DNDi
Drugs for Neglected Diseases *initiative*

CLINICAL STUDY PROTOCOL

Efficacy and Safety of Fexinidazole in Children at Least 6 Years of Age and Weighing Over 20 kg with Human African Trypanosomiasis (HAT): a prospective, multicentre, open-label study, plug-in to the pivotal study

Name of Product/Project Code	Fexinidazole
Drug Class	Antiprotozoals
Phase	II/III
Indication	Human African Trypanosomiasis (HAT) due to *Trypanosoma brucei gambiense*
Protocol Number	DNDiHATFEX006
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
Cmax	Maximal 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 or hr	Hour(s)
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 (ITT)
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
min	Minute(s)

mL	Millilitre(s)
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
WHO	World Health Organisation
δ	*delta*, difference
µL	Microlitre

Protocol Summary

Study Title	Efficacy and Safety of Fexinidazole in Children at Least 6 Years of Age and Weighing Over 20 kg with Human African Trypanosomiasis (HAT): a prospective, multicentre, open-label study, plug-in to the pivotal study
Study Phase	II/III
Indication	Human African Trypanosomiasis (HAT) due to *Trypanosoma brucei gambiense* (all stages)
Protocol number	DNDiHATFEX006
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. The clinical presentation of HAT is identical in children and adults, and the reference treatments are also the same as those used in adults, i.e. pentamidine for patients at stage 1 and the association nifurtimox-eflornithine (NECT) for patients at early and late stage 2. The present will be a plug-in to the pivotal study DNDiFEX004 (64) in adults, 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. In order to provide the results within a reasonable timeframe, the study will be open label and will include a total of 125 children 6 years of age or older with a body weight of at least 20 kg. The patients will undergo the same assessments and investigations as the adult patients in Study DNDiFEX004. Under these conditions, if there are no statistically significant differences with regard to the efficacy and safety data, the results of treatment in children will be considered to be equivalent to those in adults. Thus, the number of children needed to treat is lower than if this had been a stand-alone study. The objective is to be able to administer fexinidazole as a single treatment to all patients with HAT, without recourse to CSF-based staging of the disease. The aim of the present study is to assess the efficacy and safety of fexinidazole in children with stage-1, early stage-2 and late stage-2 HAT, stratified into three sub-groups. The study will provide an assessment of the success rate of treatment overall and by stratum, as well allowing for comparison with historical data on pentamidine in patients with stage-1 HAT.
Choice of dose	The dosing regimen is as follows: • Body weight ≥ 20 kg and < 35 kg: o 1200 mg from Day 1 to Day 4 o 600 mg from Day 5 to Day 10 • Body weight ≥ 35 kg (same regimen as for adults) o 1800 mg from Day 1 to Day 4 o 1200 mg from Day 5 to Day 10
Study Objectives	The objective of the study is to assess the efficacy and safety of an oral dosing regimen involving one daily intake for 10 days in the treatment of HAT due to *T.b. gambiense* at stage 1 or 2 in children 6 years of age or older weighing more than 20 kg. **<u>Primary Objective</u>** ▪ To demonstrate that the success rate 12 months after the end of treatment in patients with stage-1 or stage-2 HAT is greater than an acceptable rate of 80% and consistent with a target rate of 92%.

	Secondary Objectives ▪ To verify whether the success rate varies depending on the stage of the disease; if the success rate is significantly different between the 3 strata, to show that the rate is greater than 80% and consistent 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.
Primary Endpoint	**Efficacy** The primary efficacy endpoint is the outcome, i.e. success or failure, observed at the test-of-cure visit, 12 months after the end of treatment. Success means that the patient is cured, as defined by adapted WHO criteria (54). In addition, although the timepoint for assessment of the efficacy endpoint was set at 12 months after the end of treatment, patients will be followed until at least 18 months after the end of treatment.
Secondary Endpoints	**Efficacy** Outcome, i.e. success or failure, at each visit between the end of treatment and 18 months.
	Safety • Occurrence of any adverse events 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 IP and the end of the follow-up period (18 months).
	Electrocardiogram (ECG) Endpoints Categories of QT/QTc and changes on ECG tracings recorded at various timepoints.

	<u>Pharmacokinetic (PK) Endpoints</u> A series of blood samples for PK testing will be collected using dry blood spot, as well as a dry cerebrospinal fluid spot. In order to adjust to the patients' ages, the number of blood samples has been reduced, i.e. 2 samples less than adults, as follows: Whole blood: • On Day 10: 3 hours and 7 hours 15 minutes after the last intake of fexinidazole • On Day 11: 24 hours after the last intake of fexinidazole • On Day 12: 48 h hours after the last intake of fexinidazole. Cerebrospinal fluid: • On Day 11: 24 hours after the last intake of fexinidazole The lumbar puncture at D11, and therefore the PK analysis on cerebrospinal fluid was stopped in October 2014 after approximately 30 patients, as initially planned in the protocol.
Study Design	This is an open-label, single-group, multicentre, Phase II/III study. The study will be a plug-in to the pivotal study, DNDiFEX004, and will be performed at the same sites.
Inclusion and Exclusion Criteria	**Inclusion criteria:** ▪ Signed informed consent form from one parent or from the legal representative ▪ Assent from the child to participate in the study, collected in the presence of an impartial witness ▪ Between 6 and 15 years of age ▪ Body weight at least 20 Kg ▪ Male or female ▪ Able to ingest at least one complete meal per day (or at least one sachet of Plumpy'Nut®) ▪ Able to swallow the 600-mg tablets of fexinidazole ▪ Karnofsky score > 50 ▪ Evidence of trypanosomes in blood and/or lymph and/or cerebrospinal fluid. ▪ Having a permanent address and able to comply with the schedule of follow-up visits.

Exclusion Criteria:

- Refusal to participate in the study, expressed by child
- Body weight strictly less than 20 Kg;
- Severe malnutrition, defined as Body Mass Index < 16. (–2 standard deviation);
- Unable to take medication by the oral route;
- Pregnancy or breast-feeding ;
- 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 family of migrant workers, refugee status, itinerant trader, etc.;
- Active alcohol or drug addiction.
- Clinically significant laboratory test abnormality, with:
    - 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; p 41) – for girls ≥ 12 years of age; ▪ ECG abnormality as assessed by central cardiologist; ▪ 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
Study Duration	Each patient's participation will last approximately 19 months and will include: • Pre-treatment period • Treatment period of 10 days • Hospitalisation for 3 to 7 days after treatment • Additional follow-up visit at 9 weeks after D1 (between D64 and D70) • Out-patient follow-up with visits at 3, 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: • Patients with body weight ≥ 20 kg and < 35 kg: o 1200 mg (2 tablets) in one daily intake for 4 days, followed by o 600 mg (1 tablet) in one daily intake for the next 6 days. • Patients with body weight ≥ 35 kg: o 1800 mg (3 tablets) in one daily intake for 4 days, followed by o 1200 mg (2 tablets) in one daily intake for the next 6 days. The total duration of treatment will be 10 days.
Statistical Analyses	**<u>Analysis Sets</u>** Analysis of the primary efficacy endpoint will be performed on the intention-to-treat population. • Intention-to-treat population: all patients who received at least one dose of fexinidazole.

	• Per-protocol population: all patients with no major protocol violations that could interfere with the efficacy analysis. Sensitivity analyses will be performed on treatment completers, the population of evaluable patients and the per-protocol population. **Analysis** The primary analysis will be performed on the ITT population, by estimating the rate of success or failure at 12 months of follow-up. If the lower bound of the 95% confidence interval is less than or equal to 80% the study will be a failure, otherwise it will be a success. The primary test is an exact test derived from the exact confidence interval of the success rate at 12 months. **Sample Size** Determination of the sample size was based on the primary analysis. The sample size must be 125 patients having received at least one dose of fexinidazole. The sample size may be 126 patients if two patients are recruited simultaneously at the time of study discontinuation, however, it must not exceed 126 patients.

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, 68). 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.

The clinical presentation of HAT is identical in children and adults. The progression to stage 2 seems to be more rapid in children, particularly in younger children in whom HAT is generally not diagnosed until it has reached stage 2.

1.3. Diagnostic

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 21).

The diagnosis of stage-2 HAT relies on lumbar puncture. Disease staging is based on detection of parasites and on the WBC count in the CSF. In the national HAT control programmes in most countries the threshold to initiate treatment for stage-2 HAT is CSF WBC above 5/µL. As a result, a distinction is made between “early” stage-2 HAT, which is defined as CSF WBC between 5 and 20/µL, and “late” stage-2 HAT, defined as CSF WBC above 20/µL or if parasites are detected in the CSF.

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.

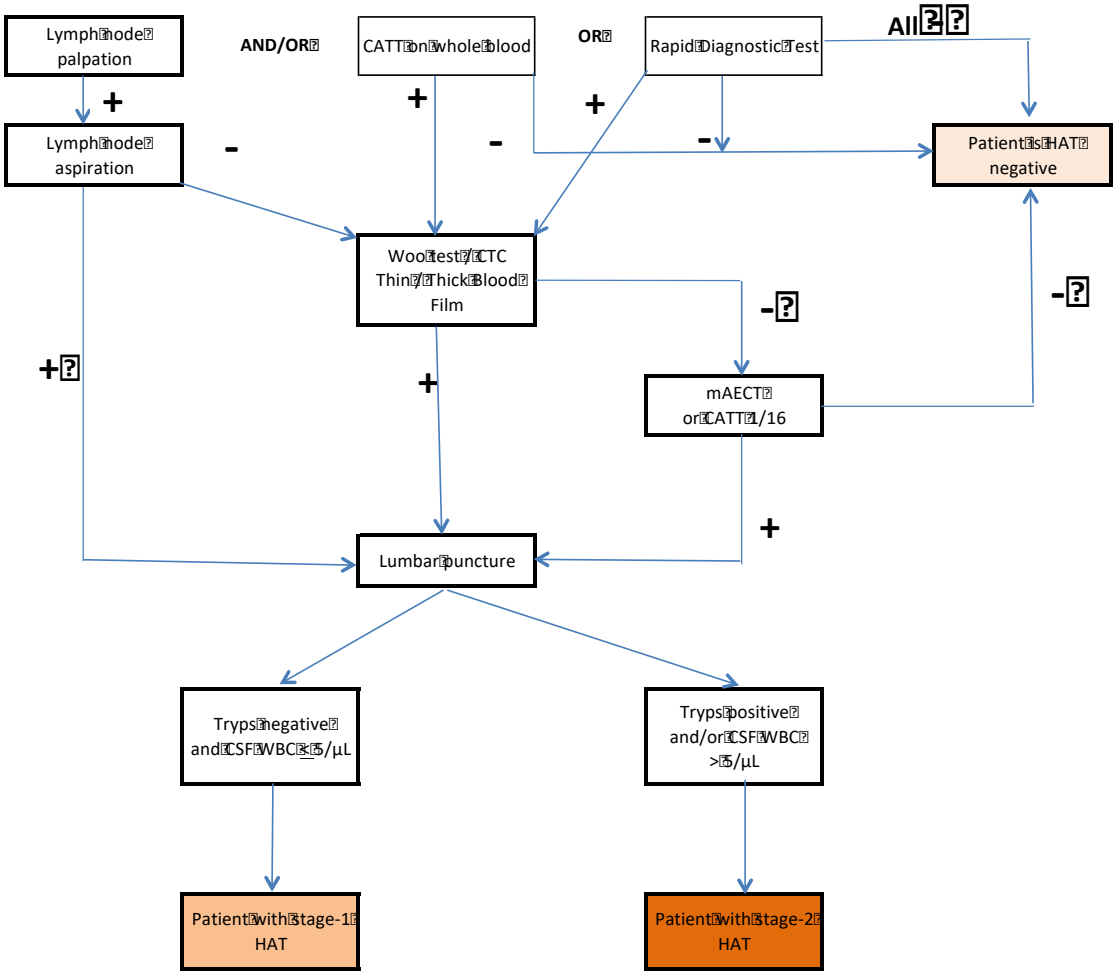
In the DRC, the mobile teams in the National HAT Control Programme usually comprise 7 people, including 3 laboratory technicians and one person who acts as a community mobiliser. The mobiliser travels through the villages a few days in advance to announce to the community that HAT screening is on the 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 (65), the Institute of Tropical Medicine in Anvers (67) and the University of Dundee (66). 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



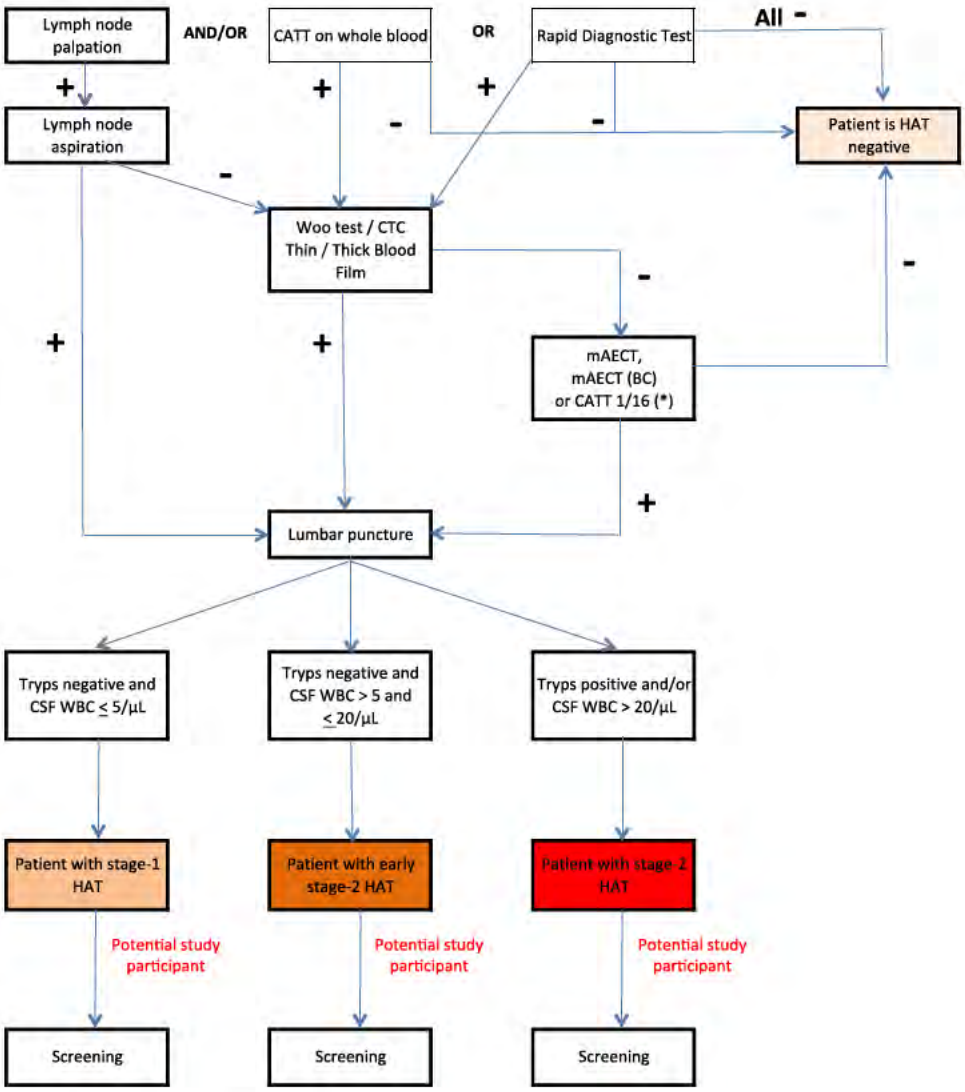
CATT = Card Agglutination Test for Trypanosomiasis
Woo test = microhematocrit centrifugation test = CTC test
mAECT = Mini-Anion Exchange Centrifugation Test
Tryps = Trypanosomes
CSF = cerebrospinal fluid WBC = white blood cells

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.

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 - Buffy Coat (BC)
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, and in April 2013, the use of NECT was extended to children in the 4th Edition of the WHO List of Essential Medicines for children, as an alternative to melarsoprol or eflornithine as single-drug therapy.

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).

Children with stage-2 HAT currently receive the same treatment as adults. NECT, which recently became the reference standard for the treatment of stage-2 HAT, was added to the WHO List of Essential Medicines for children (69) after it was administered to around 100 children included in a non-comparative study (60) and because it is used by MSF in routine programmes.

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.
Children with stage-1 HAT currently receive the same treatment as adults.

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 (M1) and fexinidazole sulfone (M2), 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. These abnormalities were not observed in volunteers exposed to fexinidazole for 10 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.

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-interval 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

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

conditions. The observed bioavailability of fexinidazole, M1 and M2 was 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, Randomised Pivotal 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).

In the DNDiFEX004 study, fexinidazole is administered orally once daily after a meal: three 600-mg tablets per day for 4 days and then two 600-mg tablets per days for the next 6 days.

Pharmacokinetic (PK) 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 CSF was 2.6 times higher than the minimum inhibitory concentration (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.

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 interval < 500ms, including at peak plasma concentration).

1.11. Choice of Dosing Regimen and Dose

The progression of HAT is identical in adults and children. The choice of the dose in children was therefore based on the results of the analysis of PK/PD data from adults, i.e. healthy volunteers and patients, and on the MIC. The dosing regimen in adults is 10 days of treatment, starting with a loading dose for 4 days followed by a maintenance dose for 6 days. Effective levels of the active drug are rapidly reached using this regimen and are maintained throughout the duration of treatment. Target blood concentrations were reached in adults. Given the PK characteristics of fexinidazole and its metabolites, a similar dosing regimen, i.e. a loading dose for 4 days followed by a maintenance dose for 6 days, can be used in children.

The factors affecting the PK of fexinidazole, such as absorption and maturation of cytochromes and of flavin mono-oxygenase (the main enzyme involved in biotransformation of fexinidazole into its active metabolites), as well as other enzyme systems, are completed before 2 years of age (59). The main metabolic pathways involved in biotransformation of fexinidazole into its metabolites are therefore considered to be the same in adults and in children over 2 years of age. In addition, there is reasonably good proportionality between the dose of fexinidazole administered and the circulating levels of fexinidazole and its metabolites.

The doses of fexinidazole to be administered in children were therefore chosen with the aim of achieving the same levels of systemic exposure, based on the quantity of fexinidazole per unit of body weight. Two points were taken into account:

- Dose administered on Day 1
- Total dose of fexinidazole administered during the entire treatment period.

The main demographic features of the 125 patients (46 women and 79 men) included in the DNDiFEX004 study at the time of the present assessment were taken into account. The age of the patients ranged from 15 to 71 years with a median of 35 years.

Mean body weight was 50.35 kg [34.5-80.0] with a median of 48 kg. It is of note that 15 patients (12 women and 3 men) weighed 40 kg or less with a minimum weight of 34.5 kg.

As mentioned above, the dosing regimen in adults is 1800 mg in a single daily intake for 4 days, followed by 1200 mg in a single daily intake for 6 days, i.e. a total dose of 14,400 mg over 10 days.

Thus:

- mean dose on Day 1 of 35.7 mg/kg [22.5-52.2];
- mean total dose administered of 28.6 mg/kg/day [18-42].

Overall, male patients are heavier than female patients, and there is therefore a minor difference, i.e. less than 15%, between the mean results in men and in women: 34.8 mg/kg on Day 1 and 27.8 mg/kg/day in men versus 40.4 mg/kg and 32.3 mg/kg/day in women.

In the potential target population of the study, i.e. 29 children diagnosed with HAT during active screening activities carried out to recruit patients to the DNDiFEX004 study, the mean age was 11 years and the mean body weight was 23.4 kg [12-40]. In the NECT-Field study (60), among 65 children between 5 and 11 years of age who were included, mean body weight was 19 kg [9-32] with a median of 18 kg.

If the mean dose on Day 1 is 35.7 mg/kg and the mean total daily dose administered is 28.6 mg/kg, the dose on Day 1 should be 1071 mg (30 × 35.7) and the desired total dose administered should be 8580 mg (28.6 × 30 × 10) for a child weighing 30 kg.

Given the usual dosing regimen and the formulations available, i.e. 600-mg tablets, the dosing regimen should be 1200 mg daily for 4 days, followed by 600 mg for 6 days, with a total dose administered of 8400 mg.

Using this dosing regimen, a child weighing 20 kg would receive:

- Dose on Day 1, 60 mg/kg, which is slightly higher than the maximum dose administered on Day 1 in the least heavy adults (52.2 mg/kg);
- Total dose: 42 mg/kg/day, which is exactly the same as the dose administered in the least heavy adults.

In conclusion, in view of the observations above and the fact that the adult the least heavy included in the DNDiFEX004 study weighed 34.5 kg, the dosing regimen is as follows:

- Body weight between [20-35] kg:
  - 1200 mg from Day 1 to Day 4
  - 600 mg from Day 5 to Day 10
- Body weight ≥ 35 kg (same as in adults)
  - 1800 mg from Day 1 to Day 4
  - 1200 mg from Day 5 to Day 10

Fexinidazole, as 600-mg tablets, will be administered orally, **after** a meal, i.e. within 30 minutes after the end of the meal.

1.12. Rationale for the Study Design

Based on the encouraging efficacy and safety results in adults in the on-going DNDiFEX004 study, it would appear that oral treatment with fexinidazole could be beneficial in children 6 years of age and older. The dosing regimen in children is based on the results in adults (see Section 1.11 Choice of Dosing Regimen and Dose p 27).

This cohort of patients will provide additional efficacy data and, because the levels of systemic exposure in children are similar to those observed in adults, will show that the safety profile of fexinidazole, based on the data currently available, remains favourable.

The present study will be a plug-in to the pivotal DNDiFEX004 study in adults, 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. In the same way, it will be possible to compare patients with stage-1 HAT in the present study to patients with stage-1 HAT in Study DNDiHATFEX005.

In order to provide the results within a reasonable timeframe, the study will be open label and will include a total of 125 children 6 years of age or older with a body weight of at least 20 kg. The patients will undergo the same assessments and investigations as the adult patients in Study DNDiFEX004. Under these conditions, if there are no statistically significant differences with regard to the efficacy and safety data, the results of treatment in children will be considered to be equivalent to those in adults. Thus, the number of children needed to treat is lower than if this had been a stand-alone study.

The objective is to be able to administer fexinidazole as a single treatment to all patients with HAT, without recourse to CSF-based staging of the disease. The aim of the present study is to assess the efficacy and safety of fexinidazole in children with stage-1, early stage-2 and late stage-2 HAT, stratified into three sub-groups. The study will provide an assessment of the success rate of treatment overall and by stratum, as well allowing for comparison with historical data on pentamidine in patients with stage-1 HAT.

1.13. Target Population

All children between 6 and 15 years of age (excluding upper limit) in whom parasites are detected in the blood, lymph or CSF will be included in the study. Only children who are able to swallow the tablets will be eligible for the study.

Given the limited number of children with HAT, all children in whom parasites are detected in the blood, lymph or CSF will be included, regardless of the stage of the disease.

The stages 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 > 5/µL and ≤ 20/µL

Patients with late stage-2 HAT

- Trypanosomes in blood and/or lymph

and

- CSF WBC > 20/µL

Or

- Trypanosomes in CSF

An informed consent form, signed by the legal representative, i.e. one of the parents or the legal representative, will be collected for each child, and assent from the child will be collected in the presence of an impartial witness (see Section 14 Ethical Considerations; p 70).

2. Study Objectives and Endpoints

2.1. Objectives

The objective of the study is to assess the efficacy and safety of an oral dosing regimen involving one daily intake for 10 days in the treatment of HAT due to *T.b. gambiense* at stage 1 or 2 in children 6 years of age or older weighing more than 20 kg.

2.1.1. Primary Objective

- To demonstrate that the success rate 12 months after the end of treatment in patients with stage-1 or stage-2 HAT is greater than an acceptable rate of 80% and consistent with a target rate of 92%.

2.1.2. Secondary Objectives

- To verify whether the success rate varies depending on the stage of the disease; if the success rate is significantly different between the 3 strata, to show that the 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.

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 patient 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 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 prinicipal visit 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 (historical data). 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), (61). 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), (61). 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 primary 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

Efficacy

Result (success or failure) at each visit from the end of treatment to month 18.

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 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).

ECG abnormalities with no clinical symptoms will not be reported as AEs. ECG changes will be analysed separately. If cardiac symptoms are present, information collected from ECG will be recorded in the eCRF.

PK Endpoints

Concentrations of fexinidazole, M1 and M2 in whole blood and CSF, and PK parameters derived from a population PK model.

- Samples of whole blood will be collected using dry blood spot (DBS) testing on venous puncture at the following timepoints:

  - On Day 10, 3 hours and 7 hours 15 minutes after the last intake of fexinidazole;
  - On Day 11, i.e. 24 hours after the last intake of fexinidazole;
  - On Day 12, i.e. 48 hours after the last intake of fexinidazole.
- Lumbar puncture will be performed at Day 11, 24 hours after intake of fexinidazole for the EOT efficacy assessment in the first 30 patients. A dry CSF spot will be collected at the same time for PK analyses in the first 30 patients.

ECG Endpoints

Triplicate ECG tracings will be recorded at 2-minute intervals to assess QT interval at the following timepoints:

- At baseline
- On Day 4, 4 hours (H4) after intake of fexinidazole, on Day 4 H23 and on Day 10 two to three hours after intake of fexinidazole.

Triplicate ECGs and a safety ECG will be collected for different purposes and will be analysed separately (see Section 6.3.2 ECG Recordings; p 46).

3. Study Design

This is an open-label, multicentre, Phase II/III study. The study will be a plug-in to the pivotal study, DNDiFEX004, and will be performed at the same sites.

4. Selection of Study Population

To be eligible for inclusion 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 approximately 8 investigational centres in the DRC and possibly in other countries suitable for the conduct of the study.

Patients may be enrolled in different ways:

a. Children may be brought to the investigational centre spontaneously by their legal representative (a relative of the child will be considered to be a legal representative) and will undergo routine assessments at the centre, including testing for *T.b. gambiense* in blood, lymph and CSF.

b. Children 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 20). Their legal representative will receive a staging certificate from the mobile team indicating what assessments were performed. If the mobile team did not perform a lumbar puncture, it will be done at the investigational site.

c. A traumatic lumbar puncture will be considered as uninterpretable by the laboratory technician if red blood cells are visible in the CSF, hindering interpretation of the analysis. In this case, lumbar puncture will not be repeated and the patient's status will be considered as undetermined as concerns disease staging. The undetermined status has no impact on the primary analysis since it is not stratified by disease stage.

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". Children who fulfil the pre-inclusion criteria, which do not require study-specific procedures, will be invited to participate in the study through their legal representative who will receive all necessary information to obtain informed consent. The children will also be informed of their right to refuse to participate in the study, taking suitable precautions and using age-appropriate language.

For patients who are under the legal age to be enrolled, their legal representative must sign the informed consent form after receiving explanations from the Investigator and before any study-specific procedures are performed. The patients will then be considered as a "screened patients".

As mentioned above, initial study-specific procedures do not include lumbar puncture, which is performed routinely. However, the project team will endeavour to provide the medical teams with the possibility of performing lumbar puncture with the use of an equimolar mixture of oxygen and nitrous oxide (EMONO), the feasibility of which is currently being assessed.

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 43). 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 for girls ≥12 years of age.

4.2. Pre-inclusion / Pre-exclusion Criteria

The pre-inclusion/pre-exclusion criteria can be checked before informed consent is obtained since no study-specific procedures are involved.

Pre-inclusion Criteria

- Between 6 and 15 years of age;
- Body weight at least 20 Kg;
- Male or female;
- Able to ingest at least one complete meal per day (or at least one sachet of Plumpy'Nut®);
- Able to swallow the 600-mg tablets of fexinidazole;
- Karnofsky score > 50 (see Appendix 2 – Karnofsky Performance Scale; p 89);
- Evidence of trypanosomes in blood and/or lymph and/or CSF;
- Having a permanent address and able to comply with the schedule of follow-up visits.

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

Patients with stage-1 HAT

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

Patients with early stage-2 HAT

- Trypanosomes in blood and/or lymph
- No evidence of trypanosomes in CSF
- CSF WBC > 5/µL and ≤ 20/µL

Patients with late stage-2 HAT

- Trypanosomes in blood and/or lymph

and

- CSF WBC > 20/µL

Or

- Trypanosomes in CSF

The strata will be self-weighted.

Pre-exclusion Criteria

- Body weight strictly less than 20 Kg;
- Severe malnutrition, defined as Body Mass Index < 16. (–2 standard deviation);
- Unable to take medication by the oral route;
- Pregnancy or breast-feeding;
- 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 family of migrant workers, refugee status, itinerant trader, etc.;
- 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 and legal representative to participate in the study and initiate the process for collecting informed consent (see Section

14.2 Informed Consent Process; p 73). 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 Criteria

- Signed informed consent form from one parent or from the legal representative;
- Assent from the child to participate in the study, collected in the presence of an impartial witness.

Exclusion Criteria

- Refusal to participate in the study, expressed by child;
- Clinically significant laboratory test abnormality, with:
  - 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; p 41) – for girls ≥ 12 years of age.
- ECG abnormality as assessed by central cardiologist.
- 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 (see Section 5.8.1 Malaria; p 40).
- Not having received appropriate treatment for soil-transmitted helminthiasis (see Section 5.8.2 Helminthiasis; p 40)

<u>The following criteria are considered to be temporary exclusion criteria</u>

- 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

Given the overall dosing regimen and formulation available, i.e. 600-mg tablet, the dosing regimen will be adapted to the child’s body weight, as follows:

- Body weight ≥ 20 kg and < 35 kg:
  - 1200 mg from Day 1 to Day 4
  - 600 mg from Day 5 to Day 10
- Body weight ≥ 35 kg (same regimen as for adults)
  - 1800 mg from Day 1 to Day 4
  - 1200 mg from Day 5 to Day 10

Fexinidazole as 600-mg tablets, will be administered by the oral route, **after** a meal, i.e. within 30 minutes after starting the meal.

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.

Patient participation in the study will be considered to be finished when the last protocol-planned visit has been performed, i.e. the last visit at M18.

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.

For patients who receive only 2 tablets, i.e. 2 x 600 mg, from Day 1 to Day 4 and 1 tablet, i.e. 1 x 600 mg, from Day 5 to Day 10, the Investigator will administer only the required number of tablets and will leave the unused tablet in the blister-pack. Study monitors will check the number of unused tablets at each monitoring visit.

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) should 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

For girls of child-bearing potential, i.e. ≥ 12 years of age, the Investigator will first decide whether or not it is appropriate to discuss contraception with the patient, i.e. depending on whether or not she is sexually active. If so, the Investigator will recommend the use of a contraceptive method or abstinence 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 of 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 eCRF, 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 eCRF, 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*	*Probabale 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
3 months	*3 months ± 1 week*	• Patient alive with no evidence of trypanosomes in any bodily fluid (no lumbar puncture at 3 months unless Investigator suspects a relapse)	• Any reason leading the Investigator to request an additional follow-up visit	• Signs or symptoms suggestive of HAT and of treatment failure leading to use of rescue treatment	• 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 between 20 and 50/µL and additional follow-up visit requested within 1 to 3 months • Any reason leading the Investigator to request an additional follow-up visit	• CSF WBC ≥ 50/µL (36) • Neurological signs or symptoms 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) • CSF WBC > 20/µL and < 50/µL and reduced 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 ≥ 50/µL • 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 • Patient with no signs of HAT who refuses to undergo lumbar puncture and who, in the opinion of the Investigator, does not require rescue treatment or an additional follow-up visit	• 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 assessments is summarised in Table 3 (p 95).

- D-15 to D-1: Patient screening with detection of *T.b. gambiense,* pre-treatment of concomitant helminthiasis and/or malaria, if any, and ECG.
- D-4 to D-1: Baseline assessment, laboratory screening.
- D1 to D10: treatment period.
- D10 to D12: sampling for PK analyses.
- D11: EOT visit.
- D13 to D18: EOH visit; if the end of hospitalisation is extended beyond D18, the EOH visit should be performed on D18 and an additional unscheduled visit should be performed at hospital discharge.
- 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 M3, M6, M12 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*
EOT visit	D11 after the Start of Treatment (SOT) (D1 after EOT)	Between D11 and D12 after SOT (D1 or D2 after EOT)
EOH visit	Between D13 and D18 after SOT (D3 and D8 after EOT)	D18 at the latest
Week 9 after D1	D64 to D70	
3 months	3 months ± 1 week after EOT	2-4 months after EOT
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 period 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; p71). 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 33).

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);
- CSF sampling for diagnosis and staging 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;
- Karnofsky Performance Score, body weight, height and vital signs including body temperature, blood pressure, heart rate and respiratory rate;
- Screening for malaria using RDT and/or thick blood smear;
- Review of inclusion and exclusion criteria;
- Digital ECG recording (CarTouch®): the recordings will be transmitted electronically for centralised reading. The central cardiologist will review the ECG and prepare a report, which will then be sent to the Investigator, stating whether or not the patient can be included in the study.

6.2.3. Baseline Assessment

The following assessments will be performed to assess the patient's baseline status and confirm the patient's eligibility to participate in the study just before 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 girls ≥12 years of age;
- Laboratory safety assessments (see Appendix 3 – Laboratory Tests; p 90) – whenever possible, all laboratory tests will be performed on fasting patients:

- 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®): triplicate tracings to assess QT interval. The recordings will be transmitted electronically for centralised reading of QT interval.

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; p51).

- Physical examination and neurological assessment, including signs and symptoms of HAT, performed only at baseline and on D11, will be performed prior to intake of fexinidazole (D-1/D1) and on D5, D8, D11 (EOT visit) and between D13 and D18 (EOH visit)
- Testing for *T.b. gambiense* in blood, lymph and CSF at the EOT visit (D11). Testing for parasites in the CSF will be performed only in the first 30 patients, except if a failure is observed among these 30 patients.
- 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

ECG recordings will be performed at the following timepoints:

To ensure the patient's safety

- At the baseline assessment: a single ECG tracing will be analysed by the central cardiologist to assess potential rhythm or conduction disorders and to assist the Investigator in screening patients.
- On D2, D3 and D4 prior to administration of fexinidazole (along with the triplicate ECG tracings on D4 H23): a single ECG will be analysed by the Investigator to check the QTcF interval (QT interval corrected using Fridericia's formula), calculated automatically. If the value for the QTcF-interval is higher than 500 ms, a second ECG tracing must be collected after a 10-to-20 minute rest. If the value is confirmed, the patient must be withdrawn from the study, and no further doses of fexinidazole are to be administered. The ECG tracings will not be reviewed systematically by the cardiologist.
- On D11 (EOT): single ECG.
- During hospitalisation and the follow-up period, additional ECG tracings may be collected at the discretion of the Investigator.

To assess QT interval

- Triplicate ECG tracings, 2 minutes apart, will be recorded at the following timepoints:
    - At the baseline assessment;
    - On D4 4 hours after intake of fexinidazole;
    - on D4H23, i.e. one hour before intake of the IP on D5, this ECG should also be used for the patient's safety assessment prior to administration of fexinidazole;
    - on D10 between 2 and 3 hours after intake of fexinidazole.

Repeat ECG

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 3-month follow-up visit.

6.3.3. Laboratory Tests

A repeat urine pregnancy test will be performed at discharge, i.e. between D13 and D18 in girls ≥ 12 years of age.

Blood biochemistry and haematology assessments will be repeated on D5, D8 and D11 (EOT visit). Safety biochemistry and haematology 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, (as well as the pregnancy test on D-1, on D18 and at 3 months in women), 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.

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 90).

6.3.4. Pharmacokinetic Analyses

PK analyses will be performed in each patient.

The sampling procedure and assay method will be described in the corresponding laboratory manual.

Approximately 2 mL of whole blood will be collected on filter paper by venous puncture for DBS testing at each of the following timepoints:

Ideal timepoint for sampling	Leeway
D10 3 hours and 7 hours 15 min after last intake of fexinidazole	± 15 min
D11 24 hours after last intake of fexinidazole	± 1 hour
D12 48 hours after last intake of fexinidazole	± 1 hour

- The timing of sample collection was optimised with WinPOPT® software using the parameters of population PK modelling pooled from the DNDiFEX001 and DNDiFEX002 studies. The timepoints for sampling were chosen in order to obtain the best predictions of pre-dose M2 concentrations.
- Lumbar puncture will be performed on D11 24 hours after the last intake of the IP, and the CSF sample will be analysed using dried spot sampling. Dried spot sampling of CSF will be performed on the first 30 patients.

The CSF dried spot samples will be stored under the same conditions (see laboratory manual).

Consequently, only 4 blood samples will be collected: one close to the C_{max} of fexinidazole and M1 and one at the transitional moment between the distribution phase of fexinidazole and M1 and the elimination phase. Both timepoints occur during the “absorption” phase of M2. The other samples will be used to measure the decline in blood fexinidazole, M1 and M2 concentrations.

The pharmacokinetic data collected in children will be incorporated *a priori* in the PK database along with the data in adults, and the consistency between the two populations will be assessed through PK population analysis.

The PK analysis will be performed in the course of the study and the first assessment will be carried out after 6 children weighing between 20 and 35 kg and 6 children weighing less than 35 kg have completed treatment in order to confirm that the target concentrations are reached in the blood and CSF.

CSF sampling will provide data on exposure to fexinidazole in the brain in this population. If the data are consistent with those obtained in adults, i.e. higher than the MIC in CSF, CSF sampling will not be performed in the entire study population. The procedure will no longer be performed after the initial results are available, i.e. after approximately 30 children have been sampled.

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 3-month Follow-up Visit

- 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;
- Testing for *T.b. gambiense* in blood and lymph for diagnosis of potential relapse;
- CSF sampling and analysis (MSC with INRB kits) only if symptoms suggesting disease progression are present;
- Urine pregnancy test in girls ≥ 12 years of age, to investigate possible exposure *in utero* (see Section 6.5.8. Exposure *in utero*; p 55);
- Additional safety assessments such as ECG, haematology, biochemistry or urine tests may be performed at the discretion of the Investigator. An ECG recording may be required at the M3 visit if the central cardiologist issued an alert at the EOH visit.

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

- Physical examination, HAT symptoms since the previous visit, neurological assessment including signs and symptoms of HAT;
- Testing for *T.b. gambiense* in blood and lymph for diagnosis of potential relapse;
- CSF sampling to test for potential relapse, with WBC count and testing for trypanosomes (Fuchs-Rosenthal/Fast Read 102® counting chamber, MSC with INRB kits);
- Additional safety assessments such as ECG, haematology, biochemistry or urine tests may be performed at the discretion of the Investigator.

6.4.4. 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, which is planned at D18, but which may take place as early as D13, 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 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 all grades combined) 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; p53).

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 fexinidazole on Day 1 until hospital discharge between D12 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 will 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, p 56.

6.5.8. Exposition *in utero*

Three pregnancy tests are planned during the study: on D-1, prior to starting treatment, at hospital discharge and at the 3-month follow-up visit. Among girls ≥ 12 years of age, i.e. 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 3-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 up to 22 or 24 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 3 to 8 days after treatment
- out-patient follow-up for 12 months
- additional follow-up until 18 months.

The total duration of the study is expected to be 36 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%;
- QTcF interval ≥ 500 msec prior to intake of fexinidazole on D2, D3, D4 or D4H23), confirmed by a second ECG recorded after the patient has been in the resting position for at least 10 to 20 min;
- 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

Determination of the sample size was based on the primary analysis (see Section 9.8.1 Primary Efficacy Analysis, p 61). With a sample size of 125 patients, the probability of rejecting H_{0A} ($\pi \leq 0.8$) is 97.5% if the true success rate is 92% with a one-sided type-I error of 0.025. The probability of rejecting H_{0B} ($\pi \geq 0.92$) is also 97.5% if the true success rate is 80% with a one-sided type-I error of 0.025. The statistical power achieved is slightly higher than the desired power, and the alpha value obtained is slightly lower than the desired value, due to the discrete distribution of the population. The sample size may be 126 patients who received at least one dose of fexinidazole if two patients are recruited simultaneously at the time of study discontinuation. If the sample size exceeds 126 patients, there is a risk of simultaneously rejecting both H_{0A} and H_{0B}. The sample size should not be less than 125 in order to avoid the risk of not rejecting either hypothesis.

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

The primary endpoint is the outcome, i.e. success or failure, of treatment at the 12-month visit. If the outcome at the 12-month visit is missing, the **primary method of imputation** will consist in imputing a probable success (considered as a success) to patients who attended the 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). 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 form 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 included patients who received at least one dose of fexinidazole.
Secondary: treatment completers	Sensitivity analysis on efficacy	All included 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, i.e. stage 1, early stage 2 and late stage 2, 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 fexinidazole (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 3, 6, 12, and 18 months.

- Number of included patients who were withdrawn from the study, listed by reason for withdrawal
- Number of included patients with at least one protocol violation, listed 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 girls ≥ 12 years of age)
- Laboratory assessments
- ECG
- Karnofsky Performance Score
- Neurological examination
- Concomitant medication

9.7. Treatment Compliance

The dosing regimen of fexinidazole is described in Section 5 Treatments, p 38.

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

<u>Primary Efficacy Endpoint</u>

The primary efficacy endpoint is the. success or failure, at 12 months after the final treatment intake. The patient's treatment 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.

Primary Analysis

The primary analysis will be performed on the 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.

The primary test is an exact test derived from the exact confidence interval (CI) of the success rate at 12 months.

Two sets of statistical hypotheses will be tested simultaneously:

H_{0A}: the true success rate is equal to or less than 80%, which is considered to be unacceptable.

H_{1A}: the true success rate is greater than 80%.

H_{0B}: the true success rate is equal to or greater than 92%, which is the target or expected success rate for fexinidazole.

H_{1B}: the true success rate is less than 92%.

If H_{0A} is rejected, then the success rate is significantly greater than 80% and the estimated rate is consistent with a rate of 92%. In this case, H_{0B} is automatically accepted, but not necessarily true.

If H_{0B} is rejected, then the success rate is significantly less than the target of 92%, and the estimated rate is consistent with the unacceptable rate of 80%. In this case, H_{0A} is automatically accepted, but not necessarily true.

If the observed success rate is equal to or greater than 87.2% (≥ 109 successes out of 125 patients), or equal to or greater than 110 successes out of 126 patients (if the sample size is equal to 126), then the study is a success since the rate is significantly greater than 80% and consistent with the target success rate of 92%.

Conversely, if the observed success rate is less than 87.2% (≤ 108 successes out of 125patients) or less than 110 successes out of 126 patients, then the study is a failure since the success rate is significantly less than the target rate of 92% and consistent with the unacceptable rate of 80%.

The unacceptable success rate of 80% is greater than the success rate of melarsoprol at 12 months, i.e. 74.8%, because the success rates of the alternative treatments, i.e. NECT and pentamidine, are considerably higher than the rate with melarsoprol, which increases the level of unacceptability.

The target or expected rate of 92% is greater than the expected value of 89% set in the pivotal study, because the success rate is evaluated at 12 months instead of 18 months (expected gain of 1.2%) and also because the success rate reported in the pivotal study is encouraging, since only one failure (a patient whose health status had been poor at inclusion) among 150 patients was observed at the EOT, and no relapses were observed among 30 patients during the 6-month follow-up period (blinded data with an allocation ratio of 2 fexinidazole for 1 NECT).

It should be noted that, in the pivotal study, a 94% success rate was expected for NECT at 18 months, and the margin of acceptable difference was set at 13%. This means that the level of the unacceptable rate for fexinidazole is81% if the success rate for NECT is truly 94%, and 80% if the success rate for NECT was 93%. This also means that the various expectations and limits are consistent across studies.

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

- The secondary analysis will be performed on the success rate at month 18.
- determine whether the success rate of treatment with fexinidazole varies depending on the stage of the disease, i.e. stage 1 versus early stage 2 versus late stage 2, using a Fisher exact test to compare the rates observed with the 3 different stages.
  If the difference between the 3 stages is significant, then the exact 95% CI of each success rate at 12 months will be calculated, and the stage that is responsible for the heterogeneity will be identified. The stage responsible for the heterogeneity will be separated from the other 2 stages, and the lower limit of the 95% CI of each of the 2 subgroups will be compared to the limit of 75%, which is slight higher than the success rate of melarsoprol at 12 months. A limit lower than 80%, i.e. 75% instead of 80%, was chosen because the sample size in each subgroup will be smaller, which will have an impact on the statistical power of each comparison. The upper limit of the CI of the success rate in patients with stage-1 HAT should be consistent with (greater than or equal to) the rate of 93%, which is the

historical success rate of pentamidine (61). The upper limit of the CI of the success rate in patients with stage-2 HAT should be consistent with the rate of 94%, which is the historical success rate of NECT.

- 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.

Data on patients with stage-1 and early stage-2 HAT in the DNDiHATFEX005 study will also be pooled. A logistic model with success at 12 months as the response and stage as covariate, as well as the study, will be used. The main results will concern the homogeneity of the success rates for the various stages. If there is heterogeneity, the success rate in patients with stage-1 HAT should not be lower than the success rate in patients with stage-2 HAT.

9.9. Safety Analysis

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.

9.10. Other Analyses

PK Data

- Fexinidazole, M1 and M2 concentrations in whole blood and CSF, as well as PK parameters derived from a population PK model.
- Analysis of all PK samples will be centralised. A population PK model will be developed using Nonmem software. The model will be fitted on rich sampling data from phase-I studies and used for sparse sampling data from phase-II studies. The model will be used to estimate population PK parameters, including clearance (CL) and volume of distribution (Vd). All of the analyses and statistical methods, including data conventions, will be described in detail in a separate SAP, which will be finalised prior to database lock.
- Correlations between blood and CSF concentrations will be described on samples collected at the EOT visit. Correlations between blood and CSF concentrations, on the one hand, and the success rate/AE rate, on the other hand, will be described.

ECG Data

- QT/QTcF interval (mean, range and categories) at the various timepoints.
- Prolongation of QT/QTcF interval in relation to baseline.

All of the analyses and statistical methods, including data conventions, will be described in detail in a separate SAP, which will be finalised prior to database lock.

10. Steering Committees

10.1. Data and Safety Monitoring Board

A Data and 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

A 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 protection.

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 83) 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 69).

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 should 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 73).

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. Collection of Informed Consent from the Child's Parent/Legal Representative

Consent must be obtained from a legal representative, who can be one of the parents or any other culturally acceptable representative of the child. The mobile teams that recruit patients in the field will request that the child be accompanied by a legal representative during visits to the investigational centre.

If both parents accompany the child, consent will be obtained from both parents, however, due to logistical constraints, if only one parent accompanies the child, consent from only one parent will be considered to be acceptable.

It is the responsibility of the Investigator to obtain voluntary written informed consent from the legal representative, after adequate presentation of aims, methods, anticipated benefits, and potential hazards of the study. This task may be performed by a designee, referred to below as "facilitator", which 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 and his/her legal representative 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 and his/her legal representative 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 fexinidazole 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's legal representative wishes, s/he will be given time to discuss the information received with members of his/her community or family before giving consent. If s/he decides to agree to participate in the study, the patient's legal representative will give written consent after the information session (or later) by signing the form, provided the facilitator is convinced that the legal representative has fully understood what was explained.

Assent will be obtained from the child (see Section 14.2.3 Collection of Assent from Child; p 75).

The 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 if the patient's legal representative is illiterate and to collect assent from the child.

If the patient's legal representative is unable to write, his/her signature can be replaced by a fingerprint and an impartial witness should be present throughout the process of collecting consent from the legal representative.

The witness should have no connection with the research team, and, whenever possible, should be chosen by the patient's legal representative. The witness must be literate, i.e. able to read. If the patient's legal representative does not know any 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 quickly, whenever necessary.

The witness will sign the consent form to attest to the completeness of the information given to the patient's legal representative, 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's legal representative has freely given informed consent for the child to participate in the study.

14.2.3. Collection of Assent from Child

No specific documentation or form will be used to collect assent from children enrolled in the study. Preference will be given to oral explanation in order to adapt the information to the child's level of understanding. Assent is difficult to obtain from children before 14 years of age since they do not clearly understand what benefits and risks entail (62). It is, however, easier for a child to refuse to participate than to accept to comply with a protocol. Refusal may be expressed when the protocol is explained to the child, or it may arise at any time during the course of the study. Indeed, the child is free to refuse, at any time, to undergo any invasive procedure planned in the protocol, even if s/he had initially agreed to participate in the study (62, 63). The child will be informed of this at the start of the study and at other appropriate moments. If the child refuses to undergo an invasive procedure, this will not jeopardise his/her overall participation in the study, provided that treatment compliance is acceptable.

Refusal to give assent will prevail over any other decision on the child's participation in the study.

14.2.4. 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 information sheet and consent form intended for the patient's legal

representative will be reviewed and updated. The legal representative of 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 for the child to participate in 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.

The PK analyses will be performed using a technique involving a dried blood spot, collected on filter paper. In children, it is preferable to use venous blood for technical reasons (see Section 6.3.3. Laboratory Tests; p 47).

CSF samples will be collected to assess exposure to fexinidazole in the brain. The analysis will be performed on the sample collected for the efficacy analyses, performed as per usual practice in the investigational centre. The PK analyses will require 5 drops of CSF and will only be performed on the first 30 children included in the study.

Samples collected on filter paper will be sent out of the countries where the study is being conducted for centralised assessment of exposure to fexinidazole. The samples will only be identified by the study reference number and the patient's code. Therefore, no identifying information will leave the patient's country.

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 and their legal representative will be reimbursed for their travel costs to and from the investigational site, however no payment will be provided for participation in the study. During the in-patient treatment phase, food will be provided 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.

In order to ensure that the child's legal representative is free to decide whether or not the child will participate in the study, all patients with HAT who are referred to the centre 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.

17. References

1. Astelbauer F, Walochnik J. “Antiprotozoal compounds: state of the art and new developments”. Int J Antimicrob Agents. 2011;38(2):118-24. doi: 10.1016/j.ijantimicag.2011.03.004.
2. Blackwelder W.C. "Proving the Null Hypothesis" in Clinical Trials. Contr Clin Trials 1982;3:345-353.
3. Blum J, Schmid C, Burri C. «Clinical aspects of 2541 patients with second stage human African trypanosomiasis”. Acta Trop 2006;97(1): 55-64
4. Brun R, Blum J, Chappuis F, Burri C. “Human African trypanosomiasis”. Lancet 2010; 375 (9709):148-59. doi:10.1016/S0140-6736(09)60829-1.
5. Bucheton B, MacLeod A, Jamonneau V. “Human host determinants influencing the outcome of Trypanosoma brucei gambiense infections”. Parasite Immunol. 2011;33(8):438-47. doi: 10.1111/j.1365-3024.2011.01287.x.
6. Büscher P, Mumba Ngoyi D, Kaboré J, Lejon V,Robays J, Jamonneau V, Bebronne N, Van Der Veken W, Biéler S. “Improved Models of Mini Anion Exchange Centrifugation Technique (mAECT) and Modified Single Centrifugation (MSC) for Sleeping Sickness Diagnosis and Staging”. PloS Negl Trop Dis 2009;3(11):e471.
7. Camara M, Camara O, Ilboudo H, Sakande H, Kaboré J, N'Dri L, Jamonneau V, Bucheton B. “Sleeping sickness diagnosis: use of buffy coats improves the sensitivity of the mini anion exchange centrifugation test”. Trop Med Int Health. 2010;15(7):796-9.
8. Checchi F, Chappuis F, Karunakara U, Priotto G, Chandramohan D. “Accuracy of Five Algorithms to Diagnose Gambiense Human African Trypanosomiasis”. PloS Negl Trop Dis 2011;5(7):e1233. Doi: 10.1371/journal.pntd.0001233.
9. Chen YH, DeMets DL, Lan KK. “Increasing the sample size when the unblinded interim result is promising”. Stat Med. 2004;23(7):1023-38.
10. CIOMS. Management of Safety Information from Clinical Trials (Report of CIOMS Working Group VI). CIOMS c/o WHO, Geneva, 2005. ISBN 92 9036 079 8.
11. Committee for Medicinal Products for Human Use (CHMP). “Guideline on the choice of the non-inferiority margin”. The European Medicines Agency 2005. EMEA/CPMP/EWP/2158/99.
12. Committee for Proprietary Medicinal Products (CPMP). “Points to consider on switching between superiority and non-inferiority”. The European Agency for the Evaluation of Medicinal Products 2000. CPMP/EWP/482/99.
13. Deborggraeve S, Büscher P. “Molecular diagnostics for sleeping sickness: what is the benefit for the patient?” Lancet Infect Dis. 2010 ;10(6):433-9.
14. Deborggraeve S, Lejon V, Ali Ekangu R, Mumba Ngoyi D, Pati Pyana P, Ilunga M, Mulunda JP, Büscher P. “Diagnostic Accuracy of PCR in gambiense Sleeping Sickness Diagnosis, Staging and Post-Treatment Follow-Up: A 2-year Longitudinal Study”. PloS Negl Trop Dis 2011;5(2):e972.
15. DNDi – Data on file – Phase 1 studies
16. DNDi. “Clinical Study to Assess the Tolerability, Feasibility and Effectiveness of Nifurtimox and Eflornithine (NECT) for the Treatment of

Trypanosoma Brucei Gambiense Human African Trypanosomiasis (HAT) in the Meningo-Encephalitic Phase (NECT-FIELD)". Accessed on January 30th, 2012, at http://www.clinicaltrial.gov/ct2/show/NCT00906880?

17. Doyle D, Hanks G, MacDonald N. "Oxford Textbook of Palliative Medicine". Oxford University Press. 845 pp, illustrated New York 1993;109. ISBN: 0-19-262028-2.
18. Durrant JD, McCammon JA. "Towards the development of novel Trypanosoma brucei RNA editing ligase 1 inhibitors". BMC Pharmacol 2011;11:9.
19. Falade C, Manyando C. "Safety profile of Coartem®: the evidence base". Malaria Journal 2009, 8(Suppl 1):S6
20. Friede T, Kieser M. "Blinded sample size reassessment in non-inferiority and equivalence trials". Stat Med. 2003;22(6):995-1007.
21. Ginsberg AM, Laurenzi MW, Rouse DJ, Whitney KD, Spigelman MK. Assessment of the effects of the nitroimidazo-oxazine PA-824 on renal function in healthy subjects. Antimicrob Agents Chemother. 2009 Sep;53(9):3726-33. doi:10.1128/AAC.00112-09
22. Harrington JM, Widener J, Stephens N, Johnson T, Francia M, Capewell P, Macleod A, Hajduk SL. "The Plasma Membrane of Bloodstream-Form African Trypanosomes Confers Susceptibility and Specificity to Killing by Hydrophobic Peptides". J Biol Chem 2010; 285(37):28659-66. doi: 10.1074/jbc.M110.151886.
23. Hasker E, Lutumba P, Mumba D, Lejon V, Büscher P, Kande V, Muyembe JJ, Menten J, Robays J, Boelaert M. "Diagnostic Accuracy and Feasibility of Serological Tests on Filter Paper Samples for Outbreak Detection of T.b. gambiense Human African Trypanosomiasis". Am J Trop Med Hyg 2010;83(2):374-9. doi: 10.4269/ajtmh.2010.09-0735.
24. Hasker E, Mitashi P, Baelmans R, Lutumba P, Jacquet D, Lejon V, Kande V, Declercq J, Van der Veken W, Boelaert M. "A new format of the CATT test for the detection of Human African Trypanosomiasis, designed for use in peripheral health Facilities" Trop Med Int Health. 2010;15(2):263-7.
25. Immtech Pharmaceuticals, Inc. "Phase IIb Trial of DB289 for the treatment of stage 1 African Trypanosomiasis". ClinicalTrials.gov 2008. Consulted on January 30th, 2012, at http://www.clinicaltrial.gov/ct2/show/NCT00803933?
26. Inojosa WO, Augusto I, Bisoffi Z, Josenado T, Abel PM, Stich A, Whitty CJ. "Diagnosing human African trypanosomiasis in Angola using a card agglutination test: observational study of active and passive case finding strategies". BMJ 2006;332(7556):1479.
27. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. "ICH Harmonised Tripartite Guideline". Accessed on www.ich.org on November 24th, 2011.
28. Jacobs RT, Plattner JJ, Nare B, Wring SA, Chen D, Freund Y, Gaukel EG, Orr MD, Perales JB, Jenks M, Noe RA, Sligar JM, Zhang YK, Bacchi CJ, Yarlett N, Don R. "Benzoxaboroles: a new class of potential drugs for human African trypanosomiasis". Future Med Chem 2011; 3(10): 1259-78.
29. Kagira JM, Maina N, Njenga J, Karanja SM, Karori SM, Ngotho JM."Prevalence and Types of Coinfections in Sleeping Sickness Patients in Kenya (2000/2009)". J Trop Med 2011;2011:248914. doi:10.1155/2011/248914.
30. Kaiser M, Bray MA, Cal M, Trunz BB, Torreele E, Brun R."Anti-

trypanosomal activity of Fexinidazole – A New Oral Nitroimidazole Drug Candidate for the Treatment of Sleeping Sickness". Antimicrob Agents Chemother. 2011. doi: 10.1128/AAC.00246-11

31. Lutje V, Seixas J, Kennedy A. "Chemotherapy for second-stage Human African Trypanosomiasis". Cochrane Database Syst Rev. 2010;(8):CD006201.
32. Lutumba P,Kande V, Boelaert M, Kayembe JM,Mampunza S. "Research capacity strengthening in the DRC". Lancet. 2010 ;375(9720):1080.
33. Malvy D, Chappuis F. "Sleeping sickness". Clin Microbiol Infect. 2011;17(7):986-95. doi: 10.1111/j.1469-0691.2011.03536.x.
34. Ministère de la Santé de la République Démocratique du Congo. « Lignes directrices pour l'évaluation éthique de la recherche impliquant des sujets humains en R. D. CONGO ».
35. Mumba D, Bohorquez E, Messina J, Kande V, Taylor SM, Tshefu AK, Muwonga J, Kashamuka MM, Emch M, Tidwell R, Büscher P, Meshnick SR. "Prevalence of Human African Trypanosomiasis in the Democratic Republic of the Congo". PloS Negl Trop Dis 2011;5(8):e1246..
36. Mumba Ngoyi D, Lejon V, N'Siesi FX, Boelaert M, Büscher P. "Comparison of operational criteria for treatment outcome in gambiense human African trypanosomiasis." Trop Med Int Health 2009;14(4):438-44.
37. Nare B, Wring S, Bacchi C, Beaudet B, Bowling T, Brun R, Chen D, Ding C, Freund Y, Gaukel E, Hussain A, Jarnagin K, Jenks M, Kaiser M, Mercer L, Mejia E, Noe A, Orr M, Parham R, Plattner J, Randolph R, Rattendi D, Rewerts C, Sligar J, Yarlett N, Don R, Jacobs R; "Discovery of Novel Orally Bioavailable Oxaborole 6-Carboxamides That Demonstrate Cure in a Murine Model of Late-Stage Central Nervous System African". Antimicrob Agents Chemother. 2010;54(10):4379-88.. doi: 10.1128/AAC.00498-10.
38. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) V4.0. Published: May 28, 2009 (v4.03: June 14, 2010). Accessed on January 13th, 2012 at http://evs.nci.nih.gov/ftp1/CTCAE/About.html
39. Ndem Amin D, Mumba Ngoyi D, Nhkwachi GM, Palomba M, Rottenberg M, Büscher P, Kristensson K, Masocha W. "Identification of Stage Biomarkers for Human African Trypanosomiasis". Am J Trop Med Hyg 2010;82(6):983-90. doi: 10.4269/ajtmh.2010.09-0770
40. Opigo J, Woodrow C. "NECT trial: more than a small victory over sleeping sickness". Lancet. 2009;374(9683):7-9. doi:10.1016/S0140-6736(09)61163-6.
41. Paliwal SK, Verma AN, Paliwal S. "Neglected Disease – African Sleeping Sickness: Recent Synthetic and Modeling Advances". Sci Pharm 2011;79(3):389-428. doi: 10.3797/scipharm.1012-08.
42. Priotto G, Chappuis F, Bastard M, Flévaud L, Etard J.-F. "Early prediction of treatment efficacy in second-stage gambiense Human African Trypanosomiasis". PLoS Neglected Tropical Diseases, *in press*.
43. Priotto G, Kasparian S, Mutombo W, Ngouama D, Ghorashian S, Arnold U, Ghabri S, Baudin E, Buard V, Kazadi-Kyanza S, Ilunga M, Mutangala W, Pohlig G, Schmid C, Karunakara U, Torreele E, Kande V. "Nifurtinox-eflornithine combination therapy for second stage African Trypanosoma Brucei gambiense trypanosomiasis: a multicentre, randomised, phase III, non –inferiority trial". Lancet 2009;374 (9683):56-64. doi:10.1016/S0140-6736(09)61117-X

44. Radwanska M. “Emerging trends in the diagnosis of Human African Trypanosomiasis”. Parasitology. 2010;137(14):1977-86. doi: 10.1017/S0031182010000211.
45. Rodgers J, Jones A, Gibaud S, Bradley B, McCabe C, Barrett MP, Gettinby G, Kennedy PG. “Melarsoprol Cyclodextrin Inclusion Complexes as Promising Oral Candidates for the Treatment of Human African Trypanosomiasis”. PloS Negl Trop Dis 2011;5(9):e1308..
46. Schag CC, Heinrich RL, Ganz PA. “Karnofsky performance status revisited: reliability, validity, and guidelines”. J Clin Oncology. 1984;2:187-193.
47. Simarro PP, Diarra A, Ruiz Postigo JA, Franco JR, Jannin JG. “The Human African Trypanosomiasis Control and Surveillance Programme of the World Health Organisation 2000–2009: The Way Forward”. PloS Negl Trop Dis 2011;5(2):e1007.
48. Sokolova AY, Wyllie S, Patterson S, Oza SL, Read KD, Fairlamb AH. “Cross-Resistance to Nitro Drugs and Implications for Treatment of Human African Trypanosomiasis”. Antimicrob Agents Chemother. 2010;54(7):2893-900. doi: 10.1128/AAC.00332-10
49. Stich A, Abel PM, Krishna S. “Human African trypanosomiasis”. BMJ 2002;325(7357):203–6.
50. Torreele E, Trunz BB, Tweats D, Kaiser M, Brun R, Mazué G, Bray MA, Pécoul B. “Fexinidazole – A New Oral Nitroimidazole Drug Candidate Entering Clinical Development for the Treatment of Sleeping Sickness”. PloS Negl Trop Dis 2010;4(12):e923..
51. Vincent IM, Creek D, Watson DG, Kamleh MA, Woods DJ, Wong PE, Burchmore RJ, Barrett MP. “A Molecular Mechanism for Eflornithine Resistance in African Trypanosomes”. PloS Pathog 2010;6(11):e1001204..
52. Wastling SL, Welburn SC. “Diagnosis of human sleeping sickness: sense and sensitivity”. Trends Parasitol. 2011;27(9):394-402. doi: 10.1016/j.pt.2011.04.005.
53. WHO (2000). "Operational Guideline for Ethics Committees That Review Biomedical Research. " World Health Organisation. TDR/PRD/ETHICS/2000.1.
54. WHO (2007). "Recommendations of the Informal Consultation on Issues for Clinical Product Development for Human African Trypanosomiasis." World Health Organisation. WHO/CDS/NTD/IDM/2007.1.
55. WHO (2011). "New cases of human African trypanosomiasis continue to drop." World Health Organisation. Consulted on January 30th, 2012, at http://www.who.int/neglected_diseases/disease_management/HAT_cases_drop/en/index.html
56. Yun O, Priotto G, Tong J, Flevaud L, Chappuis F. “NECT is next: implementing the New Drug Combination Therapy for Trypanosoma brucei gambiense Sleeping Sickness”. PloS Negl Trop Dis 2010;4(5):e720.
57. Mumba Ngoyi et al (2010).How to shorten patient follow-up after treatment for Trypanosoma brucei gambiense sleeping sickness. J Infect Dis;201(3):453-63.
58. Priotto et al 2012 Early prediction of treatment efficacy in second-stage gambiense human African trypanosomiasis. PLoS Negl Trop Dis;6(6):e1662.
59. Alcorn J. and McNamara P.J., Pharmacokinetics in the newborn, Advanced drug delivery Reviews 55 (2003) 667-686

60. NECT Field Clinical study report (draft, DNDi data)
61. M. Hümbelin (2006) Definition of Follow-Up Duration In Clinical Research Of Human African Trypanosomiasis, Thesis in pharmaceutical sciences at the University of Basel, Switzerland
62. Roth-Cline M. et al. “Parental permission and child assent in research on children”, Yale journal of biology and medicine (2013) 86: 291-301
63. Wendler, D.S. “Assent in paediatric research: theoretical and practical considerations” J Med Ethics (2006), 32:229-234
64. DNDiFEX004 trial: Efficacy and safety of fexinidazole compared to nifurtimox eflornithine combination therapy (NECT) in patients with late-stage Human African Trypanosomiasis (HAT) due to T.b. gambiense: pivotal, non-inferiority, multicentre, randomised, open-label study
65. http://www.finddiagnostics.org/media/press/121206.html
66. Sullivan L, Wall SJ, Carrington M, Ferguson MAJ (2013) Proteomic Selection of Immunodiagnostic Antigens for Human African Trypanosomiasis and Generation of a Prototype Lateral Flow Immunodiagnostic Device. PLoS Negl Trop Dis 7(2): e2087. doi:10.1371/journal.pntd.0002087
67. Büscher P. et al. Rapid Diagnostic Test for Sleeping Sickness, New England J Med 368;11 (2013)
68. Report of a WHO meeting on elimination of African trypanosomiasis (Trypanosoma brucei gambiense), Geneva, 3-5 December 2012
69. WHO Model List of Essential Medicine for Children 4th list (April 2013) http://www.who.int/medicines/publications/essentialmedicines/en/index.html

Appendices

Appendix 1 – Declaration of Helsinki

World Medical Association Declaration of Helsinki - 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 2002
(Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004
(Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008
64th W MA 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 all 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.

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for al 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.

Post-Trial Provisions

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 al 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 legal y 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 Scale

Karnofsky Performance Status Scale
Definitions 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 more serious the impairment is.

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.

Annexe 3 – Laboratory Assessments

Laboratory Assessments and Methods

All laboratory test methods will be described in a laboratory manual. Laboratory technicians have been specifically trained on these standardised methods.

Biochemistry tests: Piccolo® chemistry analyser

14 parameters will be analysed:

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

Haematology tests

- ***Hemocue® Hb 210+ or Hb301+*** *to measure haemoglobin*
- ***Microscopy****: Blood cells (visual count) using TIC® methodology (Bioanalytic GmbH) and Neubauer counting chambers*

Urine analysis

- *Dipstick analysis for safety parameters / COMBUR 9 Test®*

Leucocytes	*Nitrites*
pH	*Glucose*
Protein	*Ketone bodies*
Urobilinogen	*Bilirubin*
Blood	

- *Urine pregnancy test*

CSF Analysis

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

Blood parasitological tests

- Thin/Thick blood smear
- WOO/CTC test
- 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 190 µL (capillary blood[2)] and 4 mL (venous blood)
		WBC count	1	20 µL	
		Platelet count	1	10 µL	
		Differential WBC count	1	20 µL	
	Biochemistry	14 parameters	1	100 µL	
Urine	Urine Analysis	*COMBUR 9 Test®*	2	5 mL	5 mL

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

Baseline Assessment (D-1)

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

** Only in female patients ≥12 years of age*

Hospitalisation (D5, D8)

	Type of test	Specific test	Number of samples	Quantity per sample (approx.)	Total quantity (2 visits)
Sang	Haematology	Haemoglobin	2	20 µL	Between 340 µL (capillary blood[3]) and 8 mL (venous blood)
		WBC count	2	20 µL	
		Platelet count	2	10 µL	
		Differential WBC count	2	20 µL	
	Biochemistry	14 parameters	2	100 µL	
Urine	Urine Analysis	*COMBUR 9 Test*®	1	5 mL	5 mL

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 Biochemistry Parasitology	Haemoglobin	1	20 µL	Between 170 µL (capillary blood[3]) and 4 mL (venous blood)
		WBC count	1	20 µL	
		Platelet count	1	10 µL	
		Differential WBC count	1	20 µL	
	Parasitology	14 parameters	1	100 µL	
Lymph	Parasitology	If lymph nodes detectable			
Urine	Urine Analysis	*COMBUR 9 Test*®	1	5 mL	5 mL
CSF	Parasitology	Modified Single Centrifugation	1	4 mL	4 mL
	Haematology	WBC count	1		

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

EOH (between D13 and D18)

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

** Only in female patients ≥12 years of age*

Additional Follow-up Visit 9 weeks after D1

	Type of test	Specific test	Number of samples	Quantity per sample (approx.)	Total quantity
Sang	Haematology	Haemoglobin	1	20 µL	120 µL (capillary blood[3)]
	Biochemistry	14 parameters	1	100 µL	

Follow-up Visits (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
	Haematology	WBC count	1		

**Except at 3-month follow-up visit, unless patient has signs of symptoms of HAT*

Follow-up Visit (only M3)

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

** Only in female patients ≥12 years of age*

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
	Haematology	WBC count	1		

Quantity of biological fluid required PK analyses

Entire study (venous blood)

	Type of test	Number of samples	Quantity per sample (approx.)	Total quantity
Blood	PK	4	2 mL	8 mL
CSF	PK	1	Included in sample collected for parasitology (≤ 300 µL)	

Appendix 4 - Tables

Table 3 – Schedule of Study Procedures

Protocol-planned procedures and forms to be completed	**Pre-screening and Screening**	**Baseline**	**Treatment period**										**EOT Visit until EOH 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)*	*D12*	*D13-D18 (EOH)*	*3 – 6 – 12 – 18*
Detection of parasite in blood and/or lymph	x												x			x
Lumbar puncture (parasite and white blood cells in CSF)	x												x[2] D10H24			x[1]
Informed consent (**before any additional medicines or study-specific procedures**)	**x**	**Check**														
Pretreatment of helminthiasis (+ 3-day recovery period)	x															
Rapid diagnos ic test and/or hick blood smear for malaria	x															
Pretreatment of malaria if necessary (+ 3-day recovery period)	x															
Karnofsky score	x	Check														x
Safety ECG*	X[4]	Check		x	x	x							x			
Urine pregnancy test[3]		X (D-1)													x	x (3 months only)
Inclusion and exclusion criteria	x	x														
Demographic data	x															
Medical history	x															X[5]
Signs and symptoms of HAT		x													x	x
Vital signs	x	x					x			x			x		x	x
Physical examination		x					x			x			x		x	x
Neurological examination		x					x			x			x		x	x
Haematology/biochemistry*		x					x			x			x			x[6]
Urine analysis*		x											x			

[1] Except at 3-month visit, unless patient has signs or symptoms of HAT.

[2] Sampling at EOT to be performed on first 30 patients:

- *If no treatment failures are reported in the first 30 patients and if systemic exposure reaches the target concentrations, no sampling will be performed on subsequent patients*
- *If at least 1 failure is reported in the first 30 patients, sampling will continue in subsequent patients for follow-up on efficacy*

[3] Only female patients ≥12 years of age.

[4] ECG to be sent in electronic format for central reading – await cardiologist's report prior to including the patient in the study.

[5] Record NEW events since previous visit.

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

[7] At 6-month follow-up visit,haematology and biochemistry sampling

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

Protocol-planned procedures and forms to be completed	**Pre-screening and Screening**	**Baseline**	**Treatment period**										**EOT Visit until EOH 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)*	*D12*	*D13-D18*	3 – 6 – 12 – 18
Triplicate ECG		x				x D4H4 D4H23						x D10H2-H3				
Administration of fexinidazole			x	x	x	x	x	x	x	x	x	x				
Adverse events (AEs) [7]			x	x	x	x	x	x	x	x	x	x	x	x	x	
Serious adverse events (SAEs) (collection from signature of consent form to last study visit)		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Collection of concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Blood sampling for DBS												x D10H3 D10H7:15	x D10H24	x D10H48		

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

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 24 months
Duration of follow-up period	12 months (primary endpoint) – 18 months (follow-up)
Last patient last visit	March 2017
Final study report	December 2017

Table 5 – Overall Study Organisation

Target Country	Democratic Republic of Congo (DRC)		
Target Enrolment Rate		Screened	Included
	Total	150	125
Number of sites	At least 8 sites		
Number of patients included per site	No limitation per site		
Participation of a DSMB	A Data and Safety Monitoring Board (DSMB) will be appointed to look after safety issues (same DSMB as for DNDiFEX004		
Partners	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 MSF • Technical support • Logistical support		
Other means required for study	Mobile teams for active case detection Equipment and supplies for biochemical and haematological analyses Telecommunication means and computer hardware/software		