBP (mm Hg)	70·7 (9·4)	72·3 (9·2)
Heart rate (bpm)	78·2 (11·6)	79·8 (10·7)
Respiratory rate per min	20·2 (3.0)	20·0 (2·8)
Temperature (°C)	36·6 (0·6)	36·7 (0·50)
General health-altered	85 (32·2%)	40 (30·8%)

Data are n (%), mean (SD). bpm=beats per minute. CATT=card agglutination test for trypanosomiasis. CTC (WOO)=capillary tube centrifugation. DBP=diastolic blood pressure. HAT=human African trypanosomiasis. mAECT=mini-anion exchange centrifugation technique. SBP=systolic blood pressure.

Table 1: **Baseline characteristics**

	Fexinidazole group	Nifurtimox eflornithine combination therapy group	Difference between proportions	p value
Modified intention-to-treat	239/262 (91·2%)	124/127 (97·6%)	–6·42% (–11·22 to –1·61)	0·0029
Intention-to-treat	239/264 (90·5%)	124/130 (95·4%)	–4·85% (–10·46 to 0·76)	0·0016
Per protocol	239/262 (91·2%)	124/126 (98·4%)	–7·19% (–11·71 to –2·68)	0·0051

Data are n/N (%) or % (97·06% CI) unless otherwise stated. p value from a Blackwelder test (with a non-inferiority margin of –13%). A p value <0·0294 is significant. The CI of the difference between treatment groups was adjusted for multiplicity.

Table 2: **Treatment success rates (non-inferiority analysis) at 18 months by analysis population**

Role of funding source

The funder was responsible for the study design, data collection, data analysis, data interpretation, and writing and reviewing the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Recruitment of patients was met with difficulties. Between October, 2012, and November, 2016, more than half a million people were screened to identify 419 patients who were pre-screened. Of these, ten (2%) patients were not eligible. Of the 409 eligible patients who signed the informed consent, 14 patients were not included because they did not meet all inclusion criteria (n=12) or for another reason (n=2). Of the 395 patients included in the study, one committed suicide before randomisation. Therefore, 394 patients were randomly assigned, 264 of whom were assigned to fexinidazole and 130 to nifurtimox eflornithine combination therapy (figure 3). All randomly assigned patients received at least one dose and were included in the intention-to-treat population.

Table 1 shows the baseline characteristics of trial participants. Similar demographic characteristics were noted in the primary analysis population in both treatment groups. Medical history and clinical presentation at inclusion were consistent with late-stage g-HAT. Of note, mean bodyweight was 50·6 kg (IQR 45–56), and mean BMI was 19·2 kg/m², with 75% of patients having a BMI lower than 20·7 kg/m². At screening, nervous system disorders were recorded in 67 (25%) of patients randomly assigned to receive fexinidazole and in 34 (26%) patients randomly assigned to nifurtimox eflornithine combination therapy. The most common reported clinical signs and symptoms of HAT at the inclusion visit included headache (281 [71%]), pruritus (228 [57%]), sleepiness (218 [55%]), weight loss (217 [55%]), and asthenia (216 [55%]).

In the intention-to-treat population, 31 (8%) patients were prematurely withdrawn from the 18-month analysis, 26 (10%) in the fexinidazole group and five (4%) in the nifurtimox eflornithine combination therapy group. In the fexinidazole group, the main reasons for study withdrawal were treatment failure (administration of rescue treatment; n=12), death (n=9), loss to follow-up (n=4), and consent withdrawal (n=1). In the nifurtimox eflornithine combination therapy group, study

withdrawals were caused by loss to follow-up (n=3) or death (n=2). Apart from the two patients who died during treatment in the fexinidazole group, all patients completed treatment.

At the time of database lock (Jan 5, 2017), 371 (94%) patients had reached the primary timepoint at 18 months, 246 (93%) in the fexinidazole group and 125 (96%) in the nifurtimox eflornithine combination therapy group (figure 3). The remaining patients were withdrawn before 18 months: 18 (7%) in the fexinidazole group and five (4%) in the nifurtimox eflornithine combination therapy group (figure 3).

Success rates at 18 months were higher than expected in both treatment groups: 91·2% in the fexinidazole group (89% expected) and 97·6% in the nifurtimox eflornithine combination therapy group (94% expected). 23 (9%) patients were considered treatment failures in the fexinidazole group compared with three patients (2%) in the nifurtimox eflornithine combination therapy group. The observed difference in success rate between groups (–6·4%, 97·06% CI –11·2 to –1·6; p=0·0029]) remained within the margin of acceptable difference, set at –13% (p=0·0294; table 2). Therefore, the primary endpoint comparing treatment efficacy of fexinidazole with nifurtimox eflornithine combination therapy was met. Because of limited information about the patient's status in five debatable cases, these were reviewed by three independent experts who were masked to site and treatment allocation. In two cases, the experts deemed the outcome as a success although the conservative algorithm of classification (figure 2) had classified them as failures. In the three remaining cases, the experts confirmed the classification by the algorithm and declared the patients' outcome a success. Sensitivity analyses using different populations provided very consistent results.

Regarding the timing of the 23 treatment failures in the fexinidazole group, 16 (70%) of 23 failures occurred within 12 months after the end of treatment. Classification as failure was based on disease relapse in 15 (65%) patients, death in six (26%), loss to follow-up or absence of lumbar puncture at 18 and 24 months in one (4%) patient, and consent withdrawal in one (4%) patient. In the combination therapy group, two (67%) of three failures occurred within 12 months of treatment completion. Two patients were classified as treatment failures due to death, and one patient had no lumbar puncture at 18 and 24 months. In the sensitivity analysis done in the intention-to-treat population including Central African Republic, 239 (90%) patients showed success in the fexinidazole group versus 124 (95%) in the combination therapy group. The difference was less than 5% (–4·85%, 97·06% CI –10·46 to 0·76; p=0·0016). In the per-protocol population, excluding one patient who was a failure after nifurtimox eflornithine combination therapy but presented a deviation at inclusion (ie, severely deteriorated general status), the results were the following: 239 patients showing success (91%) in the fexinidazole group versus 124 patients (98%) in the combination therapy group (difference –7·19%, –11·71 to –2·68; p=0·0051).

	Fexinidazole group (n=264)	Nifurtimox eflornithine combination therapy group (n=130)
At least one adverse event	247 (94%) [1525]	121 (93%) [608]
At least one treatment-emergent adverse event	247 (94%) [1525]	120 (92%) [597]
At least one serious adverse event	31 (12%) [51]	13 (10%) [22]
At least one treatment-emergent adverse event resulting in death	9 (3%) [11]	2 (2%) [2]

Data are n (%) [number of events]. Dictionary used MedDRA version 16.0. A serious adverse event was defined as any adverse event that resulted in death, was life-threatening or required hospitalisation or prolongation of hospitalisation, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, or was an important medical event that might not have been immediately life-threatening or resulted in death or hospitalisation but might have jeopardised the patient or might have required intervention to prevent one of the other outcomes listed in the definition above.

Table 3: **Summary of all adverse events (intention-to-treat population)**

	Fexinidazole group (n=264)	Nifurtimox eflornithine combination therapy group (n=130)	p value
All treatment-emergent adverse events	247 (94%) [1525]	120 (92%) [597]	0·669
Nervous system disorders	158 (60%) [308]	63 (49%) [113]	0·036
Headache	92 (35%) [134]	31 (24%) [44]	0·025
Tremor	58 (22%) [68]	14 (11%) [15]	0·005
Dizziness	50 (19%) [56]	17 (13%) [22]	0·138
Convulsion	5 (2%) [5]	10 (8%) [14]	0·010
Extrapyramidal disorder	9 (3%) [9]	2 (2%) [2]	0·267
Gastrointestinal disorders	157 (60%) [353]	63 (49%) [127]	0·043
Vomiting	75 (28%) [101]	37 (29%) [46]	0·974
Nausea	68 (26%) [73]	25 (19%) [26]	0·152
Dyspepsia	34 (13%) [43]	10 (8%) [11]	0·237
Abdominal pain	25 (10%) [29]	16 (12%) [17]	0·385
Abdominal pain upper	27 (10%) [32]	6 (5%) [8]	0·049
Salivary hypersecretion	16 (6%) [17]	3 (2%) [3]	0·084
Constipation	13 (5%) [14]	2 (2%) [2]	0·076
Diarrhoea	8 (3%) [8]	5 (4%) [5]	0·669
Gastritis	8 (3%) [13]	1 (1%) [1]	0·123
Abdominal distension	8 (3%) [8]	0 [0]	0·011
Metabolism and nutrition disorders	131 (50%) [190]	64 (49%) [95]	0·970
Decreased appetite	56 (21%) [58]	24 (19%) [29]	0·532
Hyperkalaemia	27 (10%) [29]	25 (19%) [26]	0·015
Hypocalcaemia	36 (14%) [37]	3 (2%) [3]	0·000
Hyponatraemia	20 (8%) [21]	15 (12%) [18]	0·198
Hypoalbuminaemia	23 (9%) [24]	4 (3%) [4]	0·027
Hyperglycaemia	9 (3%) [9]	9 (7%) [9]	0·125

(Table 4 continues on next page)

	Fexinidazole group (n=264)	Nifurtimox eflornithine combination therapy group (n=130)	p value
(Continued from previous page)			
General disorders and administration site conditions	122 (46%) [184]	50 (39%) [83]	0·152
Asthenia	60 (23%) [73]	18 (14%) [22]	0·033
Pyrexia	23 (9%) [27]	24 (19%) [27]	0·006
Feeling hot	25 (10%) [29]	3 (2%) [4]	0·004
Chest pain	23 (9%) [25]	4 (3%) [4]	0·027
Chills	4 (2%) [4]	12 (9%) [12]	0·000
Gait disturbance	12 (5%) [13]	2 (2%) [2]	0·105
Psychiatric disorders	103 (39%) [159]	23 (18%) [31]	0·000
Insomnia	74 (28%) [83]	15 (12%) [17]	0·000
Agitation	10 (4%) [14]	1 (1%) [1]	0·058
Psychotic disorder	7 (3%) [7]	4 (3%) [5]	0·806
Anxiety	10 (4%) [10]	0 [0]	0·004
Musculoskeletal and connective tissue disorders	58 (22%) [92]	20 (15%) [28]	0·121
Back pain	30 (11%) [36]	11 (9%) [14]	0·374
Neck pain	23 (9%) [27]	7 (5%) [8]	0·232
Blood and lymphatic system disorders	29 (11%) [33]	18 (14%) [19]	0·407
Anaemia	24 (9%) [25]	14 (11%) [14]	0·591
Respiratory, thoracic, and mediastinal disorders	32 (12%) [34]	11 (9%) [18]	0·269
Cough	16 (6%) [16]	6 (5%) [6]	0·556
Vascular disorders	24 (9%) [26]	9 (7%) [10]	0·465
Hot flush	13 (5%) [13]	4 (3%) [4]	0·387
Hypertension	12 (5%) [12]	1 (1%) [2]	0·027
Infections and infestations	22 (8%) [33]	8 (6%) [10]	0·441
Skin and subcutaneous tissue disorders	22 (8%) [23]	8 (6%) [9]	0·441
Pruritus	10 (4%) [11]	4 (3%) [5]	0·722
Injury, poisoning and procedural complications	15 (6%) [18]	14 (11%) [20]	0·075
Procedural pain	7 (3%) [7]	9 (7%) [9]	0·050
Cardiac disorders	18 (7%) [21]	7 (5%) [10]	0·584
Palpitations	13 (5%) [16]	5 (4%) [5]	0·630
Renal and urinary disorders	13 (5%) [16]	7 (5%) [8]	0·839
Eye disorders	15 (6%) [18]	3 (2%) [3]	0·112
Investigations	7 (3%) [8]	10 (8%) [10]	0·025

Data are n (%) [number of events]. Dictionary used MedDRA (version 16.0).

Table 4: **Summary of treatment-emergent adverse events reported in at least 3% of patients in either group, intention-to-treat population**

According to the Kaplan-Meier approach based on the time to proven and definitive failure, the failure-free rate at 18 months was 93% with fexinidazole and 98% with nifurtimox eflornithine combination therapy (in the modified intention-to-treat population). The difference in failure-free rates of 5% in favour of nifurtimox eflornithine combination therapy is consistent with what was expected.

A similar percentage of patients who received at least one treatment dose in either treatment group experienced treatment-emergent adverse events during the study: 247 (94%) patients in the fexinidazole group compared with 120 (92%) in the nifurtimox eflornithine combination therapy group (tables 3 and 4). During the 10-day treatment period, 235 (89%) patients in the fexinidazole group and 115 (89%) in the combination therapy group experienced treatment-emergent adverse events. After end of treatment, 117 (44%) patients in the fexinidazole group experienced treatment-emergent adverse events compared with 66 (51%) in the nifurtimox eflornithine combination therapy group. HAT signs and symptoms at the 3-month follow-up timepoint had reduced markedly in both groups (figure 4).

There was no difference between groups in the proportion of treatment-emergent adverse events deemed related to treatment: 215 (81%) patients in the fexinidazole group compared with 102 (79%) in the nifurtimox eflornithine combination therapy group. Most adverse events were of mild or moderate intensity in both groups, whilst severe treatment-emergent adverse events were reported in 60 (23%) of patients in the fexinidazole group and 28 (22%) of patients in the nifurtimox eflornithine combination therapy. The most frequently reported treatment-emergent adverse events (>15% of patients overall) were: headache (123 [31%]), vomiting (112 [28%]), nausea (93 [24%]), insomnia (89 [23%]), decreased appetite (80 [20%]), asthenia (78 [20%]), tremor (72 [18%]), and dizziness (67 [17%]). Except for vomiting, which was reported in a similar percentage of patients in the fexinidazole (75 [28%]) and nifurtimox eflornithine combination therapy groups (37 [29%]), these treatment-emergent adverse events were reported in a higher percentage of patients who received fexinidazole. The largest differences between groups were reported for insomnia (74 [28%] *vs* 15 [12%]), followed by tremor (58 [22%] *vs* 14 [11%]), headache (92 [35%] *vs* 31 [24%]), asthenia (60 [23%] *vs* 18 [14%]), nausea (68 [26%] *vs* 25 [19%]), and dizziness (50 [19%] *vs* 17 [13%]). A smaller difference between groups was reported for decreased appetite (56 [21%] *vs* 24 [19%]).

73 serious adverse events were reported during the entire study, with a similar incidence in both treatment groups: 51 (12%) in patients who received fexinidazole and 22 (10%) in patients given nifurtimox eflornithine combination therapy (table 3). Most serious adverse events started after the treatment period (46 [90%] and 20 [90%], respectively) and most were considered unrelated to treatment (47 [92%] and 22 [100%], respectively). Four serious adverse events considered possibly related to treatment were reported in three patients who received fexinidazole: personality change (n=2), acute psychosis (n=1), and hyponatraemia (n=1). One of these patients with personality change died from an unrelated serious adverse event following the use of traditional medicine administered by a local healer, between end of treatment and month 3, and the three other cases recovered.

Treatment was permanently discontinued due to a serious adverse event deemed unrelated to treatment in two (1%) patients, both in the fexinidazole group; the two patients died during treatment. Treatment was temporarily interrupted due to an adverse event in three (2%) patients, all in the nifurtimox eflornithine combination therapy group. There were 11 deaths in the intention-to-treat population, in nine (3%) patients who received fexinidazole and in two (2%) patients who received combination therapy.

There were no clinically significant changes in any haematology parameters and laboratory values over the duration of treatment. The pharmacokinetic results (to be reported separately) confirmed the correct exposure of g-HAT patients in agreement with the target exposure established to cure the disease, including cerebrospinal fluid exposure. The ECG analyses (15 ECGs recorded in patients in the fexinidazole group) showed the same effect on QTcF as in the healthy volunteers study: fexinidazole treatment resulted in an increase in QTcF of 15–20 ms with an increase in heart rate of around 8 beats per min. 19 (7%) patients in the fexinidazole group had a QTcF betwen 450 and 500 ms compared with none in the nifurtimox eflornithine combination therapy group. No clinical cardiac adverse event was reported.

Discussion

Our findings show that the difference in efficacy between fexinidazole and the standard nifurtimox eflornithine combination therapy combination therapy 18 months after end of treatment was within the predetermined acceptability margin of 13% even though a difference was recorded in favour of nifurtimox eflornithine combination therapy, as was expected due to the nature of the treatments. The primary endpoint was therefore met.

In view of the advantages expected of an oral treatment (ie, the removal of the need for infusions, and systematic hospitalisation, and the direct and indirect cost advantages), we deemed some loss of efficacy versus nifurtimox eflornithine combination therapy as acceptable. Findings of the primary analysis and most sensitivity analyses showed that the recorded difference between treatments remained within the predefined acceptability limit; thus, this study confirmed the therapeutic interest of fexinidazole in late-stage g-HAT patients, provided that safety is similar.

This study used more stringent criteria for failure than the reference nifurtimox eflornithine combination therapy trial of Priotto and colleagues.[11] The intention-to-treat population in the present trial considered all deaths as failure, including those not related to the treatment or HAT. The per-protocol population considers the patients lost to follow up as failures. Those two parameters were not considered as failure in the nifurtimox eflornithine combination therapy trial.

The results of this study show that fexinidazole is fairly well tolerated compared with nifurtimox eflornithine combination therapy. There was no significant difference in the number of deaths from any reason between treatment groups, which was lower than the 5·9% fatality

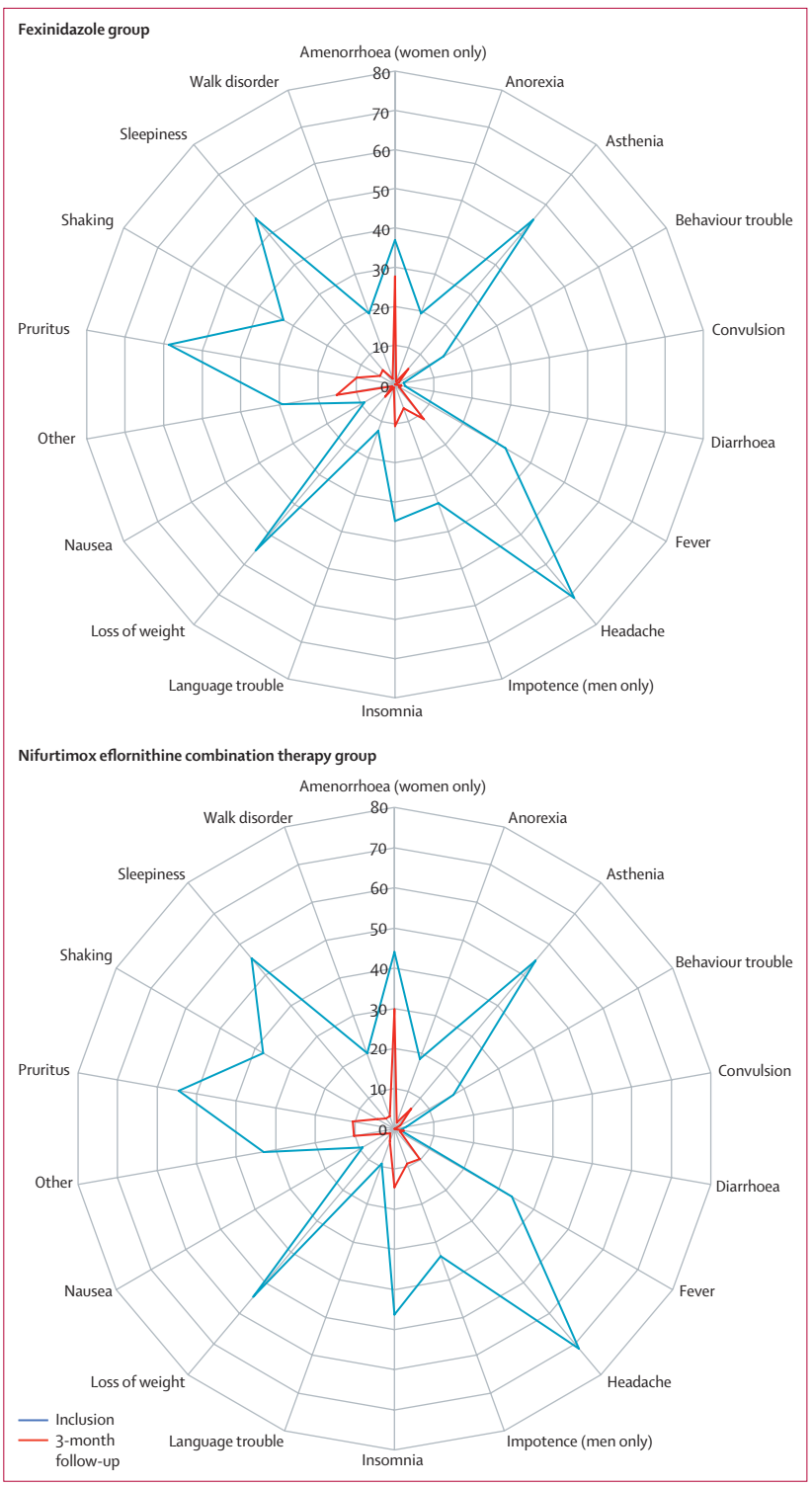

Figure 4: HAT clinical signs and symptoms from inclusion to month 3 in the intention-to-treat population
HAT=human African trypanosomiasis.

rates reported after treatment with melarsoprol,[16] the most widely used drug for treatment of HAT before the introduction of nifurtimox eflornithine combination therapy.[17] None of the 11 deaths that occurred during the study were considered related to treatment. Four serious adverse events considered possibly related to treatment were reported in three patients who received fexinidazole (personality change, acute psychosis, and hyponatraemia); one patient with personality change died later from an unrelated serious adverse event following the use of traditional medicine, and the three other cases recovered. The proportion of treatment-emergent adverse events deemed related to treatment was high in both treatment groups, and no significant differences were reported between groups. Because g-HAT is a fatal condition, and adverse events are very common during treatment, the tolerability assessment focused on major (severe) drug-related adverse events. Overall, the most frequently reported treatment-emergent adverse events that were possibly related to treatment were of mild to moderate intensity, all of which were reported in a higher percentage of patients given fexinidazole, except for vomiting.

The current study is potentially limited by its unavoidable open-label design, owing to the different methods of drug administration in the treatment groups. However, the sponsor, data management personnel, and study statisticians were kept masked to treatment until the final analysis at month 18. Moreover, quality control measures were implemented to avoid technical biases and to control for the operational bias of an open-label trial. The primary endpoint was mainly driven by objective criteria for success (up to 18 months), such as patient alive, absence of trypanosomes in any body fluid at every follow-up visit, no use of rescue medication, white blood cell count in cerebrospinal fluid 20 cells per µL or lower, and no signs and symptoms evoking a relapse. In the safety analysis, our study is strengthened by the fact that both groups had the same duration of treatment and hospitalisation of 10 days, despite the different treatments (different hospitalisation times could lead to an imbalance in the number of recorded adverse events).

HAT sleeping sickness experts have highlighted the urgent need to develop easy to use and effective treatments for late-stage g-HAT by stating that currently available options are suboptimal.[18] This study shows that fexinidazole is safe and effective for the treatment of late-stage *T b gambiense* infection. Fexinidazole is the only available oral monotherapy regimen developed and tested so far to treat patients with late-stage g-HAT. From a clinical practice perspective, use of an oral regimen with acceptable efficacy compared with the nifurtimox eflornithine combination therapy standard of care is a great advantage because its administration is much easier and is not associated with any of the potential complications relating to intravenous catheter use such as compulsory hospitalisation for treatment administration or risk of infection. A positive effect on patient management is expected. Oral treatment could benefit patients who are unwilling to be treated in hospital; in the future, these patients could receive home-based treatment. This new approach to treatment is currently being tested in a phase 3b study and could potentially increase accessibility to treatment, reaching more people in need.[19] The availability of an oral regimen should also have positive financial effects both at the patient level (removing the need to remain hospitalised; travel to a health-care centre; pay for hospitalisation-related costs, including food; and reduced interruption of employment), and at the health-care level, because oral administration requires fewer medical resources, which would simplify the logistic complexity (much lower volume of treatment supplies) and cost, alleviating the financial burden on HAT control programmes.

Contributors

The study was conceived and designed by NS-W, AT, BS, OVM, and SBl, and managed by CB, SBl, FS, SBe, and SD. The Principal Investigator (VKBKM) was responsible for the general oversight of the study. The Coordinating Investigators (WMK, DNT) were responsible for the management of the investigator team. CL and VKBKM had the overall responsibility for all clinical study sites. Clinical trial investigators (J-PFL, WK, MI, PNN, FRD, JAH, GM, LKB, AKB, PKL, JLLS, HMM, SLV) oversaw the study at the sites in Democratic Republic of the Congo and Central African Republic. OVM performed a medical review of safety data. The HAT coordinator (SD) supported site selection, organised staff trainings, and was involved in the logistic support. SBe provided study coordination and monitoring. All authors commented on a draft and approved the final version.

Declaration of interests

SBe reports grants from Drugs for Diseases *initiative* (DND*i*) during the conduct of the study and grants outside the submitted work; BS was responsible for the planned statistical strategy and received fees for this service; all other authors declare no competing interests.

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References

1 Franco JR, Simarro PP, Diarra A, Jannin JG. Epidemiology of human African trypanosomiasis. *Clin Epidemiol* 2014; **6:** 257–75.

2 Lumbala C, Simarro PP, Cecchi G, et al. Human African trypanosomiasis in the Democratic Republic of the Congo: disease distribution and risk. *Int J Health Geogr* 2015; **14:** 20.

3 Malvy D, Chappuis F. Sleeping sickness. *Clin Microbiol Infect* 2011; **17:** 986–95.

4 Stich A, Abel PM, Krishna S. Human African trypanosomiasis. *BMJ* 2002; **325:** 203–06.

5 Schmid C, Kuemmerle A, Blum J, et al. In-hospital safety in field conditions of nifurtimox eflornithine combination therapy (nifurtimox eflornithine combination therapy) for *T. b. gambiense* sleeping sickness. *PLoS Negl Trop Dis* 2012; **6:** e1920.

6 Simarro PP, Diarra A, Ruiz Postigo JA, Franco JR, Jannin JG. The human African trypanosomiasis control and surveillance programme of the World Health Organization 2000–2009: the way forward. *PLoS Negl Trop Dis* 2011; **5:** e1007.

7 Torreele E, Bourdin Trunz B, Tweats D, et al. Fexinidazole–a new oral nitroimidazole drug candidate entering clinical development for the treatment of sleeping sickness. *PLoS Negl Trop Dis* 2010; **4:** e923.

8 Kaiser M, Bray MA, Cal M, Bourdin Trunz B, Torreele E, Brun R. Antitrypanosomal activity of fexinidazole, a new oral nitroimidazole drug candidate for treatment of sleeping sickness. *Antimicrob Agents Chemother* 2011; **55:** 5602–08.

9 Tarral A, Blesson S, Mordt OV, et al. Determination of an optimal dosing regimen for fexinidazole, a novel oral drug for the treatment of human African trypanosomiasis: first-in-human studies. *Clin Pharmacokinet* 2014; **53:** 565–80.

10 Camara M, Camara O, Ilboudo H, et al. Sleeping sickness diagnosis: use of buffy coats improves the sensitivity of the mini anion exchange centrifugation test. *Trop Med Int Health* 2010; **15:** 796–99.

11 Priotto G, Kasparian S, Mutombo W, et al. Nifurtimox-eflornithine combination therapy for second-stage African *Trypanosoma brucei gambiense* trypanosomiasis: a multicentre, randomised, phase III, non-inferiority trial. *Lancet* 2009; **374:** 56–64.

12 Coleman CH, Ardiot C, Blesson S, et al. Improving the quality of host country ethical oversight of international research: the use of a collaborative 'pre-review' mechanism for a study of fexinidazole for human African trypanosomiasis. *Dev World Bioeth* 2015; **15:** 241–47.

13 WHO. Recommendations of the informal consultation on issues for clinical product development for human African trypanosomiasis. WHO/CDS/NTD/IDM/2007.1. Geneva: World Health Organization, 2007.

14 Committee for Medicinal Products for Human Use (CHMP). Guideline on the choice if the non-inferiority margin. The European Medicines Agency. 2005;EMEA/CPMP/EWP/2150/99.

15 Blackwelder WC. "Proving the null hypothesis" in clinical trials. *Control Clin Trials* 1982; **3:** 345–53.

16 Schmid C, Richer M, Bilenge CM, et al. Effectiveness of a 10-day melarsoprol schedule for the treatment of late-stage human African trypanosomiasis: confirmation from a multinational study (IMPAMEL II). *J Infect Dis* 2005; **191:** 1922–31.

17 Robays J, Nyamowala G, Sese C, et al. High failure rates of melarsoprol for sleeping sickness, Democratic Republic of Congo. *Emerg Infect Dis* 2008; **14:** 966–67.

18 WHO. Control and surveillance of human African trypanosomiasis: report of a WHO expert committee. WHO Technical Report Series No. 984. Geneva: World Health Organization, 2013.

19 Sutherland CS, Stone CM, Steinmann P, Tanner M, Tediosi F. Seeing beyond 2020: an economic evaluation of contemporary and emerging strategies for elimination of *Trypanosoma brucei* gambiense. *Lancet Glob Health* 2017; **5:** e69–79.