DNDi
Drugs for Neglected Diseases *initiative*

CLINICAL STUDY PROTOCOL

Efficacy and Safety of Fexinidazole in Patients with Stage-1 or Early Stage-2 Human African Trypanosomiasis (HAT) due to *T.b. gambiense*: a Prospective, Multicentre, Open-label, Cohort Study, Plug-in to the Pivotal Study

Name of Product/Project Code	Fexinidazole
Drug Class	Antiprotozoals
Phase	Cohort study
Indication	Human African Trypanosomiasis (HAT) due to *Trypanosoma brucei gambiense* (stage-1 or early stage-2 HAT)
Protocol Number	DNDiHATFEX005
Sponsor	DND*i*, 15 chemin Louis Dunant, 1202 Geneva, Switzerland Tel: +41 22 906 9230
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In this public version of the protocol, the signature pages have been removed.

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Abbreviations – Glossary of Terms

ACT	Artemisinin-based Combination Treatment
AE	Adverse Event
ALT	Alanine Aminotransferase (SGPT/ALAT)
AST	Aspartate Aminotransferase (SGOT/ASAT)
BMI	Body-Mass Index
CATT	Card Agglutination Test for Trypanosomiasis
CIOMS	Council for International Organisations of Medical Science
C_{max}	Maximum Concentration
CNS	Central Nervous System
CRF	Case Report Form
CSF	Cerebrospinal Fluid
CTC	Capillary Tube Centrifugation
CTCAE	Common Toxicity Criteria for Adverse Events
D	Day
DBS	Dry Blood Spot
DNDi	Drugs for Neglected Diseases *initiative*
DRC	Democratic Republic of the Congo
DSMB	Data and Safety Monitoring Board
e.g.	*exempli grati* (for example)
ECG	Electrocardiogram
EDTA	Ethylene Diamine Tetra-acetic Acid
EOH	End of Hospitalisation
EOT	End of Treatment
FDA	Food and Drug Administration
Fexi	Fexinidazole
GGT	Gamma-Glutamyl Transpeptidase
H	Hour
HAT	Human African Trypanosomiasis
i.e.	*id est* (that is to say)
ICH	International Conference on Harmonisation
INRB	*Institut National de Recherche Biomédicale* (Democratic Republic of the Congo)
ITT	Intention to Treat
IV	Intravenous
M	Month
M1	Metabolite 1 - fexinidazole sulfoxyde
M2	Metabolite 2 - fexinidazole sulfone
mAECT	Mini-Anion Exchange Column Test
mAECT-BC	Mini-Anion Exchange Column Test - Buffy Coat
MIC	Minimal Inhibitory Concentration
MSC	Modified Single Centrifugation

MSF	*Médecins Sans Frontières*
NCI	National Cancer Institute
NECT	Nifurtimox-Eflornithine Combined Therapy
PACTR	Pan African Clinical Trials Registry
p_{Fexi}	Success rate for fexinidazole
PK	Pharmacokinetic
PNLTHA	National HAT Control Programme (*Programme National de Lutte contre la Trypanosomiase Humaine Africaine*)
QT	QT interval on ECG (time interval between electrical depolarisation and repolarisation of the left and right cardiac ventricles)
QTcF	QT interval corrected by heart rate, according to the formula proposed by Fridericia
RDT	Rapid Diagnostic Test
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOT	Start of Treatment
SUSAR	Suspected Unexpected Serious Adverse Reaction
Swiss TPH	Swiss Tropical and Public Health Institute
T.b.	*Trypanosoma brucei*
ULN	Upper Limit of Normal
vs.	Versus
WBC	White Blood Cell
WHO	World Health Organisation
δ	delta, difference
µL	microlitre

Protocol Summary

Study Title	Efficacy and Safety of Fexinidazole in Patients with Stage-1 or Early Stage-2 Human African Trypanosomiasis (HAT) due to T.b. gambiense: a Prospective, Multicentre, Open-label, Cohort Study, Plug-in to the Pivotal Study
Study Phase	Cohort study
Indication	Human African Trypanosomiasis (HAT) due to *Trypanosoma brucei gambiense* at stage 1 or early stage 2
Protocol Number	DNDiHATFEX005
Study Rationale	HAT is a potentially fatal, neglected disease. HAT is caused by a parasite that initially invades the blood, the lymph nodes and then the central nervous system. At the latter stage, the treatment of HAT requires adequate drug concentrations in the brain. Patients with HAT are arbitrarily divided into two categories, stage 1 and stage 2, based on the fact that different drugs are used at each stage, i.e. pentamidine for stage 1 and nifurtimox-eflornithine combined therapy (NECT) for stage 2. Dividing the patients into two categories is based on the differing capacity of the two drugs to cross the blood-brain barrier and reach the cerebrospinal fluid and brain (NECT crosses the blood-brain barrier while pentamidine does not), as well as on their toxicity and constraints related to their use, i.e. intramuscular for pentamidine and intravenous infusion for NECT. However, the distinction between stage-1 and stage-2 HAT is not always clear and simple. Indeed, some patients with so-called “early” stage-2 HAT can be treated with pentamidine, however the risk of relapse seems to increase with the number of white blood cells in the cerebrospinal fluid (62, 63). Given the risk that patients who relapse will be lost to follow-up, most national HAT control programmes have elected to treat patients with “early” stage-2 HAT systematically with NECT. In accordance with the WHO recommendations for clinical trials intended to demonstrate treatment efficacy in patients with stage-2 HAT (64), only patients with a white blood cell count > 20/µL in the cerebrospinal fluid and/or with trypanosomes in the cerebrospinal fluid are eligible to participate in the DNDiFEX004 study. These criteria were used in the pivotal study, DNDiFEX004 (65). The present study will be a plug-in to the pivotal study DNDiFEX004 (65), which means that it will be possible to compare the results from the two studies since patients will be recruited simultaneously i.e.

	same centres and investigators, genetically homogeneous population. As of 21 November 2013, 188 patients, i.e. around 125 patients receiving fexinidazole, had been randomised in the DNDiFEX004 study. No safety issues were identified on blinded data review. A total of 11 serious adverse events were reported, 3 of which were considered as possibly related to the investigational product and which resolved without sequelae. Overall, the safety profile was similar to that observed in earlier studies in healthy volunteers, and there were no treatment discontinuations. A meeting of the Data and Safety Monitoring Board was held. No safety issues were identified, and it was recommended to continue the study with the same design. No parasites were found in any patients at the End of Treatment visit, based on blinded review, and no relapses were observed among 80 patients who attended their 6-month follow-up visit, with the exception of one patient whose health status had been poor at inclusion and who died shortly after leaving hospital (blind not lifted). In the DNDiFEX004 study, fexinidazole is administered by the oral route once daily after a meal: three 600-mg tablets daily for 4 days, followed by two 600-mg tablets daily for the next 6 days. Pharmacokinetic analysis of the first 39 patients treated with fexinidazole in the DNDiFEX004 study showed that mean exposure to the M2 metabolite, the more active metabolite, in the cerebrospinal fluid was 2.6 times higher than the minimum inhibitory concentration used as the target value based on animal data collected in preclinical efficacy studies. Blood M1 and M2 concentrations were higher in patients than in healthy volunteers. The cerebrospinal fluid-to-blood ratio was around 31% for M2 and 52% for M1.
Study Objectives	<u>Primary Objective</u> • To demonstrate that the success rate of treatment with fexinidazole at 1-year follow-up in patients with stage-1 or early stage-2 HAT is greater than 80%. An 80% success rate is considered to be inadequate and unacceptable. <u>Secondary Objectives</u> • To verify whether the success rate of treatment with fexinidazole varies depending on the stage of the disease, i.e. stage 1 or early stage 2, and, if the difference between the stages is significant, to show that the success rate is greater than 80% and consistent with the historical success rate reported with NECT in patients with early stage-2 HAT and with pentamidine in patients with stage-1 HAT.

	• To verify whether the success rate of treatment with fexinidazole varies depending on the WBC count in the CSF prior to treatment initiation. • To study changes in the success rate over time. • To assess the safety of fexinidazole and verify whether the safety profile of fexinidazole is similar to the historical safety profile reported with pentamidine.
Primary Endpoint	**Efficacy** The outcome, i.e. success or failure, observed at the test-of-cure visit, 12 months after the end of treatment.
Secondary Endpoints	**Efficacy** The outcome, i.e. success or failure, observed at each visit between the end of treatment and 18 months.
	Safety • Occurrence of adverse events at grade ≥ 3, including laboratory abnormalities, during the observation period. Adverse events will be graded according to the Common Toxicity Criteria for Adverse Events of the National Cancer Institute, Version 4.03. • Occurrence of any adverse events, at any grade, during the observation period. • Occurrence of any treatment-related adverse events (grade ≥ 3 and any grade) during the observation period. • Occurrence of any serious adverse events between the first intake of the investigational product and the end of the follow-up period (18 months).
Study Design	This is a multicentre, open-label, cohort study with a single group of patients, stratified by self-weighting into 2 strata: patients with stage-1 HAT and patients with early stage-2 HAT. At least 202 patients in at least 8 centres will participate in the study. The study is a plug-in to the pivotal study DNDiFEX004.
Inclusion and Exclusion Criteria	**Inclusion Criteria** ▪ Signed informed consent form. ▪ 15 years of age or older. ▪ Male or female. ▪ Able to ingest at least one complete meal per day (or at least one sachet of Plumpy'Nut®). ▪ Karnofsky score > 50.

- Evidence of trypanosomes in blood or lymph.
- No evidence of trypanosomes in CSF.
- Having a permanent address and able to comply with the schedule of follow-up visits.
- Willing to be hospitalised to receive treatment.

Exclusion Criteria

- Severe malnutrition, defined as Body Mass Index < 16.
- Unable to take medication by the oral route.
- Pregnancy or breast-feeding (for women of child-bearing potential, a urine pregnancy test will be performed within 24 hours prior to the start of treatment).
- Clinically significant medical condition (other than HAT) that could, in the opinion of the Investigator, jeopardise the patient's safety or interfere with participation in the study, including, but not limited to significant liver or cardiovascular disease, suspected or proven active infection (including HIV infection), CNS trauma or seizure disorder, coma or consciousness disturbances.
- Severely deteriorated general status, including as a result of cardiovascular shock, respiratory distress or end-stage disease.
- Any condition (excluding HAT-specific symptoms) that affects the patient's ability to communicate with the Investigator as required to complete the study.
- Any contraindication to imidazole drugs, i.e. known hypersensitivity to imidazoles.
- Prior treatment for HAT in the previous 2 years.
- Prior enrolment in the study or prior intake of fexinidazole.
- Foreseeable difficulty complying with follow-up, including migrant worker, refugee status, itinerant trader.
- Active alcohol or drug addiction.
- Clinically significant laboratory test abnormality, including for example:
  - alanine aminotransferase and/or aspartate aminotransferase more than 2 times the upper limit of normal (ULN),
  - total bilirubin more than 1.5 x ULN,
  - severe leukopenia at < 2000/mm^3,
  - potassium < 3.5 mmol/L,
  - any other clinically significant laboratory test abnormality (see Investigator manual for details).

	▪ Pregnancy confirmed by a positive urine pregnancy test within 24 hours prior to the start of treatment. ▪ QTcF interval ≥ 450 msec on automatic reading, if the first reading is abnormal, a second reading will be performed at least 10 to 20 min later after placing the patient in the resting position. ▪ Not tested for malaria and/or not having received appropriate treatment for malaria. ▪ Not having received appropriate treatment for soil-transmitted helminthiasis. For the purposes of the study, patients will be stratified according to the following criteria: ▪ Patients at stage 1 : CSF WBC ≤ 5/µL ▪ Patients at early stage 2: CSF WBC 6 to 20/µL For the purposes of the study, the strata will be self-weighted. It is planned to include at least 101 patients par stratum.
Study Duration	Each patient's participation will last approximately 19 months and will include: • pre-treatment period, • treatment period of 10 days (D1 to D10), • hospitalisation for 1 to 7 days after treatment, • additional follow-up visit at 9 weeks after D1, i.e. between D64 and D70), • out-patient follow-up with visits at 6, 12 and 18 months.
Investigational Product	**<u>Investigational Product</u>** Fexinidazole, 600-mg tablets to be taken by the oral route after the main meal: • 1800 mg (3 tablets) in one daily intake for 4 days, • and then 1200 mg (2 tablets) in one daily intake for 6 days. The total duration of treatment will be 10 days.
Statistical Analyses	**<u>Analysis Sets</u>** The primary analysis will be performed on: • the intent-to-treat population, comprising all patients who received at least one dose of fexinidazole; • the per-protocol population, comprising all patients who adhered to the protocol with no major violations that could interfere with the efficacy analysis.

	Sensitivity analyses will be performed on the following populations: treatment completers, evaluable patients, i.e. those with a known CSF WBC count at 12 months of follow-up or later and the per-protocol population. **Analyse** The primary analysis will be performed on the intent-to-treat population and will be based on the outcome, i.e. success or failure, of treatment with fexinidazole at 12 months of follow-up. If the lower limit of the 95% confidence interval is ≤ 80% then the study is a failure, otherwise it is a success. The 80% limit was set by substracting the 13% margin (see DNDiFEX004) to the expected global success rate with the reference treatment currently used. By combining the historical success rate for Pentamidine (stage 1) to the success rate for NECT (satge 2), a global success rate of 93% at 12 months in a hypothetical group treated with the appropriate reference treatment can be expected. The secondary analyses will assess whether the success rate varies depending on the stage of HAT, using a Fisher exact test to compare the rates in the two strata. The correlation between the success rate and the baseline CSF WBC will be investigated using a logistic regression. Finally, the time-course of the failure rate will be studied using the Kaplan-Meier method. **Sample Size** The sample size had initially been set at a minimum of 101 patients per stratum, i.e. at least 202 patients in total, with a maximum of 300 patients. However, the prevalence of stage-1 HAT is in fact seven times higher than the prevalence of early stage-2 HAT (N = 135 after 11 months of enrolment). It therefore seems unlikely that the initial objective of enrolling at least 101 patients at early stage-2 will be reached. Consequently, the objective of enrolling 101 patients will only be reached for stage 1.

1. Background and Study Rationale

1.1. Epidemiology

Human African trypanosomiasis (HAT), or sleeping sickness, is a vector-borne parasitic disease found in sub-Saharan Africa. It is transmitted by the bite of the tsetse fly (genus *Glossina*) and, if untreated, it almost invariably leads to death. HAT is caused by the protozoan parasites *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*, which are found only in foci in sub-Saharan Africa where the tsetse fly is endemic (3, 33, 49). Since 2005, human cases of trypanosomiasis due to *T.b. gambiense* have been reported in 13 countries and cases due to *T. b. rhodesiense* in 8 countries. Uganda is the only country where both species of the parasite are found. A total of 7,091 cases worldwide were reported to the WHO in 2012, 84% of which in the Democratic Republic of the Congo (DRC) alone (35, 47, 55, 66). The largest most comprehensive and accessible database of treated HAT cases was set up by MSF and is managed by Epicentre. The database compiles information from 18 programmes to control HAT in 6 countries and describes the distribution by age and by sex of a total of 31,817 patients treated for HAT up to 2010. Overall, children under 5 years of age account for 4.22% of patients, those between 5 and 9 years of age 6.63% and those between 10 and 15 years of age 12.82%. In total, children under 15 years of age account for 23.67% of the total treated population.

1.2. Clinical Presentation of HAT

There are two successive stages in the clinical course of HAT. In the first stage, called the haemolymphatic stage or stage 1, trypanosomes are present in the blood and lymphatic system. The clinical signs and symptoms are mild and non-specific, including intermittent fever, headache, pruritus and lymphadenopathy. The signs and symptoms are very similar to those of malaria, which explains why patients with stage-1 HAT are often misdiagnosed with malaria. If it is not diagnosed and treated, HAT will progress to the next stage, called the meningoencephalitic stage or stage 2, in which parasites invade the central nervous system. At this stage, patients display the classic neurological signs associated with HAT, including mental confusion, worsening sleep disturbances and, eventually, coma and death (3, 33, 49).

Dividing the patients into two categories is in fact arbitrary, and is based on the differing capacity of the two drugs currently available to cross the blood-brain barrier and reach the cerebrospinal fluid (CSF) and brain (NECT crosses the blood-brain barrier while pentamidine does not), as well as on their toxicity and constraints related to their use, i.e. intramuscular for pentamidine and twice daily intravenous infusion + oral treatment three times daily for NECT. However, the distinction between stage-1 and stage-2 HAT is not always clear

and simple. Indeed, some patients with so-called “early” stage-2 HAT can be treated with pentamidine, however the risk of relapse seems to increase with the number of white blood cells (WBC) in the CSF. Given the risk that patients who relapse will be lost to follow-up, most national HAT control programmes have elected to treat patients with “early” stage-2 HAT systematically with NECT.

1.3. Diagnosis

Current treatment options for stage-1 and stage-2 HAT are different and, for this reason, it is crucial to distinguish between the two stages before initiating treatment. HAT is diagnosed by detecting the parasite in the blood using thick or thin smear tests, or in a lymph node aspirate. Testing for *T.b. gambiense* is performed using a card agglutination test for trypanosomiasis (CATT). Patients who test positive on CATT (diluted to 1/4, 1/8, 1/16 and 1/32) and/or who have enlarged cervical lymph nodes undergo further investigations (see Figure 1; p 20).

The diagnosis of stage-2 HAT relies on lumbar puncture. The presence of parasites and/or of more than 20 WBCs per µL in the CSF confirms stage-2 HAT. In the national programmes in most countries, the threshold of positivity is a CSF WBC count of 5/µL. The presence of trypanosomes in the blood or any other bodily fluid cannot be assessed in an independent central laboratory because fixing the sample affects the sensitivity of microscopic detection. The most sensitive methods of detection are those that use concentration techniques to examine fresh centrifugated samples for motile trypanosomes.

Cure is defined as the absence of parasites in any bodily fluid and a CSF WBC count below a predetermined threshold. As a result, patients with stage-2 HAT must undergo additional lumbar punctures to confirm that they are cured. The recommendation put forward in 2004 was to assess cure up to 18 or 24 months after the end of treatment (8). Recently, a strategy to shorten follow-up was proposed by Mumba et al. (57) and ratified by Priotto (58) in a retrospective analysis of the MSF database, using two assessment timepoints at 6 months and 12 months to predict long-term success.

1.4. Routine Case Detection and Management

The routine procedure for case detection varies from one country to another and from one hospital/investigational centre to another. Patients may either present spontaneously to the hospital/investigational centre or be diagnosed in the field by mobile teams working in the context of active screening programmes.

In the DRC, the mobile teams in the National HAT Control Programme usually comprise 7 people, including 3 laboratory technicians and one person who acts

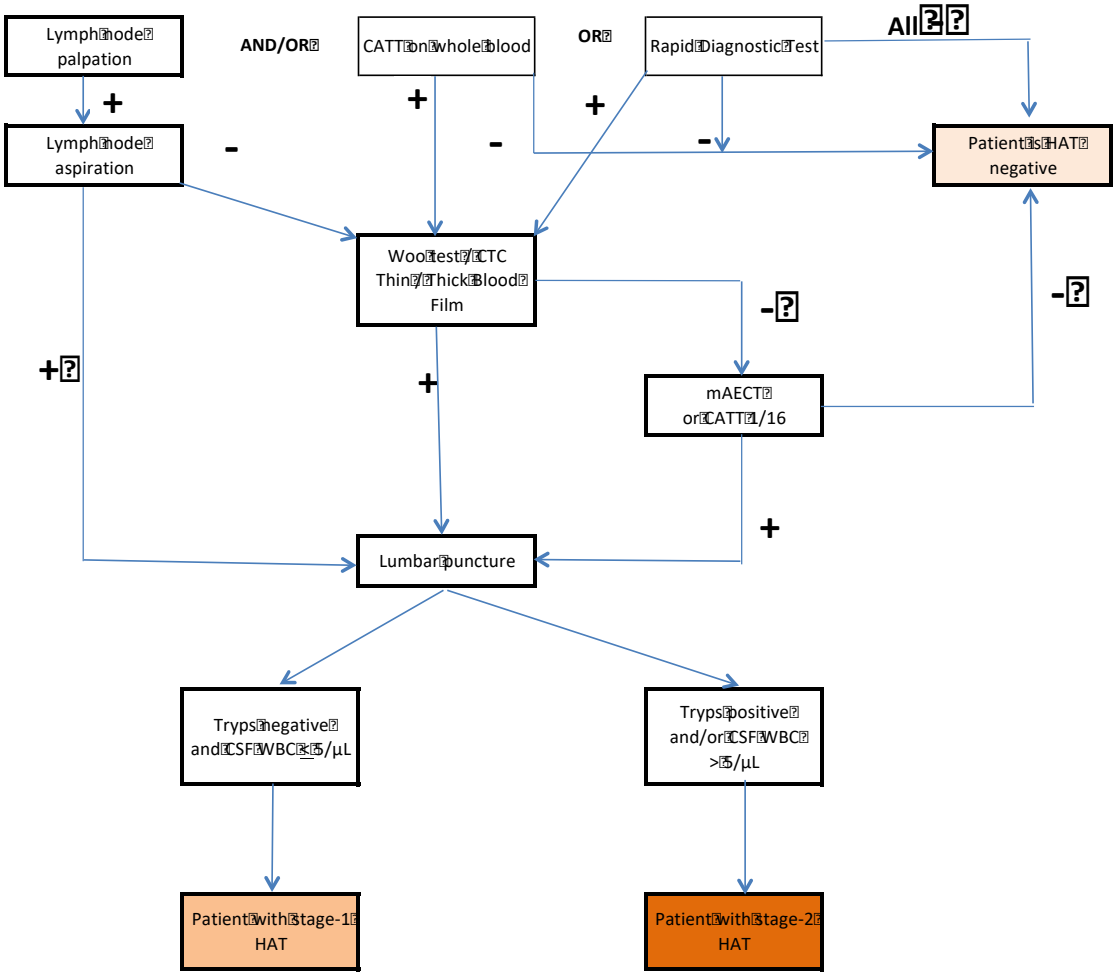
as a community mobiliser. The mobiliser travels through the villages a few days in advance to announce to the community that HAT screening is on the way.

The routine activities of the mobile teams in charge of screening and diagnosis of HAT in the DRC are described below:

- In the field or at hospital, patients initially undergo a serological assessment, i.e. CATT. Testing is then carried out to detect the parasite 1) in the blood using various methods, including the Woo test, also called the capillary tube centrifugation (CTC) test, thick or thin blood smears, and mini-anion exchange centrifugation tests (mAECT), or 2) in a fresh lymph node aspirate using a microscope, and 3) in the CSF collected on lumbar puncture for staging of the disease. CSF samples are collected only by specially trained personnel and only under specific conditions, i.e. at sites particularly remote from hospital. The mobile teams in the National HAT Control Programme or other partners are experienced and well trained.

Rapid diagnostic tests are currently being developed by various institutions, including FIND Diagnostics (67), the Institute of Tropical Medicine in Anvers (69) and the University of Dundee (68). In the coming months, these new diagnostic tools should become available as an adjunct to current methods for detecting HAT. These tests may come to replace CATT in some topographical situations, e.g. remote health facilities and passive screening in hospitals, depending on decisions taken by the national HAT control programme in each country.

Figure 1 – Decision Tree for Routine Diagnosis of HAT



CATT = Card Agglutination Test for Trypanosomiasis
Woo test = microhematocrit centrifugation test + CTC test
mAECT = Mini-Anion Exchange Centrifugation Test
Tryps = Trypanosomes
CSF = cerebrospinal fluid WBC = white blood cells

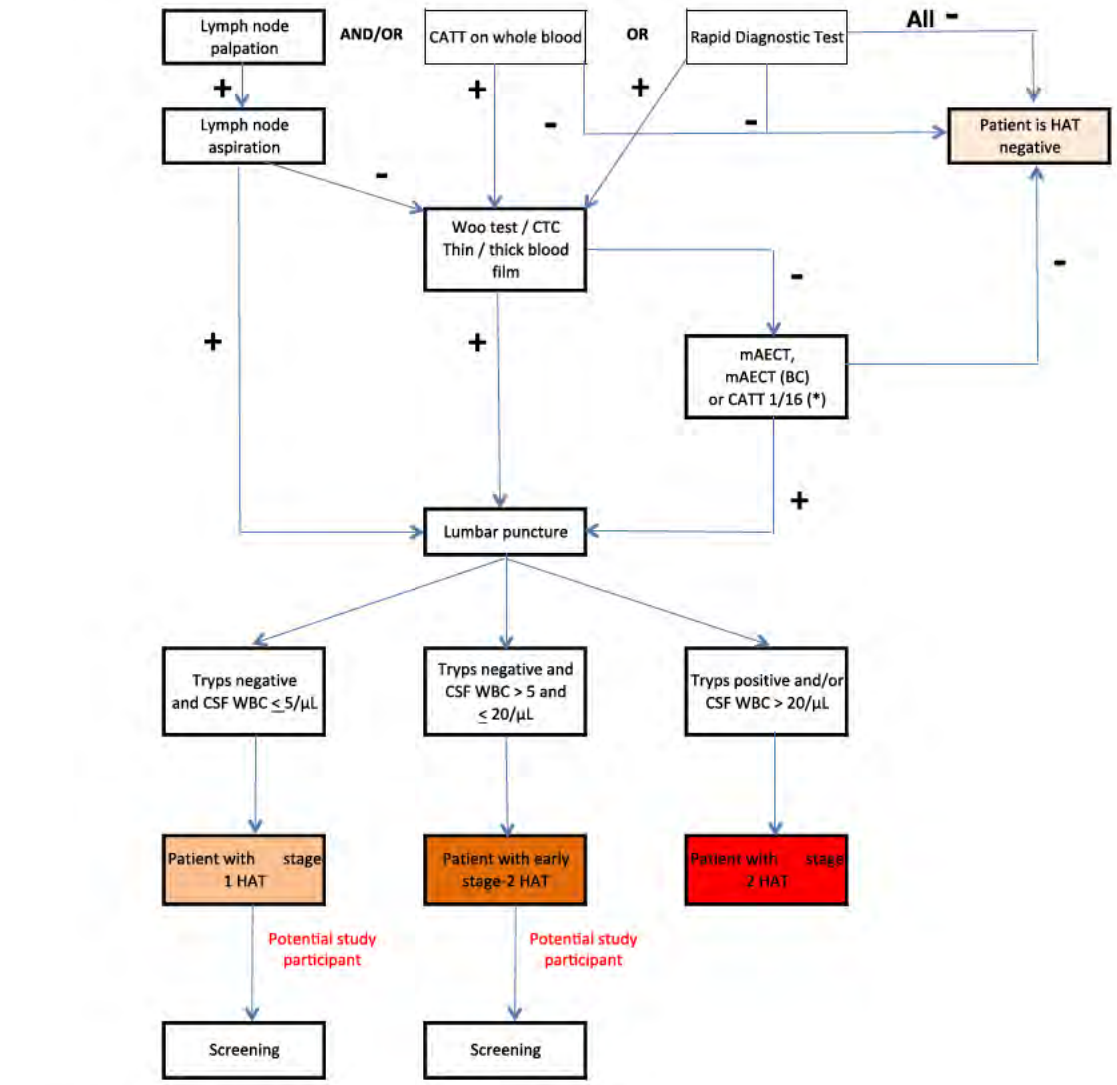
When patients are diagnosed with stage-1 HAT, they can be treated in their villages with intramuscular injections of pentamidine for 7 days, however, for the purposes of this study, they will be informed that they can participate in the study and receive treatment at the investigational centre.

Patients diagnosed with stage-2 HAT will be referred to the investigational centre by the mobile teams. They will be hospitalised for pre-treatment, if necessary, for concomitant malaria and/or helminthiasis, and for treatment of HAT.

In the present study, screening with mAECT, or the improved, more sensitive technique called the mini-anion exchange centrifugation test - buffy coat (mAECT-BC) (7), will be used whenever possible to screen CATT-positive

patients, in addition to the routine diagnostic procedures presented in the decision tree in Figure 1. In order to ensure that only patients with stage-1 or early stage-2 HAT are included in the study, patients in whom no parasites are found in the CSF must have a CSF WBC count less than to 20/µl. Only patients with evidence of trypanosomes in the blood or lymph, not in CSF, will be included (see Section 4.2 Pre-inclusion/Pre-exclusion Criteria; p31).

Figure 2 – Decision Tree for Diagnosis of HAT in the Study



CATT = Card Agglutination Test for Trypanosomiasis
Woo test = microhematocrit centrifugation test = CTC test
mAECT = Mini-Anion Exchange Centrifugation Test BC = Buffy Coat
Tryps = trypanosomes CSF = cerebrospinal fluid WBC = white blood cells
(*) CATT 1/16 positive patients without parasitological confirmation will not be eligible for inclusion in the study (routine treatment)

1.5. Current Therapeutic Options for Stage-2 HAT

Few therapeutic options are currently available to treat HAT at either stage (1, 31). Until recently, the drugs available to treat stage-2 HAT were limited to an older toxic product, melarsoprol, administered in painful IV injections for 10 days with up to 5% treatment-related mortality, and eflornithine, less toxic but difficult to manage since it requires four IV infusions daily for 14 days. NECT, a recently developed combination of oral nifurtimox for 10 days plus eflornithine, two 2-hour IV infusions daily for 7 days, was found to provide similar cure rates to the standard regimen with eflornithine, but with obvious practical advantages, including ease of administration and a shorter duration of treatment.

In May 2009, the WHO Expert Committee added NECT to the 16th Edition of the WHO List of Essential Medicines for adults, as an alternative to single-drug therapy with melarsoprol or eflornithine. In April 2013, the use of NECT was extended to children in the 4th Edition of the WHO List of Essential Medicines for children.

In keeping with the WHO recommendation, almost all of the national HAT control programmes have already adopted NECT as first-line treatment for stage-2 HAT due to *T.b. gambiense* and, in 2010, NECT became the most widely used treatment for stage-2 disease (43, 56).

NECT represents a significant improvement over current therapies, however, it is far from ideal given the conditions under which patients with HAT generally live, i.e. in poor, remote areas with little or no healthcare infrastructures and problems with logistics. Thus, there is an urgent need to develop less toxic and easier-to-use products for the treatment of this fatal disease, ideally a simplified, short-course treatment that can be administered orally at a primary healthcare facility.

1.6. Current Therapeutic Options for Stage-1 HAT

Pentamidine is the only drug currently used to treat stage-1 HAT due to *T. b. gambiense*. It was introduced into the therapeutic armamentarium in 1940. The most common dosing regimen is a single daily dose via intramuscular injection for 7 days. Pentamidine is available to mobile teams in the field who, after detecting patients with stage-1 HAT, administer the first injection and assign the remaining injections to the village nurses. Pentamidine is much better tolerated than melarsoprol, however, it still has non-negligible adverse effects, including post-injection orthostatic hypotension, the risk of sterile abscess at the site of the intramuscular injections, gastrointestinal disturbances and, less frequently, renal toxicity and diabetes.

1.7. Investigational Product and Preclinical Data

Fexinidazole is 2-substituted 5-nitroimidazole, formulated for oral administration. Fexinidazole has been shown to possess *in vitro* and *in vivo* activity against both

parasites, *T.b. rhodesiense* and *T.b. gambiense*. In mouse models of both acute and chronic infection (the latter mimicking stage-2 disease), oral administration of fexinidazole at doses of 100-200 mg/kg/day was shown to be curative and to significantly prolong survival (30). Preclinical pharmacokinetic (PK) studies have indicated that oral fexinidazole is well absorbed and is widely distributed throughout the body, including in the brain (15).

In all animal species studied, fexinidazole was rapidly metabolised through oxidation, resulting in the formation of at least two active metabolites, fexinidazole sulfoxide and fexinidazole sulfone, which have a trypanocidal activity similar to that of the parent molecule, and account for most of the pharmacodynamic activity. Toxicological studies were performed, including safety pharmacology and 4-week repeated-dose toxicokinetic studies in rats and dogs. In both species, 200 mg/kg/day was considered as the no observed adverse effect level (50). Fexinidazole was well tolerated up to 800 mg/kg/day, and no major toxicity was identified. While fexinidazole, like many nitro-heterocycles, was shown to be mutagenic in the Ames test, it is not genotoxic to mammalian cells *in vitro* or *in vivo*, and is therefore not expected to pose a genotoxic risk in humans (50).

1.8. Safety and Tolerability in Healthy Volunteers

Fexinidazole has been investigated in three phase-I studies in healthy volunteers of sub-Saharan African origin (15). In all three studies, the subjects were closely monitored, with physical examinations, vital signs, electrocardiogram (ECG) and safety laboratory tests, as well as pharmacokinetic sampling performed before, during and after dosing. A total of 118 subjects were randomised in these studies. Single doses ranged from 100 mg to 3600 mg, and multiple doses from 1200 mg to 3600 mg for a maximum of 14 days.

Administration of fexinidazole in healthy volunteers was safe when given as a single dose or as repeated doses for 14 days. As with all nitroimidazole drugs, fexinidazole primarily affects the central nervous system (CNS) and gastrointestinal system, and can cause headache and/or vomiting or other mild to moderate gastrointestinal symptoms. At the highest dose, two subjects experienced prolonged anxiety with an episode of panic attack, associated with nausea and vomiting. No specific treatment was needed. Both subjects returned to normal within 2 to 3 days after stopping the investigational product (IP).

Fexinidazole is highly metabolized. As expected with this pharmacological class, a marked, transient, quickly reversible increase in liver enzymes was observed in one volunteer just after treatment at the highest dose for 14 days. Data from these studies also suggest that there is a relationship between the dose used, as well as overall exposure (dose and duration), and the frequency and severity of abnormalities on liver function tests. These effects will be closely monitored during the study. Another important laboratory finding was an increase, within the

normal range, in plasma creatinine levels in subjects receiving the active treatment. This effect was not dose-dependent and is believed to be related to inhibition of renal tubular creatinine secretion, an effect that has previously been reported with nitroimidazole drugs (21). It is always reversible and is not accompanied by any other abnormalities on kidney function tests.

ECG recordings in studies in humans showed a limited number of cases of QTcF-interval prolongation, usually in the 30-millisecond range. QT interval corresponds to the time it takes for the left and right heart ventricles to depolarise (Q wave) and to repolarise (T wave). It is a fundamental marker in electrophysiology and in pharmacology. QT interval is corrected using a mathematical formula to take into account the heart rate (QTcF for the Fridericia formula). If the interval is abnormally prolonged or shortened, there is a risk of developing ventricular arrhythmia. In earlier studies, only one out of more than 4000 ECG recordings showed an increase of 60 ms compared to baseline. The absolute value remained within the normal range (<450 ms), however, a 24-hour Holter recording showed a mean QTcF prolongation of 16 ms compared to baseline. The prolongation was not accompanied by any clinical signs and appeared to be present from the time of staring treatment.

1.9. Pharmacokinetics and Metabolism in Healthy Volunteers

Fexinidazole is well absorbed by the oral route, and rapidly metabolised to the sulfoxide (M1) and sulfone (M2), which account for the largest proportion of drug exposure, regardless of the dose used. Elimination of the second active metabolite is a slow process. C_{max} values for both fexinidazole and M1 are reached in 3 to 6 hours, while M2 levels peak at approximately 24 hours. The mean elimination half-life of fexinidazole and M1 is approximately 10 hours versus approximately 24 hours for M2.

Plasma levels of fexinidazole, M1 and M2 increase in a non-dose-proportional manner with no major changes in their pharmacokinetic profiles.

Urinary excretion of unchanged fexinidazole, M1 and M2 is very low. Fexinidazole, M1 and M2 together account for only 3% of the total dose.

The effects of concomitant intake of food were assessed in two separate studies. In the first study, administration after a standard high-fat meal (FDA recommended) was compared to administration under fasting conditions, and in the second study, two different field meals, i.e. Plumpy'Nut®[1], and a traditional meal of rice and beans, were compared to administration under fasting conditions. The observed bioavailability of fexinidazole, M1 and M2 was

[1] Peanut-based paste in a plastic wrapper for the treatment of severe acute malnutrition, easily available in the field.

multiplied by approximately 4-fold with the high-fat meal, and by 2.5- to 3.0-fold with the two field meals (15).

The effect of food on the bioavailability of fexinidazole was taken into account in the design of studies in patients. Indeed, the dosing regimen provides for food intake prior to administration of the IP. This explains why it is particularly important to comply with the instructions on food intake.

1.10. Study DNDiFEX004 in Adults

The DNDiFEX004 study is entitled: “Efficacy and Safety of Fexinidazole Compared to the Combination Nifurtimox-eflornithine (NECT) in Patients with Stage-2 Human African Trypanosomiasis (HAT) due to *T.b. gambiense*: a Non-inferiority, Multicentre, Open-label, Randomized Pivotal Study”

In accordance with the WHO recommendations for clinical trials intended to demonstrate treatment efficacy in patients with stage-2 HAT, only patients with a WBC count of > 20/µL in the CSF and/or with trypanosomes in the CSF are eligible to participate in the study.

As of 21 November 2013, 188 patients, i.e. around 125 patients receiving fexinidazole, had been randomised in the DNDiFEX004 study. No safety issues were identified on blinded data review. A total of 11 serious adverse events (SAEs) were reported, 3 of which were considered as possibly related to the IP and which resolved without sequelae. Overall, the safety profile was similar to that observed in earlier studies in healthy volunteers, and there were no treatment discontinuations. A meeting of the Data and Safety Monitoring Board (DSMB) was held. No safety issues were identified, and it was recommended to continue the study with the same design. No parasites were found in any patients at the End of Treatment (EOT) visit, based on blinded review, and no relapses were observed among 80 patients who attended their 6-month follow-up visit, with the exception of one patient whose health status had been poor at inclusion and who died shortly after leaving hospital (blind not lifted).

Monitoring of biochemical parameters in all patients included in the DNDiFEX004 study did not show any increases in hepatic enzymes, as had been seen in healthy volunteers. As expected, a mild and reversible increase in creatinine was observed in a small number of patients. The increases were < grade 2, and none were reported as adverse events (AEs).

Monitoring of ECG parameters showed QTcF-interval prolongation, as expected, but with no clinical repercussions or treatment discontinuations (QTcF< 500ms, including at peak plasma concentration).

1.11. Choice of Dosing Regimen and Dose

All pharmacokinetic data from the first-in-man study were incorporated into a PK model simulating several regimens using different doses in order to calculate the optimal exposure. The primary objective was to achieve exposure in the brain at least twice as high as the minimum inhibitory concentration (MIC) for M2, and the secondary objective was to shorten the duration of treatment to 10 days in order to avoid exposure-related increases in liver enzymes. The food effect was used to maximise exposure over a short period of time and to reduce the dose.

The analysis came out in favour of using a once-daily dosing regimen after the main meal, starting with a loading dose for 4 days followed by a maintenance dose for 6 days.

In the DNDiFEX004 study, fexinidazole was therefore administered by the oral route once daily after a meal: three 600-mg tablets daily for 4 days, followed by two 600-mg tablets daily for the next 6 days.

Pharmacokinetic (PK) analysis on the first 39 patients treated with fexinidazole in the DNDiFEX004 study showed that mean exposure to the M2 metabolite, the more active metabolite, in the CSF was 2.6 times higher than the MIC used as the target value based on animal data collected in preclinical efficacy studies. Blood M1 and M2 concentrations were higher in patients than in healthy volunteers. The CSF-to-blood ratio was around 31% for M2 and 52% for M1.

These results are consistent with the results of the dose-finding study, DNDiFEX003, performed in healthy volunteers.

1.12. Rationale for the Study Design

To date, it has been necessary to perform a lumbar puncture in patients with HAT in order to determine whether or not a drug capable of crossing the blood-brain barrier was required. This is a painful procedure, requires a high degree of technical expertise and know-how, and is difficult to perform under field conditions. However, until a single treatment effective against both stage-1 and stage-2 HAT has been found, the procedure will remain crucial. Elimination of the preliminary procedure would represent a major improvement in the management of patients with HAT.

Because the general health status of patients with stage-1 or early stage-2 HAT is often better than that of patients at a more advanced stage, it was necessary to wait until a certain number of patients with late-stage HAT had been treated with fexinidazole in the pivotal study in order to ensure that there were no safety concerns that could jeopardise the potential benefits of treatment in patients whose general health status is better. The interim efficacy results collected at the EOT, along with the confirmation that a potentially active exposure level is

reached in the CSF, suggest that treatment efficacy should be at least as good in less seriously affected patients, since the disease is at an earlier stage.

The patient population included in the present study will provide additional efficacy data, but more importantly, it will be possible to determine, in a larger population, whether, with the same extent of exposure, the favourable safety profile of fexinidazole, based on data currently available, remains unchanged in less seriously affected patients.

In summary, the rationale for extending treatment with fexinidazole to all patients with HAT, i.e. stage 1 and early stage 2, is based on the following objectives:

- To confirm the results of the on-going DNDiFEX004 study, which involves patients with late stage-2 HAT, i.e. with CSF WBC > 20/µL;
- To achieve cost savings in terms of infrastructures, equipment and trained personnel by using the same investigational centres simultaneously;
- To document rapidly the safety of fexinidazole in patients with stage-1 HAT in order to confirm efficacy and to implement the treatment without lumbar puncture as soon as possible.

The present study will be a plug-in to the pivotal study, DNDiFEX004, which means that it will be possible to compare the results in the two studies since patients will be recruited simultaneously, i.e. same centres and investigators, with a genetically homogeneous population.

1.13. Target Population

Patients with stage-1 or early stage-2 HAT, 15 years of age or older will be included in the study. Patients with stage-1 or early stage-2 HAT are defined as follows:

Patients with stage-1 HAT

- Trypanosomes in blood and/or lymph
- No trypanosomes in CSF
- CSF WBC ≤ 5/µL

Patients with early stage-2 HAT

- Trypanosomes in blood and/or lymph
- No trypanosomes in CSF
- CSF WBC between 6 and 20/µL

Based on epidemiological data, patients 15 years of age or older account for approximately 77% of the overall population treated for HAT. From a clinical standpoint, adolescents between 15 and 17 years of age are considered to be physiologically mature, particularly as concerns hepatic and renal maturation.

Thus, the PK profiles of fexinidazole and its two main active metabolites are not expected to differ in this age group as compared to patients over 18 years of age.

Moreover, adolescents over 15 years of age are well able to understand the study objectives and constraints, and can give their assent to participation in the study (see Section 14 Ethical Considerations; p 14).

2. Study Objectives and Endpoints

2.1. Objectives

2.1.1. Primary Objective

The primary objective is to demonstrate that the success rate of treatment with fexinidazole at 1-year follow-up in patients with stage-1 or early stage-2 HAT is greater than 80%. An 80% success rate is considered to be unacceptable.

2.1.2. Secondary Objectives

The secondary objectives are:

- To verify whether the success rate of treatment with fexinidazole varies depending on the stage of the disease and, if the difference between the stages is significant, to show that the success rate is greater than 80% and compatible with the historical success rate reported with NECT in patients with stage-2 HAT and with pentamidine in patients with stage-1 HAT.
- To verify whether the success rate of treatment with fexinidazole varies depending on the WBC count in the CSF prior to treatment initiation.
- To study changes in the success rate over time.
- To assess the safety of fexinidazole and verify whether the safety profile of fexinidazole is similar to the historical safety profile reported with pentamidine.

2.2. Study Endpoints

2.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the outcome, i.e. success or failure, observed at the test-of-cure (TOC) visit, 12 months after the end of treatment (EOT).

Success at 12 months, adapted from WHO criteria (54), is defined as:

- Patient cured, i.e.:
  - patient alive,
  - AND no evidence of trypanosomes in any bodily fluid,
  - AND CSF WBC ≤ 20/µL.

A patients with no evidence of trypanosomes in any bodily fluid, but with CSF WBC > 20/µL, or who, in the opinion of the Investigator, requires rescue treatment will be considered as a probable relapse.

Patients lost to follow-up during the study and retrieved after 12 months or patients who refuse to undergo lumbar puncture at 12 months will be considered as patients probably cured, i.e. successes, if they have no clinical signs or symptoms suggestive of HAT or if their symptoms can be clearly attributed to another aetiology, provided that the outcome was favourable at the last available assessment of HAT (6-month visit or subsequent unscheduled visit). If a patient is not assessed, i.e. has no lumbar puncture, at 12 months, but has a lumbar puncture or physical examination subsequently or at 18 months, the outcome at the latter visit will prevail over that at 12 months.

Patients who die due to any cause, patients lost to follow-up and not retrieved, and patients who refuse to undergo lumbar puncture at 12 months and whose clinical outcome had previously been assessed as unfavourable, i.e. probable relapse, will be considered as failures.

The timepoint for assessment of the efficacy endpoint, i.e. success or failure, was set at 12 months after the EOT because the relapse rate between 12 and 18 months is very low and highly consistent across the various treatments administered to patients with stage-2 HAT. The success rate for melarsoprol was 74.84% at 12 months and 73.71% at 18 months, i.e. a relapse rate of 1.1% (n=3477), (59). The success rate for eflornithine was 90.3% at 12 months and 89.1% at 18 months, i.e. a relapse rate of 1.2% (n=743), (59). The relapse rate for NECT was 1.4% (n=143) between 12 and 18 months after the EOT, (43). Consequently, the overall relapse rate between 12 and 18 months after the EOT is around 1.2% for patients with stage-2 HAT, regardless of the treatment. The consistency of the findings suggests that the success rate at 12 months is predictive of the success rate at 18 months.

In addition, although the timepoint for assessment of the efficacy endpoint was set at 12 months after the EOT, patients will be followed until at least 18 months after the EOT.

2.2.2. Secondary Endpoints

Secondary Efficacy Endpoint

The secondary efficacy endpoint is the success or failure, as previously defined, at each visit between the EOT and 18 months.

Secondary Safety Endpoints

Adverse events (AEs) will be graded according to the Common Toxicity Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI), Version 4.03.

- Occurrence of any AEs at grade ≥ 3, including laboratory abnormalities, during the observation period;
- Occurrence of any AEs, at any grade, during the observation period;
- Occurrence of any treatment-related AEs (grade ≥ 3 and any grade) during the observation period;
- Occurrence of any SAEs between the first intake of the IP and the end of the follow-up period (18 months).

3. Study Design

This is a multicentre, open-label, cohort study with a single group of patients. The study is a plug-in to the pivotal study, DNDiFEX004.

4. Selection of Patient Population

To be included in the study, patients must fulfil all of the inclusion criteria and none of the exclusion criteria.

4.1. Enrolment/Inclusion Procedures

The study will be conducted in at least 8 investigational centres in the DRC and possibly in other countries suitable for the conduct of the study.

Patients will be enrolled in one of three ways:

a. Patients may present spontaneously to the investigational centre: routine assessments will be performed at the centre, including testing for *T.b. gambiense* in blood, lymph and CSF.

b. Patients may be referred to the investigational centre after being diagnosed with stage-1 or early stage-2 HAT by the mobile teams in the field (see Section 1.4 Routine Case Detection and Management; p 18). In that case, patients will not undergo a second lumbar puncture. They will receive a staging certificate from the mobile team and may participate in the study, if they so desire, without undergoing a second lumbar puncture. For ethical reasons, the lumbar puncture planned at inclusion will not be performed in these patients. However, if the staging of HAT is questionable, i.e. negative findings on CSF testing for parasite and CSF WBC between 19 and 22/µL inclusive, the patient will be asked to undergo a second lumbar puncture to confirm the stage. If the patient refuses the second lumbar puncture, s/he will be considered to have early stage-2 HAT.

c. Patients may be referred to the investigational centre by a less well-equipped mobile team that was not able to determine the stage of HAT and will then undergo assessment as described in point (a) above.

d. Each investigational centre is supplied with a new microscope, equipped with a camera that can capture video (maximum 5 seconds of video) and still images during detection of trypanosomes on the slides analysed, as well as images of cell counts in the samples analysed, i.e. the blood, lymph and CSF. The video and still images will be identified by patient, day and time of collection, and will be rendered anonymous, as with other study data, in order to ensure patient confidentiality. The images will be saved and stored on site, as well as in a specific database (Power Folder).

During the screening process prior to inclusion and before the informed consent form is signed, patients will be considered as “pre-screened patients”. Patients who fulfil the pre-inclusion criteria, i.e. not requiring any study-specific procedures, will be invited to participate in the study and will receive the information necessary to obtain their informed consent.

For patients to be enrolled in the study, they must sign an informed consent form after the Investigator or a delegate has provided explanations and prior to any study-specific procedures. Patients will then be considered as “screened patients”.

As previously mentioned, the initial study-specific procedures do not include lumbar puncture unless it is required in order to confirm the stage of HAT, when the staging based on CSF examination by the mobile team in the village is questionable.

The Investigator or a delegate must record the date of the screening visit, the patient’s initials, the patient’s number, referral source, status at the time of the screening visit, date of collection of informed consent and date of enrolment/ inclusion, as well as the treatment number or the reason for non-enrolment, if appropriate.

The enrolment/inclusion procedures must be carried out between 1 and 15 days before the planned start of treatment in the study. The procedures are described in Section 6 Schedule of Assessments (p 38). The procedures include a complete history-taking, a physical examination, testing and treatment for malaria, treatment for helminthiasis, haematological and biochemical assessments, ECG and a urine pregnancy test.

4.2. Pre-inclusion / Pre-exclusion Criteria

The pre-inclusion/pre-exclusion criteria can be checked before informed consent is obtained since the process does not involve any study-specific procedures.

Pre-inclusion Criteria

- 15 years of age or older.
- Male or female.
- Able to ingest at least one complete meal per day (or at least one sachet of Plumpy'Nut®).
- Karnofsky score > 50 (see Appendix 2 – Karnofsky Performance Scale; p82).
- Evidence of trypanosomes in blood or lymph.**
- No evidence of trypanosomes in CSF.**
- Having a permanent address and able to comply with the schedule of follow-up visits.
- Willing to be hospitalised to receive treatment.

*** As attested by the report from the mobile team indicating the tests performed and the WBC count in the CSF, or performed at the investigational centre.*

For the purposes of the study, patients will be stratified based on the following criteria:

- Patients with stage-1 HAT: CSF WBC ≤ 5/µL;
- Patients with early stage-2 HAT: CSF WBC 6 to 20/µL.

The strata will be self-weighted. A minimum of 101 patients are required per stratum.

Pre-exclusion Criteria

- Severe malnutrition, defined as Body Mass Index < 16.
- Unable to take medication by the oral route.
- Pregnancy or breast-feeding (for women of child-bearing potential, a urine pregnancy test will be performed within 24 hours prior to the start of treatment).
- Clinically significant medical condition (other than HAT) that could, in the opinion of the Investigator, jeopardise the patient's safety or interfere with participation in the study, including, but not limited to significant liver or cardiovascular disease, suspected or proven active infection (including HIV infection), CNS trauma or seizure disorder, coma or consciousness disturbances.
- Severely deteriorated general status, including as a result of cardiovascular shock, respiratory distress or end-stage disease.
- Any condition (excluding HAT-specific symptoms) that affects the patient's ability to communicate with the Investigator as required to complete the study.

- Any contraindication to imidazole drugs, i.e. known hypersensitivity to imidazoles.
- Prior treatment for HAT in the previous 2 years.
- Prior enrolment in the study or prior intake of fexinidazole.
- Foreseeable difficulty complying with follow-up, including migrant worker, refugee status, itinerant trader.
- Active alcohol or drug addiction.

4.3. Inclusion and Exclusion Criteria

Once the Investigator has checked that the patient fulfils the pre-inclusion/pre-exclusion criteria, s/he will invite the patient to participate in the study and initiate the process for collecting the patient's informed consent (see Section 14.2 Informed Consent Process; p 65). Treatment for concurrent malaria or helminthiasis will be initiated, if necessary, and further investigations will be performed.

The inclusion and exclusion criteria will then be checked, just prior to inclusion.

inclusion Criterion

- Signed informed consent form

Exclusion Criteria

- Clinically significant laboratory test abnormality, including for example:
    - alanine aminotransferase and/or aspartate aminotransferase more than 2 times the upper limit of normal (ULN),
    - total bilirubin more than 1.5 x ULN,
    - severe leukopenia at < 2000/mm^3,
    - potassium < 3.5 mmol/L,
    - any other clinically significant laboratory test abnormality (see Investigator manual for details).
- Pregnancy confirmed by a positive urine pregnancy test within 24 hours prior to the start of treatment (see Section 5.8.3 Contraception; p37.
- QTcF interval ≥ 450 msec on automatic reading, if the first reading is abnormal, a second reading will be performed at least 10 to 20 min after placing the patient in the resting position.
- Not tested for malaria and/or not having received appropriate treatment for malaria.

- Not having received appropriate treatment for soil-transmitted helminthiasis.

The following criteria are considered to be temporary exclusion criteria

- Traumatic lumbar puncture, i.e. red blood cells visible in CSF; repeat lumbar puncture can be performed 48 hours later. If the patient refuses, s/he can be included with no WBC count in the CSF.
- Recovery period after treatment for malaria and/or treatment for helminthiasis, i.e. approximately 3 days.
- Abnormalities on laboratory tests or ECG that can be controlled within a few days after the initial assessment. If the value returns to normal or is not considered clinically significant, the patient can be included in the study.

Patients who fulfil the inclusion and exclusion criteria will be referred to as “included patients”.

Patients who are excluded will be treated in accordance with usual practice in the centre, and the reasons as well as the date for exclusion from the study will be recorded.

5. Treatments

5.1. Investigational Product

Fexinidazole, 600 mg tablets, administered by the oral route **after** the main meal of the day, i.e. within 30 minutes after the start of the meal, in accordance with the following dosing regimen:

- 1800 mg (3 tablets) in a single daily intake for 4 days;
- followed by 1200 mg (2 tablets) in a single daily intake for 6 days.

The total duration of treatment will be 10 days.

Fexinidazole will be provided by DND*i*, 15 chemin Louis Dunant, 1202 Geneva, Switzerland.

5.2. Reference Treatment

Not applicable.

5.3. Treatment Allocation

All patients will receive the same treatment.

The number of the treatment pack will be recorded in the patient’s file and on the pharmacy log sheet.

5.4. Labelling and Packaging of Investigational Product

Fexinidazole tablets will be packaged in aluminium-aluminium blister packs. Each blister pack will contain the number of tablets necessary for one day of treatment, i.e. 3 tablets for the first 4 days, and 2 tablets for the next 6 days. The 10 blister packs will be packaged in an individual treatment pack for each patient.

The labelling of the secondary packaging will display the following information:

- Name of Sponsor*, name and contact details for the Coordinating Investigator or Principal Investigator
- Study number*
- Drug name* and dosage strength*
- Dosage form*, route of administration*, number of dosage units*
- Instructions for use
- Statements “For clinical study use only”* and “Keep out of reach of children”
- Batch number* and treatment pack number*
- Expiry date and storage conditions

The information items marked with an asterisk (*) will also be displayed on the primary packaging of the IP.

Information on fexinidazole will be provided in the Investigator Brochure attached to the protocol submitted to the National Authorities.

5.5. Accountability of Investigational Product

The IP will be shipped to the study coordination site (DND*i* Kinshasa), or directly to the investigational sites, depending on the logistical constraints at each site.

Study-specific forms will be used for accountability of the IP. Appropriate records concerning receipt, use, returns, loss and any other disposition of the IP will be maintained by the Investigators on site, or their delegates, under the supervision of the Principal Investigator. Study monitors will check accountability of the IP during on-site monitoring visits.

All IP must be stored in a locked room, or a locked cabinet if no specific room is available, at each investigational site, with access restricted to the nurse in charge of the pharmacy or to authorised study personnel.

The supplies of fexinidazole for the study must not be used for purposes other than the present protocol. The Investigator and the site staff may not, under any circumstances, provide other Investigators or healthcare services with the IP, or allow the IP to be used other than as described in this protocol without prior written approval from DND*i*.

5.6. Storage of Investigational Product

The IP does not require refrigerated conditions during shipping or storage.

Fexinidazole should be stored at a temperature not exceeding 30°C. Long-term stability studies have shown that fexinidazole, stored in the bottle, remains stable at 30°C under conditions of high humidity.

Fexinidazole must be protected from light. This condition is ensured by the fact that the IP is packaged in aluminium-aluminium blister packs. The stability of the tablets in the aluminium-aluminium blister packs will also be monitored in the context of regulatory stability studies.

The storage conditions, including the temperature, must be monitored by the study personnel and appropriate records should be available.

5.7. Anonymity

This is an open-label study. All persons involved in the study will know what treatment is been administered. The patient's identity will be coded, but not for the team of care-givers and the study monitors.

5.8. Concomitant Treatment

5.8.1. Malaria

All patients will undergo a test to detect malaria. All patients with a positive thick smear and/or rapid diagnostic test (RDT) will receive treatment.

Prior to starting treatment for HAT, malaria will be treated with Coartem®, unless there are individual contraindications, such as hypersensitivity to one of the components, or severe malaria. All existing artemisinin-based combination therapies against malaria have effects on the QT interval. Coartem® was chosen because its effects on QT-interval prolongation are well known, moderate and well quantified (19). The choice was also made in order to minimise confounding factors regarding the assessment of fexinidazole-related QT-interval prolongation. The Sponsor will provide Coartem® free of charge.

In patients with a contraindication to Coartem®, the Investigator can choose another antimalarial agent. The choice must be documented.

Treatment for malaria will be followed by a recovery period of at least 3 days between the last dose of the antimalarial agent and the first administration of treatment for HAT, as per usual practice in the investigational centres.

5.8.2. Helminthiasis

Treatment for helminthiasis, with mebendazole or albendazole, will be provided free of charge by the Sponsor for use as per usual practice in the investigational centres.

Treatment for helminthiasis will be followed by a recovery period of at least 3 days between the last dose of the antimalarial agent and the first administration of treatment for HAT, as per usual practice in the investigational centres.

5.8.3. Contraception

Women of child-bearing potential will be advised to use a method of contraception or to abstain from sexual relations during the treatment period and, if possible, until cure is confirmed. Medically proven methods of contraception, i.e. hormonal contraception and condoms, will be available to patients free of charge during the 18-month follow-up period.

5.8.4. Other Medication

Unless there is an urgent medical need, patients should refrain from using any medication required to treat concurrent conditions until after the end of the treatment for HAT.

Any medication used during the hospitalisation period must be recorded in the CRF, specifying the reason for use.

Information on any SAEs that may occur during the follow-up period will be collected at unscheduled visits and recorded in the CRF, specifying any medication received. Other medical events will be recorded only in the patient's medical file.

Any essential medicine required during the study period, i.e. up to the 18-month follow-up visit, will be provided to the patient free of charge. The WHO List of Essential Medicines and the MSF reference guide entitled *Essential Medicines* (2010 edition) will be used as a basis for treatment of any concurrent condition. For any chronic condition, the study team will take all necessary measures to ensure that the patient is referred to the most appropriate healthcare facility in the region.

5.9. Rescue Treatment

Patients who show no clinical response to treatment at the EOT visit, as well as patients with evidence of relapse, i.e. *T.b. gambiense* found in any bodily fluid, or of probable relapse at any time during follow-up will receive NECT, an alternative treatment for HAT, as per usual practice in the investigational centre.

The definition of probable relapse disclosed at the 6-month, 12-month or 18-month follow-up visit is provided in Table 1.

Rescue treatment for HAT will not be recorded in the "Concomitant Treatment" section of the CRF, but will be recorded as a comment on the "End of Study" page with the date of treatment start.

Table 1 – Clinical Management of Patients

Visit	*Ideal timing of visit after end of treatment*	*Success*	*Probable success*	*Probable failure*	*Proven failure*
24 hours after EOT	*Within 2 days*	• Patient alive with no evidence of trypanosomes in any bodily fluid (54)			• Evidence of trypanosomes in any bodily fluid
6 months	*6 months ± 2 weeks*	• Patient alive with no evidence of trypanosomes in any bodily fluid and CSF WBC ≤ 20/µL	• CSF WBC < 20/µL and any reason leading the Investigator to request an additional follow-up visit within 1 to 3 months	• Signs or symptoms suggestive of HAT and of treatment failure leading to use of rescue treatment.	• Evidence of trypanosomes in any bodily fluid
12 months	*12 months ± 4 weeks*	• Patient alive with no evidence of trypanosomes in any bodily fluid and CSF WBC ≤ 20/µL	• CSF WBC > 20/µL and clinically non-significant increase as compared to previous value(s) • Any reason leading the Investigator to request an additional follow-up visit within 1 to 3 months	• CSF WBC > 20/µL and clinically significant increase as compared to previous value(s) • Signs or symptoms suggestive of HAT and of treatment failure leading to use of rescue treatment.	• Evidence of trypanosomes in any bodily fluid
18 months	*18 months ± 4 weeks*	• Patient alive with no evidence of trypanosomes in any bodily fluid and CSF WBC ≤ 20/µL	• Any reason leading the Investigator to request an additional follow-up visit within 1 to 3 months	• CSF WBC > 20/µL • Signs or symptoms suggestive of HAT and of treatment failure leading to use of rescue treatment.	• Evidence of trypanosomes in any bodily fluid

An uncertain outcome may be a discrepancy between the clinical picture and the laboratory findings, or any situation that leads the Investigator and the study team to consider that an additional follow-up visit is required to decide whether or not to provide rescue treatment.

6. Schedule of Study Procedures and Assessments

6.1. Timing of Assessments

The timing of assessment presented below is summarised in Table 3.

- D-15 to D-1: Patient screening with detection of *T.b. gambiense,* pre-treatment of concomitant helminthiasis and/or malaria, if any,
- D-4 to D-1: Baseline assessment, laboratory screening

- D1 to D10: treatment period
- D11: EOT visit
- Between D11 and D18: EOH visit
- Additional follow-up visit: at 9 weeks after D1, i.e. D64 to D70, for patients who reach this visit starting in mid-December 2014
- Follow-up visits: at M6, M12 (TOC) and M18 (see Table 2 – Theoretical Schedule of Visits and Acceptable Leeway). The timing of these follow-up visits is calculated from D11 (EOT).

Table 2 – Theoretical Schedule of Visits and Acceptable Leeway

Theoretical schedule of visits	Ideal timing of visits	Acceptable leeway*
End-of-Treatment (EOT) visit	D11 after the Start of Treatment (SOT) (D1 after EOT)	Between D11 and D12 after SOT (D1 or D2 after EOT)
End-of-Hospitalisation (EOH) visit	Between D11 and D18 after SOT (D1 and D8 after EOT)	D18 at the latest
Week 9 after D1	D64 to D70	
6 months	6 months ± 2 weeks after EOT	5-9 months after EOT
12 months	12 months ± 4 weeks after EOT	10-16 months after EOT
18 months	18 months ± 4 weeks after EOT	17-21 months after EOT

* The acceptable leeway for the visits starts on the first day of the period mentioned and ends on the last day of the month mentioned.

For the purposes of the study, patients will be hospitalised from their arrival at the hospital/investigational centre until D18. They will be permitted to leave hospital from D11 onwards, if their clinical status allows it.

Any additional unscheduled visits that may take place must be recorded in the CRF.

6.2. Screening and Baseline Assessment

6.2.1. Diagnosis of HAT

The mobiliser of the mobile team will inform the communities in the villages of the HAT screening activities, as is usually the case (see Section 14.1 Information of Communities; p 63). Specific information concerning the study should be provided to the community, i.e. a brief description of the aim of the study,

explanation of the process for collecting informed consent, duration and importance of follow-up.

HAT case detection may be carried out by a mobile team.

A physical examination and, potentially, tests may be performed to collect sufficient information to suggest a diagnosis of HAT. Whenever possible, CSF sampling will be performed at the investigational centre, or by the mobile team of the National HAT Control Programmes (see Section 4.1. Enrolment/Inclusion Procedures; p 30).

6.2.2. Pre-screening and Screening

The following assessments will be performed to confirm the diagnosis of HAT, to collect medical history and to check the inclusion and exclusion criteria.

- Sampling to test for trypanosomes in the blood using Woo test/CTC, thick and thin blood smears, mAECT and mAECT-BC with INRB kits, as well as in fresh lymph node aspirate (detection using microscopy), if palpable lymph nodes are present;
- Karnofsky Performance Score;
- CSF sampling for diagnosis of HAT based on WBC and detection of trypanosomes using Fuchs-Rosenthal/Fast-Read 102® counting chamber and Modified Single Centrifugation (MSC) with INRB kits;
- Collection of full medical history;
- Demographic data and prior treatment;
- Body weight, height and vital signs including body temperature, blood pressure, heart rate and respiratory rate;
- Treatment of helminthiasis;
- Screening for malaria using RDT and/or thick blood smear (treatment to be provided if result is positive);
- Review of inclusion and exclusion criteria.

6.2.3. Baseline Assessment

The following assessments will be performed to assess the patient’s baseline status just prior to the start of treatment:

- Review of inclusion and exclusion criteria;
- Karnofsky Performance Score;
- Vital signs, including body temperature, blood pressure and heart rate;
- Verification of clinical signs and symptoms of HAT;

- Physical and neurological examinations;
- Collection of concomitant treatment;
- Urine pregnancy test for women of child-bearing potential;
- Laboratory safety assessments (see Appendix 3 – Laboratory Tests; p 83) – whenever possible, all laboratory tests will be performed on patients in fasting state:
    - Haemoglobin
    - Haematology: WBC, platelet count
    - Biochemistry: albumin (ALB), alkaline phosphatase (ALP), alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), blood urea nitrogen (BUN), chloride (Cl-), creatinine (CRE), glucose (GLU), potassium (K+), sodium (Na+), calcium (Ca2+), total bilirubin (TBIL), bicarbonates (tCO_2) and total protein (TP)
    - Urine analysis, i.e. WBC, pH, protein, urobilinogen, blood, nitrites, glucose, ketone bodies and bilirubin
- Digital ECG recording (CarTouch®).
- If the assessments mentioned in Section 6.2.2, i.e. haemoglobin, haematology, biochemistry and urine analysis, were performed within 4 days prior to the first administration, the findings will be considered as baseline values and the tests will not be repeated at the Baseline Assessment.

6.3. Assessments during Hospitalisation

6.3.1. Efficacy, Clinical Signs and Symptoms

Patients will be questioned regarding potential adverse events every day during hospitalisation and then at each subsequent visit (see Section 6.5 Safety Assessments, Definitions and Reporting of Adverse Events; p 44).

- Physical examination (including vital signs) and neurological assessment (including signs and symptoms of HAT performed only at baseline assessment and D11) will be performed at D-1 (*Note: also acceptable if done during baseline period, i.e. D-4 to D-1*), and at D5, D8, D11 (EOT visit) and between D11 and D18 (EOH visit).
- Testing for *T.b. gambiense* in blood and lymph nodes at EOT visit (D11).
- Lymph node biopsy at the EOT and at subsequent assessments is not recommended unless the Investigator considers that the procedure carries no risk for the patient.

6.3.2. ECG Recordings

Single ECGs will be recorded at the following timepoints:

- At baseline (between D-4 and D-1)
- At D11 (EOT)

A central cardiologist will review the ECGs for any rhythm or conduction disorders.

If the central cardiologist issues an alert at the last ECG assessment, e.g. for QT-interval prolongation or change in ECG pattern, the Investigator will record an additional ECG at the EOH visit, i.e. prior to discharge. If the alert is maintained at the EOH, the Investigator must record an additional ECG at the 6-month follow-up visit or schedule an interim visit.

6.3.3. Laboratory Tests

A repeat urine pregnancy test will be performed at discharge, i.e. between D11 and D18.

Blood biochemistry and haematology assessments will be repeated on D5 and D11 (EOT visit). Safety haematology and biochemistry assessments will be performed 9 weeks after intake of the first dose on D1, only in patients who reach this visit from mid-December 2014 onwards. Safety haematology and biochemistry assessments will also be performed at the 6 month follow-up visit, only in patients who reach this visit from January or February 2016 onwards. Blood samples will be analysed in the laboratory in each centre using standard equipment specifically provided for the study by the Sponsor. Whenever possible, the samples should be collected from patients in the fasting state.

Parasitology testing requires 5 mL of whole venous blood or 4 mL of CSF. The blood sample should be analysed on an mAECT column within 30 minutes after collection. The CSF sample should be examined after MSC within 15 minutes after collection. The WBC in the CSF sample should be performed within 15 minutes after collection. It is necessary to collect 5 mL of CSF to perform the two tests.

Full haematological and biochemistry analyses require at least 0.5 mL of capillary or venous blood. Capillary blood collection considerably reduces the total quantity of blood collected as compared to classical techniques. However, because it is not always feasible, collection of venous blood is permitted. For each sample, 2 mL per tube should be collected, one tube containing EDTA for haematology and one tube containing heparin lithium for biochemistry.

The urine analyses performed at the baseline assessment and at the EOT visit (D11) require only a few millilitres (5-10 mL). If any abnormalities are found, additional urine analyses will be requested for further investigation and to

determine whether or not the abnormality constitutes an AE. For women of child-bearing potential, a urine pregnancy test will be performed at D-1 and at the EOH visit, i.e. between D11 and D18.

During hospitalisation, additional safety assessments such as haematology, biochemistry or urine tests may be performed at the discretion of the Investigator in order to monitor for abnormalities.

The volume and the number of samples required for each patient are presented by visit in Appendix 3 – Laboratory Assessments (p 83).

6.4. Assessments at Follow-up Visits

If the patient changes address or is away from home during the follow-up period, the investigator together with the appropriate site personnel can make one or several follow-up visits at the new patient's address. The patient has also the option to perform one or several follow-up visits in another study site or at the Kinshasa coordination (PHLTHA and INRB).The site investigator or the coordinating investigator will take care of the patient. Documents related to these visits will be sent to the original centre so that the data can be entered into the CRF.

6.4.1. At the Additional Visit 9 Weeks after D1

- Haematology: haemoglobin, WBC count and differential, platelet count;
- Biochemistry: same as baseline assessment;
- Physical examination, including vital signs;
- Neurological examination.

6.4.2. At the 6-month, 12-month and 18-month Follow-up Visits

- Only at the 6 month visit: Haematology and Biochemistry (same as baseline assessment);
- Physical examination, HAT symptoms since discharge, neurological assessment, including signs and symptoms of HAT;
- Karnofsky Performance Score;
- Testing for *T.b. gambiense* in blood and lymph for diagnosis of potential relapse;
- CSF sampling for diagnosis of potential relapse, with WBC and testing for trypanosomes (Fuchs-Rosenthal/Fast-Read 102® counting chamber and MSC with INRB kits);
- Vital signs, including body temperature, blood pressure and heart rate;

- Additional safety assessments such as ECG, haematology, biochemistry or urine tests may be performed at the discretion of the Investigator.

6.4.3. At Unscheduled Visits

If a relapse is suspected on the basis of physical examination findings or CSF WBC count, at any visit, the patient must attend a return visit within 1 to 3 months, at the discretion of the Investigator.

The patient must also return to the investigational centre if s/he does not feel well, even if there is no apparent relationship with treatment and/or HAT.

The following assessments will be performed:

- Physical examination, HAT symptoms since the last visit, neurological assessment, including signs and symptoms of HAT;
- Investigation of any concomitant condition that may have led to the visit;
- Testing for *T.b. gambiense* in blood and lymph, if indicated;
- CSF sampling (Fuchs-Rosenthal/Fast Read 102® counting chamber, MSC with INRB kits): only if symptoms suggesting disease progression are present;
- Additional safety assessments such as ECG, haematology, biochemistry or urine tests may be performed at the discretion of the Investigator.

6.5. Safety Assessments, Definitions and Reporting of Adverse Events

The safety and tolerability of treatment will be assessed through routine monitoring of adverse events (AEs). During the observation period, the study personnel will collect AEs on a daily basis.

The **observation period** will extend from the start of treatment (D1) to hospital discharge, i.e. between D11 and D18, depending on the patient's status.

In addition, patients will be advised to return to the hospital/investigational centre at any time during the follow-up period if they experience any AEs, in order to undergo additional safety assessments.

Safety data will be reviewed at each meeting of the DSMB.

Safety endpoints will be classified as follows:

- Occurrence of any adverse events at grade ≥ 3, including laboratory abnormalities, during the observation period. Adverse events will be graded according to the NCI CTCAE, Version 4.03 (38);
- Occurrence of any adverse events, including laboratory abnormalities, (all grades combined) during the observation period;
- Occurrence of any treatment-related adverse events, including laboratory abnormalities, (grade ≥ 3 and any grade) during the observation period and during the follow-up period;
- Occurrence of any serious adverse events, including laboratory abnormalities, during the observation period;
- Occurrence of any serious adverse events, including laboratory abnormalities, between the first intake of the IP and the end of the additional follow-up period (18 months).

6.5.1. Definition of Adverse Event

An AE is defined as any untoward and unintended medical occurrence (sign, symptom or disease), including a clinically significant abnormal laboratory or ECG finding, or worsening of any pre-existing condition during the study, whether or not it is considered to be study related.

Any abnormal laboratory result on haematology, biochemistry or urine analysis must be reported as an AE if it occurs or worsens after the start of the IP, and if the CTCAE grade is > 1, unless it is associated with a previously reported clinical event. Urinary dipsticks are only indicators and are not sufficient to support reporting of an AE. They may orientate the Investigator towards further investigations that, if they show clinically significant abnormalities, may support reporting of an AE.

The Investigator or appropriate study personnel will examine any patient who experiences an AE as soon as possible. The Investigator will do whatever is medically necessary for the patient's safety and well-being. The patient will remain under observation as long as s/he is receiving the IP and up to the last day of the observation period (between D11 and D18), or longer if medically indicated in the opinion of the Investigator. All AEs observed or reported following administration of the IP will be followed until resolved or until the Investigator considers them to be "chronic" or "stable".

All identified AEs will be recorded in the appropriate AE section of the CRF using concise medical terminology, and avoiding vague, ambiguous or colloquial language. SAEs will be reported by telephone, Short Message Service (SMS) or email to Swiss TPH (see Section 6.5.5 Requirements for AE Reporting; p 47.

6.5.2. Definition of Serious Adverse Event

An SAE is any AE that:

- results in death;
- is life-threatening;
- requires in-patient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is an important medical event that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above;
- in this study, ALAT or ASAT levels higher than 3 x ULN associated with a total bilirubin level higher than 2 x ULN will be considered as SAEs.

SAEs also include any other events defined in the present protocol or by the regulatory authorities in the country in which the event occurs.

For the purposes of the present study, hospitalisation for uncomplicated delivery will not be considered as an SAE.

6.5.3. Collection of Information on Adverse Events

The Investigator is required to report all AEs s/he observes directly, as well as all AEs spontaneously reported by the patient, using concise medical terminology. In addition, during the observation period, i.e. from D1 to D18 (or earlier in the event of early discharge) and at each follow-up visit, the patient will be asked a series of questions, and a targeted physical examination will be performed, to investigate any potential AEs.

6.5.4. Adverse Event Collection Period

The periods for collection of AEs that occur in the context of the study are defined as follows:

- For **all non-serious adverse events**, the **observation period** extends from the first intake of the IP on Day 1 until hospital discharge between D11 and D18;
- For **all serious adverse events**, the **observation period** extends from enrolment of the patient in the study, i.e. after signature of the informed consent form, **until the end of follow-up** (18 months).

All AEs that occur during the AE collection period defined in the protocol must be recorded in the CRF, whether or not they are considered to be treatment related. In addition, all AEs that occur after the AE collection period, and that the Investigator considers as possibly related to the IP, must also be reported.

6.5.5. Requirements for Adverse Event Reporting

Information on AEs must be assessed by a physician. The Investigator must assess the seriousness of the AE, if necessary with the help of the Coordinating Investigator and the study monitor. The classification as serious or non-serious will determine the reporting procedure for the event.

All SAEs must be reported immediately, i.e. no later than 24 hours after the Investigator becomes aware of the SAE, to the Swiss TPH clinical study monitor, first by telephone and/or SMS, then by email using the SAE reporting form. This report must include a description of the event, onset date and type, duration, severity, relationship to the IP (with the help of the Coordinating Investigator as needed), outcome and measures taken, as well as any other relevant clinical or laboratory data. Any additional information must be sent on an SAE follow-up form as it becomes available. Follow-up reports should be submitted as soon as possible, and, if possible, within 5 working days after the new information becomes available. A close-out follow-up report must be sent after the final assessment of the case as “recovered”, “recovered with sequelae” (chronicity), “death” etc.

SAEs must also be recorded in the AE section of the CRF. It should be noted that the reporting form for SAEs (SAE form) is not the same as the form in the AE section of the CRF. The two forms must be completed in a consistent manner, using the same medical terminology.

All AEs must be recorded in the CRF.

For the purposes of this study, the Coordinating Investigator will be in charge of reporting Suspected Unexpected Serious Adverse Reactions (SUSARs) considered to be related to the IP and SAEs to the Ethical Committees in the countries and other relevant ethical committees. DND*i* will be responsible for reporting SUSARs and SAEs to the regulatory authorities.

6.5.6. Grading of Adverse Event Severity

The severity of the AE must be graded according to NCI CTCAE, version 4.03 (38) adapted for some biological parameters (i.e. haemoglobin, leukocytes, sodium, calcium and creatinin). If the AE is not described in the CTCAE, version 4.03, the Investigator will use the terms “mild”, “moderate” or “severe” to describe the maximum severity, as defined below:

Mild	does not interfere with the patient's usual activities;
Moderate	interferes to some extent with the patient's usual activities;
Severe	significantly interferes with the patient's usual activities.

The information concerning AE grading must be recorded in the AE section of the CRF.

It is important to distinguish between the severity and the seriousness of AEs: a severe AE is not necessarily an SAE.

6.5.7. Assessment of Adverse Event Causality

For all AEs, the Investigator is required to assess the possible causal relationship between the IP and the AE, with the help of the Coordinating Investigator as needed, in order to determine whether there is a reasonable possibility that the IP caused or contributed to the AE.

The causal relationship between the IP and the AE is assessed by the Investigator after a detailed analysis of the event in terms of the biological plausibility, taking into account possible unrelated causes, pre-existing medical conditions, concomitant treatments, the temporal relationship between intake of the IP and onset or worsening of the event, and known patterns of response to the IP in general.

The two types of relationships are defined as follows:

- Unrelated: there is no temporal relationship between intake of the IP and the event, and/or there is a plausible alternative explanation.
- Possibly related: any AE that is not considered as unrelated to the IP and/or for which there is no plausible alternative explanation.

The decision to interrupt, resume or permanently discontinue the IP due to an AE will be left to the discretion of the Investigator, except in situations described in Section 8 Withdrawal Criteria (50).

6.5.8. Exposure *in utero*

Two pregnancy tests are planned during the study: at D-1 and at discharge. Among women of child-bearing potential, only those who have a negative result on the pregnancy test on D-1 will be eligible to participate in the study.

The Investigator must report any pregnancy that occurs during the observation period of the study, or that is diagnosed before or at the 6-month follow-up visit,

using the appropriate pregnancy reporting form. This must be done irrespective of whether an AE occurred or not. If known, the due date must be specified.

The Investigator will monitor the patient until the term of the pregnancy, i.e. full term or preterm in the event of a miscarriage. The Investigator will provide information on the outcome of the pregnancy using the pregnancy follow-up reporting form.
A physician, preferably a paediatrician, should examine the infant at birth and submit a report using a pregnancy follow-up reporting form. The Investigator will offer the parents follow-up on infants exposed to the IP *in utero* until they reach 24 months of age. As far as possible, stillborn infants should be examined by a physician to assess the cause of death.

6.5.9. Follow-up on Adverse Events

All AEs must be followed until resolution, or until the Investigator considers them to be “chronic” or “stable”, or until the patient’s participation in the study ends, i.e. until the final report is completed for the study in which the patient was participating.

If the AE is a laboratory abnormality with a toxicity grade ≥ 3, the test must be repeated 2 to 4 days later, and then at regular intervals until the parameter reaches toxicity grade ≤ 1, or until it returns to the baseline level (see Baseline Assessment).

In addition, all SAEs and all events that the Investigator (and the Coordinating Investigator or the monitor, as needed) considers as possibly related to the IP must continue to be followed even after the end of the patient’s participation in the study. Such events should be followed until their resolution, or until the Investigator considers them as “chronic” or “stable.” The resolution of such events must be documented in the CRF, and if they are SAEs, on an SAE follow-up form.

7. Study Duration

The enrolment period is expected to last approximately 10 months. The treatment period will last 10 days.

Each patient’s participation will last approximately 19 months and will include:

- pre-treatment period (pre-screening and screening, treatment of concurrent disease)
- treatment period of 10 days
- hospitalisation for 1 to 8 days after treatment
- out-patient follow-up for 12 months, until the TOC visit
- additional follow-up until 18 months.

The total duration of the study is expected to be 28 months.

8. Withdrawal Criteria

8.1. Rules for Temporary Interruption of Treatment

Temporary interruption of treatment will not necessarily lead to withdrawal of the patient from the study. In some cases, treatment may be interrupted for a maximum of one day, i.e. one missed dose of fexinidazole, and treatment will therefore be delayed. Treatment may be reintroduced at the discretion of the Investigator responsible for the patient. One additional day of treatment will be added to make up for the missed dose. The patient should continue the visits and study procedures as planned, taking into account the delay. The reasons for interrupting treatment must be recorded in the appropriate source documents and in the CRF.

8.2. Rules for Definitive Discontinuation of Treatment

The Investigator will discontinue the IP in the following cases:

- Severe skin reaction;
- ALAT or ASAT exceeding 8 x ULN;
- ALAT or ASAT exceeding 3 x ULN accompanied by total bilirubin exceeding 2 x ULN;
- ALAT or ASAT exceeding 3 x ULN accompanied by fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia exceeding 5%;
- Any condition that, in the opinion of the Investigator, requires treatment discontinuation for medical reasons.

If a patient is withdrawn from the study before the end of treatment, the physician will make all necessary arrangements to ensure that s/he receives appropriate treatment for the condition in question.

8.3. Patient Withdrawal from the Study and Replacement of Patients

A patient may be withdrawn from the study in the following cases:

- withdrawal of consent by the patient or his/her legal representative;
- study termination by the Sponsor.

If the patient or his/her legal representative withdraws his/her consent, no further evaluations will be performed, with the exception of safety data, which must be collected whenever possible.

Data collected prior to withdrawal of the patient will be taken into account in the efficacy and safety analyses.

If a patient decides to withdraw from the study, the reason must be recorded in the CRF. If a patient is withdrawn from the study due to an AE, all measures must be taken as needed to clearly document the outcome of the AE. Patients withdrawn from the study will not be replaced.

8.4. Patients Lost to Follow-up

If a patient does not attend a protocol-planned visit, all necessary measures must be taken to contact him/her. In all cases, all necessary measures must be taken to document the outcome of the patient's condition, if possible.

9. Data Analysis and Statistical Methods

A full Statistical Analysis Plan (SAP) will be prepared prior to database lock. It will provide a detailed description of the statistical methods.

9.1. Sample Size Determination

The primary objective of the study is to demonstrate that the success rate of treatment with fexinidazole at 12 month follow-up in patients with stage-1 or early stage-2 HAT is greater than 80%. An 80% success rate is considered unacceptable.

The expected success rate with fexinidazole at 18 months in patients with late stage-2 HAT is 89% (see Study FEX004). The expected success rate at 12 months in the same population is approximately 90% since a relapse rate of around 1% can be expected between 12 and 18 months. Because the disease is less severe in patients at stage 1 and early stage 2 than in patients with late stage-2 HAT, a 91% success rate is expected in the population included in the present study. If the objective is a success rate of 91%, an exact statistical power of 91.7%, with a one-sided type-I error of 0.025 and an exact test, can be reached with a sample size of 113 patients. The minimal total sample size to include is therefore 113 patients. It is planned to enrol all patients with stage-1 and early stage-2 HAT who are diagnosed during screening for the pivotal study and who agree to participate in the present study.

The population of this study will be stratified into 2 strata: patients with CSF WBC ≤ 5/µL (stage 1) and patients with CSF WBC between 6 and 20/µL (early stage 2). The strata will be self-weighted, i.e. the number of patients in each stratum will depend solely on the number of patients who agree to participate in the study.

Because the success rate can be significantly dependent on the stage, it is planned to include a sufficiently large number of patients at stage 1 to have, with the same expected success rate at 12 months (i.e. 91%), at least 85% statistical power. Consequently, it will be necessary to include at least 101 patients at stage 1.

It was planned to include at least 101 patients at early stage-2 and a maximum of 300 patients for the entire population. It was therefore expected that there would be twice as many patients at stage 1 as compared to patients at early stage 2. However, the prevalence of stage-1 HAT is in fact seven times higher than the prevalence of early stage-2 HAT (N = 135 after 11 months of enrolment). It therefore seems unlikely that the initial objective of enrolling at least 101 patients at early stage-2 will be reached. Consequently, the objective of enrolling 101 patients will be reached only for stage 1.

Given the minimal sample size for the study, i.e. 113 patients, and the fact that 101 patients at stage 1 have already been included thus far, enrolment in the study will be stopped when approval for the present protocol amendment, i.e. Amendment 3, is obtained from the Ethics Committee and the Regulatory Authorities.

9.2. Handling of Missing Outcomes and Patients Lost to Follow-up

The primary and surrogate endpoints are based on the outcome at 12 months. If the outcome assessed at the final visit (M18) is missing, the **primary imputation method** will consist in imputing a probable success (considered as a success) to patients who attended the 12-month visit, but who refused the lumbar puncture planned for the visit, who showed no signs or symptoms of HAT at 12 months, who did not subsequently report any symptoms of relapse and for whom the outcome was considered as favourable at the last available assessment (42). In case the outcome at M18 is available but not the outcome at M12, then the outcome at M18 will be carried backwards.

If these criteria are not fulfilled, the patients will be considered as treatment failures. The outcome for patients lost to follow-up from the 12-month visit onwards will also be considered as a failure.

Two additional methods for imputing missing data will be used.

The **second method** will consist in imputing failure if there is no lumbar puncture at 12 months or later.

In the **third method**, missing data will not be imputed. All patients for whom an assessment is available at a given timepoint will be included in the estimate of the success rate at that timepoint. If a value is missing at an intermediate visit, followed by a success or a failure at one of the subsequent visits, the status at the subsequent visit will prevail over the status at the intermediate visit. In the Kaplan-Meier approach, the observation is censured at the first missing outcome, provided that all subsequent outcomes are also missing.

9.3. Handling of Centres

The primary analysis will not be stratified by centre. However, any variation in the success rate at 12 months between centres will be tested with an exact test. If the hypothesis of homogeneity is not rejected, the overall value of the result of the primary analysis is acceptable. Conversely, if the hypothesis of homogeneity is rejected (H_0), the heterogeneity may be due to atypical centres. The centres responsible for the heterogeneity will be identified and removed from the analysis in order to determine whether the success rate is higher or lower without these centres. The centre effect will also be analysed using the Glimmix procedure in order to study the time course of treatment response.

9.4. Definition of Analysis Sets

Sets used in the Analyses

Type of analysis	Aim	Definition of analysis set
Primary: ITT patients	Analysis of safety and primary efficacy analysis	All randomised patients who received at least one dose of the IP.
Secondary: treatment completers	Sensitivity analysis on efficacy	All randomised patients who completed the treatment period and who received all protocol-planned doses.
Secondary: evaluable patients	Sensitivity analysis on efficacy	ITT patients, except those who died due to causes clearly unrelated to efficacy or safety. Exclusion will be documented.
Secondary: per protocol patients	Sensitivity analysis on efficacy	ITT patients with no major protocol violations. Major violations will be described for each patient.

9.5. Patient Disposition

At the end of the study, patient disposition (overall population and by stage at diagnosis) will be presented in terms of:

- Number of patients screened
- Number of patients not included in the study because they did not fulfil the eligibility criteria, and reason for non-inclusion
- Number of patients included
- Number of included patients who received at least one dose of the IP (ITT patients)
- Number of included patients who completed the treatment period and who received all protocol-planned doses (treatment completers)

- Number of included patients who received at least one dose of the IP, except those who died due to causes clearly unrelated to the efficacy or safety of the IP (evaluable patients)
- Number of included patients with no major protocol violations (per protocol patients)
- Number of included patients who attended the following visits: screening visit, baseline assessment, visits during treatment period (D1 to D10), EOT visit, EOH visit, and follow-up visits at 6, 12 and 18 months
- Number of included patients who were withdrawn from the study, classified by reason for withdrawal
- Number of included patients with at least one protocol violation, classified by nature of violation, i.e. minor or major

9.6. Baseline Data

Descriptive summary statistics (n, mean, standard deviation, median, minimum, maximum) or frequencies and percentages will be presented for the following baseline characteristics of the study population:

- Demographic data
- Medical history
- Physical examination
- Vital signs
- Urine pregnancy test (only for women of child-bearing potential)
- Laboratory assessments
- ECG
- Karnofsky Performance Score
- Neurological examination
- Concomitant medication

9.7. Treatment Compliance

The dosing regimen of the IP is described in Section 5 Treatments (p 34).

Treatment compliance will be analysed by describing the number and percentage of patients who completed the treatment period. Patients in whom the treatment period was extended by one day (missed dose made up for at end of treatment) will be considered as having completed the treatment period. For patients who prematurely discontinued treatment, the duration of exposure will be presented.

9.8. Efficacy Analysis

9.8.1. Primary Efficacy Analysis

Primary Efficacy Endpoint

The primary efficacy endpoint is the. success or failure, at 12 months after the EOT. It will be a success if there is no evidence of trypanosomes in any bodily fluid, and the WBC count in the CSF is ≤ 20/µL. Patients with no parasitological evidence of relapse, but with a CSF WBC count > 20/µL or who, in the opinion of the Investigator, require rescue treatment, will be considered to be probable relapses and therefore as failures. Death due to any cause or use of rescue medication will be considered as a relapse, i.e. a failure. A patient who attends the follow-up visit at 12 months or later and who refuses to undergo lumbar puncture, but who has no signs or symptoms of HAT and for whom the outcome was assessed as favourable at the last assessment will be considered as a probable cure, i.e. a success, unless signs of relapse are detected on any assessment up to 18 months. In case the outcome at M18 is available but not the outcome at M12, then the outcome at M18 will be carried backwards.

Primary Analysis

The primary analysis will be performed on the intention-to-treat (ITT) population.
The primary endpoint is the success or failure of treatment, as defined above.
The primary analysis of success or failure will be performed at 12 months of follow-up.
If the exact lower limit of the 95% confidence interval is ≤ 80% then the study is a failure, otherwise it is a success.
The null hypothesis in the primary analysis is H_0: $\pi \leq 0.80$.
The alternative hypothesis in the primary analysis is: H_1: $\pi > 0.80$.
The primary analysis consists in calculating the exact 95% confidence interval of the success rate at 12 months and comparing it to 80%.

Historical yardstick and Limit of Unacceptable Success Rate

The success rate of NECT in patients with early and late stage-2 HAT (CSF WBC > 6/µL) was 94% at 18 months (143 patients assigned to the NECT group, 2 relapses and 5 deaths related or unrelated to treatment, as well as 2 patients lost to follow-up) (43). The success rate in the NECT-Field study was also 94% at 18 months (577/614, IC [91.8 – 95.7]) (60). A success rate of 94% at 18 months is a reasonable approximation of the success rate of NECT using a conservative definition, i.e. proven success.

As concerns pentamidine, Hümbelin (59) performed a meta-analysis on a sample of 2524 patients, which found a relapse rate, i.e. evidence of trypanosomes or CSF WBC ≥ 20/µL, of 5.63% in patients followed for 6 months or less, (142/2524),

of 8.20% in patients followed for 12 months or less (207/2524) and of 9.23% in patients followed for 18 months or less. The failure rate was slightly lower in the Balasegaram study (61): 5.05% in 454 patients followed for 6 months and 371 patients followed for 12 months. A success rate no higher than 92% is expected at 12 months and of 91% at 18 months, since Balasegaram's results were derived from a smaller sample size and are not based on patients followed for at least X months, but for patients followed for X months or less.

By combining the historical success rates of NECT and pentamidine in patients with stage-1 and early stage-2 HAT, an overall success rate of 93% at 12 months is expected if each treatment was used for its respective stratum of patients.

The acceptable limit of the difference in efficacy between fexinidazole and NECT was set at 13% in the pivotal study on fexinidazole in patients with late stage-2 HAT. The limit was estimated based on a survey conducted among field practitioners. The possible 13% lower efficacy is compensated for by the advantage of having an oral formulation that does not require elaborate healthcare infrastructures. As discussed above, the major advantage of fexinidazole in patients with stage-1 and stage-2 HAT is the oral route of administration and the fact that painful lumbar punctures are not required for staging the disease and choosing the appropriate treatment. It should be noted that the potentially lower efficacy is not a major issue for these patients in whom the disease is not life-threatening in the short term since a second-line treatment can be administered if necessary. In the randomised pivotal study, the maximum acceptable difference in efficacy in relation to the comparator was 13%; in the present non-randomised study, an equivalent acceptable difference in efficacy has been chosen. Using a success rate of 93% at 12 months and an acceptable margin of difference of 13%, the unacceptable limit of efficacy is 80%, which is still higher than the success rate of melarsoprol at 12 and 18 months, i.e. 74.84%-78.98% and 73.71%-78.63% respectively, n = 3477 (59).

9.8.2. Sensitivity Analyses

Several sensitivity analyses will be performed to assess the robustness of the results of the primary analysis and to facilitate interpretation. They will be performed on the population of treatment completers, the population of evaluable patients and the per-protocol population. Additional sensitivity analyses will be described in the SAP.

9.8.3. Secondary Efficacy Analyses

- A comparison will be performed in order to determine whether the success rate varies depending on the stage of HAT; three stages will be compared: stage 1, early stade-2 and late stage-2 from the FEX004 study. A likelihood ratio test will be used to compare the three rates. If the hypothesis of

homogeneity is not rejected, stage 1 will be compared directly to early and late stage 2 combined since the sample size of patients at early stage 2 is expected to be small, which will affect the overall power of the test. If the hypothesis of homogeneity is rejected, pair-wise comparisons will be performed to identify the groups that differ.

- A test will also be performed to determine whether the observed rate for stage 1 and early and late stage 2 combined are significantly different from the limit of 80%, which is considered unacceptable.
- The correlation between the success rate and the WBC count in the CSF will be estimated using a logistic regression. The WBC count will be a quantitative covariate. Another analysis will be performed using a logistic regression with a random intercept to take into account the centre effect. A trend test will also be performed using the Bartholomew's test. Another analysis will be performed after pooling patients with late stage-2 HAT treated with fexinidazole in the pivotal study with patients in this study. The correlation between the success rate and the baseline WBC count will be adjusted with a logistic regression model using the centre as covariate.
- The time-course of the cumulative rate of definitive failure (from the start of treatment to the definitive failure) will be estimated using the Kaplan-Meier method, and patients lost to follow-up will be considered as censures.
- The success rate at each timepoint will be estimated and compared using a Cochran Q-test. The logistic model for repeated measures (Glimmix procedure in SAS®) will be used to test the time effect adjusted by centre.

9.9. Safety Analyses

All patients who received at least one dose of fexinidazole will be included in the safety analyses.

The percentage of patients with SAEs and/or AEs leading to treatment discontinuation will be presented by system-organ class, using appropriate MedDRA preferred terms, according to NCI CTCAE, version 4.03.

The percentage of patients with at least one AE will be described. If a patient experienced several AEs described using the same preferred term, the AE with the maximum severity will be used in the analysis of severity. For recurrent AEs, the frequency of occurrence of the AEs by patient will be presented. In addition, each SAE will be presented in a narrative describing all aspects of the medical event.

AEs not leading to treatment discontinuation will be presented for each treatment group using the same classification as presented above.

The incidence of SAEs and AEs, along with the respective 95% confidence intervals will be presented for the entire population, by stratum, by category and by frequency. In other cases, only descriptive statistics will be presented.

Laboratory safety parameters, i.e. haematology and biochemistry, will also be presented individually, indicating the percentage of patients, the size of the increase in the value in relation to the ULN and baseline value, and changes in blood levels over time. Shift tables will be presented. A listing of patients with laboratory abnormalities will be provided.

ECG abnormalities will be presented at each timepoint and for each stratum.

10. Steering Committees

10.1. Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) consisting of at least 3 members independent from the Investigators and Sponsor, will be set up prior to study initiation. The DSMB will monitor the study in order to ensure that any harm to the patients included in the study is minimized. The DSMB will review safety data at pre-determined intervals, review all information related to the occurrence of SAEs and AEs leading to treatment discontinuation, and issue recommendations about the study if the current benefit-to-risk ratio for patients in the study seems to be unfavourable. The data and intervals will be agreed prior to, or soon after, study initiation and documented in the DSMB Charter.

The organisation of the DSMB and its operating methods will be described in the DSMB Charter, which will have been prepared and approved at the first meeting.

The DSMB of the pivotal study, DNDiFEX004, will also be in charge of studies DNDiHATFEX005 and DNDiHATFEX006.

Additional *ad hoc* members may be invited to join the DSMB if any safety concerns emerge, in order to give additional support to the competencies already present.

10.2. Pre-database Lock Review Committee

Pre-database Lock Review Committee, comprised of persons involved in the conduct of the study and data processing, will be responsible for assessing the consistency of the rules used to define patient disposition:

- per-protocol patients versus major violations**;**
- success versus failure.

11. Quality Assurance and Quality Control Procedures

The Investigator must maintain appropriate accurate records to ensure that all aspects of conducting the study are fully documented, and that study data can be verified at the end of the study. These documents include the Investigator Site File, the patients' clinical source documents, screening/enrolment logs and other study-specific forms.

11.1. Investigator Site File

The Investigator's Site File must contain the protocol and protocol amendments, IEC and regulatory approval with all correspondence, a copy of the patient information and informed consent form, drug accountability records and curriculum vitae for study personnel, as well as authorisation forms and any other relevant documents or correspondence.

11.2. Case Report Forms

Data will be collected by laboratory technicians, physicians, nursing staff or care-givers authorised by the Investigator. Data collection will be supervised by the Investigator. Study-specific information will be entered in a case report form (CRF). Data generated from this information must be consistent with the source documents, and any discrepancies must be accounted for. Some data may be collected directly in the CRF, in which case, this will be described in the Investigator manual. All data that are recorded in the CRF must be rendered anonymous, i.e. such that they are only identified by the patient's code.

The Investigator must ensure the accuracy, completeness, legibility and timely entry of all data reported to the Sponsor via the CRF, and any other additional information that is requested. The Investigator is responsible for ensuring that all informed consent forms and screening forms for all patients are stored in a secure location. Data will be entered in the CRF after each patient visit. The CRF will be signed by the Investigator.

11.3. Source Documents

The data in the CRF must be verified by direct inspection of the source documents. The source documents are the patients' medical files, the physicians' and nursing staff's notes, appointment books, originals of laboratory test results, ECG tracings, reports on specific assessments, signed informed consent forms and patient screening/enrolment logs. Some data collected directly in the CRF may be considered as source data, in which case the data concerned will be described in detail in the Investigator Manual.

The Investigator must keep the source documents up to date, i.e. reports on laboratory tests and consultations, records of medical history and physical

examination reports, so that they can be examined and/or audited by DND*i* or its designated clinical monitors and/or by the Regulatory Authorities.

11.4. Retention of Documents

The Investigator must retain all essential documents for at least two years after approval of the last marketing authorisation is obtained, and until there are no on-going or planned applications for marketing authorisation, or until at least 15 years after the official stop date of clinical development of fexinidazole. However, study documents may need to be retained for a longer period of time if required by local regulations in effect or by agreement with DND*i*. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained. After that date, the documents may be destroyed with prior permission from DND*i*, subject to local regulations.

DND*i* must be notified in advance if the Investigator plans to assign the study records to another party or move them to another site.

11.5. Monitoring

Clinical monitors will perform regular monitoring visits during which they will verify source data, Informed Consent Forms, medical records, laboratory results, imaging reports, CRFs, drug dispensing logs and protocol violations. The monitors will be given access to the corresponding source documents for each patient on condition that that the patient's confidentiality is maintained in accordance with local regulations.

Monitoring visits at the investigational sites will be performed periodically by *DNDi* representatives or designated clinical monitors to ensure compliance with Good Clinical Practice and all aspects of the protocol. Source documents will be reviewed for verification of consistency with the data in the CRFs. It will be the clinical monitor's responsibility to inspect the CRFs at regular intervals. The Investigator will ensure that DND*i* designated representatives have direct access to source documents. It is important that the Investigators and the personnel concerned are available during monitoring visits. The Investigator agrees to cooperate with the clinical monitor to ensure that any problems detected during monitoring visits are resolved.

The monitoring visits provide DND*i* with the opportunity to assess progress of the study, to verify the accuracy and completeness of the CRFs and to resolve any inconsistencies in the study records, as well as to ensure compliance with all protocol requirements, applicable regulations and Investigator obligations.

Four types of visits are planned: site evaluation visit, site initiation visit, monitoring visit and site closure visit.

11.6. Audits and Inspections

The investigational centres may also be subject to quality assurance audits by DND*i* or designated representatives, and/or to inspection by regulatory authorities or IEC members.

The purpose of the inspections is to verify adherence to the protocol and to ensure the study is being conducted in accordance with Good Clinical Practice. It is important that the Investigators and the personnel concerned are available for any audits or inspections.

11.7. Data Management

A CRF must be completed for each patient who has given informed consent. The present clinical study will use a CRF. The study data will be stored in a computer database maintaining confidentiality in accordance with national legislation on data protections.

All data will be entered in the CRF under the responsibility of the Investigator or a qualified designated staff member.

Data will be reviewed by the clinical monitor. Data queries will be generated, documented and resolved on a regular basis throughout the study.

11.8. Confidentiality of Information, Study Documents and Patients' Files

The Investigator will ensure that the anonymity of patients is maintained and that their identity is protected from unauthorised third parties. Patients must not be identified by their names in the CRF or on any other documents submitted to the Sponsor. Only the patient number should appear. The Investigator must keep a patient enrolment log containing the patients' number, name and address. The Investigator must ensure the confidentiality of all documents submitted to the Sponsor's authorised representatives, including the signed informed form.

The findings of any assessments, including laboratory tests, will remain strictly confidential to the patient him/herself. This includes patients under legal age and vulnerable patients. Particular attention will be paid to the confidentiality of the results of pregnancy tests and tests related to concomitant diseases.

12. Protocol Amendments

The Investigators will ensure that the study is conducted in strict compliance with the protocol, and that all data are collected and recorded in the CRF.

All protocol modifications must be documented in writing. A protocol amendment can be initiated by either the Sponsor or any Investigator. The Investigator will provide the reasons for the proposed amendment in writing and will discuss it with the Sponsor and the Principal Investigator.

Any protocol amendment must be approved and signed by the Sponsor and the Principal Investigator, and must be submitted to the appropriate IEC for information and approval in accordance with local requirements, and to regulatory agencies, if required. Approval must be received from the IEC, and the regulatory authorities, if applicable, before any changes can be implemented, with the exception of changes required to avert an immediate risk for study participants, or when the change involves only logistical or administrative aspects of the study, e.g. changes in telephone numbers.

13. Early Termination of Study

Both the Sponsor and the Principal Investigator will have the right to terminate the study early, i.e. at any time prior to inclusion of the planned number of patients, but they may exercise this right only for valid scientific or administrative reasons. If this is necessary, the two parties will define the procedures for terminating the study after consultation. The Sponsor and the Principal Investigator will ensure that early termination of the study takes place in such a way as to protect of the patients' interests.

Reasons for which the study may be terminated by the Sponsor include, but are not limited to:

- insufficient enrolment rate;
- protocol violations;
- inaccurate or incomplete data;
- dangerous or unethical practices;
- on recommendation from the DSMB or IEC.

Reasons for which the study may be terminated by the Investigator include, but are not limited to:

- insufficient time or resources to conduct the study;
- lack of eligible patients.

If the study is terminated early by the Sponsor or the Investigator, the latter must:

- complete all CRFs to the largest extent possible;
- return all study-related articles and equipment to the Sponsor who provided them;
- answer all queries from the Sponsor, or delegated representatives, related to data on patients enrolled by the site prior to study termination;
- ensure that patients enrolled in the study who have not yet attended any follow-up visits receive all necessary medical care;
- provide the IEC, the regulatory authorities and, if appropriate, the Sponsor with a written explanation of the decision to terminate the study.

14. Ethical Considerations

The protocol for this study was prepared in accordance with the general ethical principles set out in the Declaration of Helsinki of the World Medical Association (see Appendix 1 – Declaration of Helsinki; p 76) and ICH guidelines for Good Clinical Practice (ICH Harmonised Tripartite Guideline - Guideline For Good Clinical Practice E6(R1) - current step 4 version, dated 10 June 1996). DNDi commits to respect all applicable laws for the protection of the rights and welfare of human subjects.

The protocol will be officially submitted by the Principal Investigator for approval from the IEC of the Ministry of Health of the DRC (Clinique Ngaliema).

Approval from the IEC must be received prior to undertaking any protocol-specific procedure in any patient.

In addition, the protocol will be reviewed by the MSF Ethics Review Board prior to study initiation in the sites concerned, since MSF is involved in the study as an implementation partner.

Any modification made to the protocol after receipt of the IEC approval must also be submitted in writing by the National Investigator to the IEC, in accordance with local procedures and regulatory requirements (see Section 12 Protocol Amendments ; p 61).

The protocol will be submitted along with appendices relevant to the information and safety of patients, such as the patient information sheet & consent/assent form, and the Investigator Brochure. The set of images provided to the Investigators as visual aids to explain the study procedures will be presented to the IEC. The patient information sheet and consent/assent form must be formally agreed upon by each IEC separately.

The protocol will be submitted for opinion from the IEC of Necker Hospital in Paris, France.

14.1. Information of Communities

The PNLTHA (National HAT Control Programme) in the DRC is responsible for all prevention and treatment activities regarding HAT within the country, and in particular for the supervision and coordination of the mobile teams in charge of HAT screening activities. PNLTHA is fully involved in the design and implementation of the study on fexinidazole in the DRC.

Information of the communities participating in the study will be provided at three different levels.

Firstly, the study will be presented to the public health representatives of the provinces concerned, namely the Provincial Medical Inspectors (*Médecins*

Inspecteurs Provinciaux) and District Medical Officers (*Médecins Chefs de Zones*), as well as the District Administrators prior to any study-related activity in their respective geographic areas of responsibility. Information on the study will be provided by the Provincial Coordinators of the PNLTHA (*Médecins Coordinateurs*), if possible in conjunction with a DNDi representative. The information will be based on the study protocol summary, the patient information sheet and consent form, and a summary of the Investigator Brochure.

Secondly, and before starting screening activities for the study in a given area or health zone, an adequate, HAT-experienced person with good knowledge of the area and local culture and good communication skills, i.e. either a member of a mobile team and/or a community mobiliser, will visit the local authorities, and tribal or village chiefs a few days before arrival of the mobile team, and inform them about the study and the related activities. In agreement with the local chiefs, an additional information session for the local population may be held, possibly during the usual community information session, which routinely takes place just before the start of screening activities by mobile teams. HAT is endemic in the regions where the study is to be conducted, and therefore, individuals already have a basic knowledge of the disease. In addition, most of the community mobilisers and many mobile team members have undergone specific training in community communication and HAT and will also receive additional study-specific training. Their experience and knowledge will therefore be extremely valuable in promoting a good understanding of the study.

The following information on the study will be disseminated at the community level:

- Routine procedures for detection and diagnosis of HAT;
- Primary objective of the study, i.e. to develop a safe oral drug to treat HAT that will be made available to the local population;
- Information on the new drug, the reference treatment as an alternative outside the study, the availability of a rescue treatment and on concomitant treatments as needed;
- Information on the duration of hospitalisation, number of follow-up visits up to 18 months as compared to routine treatment, importance of attending follow-up visits and possibility of visits by study staff at village level if the patient does not attend the follow-up visits at the centre;
- Information on provision of food to all HAT patients treated at the sites, regardless of whether or not they are included in the study;
- Information on organisation of transport and/or reimbursement of transport costs for patients included in the study;
- Importance of the freedom of each individual to accept or to refuse to take part in the study, after full explanation of the study. Availability of treatment in either case;

- Need for minors and patients with impaired cognitive capacities to come to the centre accompanied by a legal guardian/representative.

The third level of information concerns the individual consent of each patient (see Section 14.2. Informed Consent Process; p 65).

At the end of the study, the community will receive information on the results using the same means of communication, i.e. community mobilisers.

14.2. Informed Consent Process

14.2.1. General Process

The patient will not be included in the study until after s/he has given informed consent in writing. It is the responsibility of the Investigator to obtain, for each individual who participates in the study, voluntary written informed consent after having provided adequate explanation of the aims, methods, expected benefits and potential risks of the study. This task can be performed by a designee, referred to below as a “facilitator”, who may be a study nurse.

The written informed consent document will be translated into the local language or a language understood by the patients, and submitted to the IEC in each country for approval.

The facilitator will be chosen within the team for her/his good knowledge of the patients’ preferred local language, and for his/her skills in interacting with patients. More than one facilitator may be chosen in each centre to cover all local languages and dialects.

Visual aids, including photographs, drawings and samples, will also be made available to the facilitator, describing the activities performed during the study, i.e. lumbar puncture, finger pricks, ECG, etc., and will be submitted to the IEC for approval.

The patient will be invited to attend the information session alone or together with family or friends if s/he wishes. The session will be held in a separate room in order to ensure patient confidentiality, with only one facilitator present.

The patient will first be informed about the disease, i.e. HAT, with a clear description of the signs and symptoms.

The information provided during the session will address the following topics:

- currently available treatments;
- study objective and need for scientific evaluation of a new drug;
- information on the new drug from previous studies (efficacy, safety…);

- number of patients to be enrolled and the duration of the study;
- criteria to fulfil to be eligible for inclusion in the study;
- patient's commitments during the study, i.e. time, compliance with study-specific procedures and attendance at follow-up visits;
- samples to be collected for laboratory tests and purpose of tests;
- benefits and risks associated with study participation;
- compensation for travel costs and provision of food during hospitalisation;
- patients' rights regarding withdrawal, rescue treatment, additional information, etc.

If the patient wishes, s/he will be given time to discuss the information received with members of his/her community or family before giving consent. Written consent will be given after the information session (or later) by signing the form, provided the facilitator is convinced that the patient has fully understood what was explained.

All informed consent forms have been translated into the following local/national languages/lingua franca spoken in the areas where the study is being conducted: Lingala, Kituba/Kikongo and Tshiluba. If the patient does not speak any of the national/local languages/lingua franca and if pre-specified and authorised staff with knowledge of the dialect/local language are present, an *ad hoc* oral translation may be acceptable. The oral translation will be supported by the use of the available visual aids. The document signed by the patient will be the form in the lingua franca of his/her country/region. The procedures for illiterate patients should apply. The oral translation should be documented on the signed consent form, i.e. the person who did the translation will indicate her/his name and the language/dialect used, and will sign the form.

14.2.2. Impartial Witness

The presence of an impartial witness is mandatory when illiterate patients are recruited and/or the legal representative is illiterate (see Section 14.2.2. Impartial Witness; p 66). Other situations may also require such a witness (see Section 14.2.3. Illiterate Patients; p 67 and Section 14.2.4. Patients Unable to Give Consent; p 67).

The witness should have no connection with the research team, and, whenever possible, should be chosen by the patient. The witness must be literate, i.e. able to read. If the patient does not know an appropriate witness, the team will propose someone from the hospital staff who is not working in the HAT clinical unit, or any literate person from the neighbourhood who is willing to act as a witness. The study team will take all necessary measures to prepare a list of possible

witnesses before the start of the study and keep this list updated, in order to find a witness at short notice, whenever necessary.

The witness will sign the consent form to attest to the completeness of the information given to the patient, and its compliance with the written information in the patient information sheet. The witness must be present throughout the entire information session.

The witness will confirm that the patient has freely given his/her informed consent to participate in the study.

14.2.3. Illiterate Patients

If the patient is illiterate, an impartial witness must be present throughout the information session.

The facilitator will explain the information contained in the written document to the patient and ask whether he/she gives his/her consent to participate. The patient's consent will be documented with his/her fingerprint on the form, and the witness will sign the form.

14.2.4. Patients Unable to Give Consent

Some patients with HAT may already have impaired cognitive capacities or behavioural abnormalities that preclude them from giving free and informed consent.

Considering the frequency of such symptoms in HAT, exclusion of these patients could jeopardise the capacity to complete the study.

Consequently, for patients who present with symptoms of psychological or behavioural disturbances and/or with impaired mental status, such as memory, alertness, disorientation, etc., consent will be requested from an accompanying family member, acting as legal representative.

As is the case with minors, non-consent from the patient will prevail if s/he refuses to participate in the study.

The consent process should be conducted in the presence of an impartial witness who will attest that the patient's will and best interests have been respected.

As soon as the patient has recovered his/her capacity to decide, s/he will be asked to confirm his/her desire to participate in the study, usually during the hospitalisation period, attested by the signature of an additional consent form.

14.2.5. Patients Under Legal Age

For patients under legal age, i.e. between 15 and 18 years old, considered as adolescents/young adults, the consent of one of their parents or another culturally

acceptable legal representative will be required in addition to their own personal assent. During field visits by the mobile team, adolescents/young adults will be advised to come to the study centre accompanied by a legal representative.

No specific patient information sheet or specific form will be used to collect assent from adolescents/young adults recruited to the study, since the data in the patient information sheet is considered to be understandable by both adolescents and adults.

The form will be signed by both the adolescent/young adult and his/her legal representative. If the patient or the legal representative is illiterate, a fingerprint should replace the signature. If the legal representative is illiterate, an impartial witness must attend the assent process and the consent process for the legal representative (see Section 14.2.2. Impartial Witness; p 66).

For young adults considered as emancipated because they are already married, the legal representative may be the husband or wife. If they are not married but are living on their own, they may be included with their own consent, provided an impartial witness is present during the consent process to confirm their understanding of the study, to confirm the probability that they are indeed emancipated and to sign the consent form along with them.

14.2.6. Changes in the Benefit-to-Risk Assessment during the Study

If new safety information results in significant changes in the benefit-to-risk ratio, the patient information sheet and consent form will be reviewed and updated. Patients currently being treated will be informed of the new information, given a copy of the revised patient information and asked to renew their consent to continue the study.

14.3. Ethical Aspects of Study Treatment and Sampling for Laboratory Tests

Experimental data suggest that fexinidazole has significant potential for the treatment of *T.b.* gambiense infections. Phase-I studies in healthy volunteers who received fexinidazole suggest that the benefit-to-risk ratio of the dose selected is acceptable.

No screened patients will be left without treatment. Patients not eligible for the study will be offered alternative treatment.

Sampling will be performed only for the purposes of safety assessments and PK analyses. The volume of blood collected will be reduced to a minimum. The discomfort of blood collection can be reduced using capillary sampling instead of venous blood sampling. However, if the skin is thick and hard, which is often the

case in rural populations, this sampling method may become painful due to the need for several pricks. In such cases, venous sampling may be preferable.

CSF samples will be collected in order to assess efficacy, collected as per usual practice in the investigational centre.

None of the samples will be retained after the end of the study. No bank of biological material will be set up. All remaining biological material will be destroyed, and the procedure will be documented with a certificate of destruction.

14.4. Costs for Patients

Patients will be reimbursed for their travel costs to and from the investigational site, but will not receive any payment for participation in the study. During the in-patient treatment phase, food will be provided to the patient free of charge. Following usual practice at each investigational site, food will be cooked or not. If not, the family will prepare it. Enough food will be provided in order to cover the needs of the relatives accompanying the patient during hospitalisation.

For follow-up visits, the patients' travel costs will be covered by the Sponsor, based on site-specific procedures, i.e. payment of taxi, use of specific study vehicle, transport by mobile teams, reimbursement at flat rate, etc. Food will be provided for the patient during his/her stay in hospital. The lost days of work due to travel for follow-up visits may be compensated, depending on requirements from local IECs.

Any essential medication that is required during the study will be provided free of charge to the patient. The WHO essential medicine list and the MSF guide *Essential Medicines* (2010 edition) will be used as a reference for the treatment of any concurrent condition. For any chronic disease, the study team will take all necessary measures to have the patient referred to the most appropriate local medical centre.

To ensure that participation in the study is voluntary, all HAT patients sent to hospital for treatment will be given food during the in-patient treatment phase, even if they are not included in the study, whether this is because they do not fulfil the selection criteria or because they do not wish to participate in the study.

15. Insurance and Liability

DND*i* will take out an insurance policy to cover any claims arising from the study, except for claims that arise from malpractice and/or negligence, in which case the Investigator or the institution will be held liable. In addition, DND*i* will cover the costs of treating patients in the study in the event of study-related injuries, in accordance with applicable local regulatory requirements.

16. Reports and Publications

The study will be registered with a recognised international clinical trial registry, such as www.clinicaltrials.gov or the Pan African Clinical Trials Registry.

The results of the study may be published or presented at scientific meetings. If this is the case, the Investigator agrees to submit all manuscripts or abstracts to DND*i* prior to publication.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of the results of multicentre studies only in their entirety and not as individual centre data. Any formal publication on the study in which input from DND*i* personnel exceeded that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate DND*i* personnel. Authorship will be decided by mutual agreement.

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Appendices

Appendix 1 – Declaration of Helsinki

Declaration of Helsinki of the World Heath Associations - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington, USA, 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo, Japan, 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of al other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient’s best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician’s knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best-proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for al human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burden and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol

should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be al owed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor on-going studies. The researcher must provide monitoring information to the committee, especial y information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formal y documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mental y incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient- physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best-proven intervention(s), except in the following circumstances:

- where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

- where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

- and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Appendix 2 – Karnofsky Performance Scale

KARNOFSKY PERFORMANCE STATUS SCALE
DEFINITIONS OF RATING CRITERIA (%)

The Karnofsky Performance Scale Index allows patients to be classified as to their functional impairment (46, 17). This can be used to compare effectiveness of different therapies and to assess the prognosis in individual patients. The lower the Karnofsky score, the worse the survival for most serious illnesses.

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead.

Appendix 3 – Laboratory Assessments

Laboratory Tests and Methods

All laboratory assessments will be described in a laboratory manual. Laboratory technicians have received specific training on these standard methods.

Biochemical tests: Piccolo® chemistry analyser

14 parameters will be analysed:

Albumin (ALB)	*Calcium (CA)*
Alkaline phosphatase (ALP)	*Glucose (GLU)*
Alanine aminotransferase (ALAT)	*Bicarbonates (tCO_2)*
Aspartate aminotransferase (ASAT)	*Blood urea nitrogen (BUN)*
Total bilirubin (TBIL)	*Sodium (Na+)*
Total protein (TP)	*Chloride (Cl-)*
Creatinine (CRE)	*Potassium (K+)*

Haematological tests

- ***Hemocue® Hb 210+ or Hb301+****: to measure haemoglobin level*
- ***Microscopy*** *: full blood cell count (visual count) using the TIC® system (Bioanalytic GmbH) and Neubauer counting chambers.*

Urine analysis

- *Urine dipstick analyses for safety parameters/COMBUR 9 TEST®*

White blood cells	*Nitrites*
pH	*Glucose*
Protein	*Ketone bodies*
Urobilinogen	*Bilirubin*
Blood	

- *Urine Pregnancy Test*

CSF Analysis

- Modified Single Centrifugation (MSC) with INRB kits: detection of parasite
- Fuchs-Rosenthal/Fast Read 102® counting chamber: WBC count

Blood parasitology tests

- Thick/thin blood smears
- Woo test/CTC
- mAECT with INRB kits
- mAECT-BC with INRB kits

Quantity of biological fluid required at each sampling timepoint

Screening Visit (between D-15 and D-1)

	Type of test	Specific test	Number of samples	Quantity per sample (approx.)	Total quantity
Blood	Parasitology	Woo/CTC	1	100 µL	≤ 400 µL
		Thin/thick blood smear	1	≤ 300 µL	
		mAECT (±BC)	1	5 mL	5 mL
Lymph	Parasitology	If lymph nodes detectable			
CSF	Parasitology	Modified Single Centrifugation	1	4 mL	4 mL
	Haematology	White blood cell count	1		

Baseline Assessment (between D-4 and D-1)

	Type of test	Specific test	Number of samples	Quantity per sample (approx.)	Total quantity
Blood	Haematology	Haemoglobin	1	20 µL	Between 120 µL (capillary blood[2)] and 4 mL (venous blood)
	Biochemistry	14 parameters	1	100 µL	
Urine	Pregnancy*		1	5 mL	5-10 mL
	Urine Analysis	*COMBUR 9 Test®*	2	5 mL	

* Must be on Day -1

[2] *All haematological and biochemical analyses can be performed using a single finger-prick with a Tenderlett® device or similar.*

Hospitalisation (D5)

	Type of test	Specific test	Number of samples	Quantity per sample (approx.)	Total quantity (1 visit)
Blood	Haematology	Haemoglobin	1	20 µL	Between 120 µL (capillary blood[6)] and 4 mL (venous blood)
	Biochemistry	14 parameters	1	100 µL	

EOT (D11)

	Type of test	Specific test	Number of samples	Quantity per sample (approx.)	Total quantity (1 visit)
Blood	Parasitology	Woo/CTC	1	100 µL	≤ 400 µL
		Thin/thick blood smear	1	≤ 300 µL	
		mAECT (±BC)	1	5 mL	5 mL
	Haematology	Haemoglobin	1	20 µL	Between 120 µL (capillary blood[6)] and 4 mL (venous blood)
	Biochemistry	14 parameters	1	100 µL	
Lymph	Parasitology	If lymph nodes detectable			
Urine	Urine Analysis	*COMBUR 9 Test®*	1	5 mL	5 mL

EOH (between D11 and D18)

	Type of test	Specific test	Number of samples	Quantity per sample (approx.)	Total quantity
Urine	Pregnancy		1	5 mL	5 mL

Additional Follow-up Visit 9 weeks after D1

Blood	Type of test	Specific test	Number of samples	Quantity per sample (approx.)	Total quantity
	Haematology	Haemoglobin	1	20 µL	

	Biochemistry	14 parameters	1	100 µL	120 µL (capillary blood[6)]

Follow-up Visit 6M

	Type of test	Specific test	Number of samples	Quantity per sample (approx.)	Total quantity per visit
Blood	Parasitology	Woo/CTC	1	100 µL	≤ 400 µL
		Thin/thick blood smear	1	≤ 300 µL	
		mAECT (±BC)	1	5 mL	5 mL
	Haematology	Haemoglobin	1	20 µL	120 µL (capillary blood)
	Biochemistry	14 parameters	1	100 µL	
Lymph	Parasitology	If lymph nodes detectable			
CSF	Parasitology	Modified Single Centrifugation	1	4 mL	4 mL

Follow-up Visits 12 M and 18 M (per visit)

	Type of test	Specific test	Number of samples	Quantity per sample (approx.)	Total quantity per visit
Blood	Parasitology	Woo/CTC	1	100 µL	≤ 400 µL
		Thin/thick blood smear	1	≤ 300 µL	
		mAECT (±BC)	1	5 mL	5 mL
Lymph	Parasitology	If lymph nodes detectable			
CSF	Parasitology	Modified Single Centrifugation	1	4 mL	4 mL

Appendix 4 - Tables

Table 3 – Schedule of Study Procedures

Protocol-planned procedures and forms to be completed	**Pre-screening and Screening**	**Baseline**	**Treatment period**										**End-of-Treatment Visit until End-of-Hospitalisation Visit**		**Follow-up period (months)**
Timepoint →	D-15 to D-1	*D-4 to D-1*	*D1*	*D2*	*D3*	*D4*	*D5*	*D6*	*D7*	*D8*	*D9*	*D10*	*D11 (EOT)*	*D11-D18 (EOH)*	6 – 12 – 18 months
Detection of parasite in blood and/or lymph	x												x		x
Lumbar puncture (parasite and white blood cells in CSF)	x														x
Informed consent (**before any additional medicines or study-specific procedures**)	**x**	**Check**													
Pretreatment of helminthiasis (+ 3-day recovery period)	x														
Rapid diagnostic test and/or thick blood smear for malaria	x														
Pretreatment of malaria if necessary (+ 3-day recovery period)	x														
Karnofsky score	x	x											x		x
Urine pregnancy test		X**												x	
Inclusion and exclusion criteria	x	x													
Demographic data	x														
Medical history	x														X [1]
Signs and symptoms of HAT		x												x	x
Vital signs	x	x					x			x			x	(x)*	x
Physical and neurological examina ion		x					x			x			x	(x)*	x
Haematology and biochemistry §		x					x						x		X[4]
Urine analysis §		x											x		
Safety ECG §		x											x		
Administration of fexinidazole			x	x	x	x	x	x	x	x	x	x			
Adverse event (AE)[2] collection			x	x	x	x	x	x	x	x	x	x	x	(x)*	
Serious adverse event (SAE) collection from signature of consent form to last study visit		x	x	x	x	x	x	x	x	x	x	x	x	(x)*	x
Collection of concomitant medica ion	X[3]	x	x	x	x	x	x	x	x	x	x	x	x	(x)*	

** Assessments to be performed only if EOH visit is different from EOT visit.*

§ Repeat tests possible, if needed, i.e. if result was abnormal on previous assessment.

*** Pregnancy test to be performed on D-1 (i.e. within 24 hours prior to the start of fexinidazole.*

1 *Record new events since previous visit.*

2 *In addition, any adverse event that occurs after the AE reporting period and considered as possibly treatment-related by the Investigator must be reported.*

3 *Including prior medication.*

4 *At 9 weeks after D1, only sampling for haematology and biochemistry, physical examination (including vital signs) and neurological assessment are to be performed.*

5 At 6M visit, sampling for haematology and biochemistry

Table 4 – Study Schedule

Final version of protocol	Version 1.0 - December 2013 version 2.0 – March 2014
Investigational Product available	January 2014
First patient first visit	April 2014
Duration of enrolment period	Approximately 10 months
Duration of follow-up period	12 months (primary endpoint) – 18 months (follow-up)
Last patient last visit	December 2015 (primary endpoint) – June 2016 (follow-up)
Final study report	April 2016 (primary endpoint) – September 2016 (follow-up)

Table 5 – Overall Study Organisation

<table>
<tr><td>Target Country</td><td colspan="3">Democratic Republic of Congo (DRC)</td></tr>
<tr><td rowspan="2">Target Enrolment Rate</td><td></td><td>Screened</td><td>Included</td></tr>
<tr><td>TOTAL</td><td>300</td><td>202 to 300</td></tr>
<tr><td>Number of sites</td><td colspan="3">At least 6 sites</td></tr>
<tr><td>Number of patients included per site</td><td colspan="3">No limitation per site</td></tr>
<tr><td>Participation of a DSMB</td><td colspan="3">A Data and Safety Monitoring Board (DSMB) will be appointed to look after safety issues (same DSMB as for pivotal study)</td></tr>
<tr><td>Partners</td><td colspan="3">Swiss Tropical and Public Health Institute, Basel, Switzerland
▪ Monitoring
▪ Logistics (Swiss TPH/DNDi Kinshasa)

Ministry of Health, Kinshasa, DRC
• Principal Investigator

PNLTHA, Kinshasa, DRC
• Supervision of teams and investigational sites
• Coordination of supplies and active case detection teams

CBCO
• Management of an investigational site

MSF
• Technical support
• Logistical support</td></tr>
<tr><td>Other means required for study</td><td colspan="3">Mobile teams for active case detection
Equipment and supplies for biochemical and haematological analyses
Telecommunication means and computer hardware/software</td></tr>
</table>