DNDi
Drugs for Neglected Diseases *initiative*

CLINICAL STUDY PROTOCOL

An open-label study assessing effectiveness, safety and compliance with fexinidazole in patients with human African Trypanosomiasis due to *T.b. gambiense* at any stage

Name of Investigational Product	Fexinidazole
Therapeutic class	Antiprotozoal
Phase	IIIb Cohort study
Indication	Human African Trypanosomiasis (HAT) due to *Trypanosoma brucei gambiense* at any stage
Protocol number	DNDi-FEX-09-HAT
Registration number	NCT03025789
Sponsor	Drugs for Neglected Diseases initiative (DND*i*) 15 chemin Louis Dunant, 1202 Geneva, Switzerland Tel: +41 22 906 9230
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Protocol version / date	Version 3.0 / 26 June 2020
Protocol amendment	N°2, *26 June 2020*

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I will provide copies of the protocol and all relevant information to all individuals participating in the study under my responsibility. I will ensure that they are given all of the necessary information on the study treatment and the procedures of the study.
I will use only the informed consent form approved by the Sponsor or its representative, and I agree to submit all relevant documentation to the Independent Ethics Committee (IEC) responsible for the study.
I also agree that the Sponsor or its representatives shall have access to all source documents from which data entered in the case report forms was generated.

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Abbreviations – Glossary of Terms

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	Body mass index
BUN	blood urea nitrogen
CATT	card agglutination test for trypanosomiasis
CI	confidence interval
CRF	Case report form
CSF	cerebrospinal fluid
CTC	capillary tube centrifugation
CTCAE	Common Toxicity Criteria for Adverse Events
D	day
DART	Development and Reproductive Toxicology
DNDi	Drugs for Neglected Diseases *initiative*
DRC	Democratic Republic of the Congo
DSMB	Data and Safety Monitoring Board
e.g.	*exempli gratia* (for example)
ECG	electrocardiogram
EoH	end of hospitalisation
EoT	end of treatment
g-HAT	Human African Trypanosomiasis due to *T.b. gambiense*
GCP	Good Clinical Practice
H	hour
HAT	human African trypanosomiasis
i.e.	*id est* (that is to say)
ICH	International Council on Harmonisation
IMP	investigational medicinal product
ITT	intention to treat
M	month
mAECT	mini-anion exchange column test
mAECT-BC	mini-anion exchange column test - buffy coat
MedDRA	Medical Dictionary for Regulatory Affairs
mITT	modified intention to treat
NCI	National Cancer Institute
NECT	Nifurtimox-Eflornithine Combination Therapy
PK	pharmacokinetic
PNLTHA	*Programme National de Lutte contre la Trypanosomiase Humaine Africaine*

PP	*per protocol*
QT	QT interval on electrocardiogram (time interval between electrical depolarisation and repolarisation of the left and right cardiac ventricles)
RDT	rapid diagnostic test
SAE	serious adverse event
SAP	statistical analysis plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
T.b.	*Trypanosoma brucei*
ULN	upper limit of normal
WBC	White blood cell or white blood cell count
WHO	World Health Organisation
Y	year
µL	microlitre

Protocol Summary

Study Title	An open-label study assessing effectiveness, safety and compliance with fexinidazole in patients with human African Trypanosomiasis due to *T.b. gambiense* at any stage
Study Phase	IIIb Cohort study
Indication	Human African Trypanosomiasis (HAT) due to *Trypanosoma brucei gambiense* at any stage
Protocol Number	DNDi-FEX-09-HAT
Study Rationale	Human African Trypanosomiasis (HAT) is a potentially fatal, neglected disease. Currently, the choice of drug used to treat HAT due to *T.b. gambiense* is based on the stage of the disease: pentamidine in patients with early-stage HAT and nifurtimox-eflornithine combined therapy (NECT) for patients with late-stage HAT. Patients with HAT must therefore undergo lumbar puncture for disease staging before treatment can begin. Fexinidazole is a 2-substituted 5-nitroimidazole, orally active *in vitro* and *in vivo* against the two parasites that cause HAT. The aim of the present study is to provide additional information on the effectiveness and safety of fexinidazole and to assess its use under conditions as close as possible to those in real life, both in patients treated on an out-patient basis and in the hospital setting, depending on clinical status.
Study Objectives	**<u>Primary Objective</u>** o To assess the effectiveness of fexinidazole administered to in- and out-patients with g-HAT at all stages of the disease. **<u>Secondary Objectives</u>** o To assess the safety of fexinidazole in patients with g-HAT at all stages, treated in hospital or as out-patients. For patients treated on an out-patient basis: o To assess treatment compliance; o To assess the feasibility of treatment management by the patient him/herself or with the help of a caregiver under the recommended conditions; o To assess the acceptability of the proposed final packaging and understanding of the instructions for use. For patients treated in hospital: o To assess the PK of fexinidazole and its main metabolites in the blood.
Primary Endpoint	**<u>Effectiveness</u>**

	Outcome (success or failure) at 12 months and 18 months after the end of treatment. Success is defined as a cure, according to the criteria adapted from the WHO (21).
Secondary Endpoints	**Safety** ▪ Occurrence of grade ≥ 3 adverse events (AEs), including laboratory and haematological abnormalities (if considered clinically significant), between the first intake of fexinidazole and the end of the observation period* or the follow-up period (18 months) for non-serious AEs assessed as related to fexinidazole. AE severity will be graded according to the National Cancer Institute (NCI) Common Toxicity Criteria for AEs (CTCAE), Version 4.03 (14) and, for certain laboratory parameters, modified CTCAE will be used. ▪ Occurrence of any serious adverse event (SAE) between the first intake of fexinidazole and the end of the follow-up period (18 months). ▪ Number of patients who discontinued treatment or were hospitalised during treatment for reasons related to safety, including overdose. * The observation period extends from the first intake of fexinidazole on Day 1 until the end-of-hospitalisation visit (between Day 13 and Day 18) for patients treated in hospital. For out-patients, the observation period extends to the end-of-treatment visit on Day 11. **Treatment Compliance in Out-patients** ▪ Presence of fexinidazole and/or its metabolites in the blood sample collected on Day 11 and/or at any unscheduled visit between Day 1 and the EoT visit, number of patients who brought unused tablets back at end of treatment, number of tablets brought back at the end of treatment (D11) and patients' responses to the questionnaire at the compliance interview. **Feasibility of Out-patient Treatment** ▪ On the basis of examination of packaging at the end of treatment and on interview with patients and/or the caregiver: number of patients who temporarily interrupted treatment, number of patients who prematurely discontinued treatment, number of patients who delayed starting treatment, number of patients who mislaid treatment units, number of patients who were hospitalised during treatment for reasons related to non-compliance, number of patients who took treatment regularly, according to the patients themselves, number of patients who understood the instructions concerning the dosing regimen of fexinidazole (questionnaire on Day 0), number of patients who complied with the dosing regimen (questionnaire on Day 11).

	<u>Acceptability of Packaging in Out-patients</u> ▪ Questionnaire on Day 0 and Day 11 (patients and/or caregivers*) **<u>Pharmacokinetics (PK) Parameters in Patients Treated in Hospital</u>** ▪ PK parameters for fexinidazole and its metabolites in whole blood, measured in all patients treated in hospital. * *Caregiver definition: accompanying person designated to take care of the patient during the treatment period and, more specifically, to ensure that fexinidazole is taken according to instructions. If several persons accompany the patient, a choice must be made by the patient (if possible) together with the Investigator to designate the most suitable person to fulfil the role*.
Study Design	This is a prospective, multicentre, open-label, study, assessing the effectiveness of fexinidazole in a cohort of adults and children with HAT at any stage, with follow-up over 18 months. It is planned to include 174 patients in 4 centres or more in the Democratic Republic of the Congo and in Guinea. The duration of treatment is 10 days. Patients will be treated on an out-patient basis or in hospital.
Inclusion and Exclusion Criteria	<u>Inclusion Criteria</u>: ▪ Male or female patient, including breastfeeding or pregnant women in the second or third trimester. ▪ ≥ 6 years of age. ▪ ≥ 20 kg body weight. ▪ Signed Informed Consent Form and Assent Form for patients less than 18 years of age. ▪ Trypanosomes detected in any body fluid. ▪ Physically able to ingest at least one solid meal per day. ▪ Able to take oral medication. ▪ Karnofsky Performance Status > 40%. ▪ Able to comply with the schedule of follow-up visits and with the study constraints. ▪ Easily reachable during the out-patient follow-up period. ▪ Willing to undergo lumbar punctures. <u>Non-inclusion Criteria</u>: ▪ Active clinically relevant medical conditions other than HAT that, in the Investigator's opinion, could jeopardise patient safety or interfere with participation in the study, including but not limited to significant liver or cardiovascular diseases, HIV infection, CNS trauma or seizure disorders, coma or altered consciousness not related to HAT. ▪ Severe renal or hepatic impairment defined as:

	○ elevated creatinine at > 3 times the upper limit of normal (ULN) ○ elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST) or bilirubin at > 3 ULN ▪ Severely deteriorated general condition, such as cardiovascular shock, respiratory distress or terminal illness. ▪ Any condition (except symptoms of HAT) that compromises ability to communicate with the Investigator as required for completion of the study. ▪ Any contraindication to imidazole products (known hypersensitivity to imidazoles). ▪ Treatment for HAT within 2 years prior to inclusion. ▪ Prior enrolment in the study or prior intake of fexinidazole. ▪ Foreseeable difficulty in complying with the schedule of follow-up visits (migrants, refugees, itinerant traders, etc.). <u>Temporary Non-inclusion Criteria</u>: ▪ Recovery period after antimalarial treatment and/or treatment of helminthiasis (at least 3 days). ▪ Uncontrolled diabetes or hypertension or any patients requiring clinical stabilisation; wait until appropriate treatment to control the disease has been initiated. ▪ First trimester of pregnancy. ▪ Traumatic lumbar puncture at Screening, that is to say (i.e). red blood cells visible in cerebrospinal fluid (CSF); wait for 48 hours before repeating lumbar puncture. <u>Eligibility Criteria for Out-patient Treatment</u>: ▪ Accepting to be treated on an out-patient basis. ▪ Karnofsky Performance Status > 50%. ▪ Good understanding of the method of administration of fexinidazole by the patient and/or caregiver (checked using a questionnaire at the time of IMP dispensing). ▪ Residing close to the investigational centre, i.e. at most one hour by road and/or boat, during the treatment period*. ▪ Easily reachable during the treatment period. ▪ No medical or psychiatric contraindications for treatment as out-patient. ▪ No pregnancy or breastfeeding. ▪ No neurological symptoms. * The patient (and caregiver) is permitted to reside in a place different from his/her main place of residence during the treatment period.
Study Duration	Based on an enrolment period of approximately 36 months and a follow-up period of 18 months, the total duration of the study will be 54 months. Each patient's participation in the study will last approximately 19 months, i.e. Screening (1 to 15 days), Treatment Period (10 days) and Follow-up Period (18 months).

Investigational Medicinal Product	**Investigational Medicinal Product** Fexinidazole, 600 mg tablets, to be taken by the oral route in a single intake during the main meal of the day at the daily dose of: Adult patients and children with body weight equal to or above 35 kg: ▪ 1800 mg (3 tablets) for 4 days, followed by ▪ 1200 mg (2 tablets) for 6 days. Children with body weight of at least 20 kg and below 35 kg: ▪ 1200 mg (2 tablets) for 4 days, followed by ▪ 600 mg (1 tablet) for 6 days. The total duration of treatment will be 10 days.
Study Schedule	▪ Screening and baseline assessment: Day -15 to Day -1 Patients treated in hospital: ▪ Treatment period: Day 1 to Day 10 ▪ End-of-treatment Visit: Day 11 ▪ End-of-hospitalisation Visit: between Day 13 and Day 18 Patients treated on an out-patient basis: ▪ Visit for dispensing prior to first intake of IMP: Day 0 ▪ End-of-treatment Visit at investigational centre: Day 11 Follow-up visits for all patients ▪ 3 months, 6 months, 12 months and 18 months.
Statistical Analyses	**Primary Analysis** The primary analysis will be performed on the modified intention-to-treat (mITT) population. The success rate at 12 months and the success rate at 18 months will be estimated, bearing in mind that 18 months provides a more reliable estimate of the cure rate. The 95% exact confidence interval will be provided. **Secondary Analyses** The success rates at 12 and 18 months will be estimated in the subgroup of early-stage patients, as well as the subgroup of late-stage patients. Secondary analyses concerning safety, compliance, feasibility of out-patient treatment, correct understanding of packaging and PK parameters will be performed. **Interim Analyses on Safety and Compliance** Interim analyses on safety and compliance will be performed during the study in order to supplement the registration file for fexinidazole with data from patients who have completed the treatment period, as well as data from patients treated in hospital who have completed the hospitalisation period. Data from follow-up visits completed at the time of data base lock will also be included in the analysis. **Sample Size Determination**

	The sample size determination is based on the primary analysis. The expected success rate is between 87% and 91% depending on the percentage of early-stage patients included in the sample. The success rate for patients with late-stage HAT should be slightly below the expected success rate of 89% in the pivotal study, DNDiHATFEX004, which has a restricted, more homogeneous population. As concerns early-stage patients, a meta-analysis (11) performed on a sample of 2524 patients treated with pentamidine and indexed in 4 databases maintained by non-governmental organisations showed a relapse rate (presence of trypanosomes or CSF WBC ≥ 20/µL) of 5.63% in patients followed for 6 months or less (142/2524), 8.20% in patients followed for 12 months or less (207/2524) and 9.23% in patients followed for 18 months or less. The expected success rate for early-stage patients should be close to 92%. A sample size of 174 patients at all stages of the disease provides a precision of 5% in the estimate if the expected success rate is 87% and if a Wald confidence interval is used. Because the confidence interval will be calculated with an exact method (Clopper-Pearson approach) the length of the lower arm of the 95% CI will be larger than that of the upper arm. The precision for the lower arm will be close to 6% and that of the upper arm will be close to 4.5 % if we consider an expected success rate of 87%. The precision will be greater if the success rate is higher.

1. Background and Study Rationale

1.1. Epidemiology

Human African trypanosomiasis (HAT), or sleeping sickness, is a vector-borne parasitic disease that is present in sub-Saharan Africa. It is transmitted by the bite of the tsetse fly and, if left untreated, it invariably leads to the patient's death. The parasites responsible for HAT are the protozoa, *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*, which are found only in foci in regions of sub-Saharan Africa where the tsetse fly is endemic (1, 12, 18). Twenty-four countries are considered to be endemic for HAT due to *T.b. gambiense* (g-HAT), however, since 2005, cases have been reported in only 14 of these countries. Thirteen countries are considered to be endemic for HAT due to *T.b. rhodesiense*, however cases have been reported in only 6 of the countries. Uganda is the only country where both subspecies of parasite are found. In 2014, the WHO identified 3 796 cases of g-HAT worldwide, 87% of which in the Democratic Republic of the Congo (DRC) alone (13, 17, 22, 23). According to the same source, however, the actual number of cases may be as high as 20,000 and as many as 65 million people may actually be exposed to the disease. With nearly a hundred cases reported every year, Guinea is now the West African country the most affected by sleeping sickness.

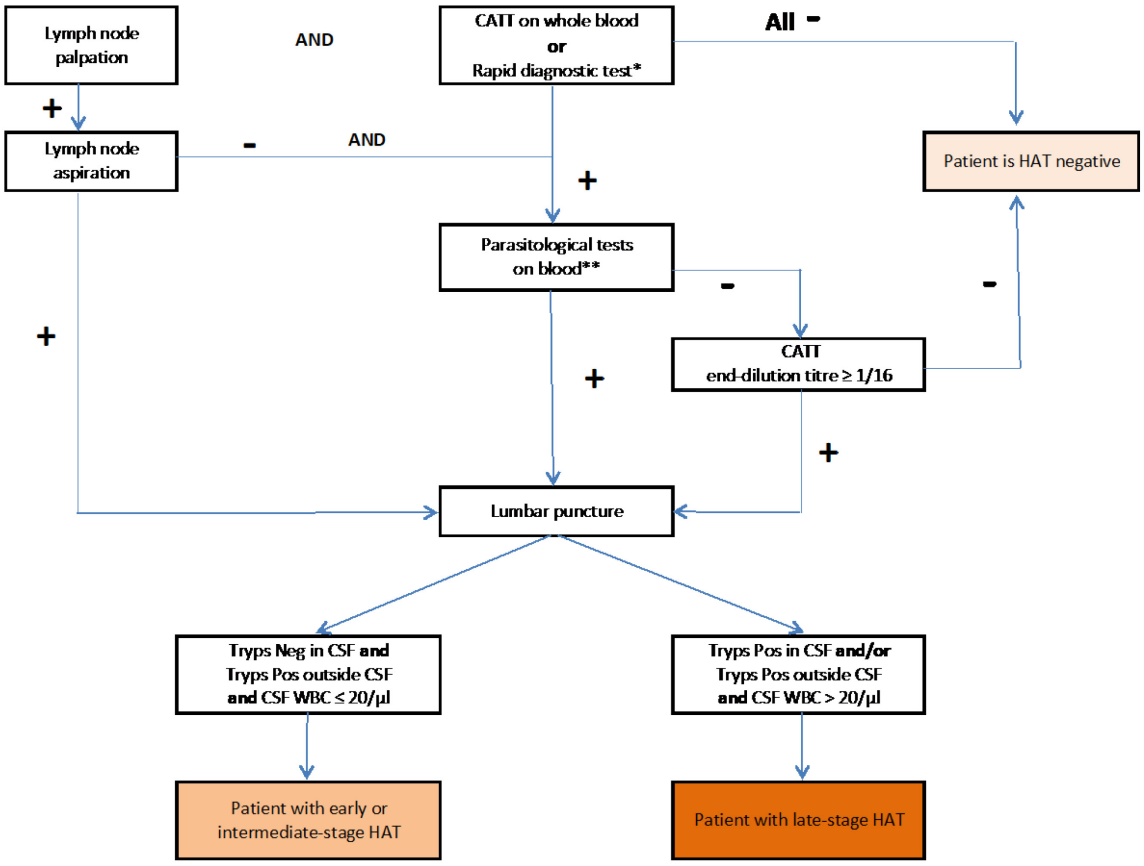
1.2. Clinical Presentation of HAT

There are two successive stages in the clinical course of HAT. In the first stage, called the haemolymphatic or early stage, trypanosomes are present only in the blood and lymphatic system. The clinical signs and symptoms are mild and non-specific, including bouts of fever, headache, joint pain, itching and lymph node enlargement. Patients diagnosed with early-stage HAT due to *T.b. gambiense* (g-HAT) receive intramuscular injections of pentamidine for 7 days. If left undiagnosed and untreated, patients progress to the next stage, called the meningoencephalitic stage or late stage, in which parasites invade the central nervous system. At this stage, patients display neurological signs including mental confusion, behavioural changes, sensory disturbances, sleep disturbances and, eventually, coma and death. Patients diagnosed with late-stage HAT are hospitalised for treatment with nifurtimox-eflornithine combination therapy (NECT). There is also an intermediate stage in which no parasites are detected in the cerebrospinal fluid (CSF), however the white blood cell count (WBC) in the CSF is between 6 and 20/µL (1, 12, 168). Patients with intermediate-stage HAT can be treated with pentamidine.

1.3. Diagnostic Process for Patients in the Study

HAT due to *T.b. gambiense* may be diagnosed either in the context of passive screening in patients who present spontaneously to the hospital or to one of the outlying healthcare centres or in the context of active screening by mobile teams or prospections in the field. Whatever the context, the diagnostic process will consistently include the following three steps: screening for potential infection using clinical and serological assessments, detection of the parasite and staging of the disease by lumbar puncture and CSF analysis (see Figure 1).

Figure 1 – Decision Tree for the Diagnosis of HAT in the Context of the Study



* Preferably CATT for active screening and RDT for passive screening
** Preferably in the following order: mAECT-BC (passive); mAECT (active); CTC/Woo test; Thick blood smear
CATT: Card Agglutination Test for Trypanosomiasis
Tryps: Trypanosomes CSF: Cerebrospinal Fluid WBC: White Blood Cell count
Pos: Positive
Neg: Negative

Screening, which consists in investigation of potential infection, will be performed by assessing clinical signs, including the presence of swollen cervical lymph nodes, and by serological tests. In the community, outlying healthcare centre or hospital, serological screening will be performed using a rapid diagnostic test (RDT) (3) or the card agglutination test for trypanosomiasis (CATT) (10).

For patients with a positive result on serological screening, tests to detect the parasite will be performed on fresh samples, i.e. on lymph node aspirate collected

by needle biopsy and in the blood preferably using one of the concentration methods that allow for microscopic detection of motile parasites using the Woo test (capillary tube centrifugation) or the mini-anion exchange centrifugation test (mAECT) (2) or, if concentration methods are not available, by examination of a stained thick blood smear.

In the context of the study, the improved technique, called the “mini-anion exchange centrifugation test on buffy coats” (mAECT-BC) (4), will be used whenever possible in patients with positive serological tests and negative findings on the usual parasitological tests, i.e. Woo test or mAECT, in addition to the usual procedures.

Because the serological tests currently available are not 100% reliable, an individual may have negative serological tests, but still show clinical signs suggestive of HAT. In this case, the individual will undergo the parasitological tests described above.

The diagnostic tests will be performed in the investigational centre for all patients, including patients diagnosed outside the centre. Lumbar puncture for disease staging will be performed only at the investigational centre. It is planned to perform lumbar puncture, whenever possible, using a local anaesthetic cream, i.e. an Emla® patch, as well as an atraumatic needle. Parasitological tests will be performed after modified single centrifugation (MSC) of the CSF using Pasteur disposable plastic pipettes.

Only patients in whom the presence of parasites is confirmed by at least two team members at the investigational centre and approved by the Investigator, will be included in the study, regardless of the findings reported by the mobile teams. For quality control purposes, it is planned to record digital images of the parasitological tests and CSF WBC counts at the time of the initial diagnosis, as well as during follow-up visits.

In the context of the study, a CSF WBC count of 20/µL, as well as the presence of parasites in any body fluid, will be used to stage the disease, in accordance with the WHO guidelines for clinical studies assessing treatments for late-stage HAT (21).

All patients included in the study will receive fexinidazole, regardless of the stage of the disease. Disease staging based on analysis of CSF obtained on lumbar puncture is necessary because the treatments currently available are not the same for early-stage and late-stage HAT and, in the context of the study, it will provide confirmation of the efficacy of fexinidazole against both stages of HAT.

The end-of-treatment assessment of patients will be based on parasitological tests on the blood and/or lymph on Day 11 and at the 3-month, 6-month, 12-month and 18-month visits, in accordance with the WHO guidelines (21). At the 3-month follow-up visit, lumbar puncture will be performed only in patients with clinical signs of relapse. Lumbar puncture will be routinely performed at the 6-, 12- and 18-month follow-up visits, unless the patient explicitly refuses the test.

1.4. Investigational Medicinal Product

Fexinidazole is a 2-substituted 5-nitroimidazole, orally active *in vitro* and *in vivo* against the two parasites *T.b. rhodesiense* and *T.b. gambiense*. The compound acts primarily as a biologically active prodrug, with the sulfoxyde and sulfone metabolites providing most of the trypanocidal activity. The efficacy of fexinidazole and of its metabolites in the treatment of HAT has been demonstrated in an extensive programme of preclinical and phase-I studies (179, 7).

Fexinidazole has received a positive opinion from the European Medicines Agency (EMA) and its use has been approved by the Democratic Republic of the Congo and Guinea.

To date, approximately 617 patients have received fexinidazole in the three studies, including 322 patients (52%) with late-stage HAT and 295 patients (48%) with early- or intermediate-stage HAT. Initial data on the safety of fexinidazole from the on-going studies in HAT indicate that the overall safety profile is satisfactory. No treatment interruptions have been reported. The most frequently observed adverse reactions in phase-I studies, which included a total of 154 healthy volunteers, primarily involved the central nervous system (headache) and gastrointestinal tract (nausea, vomiting, diarrhoea). In a phase-II/III study on fexinidazole for the treatment of Chagas disease, adverse reactions involving liver function, as well as cases of transient, reversible, asymptomatic neutropenia at grade 3 and 4, were reported (7).

1.5. Choice of the Dose and Dosing Regimen

The dose and the dosing regimen were chosen on the basis of phase-I studies in healthy volunteers. In particular, the DNDiFEX003 study demonstrated that the optimal dosing regimen should include a loading dose of 1800 mg for 4 days, followed by a maintenance dose of 1200 mg for 6 days in order to rapidly reach exposure levels in the brain at least twice as high as the minimal inhibitory concentration for M2. Use of a loading dose also leads to a shorter duration of treatment, which in turn avoids fexinidazole-related increases in liver enzyme levels. The optimal dosing regimen should also include concomitant intake of food in order to maximise exposure over a short period of time and to reduce the dose administered. Pharmacokinetic (PK) findings in adults and children included in the on-going clinical studies confirmed the dosing regimen chosen (7).

1.6. Rationale for the Study Design and Target Population

The decision to conduct an open-label study was prompted by the need to collect additional information on the efficacy and safety of fexinidazole under clinical

conditions close to those in real life and thus to confirm the feasibility of treating patients outside the hospital setting.

It is also necessary to collect information on the effectiveness and safety of fexinidazole in a wider set of patients who are more representative of the patients who will be treated in the future. Thus, the target population will include patients who were not included in the earlier studies, such as breastfeeding and pregnant women. This decision is supported by data from the full development and reproductive toxicology (DART) studies showing that there is no risk of toxicity on foetal or post-natal development with fexinidazole:

A full programme of regulatory-compliant DART studies was conducted in rats and rabbits. Doses of 0 (vehicle alone), 50, 200 and 800 mg/kg/day in rats and of 0 (vehicle alone), 10, 20 and 40 mg/kg/day in rabbits were administered from gestation day 6 to gestation day 20.

All of the findings presented in the full report on the DART studies clearly indicate that fexinidazole and its two metabolites:

- do not cause any disturbances in fertility in male or female rats. This is consistent with the findings from repeated-dose toxicity studies;
- do not cause any disturbances in gestation in rats or rabbits or any adverse effects on conceptuses, and no evidence of teratogenic potential was noted at any dose;
- do not cause any adverse effects on pregnant or lactating females, on the development of the embryo or foetus, or on newborns up to weaning.

These findings therefore confirm that fexinidazole can be tested in pregnant women. All of the findings of reproduction studies, as well as from a standard battery of genotoxicity tests, are available, as required by International Council on Harmonization (ICH) Topic M3 (2008). The findings from preclinical studies show that fexinidazole and/or its metabolites do not induce any toxicity on reproductive function.

A study on fexinidazole concentrations in milk was conducted on lactating female albino rats after the administration of 800 mgeq/kg of [14C]-fexinidazole. Radioactive drug-related material was detected in milk at a concentration similar to that in plasma and in blood. Exposure to the radioactive drug-related material was approximately 80% of that measured in plasma, in terms of both C_{max} and AUC values.

On the basis of these findings, the same extent of exposure can be expected in breastfed human newborns. Median and maximum plasma exposure to M2, the main metabolite, observed in women participating in the FEX004 study were 529 and 930 µg•h/mL respectively. This corresponds to a plasma M2 concentration of approximately 22 to 39 µg/mL, from which it can be inferred that the concentration in breast milk will be from 18 to 31 µg/mL. Thus, for newborns with a mean weight

of 3 kg who consume around 500 mL of breast milk per day, this corresponds to total exposure to M2 in the range of 9.0 to 15.5 mg/day, i.e. 3.0 to 5.2 mg/kg.

Nevertheless, as a precautionary measure, pregnant women will be eligible to participate in the study only once they have reached the second trimester of pregnancy and will not be eligible for treatment on an out-patient basis.

The target population will also include patients whose health status is not as good as in earlier studies, within medically acceptable limits, as this is likely to be the case for some patients who will be treated in the future. Thus, the eligibility criteria for patients in the study are less strict that those in earlier studies on fexinidazole with, in particular, deletion of some criteria based on laboratory tests and on body-mass index (BMI).

As in early studies, in particular DNDiHATFEX006, children under 6 years of age will not be part of the target population for practical reasons related to the size of the tablets and difficulty in swallowing them.

Lastly, the study will provide additional laboratory data at 3 months and 6 months to supplement the existing laboratory safety database, with a particular focus on haematological and hepatic functions.

2. Study Objectives and Endpoints

2.1. Objectives

2.1.1. Primary Objective

- To assess the effectiveness of fexinidazole administered to in- and out-patients with g-HAT at all stages of the disease.

2.1.2. Secondary Objectives

- To assess the safety of fexinidazole in patients with g-HAT at all stages, treated in hospital or as out-patients.

For patients treated on an out-patient basis:

- To assess treatment compliance;
- To assess the feasibility of treatment management by the patient him/herself or with the help of a caregiver under the recommended conditions;
- To assess the acceptability of the packaging and understanding of the instructions for use.

For patients treated in hospital:

- To assess the PK of fexinidazole and its main metabolites in the blood.

2.2. Study Endpoints

2.2.1. Primary Endpoint – Effectiveness

The primary endpoint for the assessment of effectiveness will be:

- Outcome (success or failure) at 12 months and 18 months after the end of treatment. Success is defined as a cure, according to the criteria adapted from the WHO (21).

2.2.2. Secondary Endpoints - Safety

The secondary endpoints for the assessment of the safety of fexinidazole will be:

- Occurrence of grade ≥ 3 adverse events (AEs), including laboratory and haematological abnormalities (if considered clinically significant), between the first intake of fexinidazole and the end of the observation period* or the follow-up period (18 months) for non-serious AEs assessed as related to fexinidazole. AE severity will be graded according to the National Cancer Institute (NCI) Common Toxicity Criteria for AEs (CTCAE), Version 4.03 (12) and, for certain laboratory parameters, modified CTCAE will be used.
- Occurrence of any serious adverse event (SAE) between the first intake of fexinidazole and the end of the follow-up period (18 months).
- Number of patients who discontinued treatment or were hospitalised during treatment for reasons related to safety, including overdose.

*The observation period extends from the first intake of fexinidazole on Day 1 until the end-of-hospitalisation visit (between Day 13 and Day 18) for patients treated in hospital. For out-patients, the observation period extends to the end-of-treatment visit on Day 11.

2.2.3. Secondary Endpoints - Compliance

The secondary endpoints for the assessment of compliance with treatment in patients treated on an out-patient basis will be:

- Presence of fexinidazole and/or its main metabolites in the blood sample collected on Day 11 and/or at any unscheduled visit between Day 1 and the end-of-treatment (EoT) visit;
- Number of patients who brought unused tablets back at the end of treatment;
- Number of tablets brought back at the end of treatment (D11)
- Patients' responses to the questionnaire at the compliance interview.

2.2.4. Secondary Endpoints - Feasibility

In patients treated on an out-patient basis, the secondary endpoints for assessment of the feasibility of self-management of treatment intake, or with the assistance of the caregiver* under recommended conditions, will be:

- Number of patients who temporarily interrupted treatment;
- Number of patients who prematurely discontinued treatment;
- Number of patients who delayed starting treatment;
- Number of patients who mislaid treatment units;
- Number of patients who were hospitalised during treatment for reasons related to non-compliance;
- Number of patients who took treatment regularly, according to the patients themselves (compliance interview at Day 11);
- Number of patients who understood the instructions concerning the dosing regimen of fexinidazole (questionnaire on Day 0);
- Number of patients who complied with the dosing regimen, including intake of treatment during a meal (questionnaire on Day 11).

* *Caregiver definition: accompanying person designated to take care of the patient during the treatment period and, more specifically, to ensure that fexinidazole is taken according to instructions. If several persons accompany the patient, a choice must be made by the patient (if possible) together with the Investigator to designate the most suitable person to fulfil the role*.

2.2.5. Secondary Endpoints - Packaging

The secondary endpoint for assessment of understanding and acceptability of the packaging by out-patients will be:

- Questionnaire on Day 0 and Day 11 (patients and/or caregivers)

2.2.6. Secondary Endpoints - PK

The secondary endpoint for the PK assessment will be:

- PK parameters of fexinidazole and its metabolites in whole blood, measured in all patients treated in hospital.

3. Study Design

This is a prospective, multicentre, open-label study, assessing the effectiveness of fexinidazole in a cohort of adults and children with HAT at any stage, with follow-up over 18 months.

It is planned to include 174 patients in 4 investigational centres or more in the DRC and in Guinea that have experience in the treatment of patients with HAT.

The duration of treatment is 10 days. Patients will be treated on an out-patient basis or in hospital, in accordance with pre-set inclusion and non-inclusion criteria.

The end of study corresponds to the last visit of the last patient.

4. Eligibility Criteria

4.1. Inclusion Criteria

To be included in the study, the patient must fulfil all of the following criteria:

- Male or female patient, including breastfeeding or pregnant women in the second or third trimester;
- ≥ 6 years of age;
- ≥ 20 kg body weight;
- Signed Informed Consent Form and Assent Form for patients less than 18 years of age;
- Trypanosomes detected in any body fluid;
- Physically able to ingest at least one solid meal per day;
- Able to take oral medication;
- Karnofsky Performance Status > 40% (see Appendix 2 - Performance Status Scale, p74);
- Able to comply with the schedule of follow-up visits and with the study constraints;
- Easily reachable during the out-patient follow-up period;
- Willing to undergo lumbar punctures.

4.2. Non-inclusion Criteria

To be included in the study, the patient must not fulfil any of the following exclusion criteria:

- Active clinically relevant medical conditions other than HAT that, in the Investigator's opinion, could jeopardise patient safety or interfere with participation in the study, including but not limited to significant liver and cardiovascular diseases, HIV infection, CNS trauma or seizure disorders, coma or altered consciousness not related to HAT;
- Severe renal or hepatic impairment defined as:
    - elevated creatinine at > 3 times the upper limit of normal (ULN);
    - elevated ALT, AST or bilirubin at > 3 X ULN;

- Severely deteriorated general condition, such as cardiovascular shock, respiratory distress, or terminal illness;
- Any condition (except symptoms of HAT) that compromises ability to communicate with the Investigator as required for completion of the study;
- Any contraindication to imidazole products (known hypersensitivity to imidazoles);
- Treatment for HAT within 2 years prior to inclusion;
- Prior enrolment in the study or prior intake of fexinidazole;
- Foreseeable difficulty in complying with the schedule of follow-up visits (migrants, refugees, itinerant traders, etc.).

The following criteria are considered as temporary non-inclusion criteria:

- Recovery period after antimalarial treatment and/or treatment of helminthiasis (at least 3 days);
- Uncontrolled diabetes or hypertension or any patients requiring clinical stabilisation; wait until appropriate treatment to control the disease has been initiated;
- First trimester of pregnancy (based on date of last menstrual period);
- Traumatic lumbar puncture at Screening i.e. red blood cells visible in CSF; wait for 48 hours before repeating lumbar puncture.

Ineligible patients will be treated according to the protocol of the National HAT Control Program (PNLTHA) and will receive the same support from the Sponsor during the treatment period.

4.3. Eligibility Criteria for Out-patient Treatment

To be eligible for treatment on an out-patient basis, the patient must fulfil all of the following criteria:

- Accepting to be treated on an out-patient basis;
- Karnofsky Performance Status > 50%;
- Good understanding of the method of administration of fexinidazole by the patient and/or caregiver (checked using a questionnaire at the time of dispensing fexinidazole);
- Residing close to the investigational centre, i.e. at most one hour by road and/or boat, during the treatment period*;
- Easily reachable during the treatment period;
- No medical or psychiatric contraindications for treatment as out-patient;
- No pregnancy or breastfeeding;

- No neurological symptoms.

* *The patient (and caregiver) is permitted to reside in a place different from his/her main place of residence during the treatment period*.

5. Study Treatment

5.1. Investigational Medicinal Product

The investigational medicinal product (IMP) is fexinidazole as 600-mg tablets, to be taken orally in a single intake during the main meal of the day at the daily dose of:

Adult patients and children with body weight equal to or above 35 kg:

- 1800 mg (3 tablets) for 4 days, followed by
- 1200 mg (2 tablets) for 6 days.

Children with body weight of at least 20 kg and below 35 kg:

- 1200 mg (2 tablets) for 4 days, followed by
- 600 mg (1 tablets) for 6 days.

The total duration of treatment will be 10 days.

5.2. Treatment Allocation

All patients who give informed consent/assent to participate in the study and who fulfil the eligibility criteria will receive the IMP.

5.3. Packaging of IMP

The tablets of fexinidazole will be presented in the commercial packaging that has been designed for use once the product has obtained marketing authorisation. The packaging will be different depending on the body weight and age of the patient. The tablets will be packaged in aluminium/aluminium blister packs and presented as a wallet, i.e. a cardboard pack with three folding panels. Each pack contains the number of tablets required for 10 days of treatment.

Mock-ups of the packaging intended for patients are presented in Appendix 5, Packaging of IMP, p79.

5.4. Accountability of IMP

Fexinidazole will be sent to the study coordination sites.

Study-specific forms will be used for accountability of fexinidazole and will be kept up to date by the person designated as responsible for the pharmacy in the investigational centre, under the responsibility of the Investigator, or by the Investigator him/herself. During on-site monitoring, the study monitors will check

that the forms are up to date. In the course of the study, the monitors will perform reconciliation between the quantities of fexinidazole delivered to the centre and the quantities dispensed to patients, as well as used and unused quantities.

Fexinidazole must not under any circumstances be used outside the context of the study without prior written approval from the Sponsor.

Each patient who is to be treated on an out-patient basis (or the caregiver) will be given the appropriate size pack, based on age and weight, containing sufficient quantity of fexinidazole for 10 days of treatment. The patient will also be given precise instructions on how to store fexinidazole and how to take the tablets. At the EoT visit (Day 11), the patient and/or the caregiver must return the original treatment pack to the centre so that treatment compliance can be checked and recorded.

For patients treated in hospital, accountability of fexinidazole will be ensured by the person responsible for the pharmacy in the investigational centre, under the responsibility of the Investigator, or by the Investigator him/herself.

5.5. Storage of IMP

Fexinidazole should be stored at a temperature not exceeding 30°C. Regulatory-compliant stability studies are currently on-going. Data currently available indicate that fexinidazole remains stable for 18 months when stored at 30°C with 75% relative humidity and for 6 months at 40°C with 75% relative humidity.

Fexinidazole will be stored in a locked room at the investigational centre, or a locked cabinet, with access restricted to the person responsible for the pharmacy and/or the Investigator. The storage conditions, including the temperature, must be monitored by the person responsible for the pharmacy in the centre. Appropriate records must be available.

Patients who are eligible for treatment on an out-patient basis will receive precise instructions on how to store the IMP and on the recommended dosing regimen.

5.6. Concomitant Treatment

5.6.1. Malaria

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

Prior to starting treatment with fexinidazole, malaria will be treated for 3 days with the combination artemether-lumefantrine (Coartem®) unless the patient has personal contraindications, such as severe malaria or hypersensitivity to one of the components, i.e. artemether or lumefantrine. All of the existing artemisinin-based combination therapies used against malaria have effects on the QT interval. Coartem® was chosen because its effects on QT-interval prolongation are known

to be moderate and well quantified (9). The choice was made to minimise confounding factors in the assessment of fexinidazole-related QT-interval prolongation. Coartem® will be provided free of charge by the Sponsor.

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

Treatment will be followed by a recovery period of at least 3 days between the last dose of Coartem® and the start of treatment with fexinidazole.

5.6.2. Helminthiasis

All patients will receive treatment for helminthiasis, with mebendazole or albendazole, in accordance with the usual practice in the centre. The Sponsor will cover the cost of treatment.

Treatment for helminthiasis must be followed by a 3-day recovery period before starting treatment with fexinidazole, in accordance with the usual practice in the centres.

5.6.3. Contraception

Women of child-bearing age will be advised not to become pregnant and therefore to use a method of contraception or sexual abstinence throughout the entire treatment period and, if possible, until 48 hours after the EoT.

5.6.4. Other Medicines

Any medicines required to treat concomitant chronic conditions should remain unchanged during the treatment period with fexinidazole.

The list of medicines showing to have interactions with fexinidazole is described in the Investigator's Brochure for fexinidazole.

For patients treated in hospital, any medicine used between the Screening visit (Day -15 to Day -1) and the EoH visit (Day 13 to Day 18) must be recorded in the CRF, specifying the reason for use. For patients treated on an out-patient basis, any medicines taken during the Screening visit (Day -15 to Day -1) will be recorded in the same manner as for patients treated at hospital, while any medicines taken during the treatment period will be collected at the EoT visit and recorded in the CRF, specifying the reason for use.

Any medicines administered to treat an SAE during the follow-up period, i.e. up to the visit at 18 months, must be recorded in the CRF (see Section 6.8 Safety Assessments, Definitions; p 40). Other medicines used to treat other non-serious medical events will be recorded only in the patient's medical file.

Any medicine required during the study, i.e. at any time up to the visit at 18 months will be provided free of charge to the patient. The WHO List of Essential Medicines

and the *Essential Drugs* guide (2010 edition) published by *Médecins Sans Frontières* will be used as a reference for the treatment of any concomitant condition. The study team will take all necessary measures to ensure that the patient receives appropriate care for any concomitant condition during the course of the study.

5.6.5. Rescue Treatment

Patients in whom no response is observed on parasitological testing at the EoH visit, as well as patients who show signs of relapse at any time during follow-up, will receive the treatment recommended by the PNLTHA.

If a patient treated on an out-patient basis interrupts treatment with the IMP after Day 4, s/he will be followed up in the usual manner by the investigational centre in order to detect a possible relapse. In this situation, rescue treatment will be the treatment recommended by the PNLTHA.

If a patient treated on an out-patient basis interrupts treatment with the IMP before Day 4, s/he will receive rescue treatment with NECT if s/he has late-stage HAT or with pentamidine if s/he has early-stage HAT.

Rescue treatment for HAT must be recorded in the appropriate section of the CRF and not as concomitant medication.

Probable relapse at the 6-month, 12-month or 18-month follow-up visit is defined as shown below.

Table 1 – Clinical Classification of Patients

Visit	*Ideal timing of visit after end of treatment*	*Favourable outcome*	*Uncertain outcome*	*Probable relapse*	*Proven relapse*
24 hours after EoT	*24 hours after the End of Treatment (EoT)*	• Patient alive with no evidence of trypanosomes in any body fluid (19)			• Evidence of trypanosomes in any body fluid
3 months	*3 months ± 1 week*	• Patient alive with no evidence of trypanosomes in any body fluid (no lumbar puncture at 3 months unless Investigator suspects relapse)	• Any reason prompting the Investigator to request an additional follow-up visit	• Neurological signs or symptoms leading to use of rescue treatment	• Evidence of trypanosomes in any body fluid
6 months	*6 months ± 1 week*	• Patient alive with no evidence of trypanosomes in any body fluid and CSF WBC ≤ 20/µL	• CSF WBC between 20 and 50/µL and additional visit requested within 1-3 months • Any reason prompting the	• CSF WBC ≥ 50/µL (**24**) • Neurological signs or symptoms leading to use of rescue treatment	• Evidence of trypanosomes in any body fluid

			Investigator to request an additional follow-up visit		
12 months	*12 months ± 4 weeks*	• Patient alive with no evidence of trypanosomes in any body fluid and CSF WBC ≤ 20/µL • CSF WBS between 20 and 50/µL, and lower as compared to prior value(s)	• CSF WBC > 20/µL and non-significant increase from a clinical standpoint in relation to prior value(s) • Any reason prompting the Investigator to request an additional follow-up visit	• CSF WBC > 20/µL and significant increase from a clinical standpoint in relation to prior value(s) • Neurological signs or symptoms leading to use of rescue treatment	• Evidence of trypanosomes in any body fluid
18 months	*18 months ± 4 weeks*	• Patient alive with no evidence of trypanosomes in any body fluid and CSF WBC ≤ 20/µL • Patient with no signs of HAT and 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 prompting the Investigator to request an additional follow-up visit	• CSF WBC > 20/µL • Neurological signs or symptoms leading to use of rescue treatment	• Evidence of trypanosomes in any body fluid

6. Schedule of Study Procedures and Assessments

6.1. Timing of Assessments

Study procedures will be performed in accordance with the following schedule (see also Table 2 – Theoretical Schedule of Visits and Acceptable Leeway):

- Day -15 to Day -1: screening and baseline assessment

Then, depending on the type of patient:

Patients treated in hospital:

- Treatment period: Day 1 to Day 10
- EoT visit: Day 11
- EoH visit: between Day 13 and Day 18

Patients on an out-patient basis:

- IMP dispensing visit prior to first intake of IMP: Day 0
- Compulsory EoT visit at investigational centre: Day 11

Out-patient follow-up visits for all patients:

- 3 months, 6 months, 12 months and 18 months

The schedule of visits is calculated from the first day of treatment (Day 1).

Table 2 - Theoretical Schedule of Visits and Acceptable Leeway

Type of Visit	Schedule of Visits and Acceptable Time Window	Acceptable leeway*
EoT Visit	Day 11	Day 11 + 1 day
End-of-Hospitalisation Visit, only for patients treated in hospital	Between Day 13 and Day 18	Day 18 at the latest
3-month follow-up visit	3 months ± 1 week after Day 1	2 to 4 months, i.e. 60 to 149 days, after Day 1
6month follow-up visit	6 months ± 1 week after Day 1	5 to 9 months, i.e. 150 to 299 days, after Day 1
12-month follow-up visit	12 months ± 4 weeks after Day 1	10 to 16 months, i.e. 300 to 509 days, after Day 1
18-month follow-up visit	18 months ± 4 weeks after Day 1	17 to 21 months, i.e. 510 to 659 days, after Day 1

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

Additional unscheduled visits may take place and must be recorded in the CRF.

See also Appendix 7 - Schedule of Study Events (p 82).

6.2. Screening and Baseline Assessment

6.2.1. Screening

Patients who are to participate in the study will be recruited either through active screening, i.e. patients already diagnosed by the mobile teams and referred to the investigational centre, or through passive screening, i.e. patients diagnosed at the investigational centre or nearby.

- In the context of active screening, 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 the Communities; p 59). Specific information concerning the study will 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.
- In the context of passive screening, specific information concerning the study will be provided by static healthcare structures located near the investigational centre in order to refer patients to the investigational centre.

- Diagnosis of HAT and staging of the disease will be performed at the investigational centre.

The following diagnostic tests will be performed at the investigational centre between Day -15 and Day -1 to confirm the diagnosis of HAT:

- Serological testing (RDT or CATT);
- Collection of blood and/or lymph samples for testing for parasites;

If a patient has been diagnosed as HAT-positive in the context of another clinical study sponsored by DNDi, the results of diagnostic tests, i.e. blood and/or lymph samples or lumbar puncture, can be used in the present study if they were performed less than 7 days before Screening.

Patients will be invited to participate in the study and the Investigator (or a designee) will provide the information required to collect the patient's informed consent. Once the patient has signed the informed consent, s/he will be considered as a "screened patient" and s/he will receive a patient ID number.

6.2.2. Baseline Assessment

Whether the patient is being considered for treatment in hospital or as an out-patient, the following procedures will be performed between Day -15 and Day -1 in order to stage the disease, to collect medical history and safety data, and to check the inclusion and non-inclusion criteria.

- Collection of informed consent / assent prior to administering any additional medication or to performing any non-routine assessment;
- Collection of CSF sample for WBC and disease staging;
- Karnofsky Performance Status,
- Review of inclusion and non-inclusion criteria
- Collection of demographic data;
- Collection of full medical history;
- Collection of signs and symptoms of HAT, in particular severity and time since the start of symptoms;
- Vital signs: body temperature, blood pressure, heart rate and respiratory rate;
- Diagnosis of malaria using RDT and/or thick blood smear and, if the result is positive, administration of antimalarial treatment;
- Treatment of helminthiasis, according to routine practices;
- Collection of concomitant medication;
- Physical and neurological examinations;

- Laboratory safety assessments (see Appendix 3 – Laboratory Tests; p 75) – when possible, samples will be collected in the morning from patients in the fasting state;
  - Haemoglobin;
  - Haematology: WBC, platelet count;
  - Biochemistry: albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), chloride, creatinine, glucose, potassium, sodium, calcium, total bilirubin, bicarbonates and total protein;
  - Urine analysis (leucocytes, nitrites, pH, protein, glucose, ketone bodies, urobilinogen, bilirubin, blood and haemoglobin);
- Urine pregnancy test for women of child-bearing potential, to be done on Day -1;
- Triplicate digital ECG (CarTouch®), to be done on Day -1;
- Collection of SAEs.

6.3. IMP Dispensing: Day 0

If the patient is to be treated on an out-patient basis, the following procedures will be performed before s/he returns home to begin treatment.

- Check that all procedures for baseline assessment have been performed.
- Dispensing of IMP and, before returning home, reminder concerning instructions for taking the IMP and interview with Investigator to collect responses to questionnaire and ensure good understanding of the instructions by the patient and/or the caregiver;
- Collection of SAEs since signature of informed consent.

6.4. Procedures during Treatment Period for Patients Treated In Hospital: Day 1 to Day 10

6.4.1. Clinical Signs and Symptoms

- Patients will be questioned each day concerning possible AEs during the hospitalisation period and at each subsequent follow-up visit (see Section 6.8 Safety Assessments, Definitions; p 40);
- Collection of concomitant medication.

If indicated by the patient's clinical status, the following procedures will be performed on Day 8:

- Vital signs: body temperature, blood pressure, heart rate and respiratory rate;

- Physical and neurological examinations.

6.4.2. ECG Recordings

Two digital ECGs (CarTouch®) will be recorded in triplicate to assess QT-interval:

- 4 hours after intake of IMP on Day 4;
- 23 hours after intake of IMP, i.e. 1 hour before intake of IMP on Day 5.

6.4.3. PK Analyses

The procedure for sampling and the assay method will be described in the Laboratory Manual.

During the treatment phase, four samples will be collected for PK analyses.

Whole blood, approximately 2 mL each time, collected by venipuncture will be deposited on filter paper using the dry blood spot (DBS) technique at the following timepoints:

Table 3 – PK Sampling Times during the Treatment Period

Ideal timing for sample collection	Acceptable leeway
Day 8: 3 hours 15 minutes after intake of the IMP	± 15 min
Day 9: 3 hours after intake of the IMP	± 15 min
Day 10: 3 hours and 7 hour 15 minutes after intake of the IMP	± 15 min

6.5. Treatment Period for Patients Treated on an Out-patient Basis

Patients treated on an out-patient basis who require hospitalisation, for whatever reason, will undergo the same procedures as patients initially treated in hospital, up to the end of the hospitalisation period, as provided for in the protocol. During this period, and up to Day 13 or Day 18, the reasons for hospitalisation will not be considered to be SAEs solely based on the criterion of hospitalisation, but may be considered to be SAEs based on other criteria (see Section 6.8.1).

PK sampling should be performed at any unscheduled visit between Day 1 and Day 10, regardless of the day on which the visit takes place.

6.6. Procedures at the EoT Visit – Day 11

Whether the patient is being treated in hospital or as an out-patient, the following procedures will be performed at the EoT visit on Day 11:

- Collection of blood and/or lymph samples for testing for parasites;
- Collection of signs and symptoms of HAT, if any;
- Karnofsky Performance Status;
- Vital signs: body temperature, blood pressure, heart rate and respiratory rate;
- Physical and neurological examinations;
- Collection of concomitant medication and AEs;
- Urine pregnancy test for women of child-bearing potential;
- Laboratory safety assessments (see Appendix 3 – Laboratory Tests; p 75) – when possible, samples will be collected in the morning from patients in the fasting state;
  - Haemoglobin;
  - Haematology: WBC, platelet count;
  - Biochemistry: albumin, ALP, ALT, AST, BUN, chloride, creatinine, glucose, potassium, sodium, calcium, total bilirubin, bicarbonates and total protein;
  - Urine analysis (leucocytes, nitrites, pH, protein, glucose, ketone bodies, urobilinogen, bilirubin, blood and haemoglobin);
- Triplicate digital ECG (CarTouch®);
- Collection of blood sample 24 hours after the last intake of the IMP (Day 11) for PK analyses. If the patient was treated on an out-patient basis, the sample will be used to check treatment compliance. If the patient was treated in hospital, a second blood sample will be collected 48 hours (Day 12) after the last intake of the IMP for PK analyses.

Table 4 – PK Sampling Times at the End of the Treatment Period

Ideal timing for sample collection	Acceptable leeway
Day 11: 24 hours after the last intake of the IMP	± 1 hour
Day 12: 48 hours after the last intake of the IMP (only for patients treated in hospital)	± 1 hour

If the patient was treated on an out-patient basis, the following procedures will be performed:

- Interview for collection of AEs observed by the patient during the treatment period and collection of concomitant medication;
- Interview for compliance with accountability of fexinidazole tablets;
- Questionnaire to assess acceptability of packaging of IMP.

6.7. Procedures at Follow-up Visits

6.7.1. Procedures at EoH Visit - Day 13 to Day 18

If the patient was treated in hospital, the following procedures will be performed on the day of discharge:

- Vital signs: body temperature, blood pressure, heart rate and respiratory rate;
- Physical and neurological examinations;
- Collection of concomitant medication and AEs.

6.7.2. Procedures at Follow-up Visits at 3, 6, 12 and 18 months

Whether the patient is being treated in hospital or as an out-patient, the following procedures will be performed at Follow-up Visits at 3, 6, 12 and 18 months:

- Collection of blood and/or lymph samples for testing for parasites;
- Collection of CSF for WBC and detection of trypanosomes. At the 3-month follow-up visit, lumbar puncture will be performed only if indicated by the patient's clinical status;
- Collection of signs and symptoms of HAT, if any;
- Karnofsky Performance Status;
- Vital signs: body temperature, blood pressure, heart rate and respiratory rate;
- Physical and neurological examinations;
- Urine pregnancy test for women of child-bearing potential, only at 3-month and 6-month visits;
- Collection of SAEs
- Collection of non-serious AEs assessed as related to fexinidazole;
- Laboratory safety assessments (see Appendix 3 – Laboratory Tests; p 75) – when possible, samples will be collected in the morning from patients in the fasting state:
  - Haemoglobin;
  - Haematology: WBC, platelet count;

- Biochemistry: albumin, ALP, ALT, AST, BUN, chloride, creatinine, glucose, potassium, sodium, calcium, total bilirubin, bicarbonates and total protein.

Laboratory safety assessments will be performed at the 12-month and 18-month visits only if indicated by the patient's clinical status.

In the event that a patient moves house or is travelling away from home during the follow-up period, the Investigator accompanied by any necessary study team members may travel to the patient's new place of residence in order to perform one or more follow-up visits.

The patient could also attend one or more follow-up visits in another investigational centre or in a satellite centre. The patient would then be managed by the Investigator in the other investigational centre or by the Coordinating Investigator at the PNLTHA.

The site investigator and his/her study team can also travel to the satellite site to monitor the patient.

In that case, the Investigator in the patient's original investigational centre should inform the Coordinating Investigator and the person in charge of monitoring that a visit is planned to take place in a different investigational centre.

Data collected at such visits will then be sent, within a reasonable timeframe after the visit, to the patient's original investigational centre in order to be recorded in the CRF.

The patient's original investigational centre is responsible for entry of the data and retains medical responsibility for the patient.

6.7.3. Procedures at Unscheduled Visits

At any time during the study, the patient may make unscheduled visits to the investigational centre, as required by his/her clinical status. The following procedures may be performed, at the Investigator's discretion:

- Physical and neurological examinations;
- Collection of signs and symptoms of HAT, if any, since the previous visit;
- Investigation of any concomitant condition that could have prompted the visit;
- Collection of blood and/or lymph samples for testing for parasites, if indicated;
- Collection of CSF, only if symptoms suggesting a relapse of HAT are present;
- Additional safety assessments such as ECG, haematology, biochemistry or urine analysis.
- Collection of AEs, in accordance with Section 6.8.4.
- For patients treated on an out-patient basis, blood sampling for PK analysis in the event of an unscheduled visit between Day 1 and Day 11.

6.8. Safety Assessments

6.8.1. Definitions

Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory test or ECG finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The definition of an AE includes worsening of any pre-existing conditions or any abnormality on a test procedure (e.g. ECG) or laboratory test (haematology, biochemistry) that occurs or worsens (in severity or frequency) after starting the IMP and that the Investigator considers to be clinically significant, unless it is associated with a previously reported clinical event.

Of note, lack of efficacy is not an AE.

Laboratory test abnormalities may be considered to be “clinically significant”, and should therefore be reported as AEs, if they fulfil any of the following criteria:

- The abnormality suggests a disease and/or organ toxicity and the abnormality was not present at baseline or is considered to have worsened abnormally from baseline,
- The abnormality leads to discontinuation of the IMP,
- The abnormality requires a medical intervention or treatment.

Serious Adverse Event

A serious adverse event (SAE) is any event that:

- results in death;
  - i.e. causes or contributes to death;
- is life-threatening;
  - i.e. in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it had been more severe;
- requires hospitalisation or prolongation of existing hospitalisation;
  - i.e. the AE required hospitalisation for at least 24 hours or prolonged hospitalisation beyond the duration initially expected. Hospitalisation for surgery planned prior to study entry, for social reasons, for elective surgery

(e.g. cosmetic surgery) or in the context of usual management of the disease (including treatment adjustment) will not be considered as an SAE. Similarly, hospitalisation of patients initially treated on an out-patient basis will not be considered as an SAE solely based on the criterion of hospitalisation because, in accordance with Section 6.5, they are to remain in hospital, as are patients initially hospitalised, up to Day 13 or 18. The other seriousness criteria remain valid. This includes hospitalisation for reasons related to non-compliance with treatment, including for a non-serious AE based on the other seriousness criteria;

- results in persistent or significant disability or incapacity;
  - i.e. an AE that leads to significant impairment of the patient's ability to carry out normal activities;
- is a congenital anomaly or birth defect in the child or foetus of a female patient exposed to treatment prior to conception or during pregnancy;
- is an important medical event, i.e. an event that may not be immediately life-threatening or result in death, but that jeopardises the patient's safety or requires an intervention to prevent one of the outcomes above.

In the study, ALT or AST levels above 3 ULN associated with total bilirubin above 2 ULN will be considered to be SAEs.

Any suspected transmission of an infectious agent via the IMP will also be considered as an SAE.

Any other event defined as serious in the protocol will be reported as an AE and as an SAE in accordance with the procedure described in Section 6.8.5.

For the purposes of the study, hospitalisation for non-complicated delivery will not be considered as an SAE.

6.8.2. Collection of Information on AEs

AEs may be observed directly by the medical personnel or spontaneously reported by the patient or his/her caregiver. For patients treated in hospital, potential AEs will be collected by the medical personnel each day during the treatment period and up to the EoH visit. The Investigator or qualified study personnel should examine any patient who experiences an AE as soon as possible. All medical measures necessary to ensure the patient's safety and well-being must be implemented. For patients treated on an out-patient basis, potential AEs that occur during the treatment period will be collected at the EoT visit, i.e. Day 11, or at any unscheduled visit to the centre between Day 1 and Day 11.

After the end of the periods mentioned above, AEs will be collected as described in Section 6.8.4.

Information on AEs will be recorded in the corresponding section of the CRF using concise medical terms and avoiding vague, ambiguous or colloquial language. When a clinically significant laboratory abnormality is reported, whenever possible, a clinical diagnosis should be reported as the AE rather than simply an abnormal value, e.g. “anaemia” instead of “reduced red blood cell count”.

6.8.3. Follow-up on AEs

Any AE must be followed up until it resolves, until the Investigator considers it to be “stable” or “chronic”, or until the end of the patient’s participation in the study, i.e. until the end-of-study page of the CRF for the patient has been completed.

If the AE is a clinically significant laboratory test abnormality, a repeat test is to be performed 2 to 4 days later and then at regular intervals until the value returns to normal or to the baseline level.

6.8.4. AE Collection Period

The collection period for AEs that occur in the context of the study is defined as follows:

- For **any AE** that is not considered to be an SAE: from the first intake of fexinidazole on Day 1 **until the EoH visit** (Day 13-18) for patients treated in hospital. For patients treated on an out-patient basis, the observation period extends to the EoT visit (Day 11).
- For **any SAE**: from the time of enrolment of the patient in the study (i.e. after signing the informed consent) and **until the end of follow-up** (18 months).

AEs that occur during the Screening period (after signing the informed consent) prior to the start of treatment and that are considered to be related (i.e. a reasonable possibility) to participation in the study, will also be collected by the medical personnel and recorded in the CRF.

In addition, any non-serious AE that occurs after the collection period and that the Investigator considers to be related (i.e. a reasonable possibility) to the IMP, must also be collected.

6.8.5. Reporting Requirement for AEs

Information on AEs must be assessed by a physician. The Investigator must determine whether the AE is considered to be serious or not, if necessary with the assistance of the Coordinating Investigator and the study monitor. This classification will determine the reporting procedure for the event.

All SAEs must be reported to the study monitor **immediately, and at the latest 24 hours** after the Investigator becomes aware of the event. The information must be reported, initially, by telephone and/or Short Messaging Service (SMS), and then using the SAE reporting form, which is to be sent by e-mail. The report must

include the nature of the SAE (if possible a clinical diagnosis), the date and nature of onset, duration, severity, relationship to IMP (assessed with the assistance of the Coordinating Investigator, as needed; reasonable possibility see Section 6.8.7.), measures taken and outcome, as well as any other relevant clinical or laboratory data.

Additional information must be sent as soon as it becomes available, using the SAE follow-up reporting form. All follow-up reports must be sent as quickly 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, specifying the outcome of the SAE as “recovery”, “recovery with sequelae”, “death” etc.

SAEs must be reported using the AE reporting form in the CRF and the SAE reporting form. It should be noted that the SAE reporting 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 responsible for reporting suspected unexpected serious adverse reactions (SUSARs), considered to be related to the IMP (reasonable possibility), as well as all SAEs, to the Ethics Committee of the country and to other appropriate governing bodies in accordance with national regulatory requirements.

The Sponsor will be responsible for reporting SUSARs and SAEs to the regulatory authorities in accordance with current regulations. The Investigator Brochure will be used as the reference safety information on the IMP, and the expectedness of Aes will be assessed by the Sponsor using this information.

6.8.6. Grading of AE Severity

The severity of the AE will be graded according to NCI CTCAE, version 4.03 (14) and, for certain laboratory parameters, modified CTCAE (see Appendix 6- CTCAE v4.03 adapted, p 81). 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	The patient is conscious of the event or symptom, which is easily tolerated; the event does not lead to any reduction in the patient’s activities of daily life.
Moderate	The patient feels discomfort such that it reduces or interferes with the patient’s activities of daily life.
Severe	Significant functional impairment: the patient is unable to carry out activities of daily life and/or the event is life threatening.

Information on the severity of the AE must be recorded in the Adverse Events section of the CRF.

It is important to distinguish between the severity and the seriousness of an AE: a severe AE is not necessarily a serious AE, since the criteria for seriousness (see Section 6.8.1 Definitions, Serious Adverse Event; p 40) are different from the criteria for severity.

6.8.7. Assessment of AE Causality

For each AE, the Investigator must assess the possible causal relationship between the IMP and the AE, with the assistance of the Coordinating Investigator, in order to determine whether there is a reasonable possibility that the IMP caused or contributed to the AE.

The causal relationship between the IMP 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 medication, the temporal relationship between intake of the IMP and onset or worsening of the AE, and the known patterns of response to fexinidazole in general.

The two types of causal relationships are defined as follows:

- Not related: there is no reasonable possibility of a causal relationship.
- Related: there is at least a reasonable possibility of a causal relationship between the IMP and the AE. This means that there are facts (evidence) or features that suggest a causal relationship.

6.8.8. Exposure *in utero*

Four pregnancy tests are planned during the study: at Screening (Day -1), at the EoT visit (Day 11), and at the 3-month and 6-month follow-up visits. Pregnancy is not a non-inclusion criterion. Women in the second or third trimester of pregnancy will be allowed to participate in the study, however they will be treated in hospital. First-trimester pregnancy is considered to be a temporary non-inclusion criterion (see Section 4.2 Non-inclusion Criteria; p 26).

Pregnancy is not considered to be an AE, regardless of when it is detected.

Nevertheless, the Investigator must report any pregnancy that occurs during the treatment period or that is detected at the 3-month or 6-month follow-up visits, using the appropriate Pregnancy Reporting Form. The pregnancy must be reported whether or not an AE occurred. If known, the due date should be specified.

The Investigator must monitor the patient until the term of the pregnancy, i.e. full term or preterm, in the event of a miscarriage. The Investigator must 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 Newborn Follow-up Form. The child's age must be collected and recorded on the form. The child will undergo diagnostic testing, in accordance with PNLTHA procedures, in order to rule out vertical transmission of the parasite. If the child is found to be HAT-positive, s/he will be managed by the PNLTHA.

The Investigator will offer the patient follow-up on infants exposed to the IMP *in utero* until they reach 24 months of age. As far as possible, stillborn infants should be examined by a physician to ascertain the cause of death.

Any SAE that occurs in a pregnant patient (exposed to the IMP or who is found to be pregnant any time up to the 18-month visit) or that concerns the pregnancy or the foetus, will be reported using the SAE reporting form in the same manner as any other SAE. Any non-serious AE concerning a pregnant patient that occurs during the AE reporting period will be collected using the AE form in the CRF (see Section 6.8.4. AE Collection Period, p 42).

6.8.9. Exposure During Breastfeeding

The Investigator will offer the patient follow-up on infants exposed to the IMP via breastfeeding, until they reach 24 months of age. Follow-up will be recorded using the Newborn Follow-up Form, where the child's age must be recorded.

The child will undergo diagnostic testing, in accordance with routine practice, in order to rule out transmission of the parasite via the mother's milk.

If the child is found to be HAT-positive, s/he will be managed by the PNLTHA.

7. Study Duration

Based on an enrolment period of approximately 36 months and a follow-up period of 18 months, the duration of the study will be 54 months.

Each patient's participation in the study will last approximately 19 months and will include:

- a Screening period (including treatment of concomitant disease) of up to 15 days;
- a treatment period of 10 days;
- an in-hospital follow-up period of 3 to 8 days;
- an out-patient follow-up period of 18 months.

8. Withdrawal Criteria

8.1. Temporary Interruption of Treatment

Patients treated on an out-patient basis must not under any circumstances discontinue treatment, even temporarily. However, if temporary interruption of treatment seems inevitable, the patient must contact the Investigator or come to the investigational centre before interrupting treatment. The Investigator will decide on the appropriate course of action and will inform the Sponsor as quickly as possible.

Temporary interruption of treatment will not necessarily lead to patient withdrawal 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. One additional day of treatment will be added to make up for the missed dose, and the EoT visit will take place on Day 12. 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 CRF.

8.2. Definitive Discontinuation of Treatment

The Investigator, in agreement with the Principal Investigator, will discontinue the study treatment in the following cases:

- Severe skin reaction;
- ALT or AST > 8 ULN;
- ALT or AST > 3 ULN in association with total bilirubin > 2 ULN;
- ALT or AST > 3 ULN in association with fatigue, nausea, vomiting, abdominal pain or tenderness in the right upper quadrant, fever, rash and/or eosinophilia (> 5%);
- Any condition that requires treatment discontinuation for medical reasons, as decided by the Investigator.

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 the 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 withdraws his/her consent, the Investigator must ensure the patients safety and well-being and take appropriate measures. When possible, the Investigator should perform an end-of-study examination.

If a patient decides to withdraw from the study, the Investigator must ensure that withdrawal is not related to an AE. If a patient withdraws from the study due to an AE, all measures must be taken as needed to clearly document the outcome of the AE.

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

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 possible measures must be taken to contact him/her. In all cases, the Investigator must take all possible measures to document the course of the patient's condition.

9. Data Analysis and Statistical Methods

A first draft of the full Statistical Analysis Plan (SAP) will be prepared. It will provide a more detailed description of the statistical methods. The SAP will be reviewed and, if necessary, amended prior to final database lock. Successive versions will be dated and numbered.

9.1. Sample Size Determination

The sample size determination is based on the primary analysis. The expected success rate is between 87% and 91% depending on the percentage of early-stage patients included in the sample. The success rate for patients with late-stage HAT should be slightly below the expected success rate of 89% in the pivotal study, DNDIHATFEX004, which has a restricted, more homogeneous population.

As concerns early-stage patients, a meta-analysis performed by Hümbelin (11), on a sample of 2524 patients treated with pentamidine and indexed in the databases of four non-governmental organisations showed a relapse rate (presence of trypanosomes or CSF WBC ≥ 20/µL) of 5.63% in patients followed for 6 months or less (142/2524), 8.20% in patients followed for 12 months or less (207/2524) and 9.23% in patients followed for 18 months or less. The expected success rate for early-stage patients should be close to 92%.

A sample size of 174 patients provides a precision of ± 5% in the estimate if the expected success rate is 87% and if a Wald confidence interval is used.

Because the confidence interval will be calculated with an exact method (Clopper-Pearson approach) the lower arm of the 95% CI will be longer than the upper arm. The precision for the lower arm will be close to 6% and that of the upper arm will be close to 4.5 % if we consider an expected success rate of 87%. The precision will be greater if the success rate is higher.

9.2. Definition of Study Populations included in the Analyses

Three patient populations will be used in the statistical analyses, as follows:

- The intent-to-treat (ITT) population, comprising all patients included in the study, regardless of whether or not they took the IMP;
- The modified intent-to-treat (mITT) population, comprising all patients who took at least one tablet of fexinidazole;
- The per protocol (PP) population, comprising all patients who completed the study in accordance with the protocol with no major violations that could interfere with the efficacy evaluation. Premature withdrawal from the study due to treatment inefficacy or intolerance will not be considered as a protocol violation.

9.3. Patient Disposition

At the end of the study, the following categories of patients will be described:

- Number of patients who underwent Screening;
- Number of patients who were not included in the study due to non-fulfilment of eligibility criteria, and reasons for non-inclusion;
- Number of patients included (i.e. who signed the Informed Consent form, ITT patients);
- Number of patients included by stage of HAT and by treatment modality, i.e. in hospital or on an out-patient basis;
- Number of patients included who took at least one tablet of fexinidazole (mITT patients) by disease stage;
- Number of patients included, by disease stage, who completed treatment and who received all of the protocol-planned doses (treatment completers);
- Number of patients included, by disease stage, who took at least one tablet of fexinidazole, excepting those who died for reasons clearly unrelated to efficacy or safety of the IMP (evaluable patients);
- Number of patients included, by disease stage, with no major protocol violations (PP patients);
- Number of patients included, by disease stage, treated on an out-patient basis, who:
    - temporarily interrupted treatment,
    - prematurely discontinued treatment,
    - were hospitalised for reasons related to non-compliance,
    - were hospitalised for a safety problem (non-exhaustive list);

- Number of patients included, by disease stage, who underwent the following visits:
  - Screening,
  - Dispensing (Day 0), for patients treated an out-patient basis,
  - Visits during Treatment Period (Day 1 to Day 10),
  - EoT Visit,
  - EoH Visit (Day 13 to Day 18), for patients treated in hospital,
  - 3-month Follow-up Visit,
  - 6-month Follow-up Visit,
  - 12-month Follow-up Visit,
  - 18-month Follow-up Visit.
- Number of patients included, by disease stage, withdrawn from the study, categorised by reason for withdrawal.

9.4. Description of Patients at Baseline

Descriptive statistics (n, mean, standard deviation, median, minimum, maximum) or frequencies and percentages will be presented for the following patient baseline characteristics, by disease stage and overall:

- Demographic data
- Medical history
- Physical examination
- Vital signs
- Urine pregnancy test (for women of child-bearing potential)
- Laboratory tests
- Karnofsky Performance Status (separating patients treated on an out-patient basis and patients treated in hospital)
- Neurological examination
- Concomitant medication

9.5. Effectiveness Analyses

9.5.1. Primary Analysis - Effectiveness

The primary analysis will be performed on the mITT population. The success rate at 12 months and the success rate at 18 months will be estimated, bearing in mind that 18 months provides a more reliable estimate of the cure rate. The 95% exact confidence interval of the percentage will be provided.

9.5.2. Sensitivity Analysis

The success rates at 12 and 18 months will be estimated along with the 95% exact confidence intervals on the per protocol population of patients.

9.5.3. Secondary Analysis - Effectiveness

The success rates at 12 and 18 months will be estimated in the sub-group of early-stage patients as well as the sub-group of late-stage patients. The Clopper-Pearson (exact) 95% confidence interval will be provided. The expected success rate in late-stage patients is slightly higher than that in early-stage patients, however, given the precision of the estimates, the observed rate may be lower. The proportion of early-stage patients in the study sample will also be estimated.

9.6. Secondary Analyses

9.6.1. Secondary Analysis - Safety

The secondary safety analyses will be performed on the mITT population, i.e. all patients who took at least one tablet of fexinidazole.

The proportion of patients who experienced an SAE and/or an AE leading to treatment discontinuation will be described by system-organ class using Medical Dictionary for Regulatory Affairs (MedDRA) terms and/or NCI CTCAE, version 4.03 (14) and, for certain laboratory parameters, modified CTCAE will be used (see Appendix 6 – CTCAE v4.03 adapted, p 81).

The proportion of patients who experienced at least one AE will be described. Events described using the same term and that occur several times in the same patient will be counted only once. If a patient experiences several events described with the same term, the event with the maximal severity will be included in the analysis. In addition, each SAE will be described in a narrative presenting all aspects of the medical event and the causality assessment.

The incidence of AEs and of SAEs and their respective 95% confidence intervals will be presented 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 described individually, indicating the proportions of patients by category corresponding to the size of the increase in relation to the ULN for liver function tests (< 1 ULN, 1–2 ULN, 2–3 ULN etc.). Scatter graphs with baseline values on the x-axis and post-treatment values on the y-axis with the bisector indicating the absence of change will be presented. Changes in blood levels over time will be presented in graphs. Shift tables will be provided to supplement signal detection. A listing of patients with clinically significant increases in laboratory parameters will be provided.

Abnormalities, if any, on ECG tracings recorded on Day 11 will be described.

The proportion of patients hospitalised for a safety problem, including overdose, will also be presented.

9.6.2. Secondary Analysis - Compliance

Compliance will be assessed on the sub-group of out-patients from the ITT population, i.e. all patients who were considered as eligible for treatment on an out-patient basis and to whom the IMP was dispensed, regardless of whether or not they took the IMP.

The number and percentage of patients in whom the presence of fexinidazole or its main metabolites was detected in the blood sample collected on D11 will be presented, as well as the success rate in this sub-group of patients and in the sub-group of patients in whom no trace of fexinidazole or its main metabolites was detected. The distribution of the frequency of patients with unused tablets remaining at the end of the treatment period will be presented, and the relation between the success rate and the number of tablets remaining will be determined using a logistical regression or a sub-group analysis. The distribution of the frequencies of responses from patients during the compliance interview will be presented.

The information provided by the PK analyses, the number of tablets remaining and the questionnaire will be combined to define perfect compliance and non-compliance. Perfect compliance corresponds to a patient in whom fexinidazole is detected in the blood, who has no remaining tablets and whose report on full compliance with treatment seems unquestionable. The success rate in patients with perfect compliance will be compared to that in non-compliant patients.

9.6.3. Secondary Analysis - Feasibility

The secondary analyses concerning the feasibility of patient self-management of treatment intake under recommended conditions will be performed on the sub-group of out-patients from the ITT population, i.e. all patients who were considered as eligible for treatment on an out-patient basis and to whom the IMP was dispensed, regardless of whether or not they took the IMP. The endpoints analysed will be as follows:

- Number and proportion of patients who temporarily interrupted treatment;
- Number and proportion of patients who prematurely discontinued treatment;
- Number and proportion of patients who delayed starting treatment;
- Number and proportion of patients who mislaid treatment units;
- Number and proportion of patients who were hospitalised for reasons related to non-compliance.

For each of the endpoints, the proportion of patients will be presented with the 95% Confidence Interval (CI).

9.6.4. Secondary Analysis - Packaging

Descriptive results will be presented for the questionnaire completed by the patient and/or caregiver at the dispensing visit (Day 0) and at the EoT visit (Day 11) for the patients treated on an out-patient basis (sub-group of out-patients from the ITT population).

9.6.5. Secondary Analysis - PK

The secondary analyses concerning PK will be performed on the sub-group of patients treated in hospital. Concentrations of fexinidazole and its metabolites in whole blood, as well as estimates of PK parameters derived from a population model will be presented. The data will provide confirmation of data from phase-I studies on a larger scale and, in particular, will provide confirmation that data in patients not included in earlier studies (e.g. pregnant or breastfeeding women) are consistent with those in patients in other studies. PK parameters in patients considered to be treatment failures or who experienced intolerance to fexinidazole will be described individually.

9.7. Interim Analyses

No interim analysis is planned for this study.

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

The endpoints are based on the outcome at 18 months.

For patients who attended the 18-month visit, but who refused the lumbar puncture planned at the visit, the **primary imputation method** will consist in checking for signs or symptoms of HAT. If no signs or symptoms of HAT are present and trypanosomes are negative, and if the outcome was considered as favourable at the last available assessment, the patients will be considered as treatment successes.

If these criteria are not fulfilled, the patients will be considered as treatment failures. The outcome for patients who did not attend the 18-month visit or later will also be considered as a failure, except for patients who fled the region due to armed conflict or natural disaster.

For the analysis at 12 months, if the lumbar puncture at 12 months is missing, data from the last available assessment will be used:

- the outcome at 18 months will be used, if a lumbar puncture was performed at that visit.

- if a lumbar puncture was performed at 6 months, but not at 18 months, the patient will be considered as a success if the CSF WBC was ≤ 5/µL and lower as compared to prior values, if no trypanosomes were detected and if no HAT-related symptoms were present at 12 months.
- if a lumbar puncture was performed at 6 months and at 18 months, the outcome at 18 months will prevail.

In situations other than those described above and if no lumbar puncture is available after the start of treatment, the patients will be considered as failures.

9.9. Handling of Centres

The primary analysis will not be stratified by centre because the weight of each centre in the overall population is unknown. Nevertheless, the results by centre will be presented and a test of homogeneity (a likelihood-ratio test) will be performed on the success rates. A centre effect is entirely possible. In this case, an estimate of the overall success rate will also be provided, giving equal weight to each centre rather than weighting the centres based on the number of patients. The estimate of the rate will be given by $p = \sum W_h\, p_h$ where W_h is the weight of each centre, i.e. the inverse of the number (k) of the centre (k^{-1}). La variance of the estimator will be equal to $Var(P_h) = \sum W_h^2.\ p_h(1-p_h) / n_h$ where n_h is the number of patients in centre h. In addition, a Forest plot will be presented to determine whether the heterogeneity is quantitative (dispersion around a central value) or qualitative (presence of entirely atypical centres).

10. Data and Safety Monitoring Board

A DSMB, composed of at least 3 members independent of the Investigators and the Sponsor, will be set up prior to the start of the study. The DSMB will monitor the study in order to minimise any risk of harm to the patients included in the study. At each of its meetings, the DSMB will examine safety data at predetermined intervals and all information related to SAEs, and will issue recommendations regarding the study if the benefit-to-risk ratio for patients seems to be in jeopardy. The data and the intervals for review will be decided before, or shortly after the start of the study and will be recorded in the DSMB Charter.

The organisation of the DSMB will be described in the DSMB Charter, which will be prepared and approved prior to the first planned meeting.

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.

11. Quality Assurance and Quality Control Procedures

11.1. Investigator Site File

The Investigator must maintain appropriate accurate records to ensure that all aspects of study conduct 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.

The Investigator's Site File must contain the protocol and protocol amendments, Independent Ethics Committee (IEC) and regulatory approval with all correspondence, a copy of the patient information and informed consent form, the Investigator Brochure, drug accountability records, Curriculum Vitae (CV) for study personnel, as well as authorisation forms and any other relevant documents or correspondence in accordance with Good Clinical Practice (GCP) and the Sponsor's standard operating procedures.

11.2. Case Report Forms

Data will be collected by laboratory technicians, physicians, nursing staff or care-providers authorised by the Investigator. Data collection will be supervised by the Investigator. Study-specific information will be entered in a CRF in paper format. Data generated from this information must be consistent with the source documents and any discrepancies must be accounted for. All data that are recorded directly in the CRF must be rendered anonymous, i.e. such that they can only be identified by the patient's number.

The Investigator must ensure the accuracy, completeness, legibility and timely entry of all data reported to the Sponsor via the CRF, as well as any additional information that may be requested. The Investigator is responsible for ensuring that all informed consent forms and screening forms for all patients are stored in a secure location. After each visit, data will be entered in the CRF, scanned and sent by Internet to the data manager for entry (double data entry) in the database. The CRF will be signed by the Investigator as the study advances and the CRF pages are sent.

11.3. Source Documents

The data in the CRF must be verified by direct inspection of the source documents. The source documents are the patient's 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, recorded images of microscopic examinations and patient screening/enrolment logs. The questionnaires on D0 and D11 on product packaging are also considered as source documents.

In the study, 100% source document verification will not be carried out. Instead, the focus will be on monitoring for data consistency (cf. the monitoring plan).

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 the Sponsor / designated clinical monitors and/or by the Regulatory Authorities, if appropriate.

11.4. Retention of Documents

The Investigator must retain all essential documents for at least 25 years after the official stop date of clinical development of the IMP. 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 the Sponsor. 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 the Sponsor, subject to local regulations.

The Sponsor must be notified in advance if the Investigator plans to assign the study records to another party or move them to another location.

11.5. Monitoring

Clinical monitors will perform regular monitoring visits during which they will verify source data, Informed Consent Forms, medical records, laboratory test 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 representatives of the Sponsor 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 and SAE forms or information provided in response to queries from the Pharmacovigilance Unit at DNDi. The clinical monitor will be responsible for inspecting the CRFs at regular intervals. The Investigator will ensure that the Sponsor’s 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 the Sponsor 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 visit are planned: a site assessment visit, an initiation visit, monitoring visits and a close-out visit.

In addition, data quality will be checked on a regular basis by representatives of the Sponsor in the context of centralised monitoring in order to detect any missing data, inconsistencies, discrepancies and deviations, with analysis of the performance of the investigational centres in order to adapt and/or optimise the monitoring visits and to implement corrective and/or preventive actions, including the need for training, depending on the risks identified and/or deficiencies observed.

11.6. Audits and Inspections

The investigational centre may also be subject to quality assurance audits by the Sponsor or designated representatives, and/or to inspection by regulatory authorities or IEC members.

The purpose of the audits and/or inspections is to verify adherence to the protocol and to ensure that 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 gives informed consent to participate in the study. A paper CRF will be used in the study. The study data will be stored in a computer database that ensures confidentiality of the data, in accordance with national legislation on data protection.

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

The clinical monitor will monitor the data continuously. Data queries will be generated, documented and resolved continuously throughout the study.

11.8. Data Confidentiality

The Investigator must 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 or imaging submitted to the Sponsor. Only the patient number should appear. The Investigator must keep a patient enrolment log containing the number, name and address of patients. The Investigator must ensure the confidentiality of all documents submitted to the Sponsor’s authorised representatives, including the signed informed consent form.

The findings of any assessments, including laboratory tests, will remain strictly confidential to the patient him/herself, except in the case of patients under legal age and vulnerable patients whose findings will also be communicated to the legal representative. 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. A favourable opinion 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 danger 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 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;
- 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 fullest 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 centre 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 68) and International Council on Harmonisation (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 submitted by the Principal Investigator for official approval to the Ethics Committee of the Protestant University in Congo and to the National Ethics Committee for Health Research in Guinea (CNERS) .

Approval must be received from the Ethics Committee prior to performing any study-specific procedures on any patient.

Any changes made to the protocol after it has been approved by the IEC must be submitted in writing to the IEC by the Principal Investigator in accordance with local procedures and regulatory requirements in effect (see Section 12 Protocol Amendments; p57).

The protocol must be submitted along with the appendices related to the information and safety of patients, including the Patient Information Sheet, the Informed Consent/Assent Form and the Investigator Brochure. The set of photo cards provided to Investigators as a visual aid to explain the study procedures will be presented the Ethics Committees. The information sheet for patients and the informed consent/assent form, translated into the local language or a language

understood by the patients will be submitted for official approval from the Ethics Committee.

The protocol has received a positive opinion from the Committee for the Protection of Persons at the Hôpital Necker in Paris, France.

14.1. Information of Communities

The study will be conducted in collaboration with the National Sleeping Sickness Control Program (PNLTHA). The program brings together all activities related to the prevention and treatment of HAT in the DRC, in particular the supervision and coordination of the teams in charge of HAT screening activities (mobile teams and prospect activities). The PNLTHA is fully involved in the design and implementation of the study.

Information of the communities participating in the study will follow the procedures of the PNLTHA.

The following information on the study will be disseminated to the community at various levels:

- 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 availability of a rescue treatment and on concomitant medication 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 for patients treated at hospital;
- Information on organisation of transportation and/or reimbursement of travel costs from their village to the investigational centre for patients included in the study, as well as for the caregiver for patients treated on an out-patient basis;
- 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.

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. Overall Procedure

The patient will not be included in the study until after s/he has given informed consent in writing. It is the responsibility of the Investigator to obtain, for each individual who participates in the study, voluntary written informed consent after having provided adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. For patients under legal age, consent must be obtained from the patient's legal representative. During their visits in the field, the mobile teams will inform the communities of the necessity for children to be accompanied by a legal representative during visits to the investigational centre.

The patient information and the informed consent form will be available in the following national/local languages or the lingua franca : French, Lingala, and Kituba/Kikongo and Tshiluba, corresponding to the languages spoken in the regions where the study is to be conducted. The document will be submitted to the IEC for approval. If the patient does not speak any of the national/local languages or the lingua franca and if a member of the study personal who speaks the patient's local language/dialect has been identified and approved in advance, an *ad hoc* oral translation will be acceptable. The oral translation will be supported by use of the visual aids available. The patient will sign the document corresponding to the lingua franca in his/her country or region. The procedures followed for illiterate patients should be applied. The translation should be documented on the signed consent form (the person who provided the translation will indicate his/her name and the language/dialect used, and will sign the form).

Each centre will ensure that patients fully understand the information and to that end may call upon a "facilitator" who is known to the study team for his/her knowledge of the local language used by patients and for his/her communication skills with patients. Several facilitators may be designated in each centre to cover all local languages/dialects. Visual aids, including photographs, drawings and samples, will also be made available to the Investigator and the facilitator, describing the activities performed during the study, i.e. lumbar puncture, finger pricks, ECG, etc.

The information session will be held in a separate room in order to ensure patient confidentiality, with only one facilitator present.

The patient and his/her caregiver 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 treatment;
- Information on the new drug from prior and on-going studies (safety, PK/PD…)
- 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, compliance with out-patient treatment 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 for patients treated at hospital:
- Patients' rights regarding withdrawal, rescue treatment, additional information, etc.

If the patient or, in the case of patients under legal age, the 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 chooses to take part in the study, the patient or, in the case of patients under legal age, the legal representative will give written consent by signing the form, provided that the Investigator and/or the facilitator is convinced that the patient has fully understood what was explained. If applicable, assent may be requested from children (see Section 14.2.6 Collection of Assent from Children; p 63).

14.2.2. Impartial Witness

An impartial witness must be present when illiterate patients are recruited and/or if the legal representative is illiterate or if the patient is unable to give consent (see Section 14.2.3. Illiterate Patients; p62; Section 14.2.4. Patients Unable to Give Consent; p62; Section 14.2.5. Patients Under Legal Age p62; and Section 14.2.6. Collection of Assent from Children; p63).

The witness should have no connection with the study team, and, whenever possible, should be chosen by the patient. The witness must be literate, i.e. able to read. If the patient does not know 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, and its compliance with the written information in the patient information sheet. The witness must be present throughout the entire information session.

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

14.2.3. Illiterate Patients

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

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

14.2.4. Patients Unable to Give Consent

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

Considering the frequency of such symptoms in late-stage HAT, non-inclusion of these patients could jeopardise the capacity to complete the study.

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

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

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

14.2.5. Patients Under Legal Age

For patients under legal age, i.e. between 15 and 18 years old, considered as adolescents/young adults, the consent of one of their parents or another culturally acceptable, legal representative will be required in addition to their own personal assent. During field visits by the mobile team, adolescents/young adult patients will be advised to come to the study centre accompanied by a legal representative.

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

The form must be signed by both the adolescent/young adult and his/her legal representative. If the patient or the legal representative is illiterate, a fingerprint should replace the signature. If the legal representative is illiterate, an impartial

witness must attend the assent process and the consent process for the legal representative (see Section 14.2.2 Impartial Witness; p 61).

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

14.2.6. Collection of Assent from Children

No specific patient information sheet or specific form will be used to collect assent from children recruited to the study. Instead, priority will be given to oral information in order to adapt the information to what the child is able to understand. It is difficult to obtain assent from children under 14 years of age as children have difficulty weighing up benefits and risks (15). It is, however, easier for a child to refuse to participate than to accept to comply with a protocol. The refusal may be expressed at the time when the protocol is explained or at any time during conduct of the study. Indeed, at any time, the child should be entitled to refuse to undergo an invasive protocol-related procedure, even after having agreed to take part in the study (15, 20). Children will be informed of this at the start of the study and at other appropriate times during the study. If the child subsequently refuses to undergo an invasive procedure, this will not be prejudicial to his/her continued participation in the study, provided that treatment is correctly followed.

Non-assent from the child will prevail if s/he refuses to take part in the study.

14.2.7. Changes in the Benefit-to-Risk Ratio during the Study

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

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

Experimental data suggest that fexinidazole has significant potential for the treatment of *T.b. gambiense* infections.

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

None of the samples will be retained after the end of the study. No biobank is to be set up. All remaining biological material will be destroyed and the destruction procedure will be recorded in a certificate of destruction.

14.4. Costs for Patients

Travel costs to and from the investigational centre will be reimbursed for patients and for the caregivers of patients treated on an out-patient basis, however no compensation will be provided for their participation in the study. For patients treated at hospital, food will be provided free of charge for the in-patient treatment phase. Food may or may not be prepared for the patients, depending on usual practice in each investigational centre. If not, the family will prepare the food. Sufficient food will be provided to cover the needs of the relatives accompanying the patient during hospitalisation.

For follow-up visits, the patients' travels costs will be covered depending on the particular practices in each investigational centre with regard to payment of taxi fares, use of a study-specific vehicle, transport by mobile teams, reimbursement at a flat rate, etc. Missed days of work due to travel for follow-up visits may be compensated, depending on requirements from local IECs.

To ensure that patients are free to decide whether or not to participate in the study, all patients who are diagnosed with HAT and who are treated at hospital will receive food during the in-hospital treatment phase, even if they are not included in the study, regardless of whether this is because they do not fulfil the inclusion criteria or because they do not wish to participate in the study.

Any medication that is required during the study will be provided to the patients free of charge. The WHO List of Essential Medicines and the guides entitled "Clinical Guidelines" and "Essential Medicines" (2013 edition), published by Doctors Without Borders, will be used as reference guides for the treatment of all concomitant conditions. For chronic conditions, the study team will take all necessary measures to ensure that the patient is referred to the most appropriate local healthcare facility in the region for treatment free of charge.

15. Insurance and Liability

DND*i* will take out an insurance policy to cover any claims arising from the study, with the exception of 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. Rapports and Publication

The study will be registered with a recognised international registry of clinical trials, i.e. www.clinicaltrials.gov or the Pan-African Clinical Trials Register.

As a general rule, DND*i* supports the timely communication of all research it sponsors, in accordance with its Policy for External Scientific and Clinical Communications. Thus, the Sponsor will facilitate publication of the findings of this study and/or presentation of the findings during scientific meetings. In this situation, the Investigator agrees to submit any manuscripts or abstracts to the Sponsor in advance. The Sponsor will promote communication of the overall study findings and not of individual findings related to a single investigational site. Any official publication of the study findings for which Sponsor personnel played a more important role than simple monitoring of study conduct will be considered as a joint publication by the Investigator and the Sponsor personnel concerned. The list of authors will be decided by mutual agreement in accordance with the authorship rules of international scientific journals.

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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
53rd WMA General Assembly, Washington, DC, USA, October 2002
55th WMA General Assembly, Tokyo, Japan, October 2004
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

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

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of 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, well-being and rights 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 all 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, Burdens 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 allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially 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 formally 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 mentally 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

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

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

Post-Trial Provisions

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

Research Registration And Publication And Dissemination Of Results

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

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

Unproven Interventions In Clinical Practice

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

Appendix 2 – Karnofsky Performance Status Scale

KARNOFSKY PERFORMANCE STATUS SCALE

Definitions of Rating Criteria (%)

The Karnofsky Performance Scale Index allows patients to be classified in terms of their functional impairment. (16, 8). This can be used to compare effectiveness of different therapies and to assess the prognosis in individual patients. The lower the Karnofsky score, the worse the survival for most serious illnesses.

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

Appendix 3 – Laboratory Tests

Laboratory Tests and Methods

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

Biochemical tests

14 parameters will be analysed:

Albumin	*Calcium*
Alkaline phosphatase	*Glucose*
Alanine aminotransferase	*Bicarbonates*
Aspartate aminotransferase	*Blood urea nitrogen*
Total bilirubin	*Sodium*
Total protein	*Chloride*
Creatinine	*Potassium*

Haematological tests

- *Haemoglobin assay*
- ***White blood cells:*** *count and differential count*
- ***Platelets:*** *count*
- ***Microscope****: full blood cell count (visual count) (see Investigator Manual)*

Urine analysis

- *Urine dipsticks for laboratory safety analyses / Combur 9 Test®*

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

- *Urine pregnancy test*

CSF analysis (see Investigator Manual)

- *Modified Single Centrifugation (MSC): detection of parasites*
- *Counting chamber: WBC count*

Blood parasitology tests (see Investigator Manual)

- *Thick/thin blood smears*
- *Woo test /CTC*
- *mAECT*
- *mAECT-BC*

Quantities of biological fluids required at each sampling timepoint

Screening Visit (Day -15 to Day -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
	Haematology	Haemoglobin	1	20 µL	170 µL (capillary blood[1)])
		WBC	1	20 µL	
		Platelet count	1	10 µL	
		Differential WBC	1	20 µL	
	Biochemistry	14 parameters	1	100 µL	
Lymph	Parasitology	If lymph nodes detectable			
CSF	Parasitology	Modified Single Centrifugation	1	4 mL	4 mL
Urine	Pregnancy		1	5 mL	10 mL
	Urine analysis	Combur 9 Test®	1	5 mL	

End-of-Treatment Visit (Day 11)

	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
	Haematology	Haemoglobin	1	20 µL	170 µL (capillary blood[1)])
		WBC	1	20 µL	
		Platelet count	1	10 µL	
		Differential WBC	1	20 µL	
	Biochemistry	14 parameters	1	100 µL	
Lymph	Parasitology	If lymph nodes detectable			
Urine	Pregnancy		1	5 mL	10 mL
	Urine analysis	Combur 9 Test®	1	5 mL	

Follow-up Visits at 3, 6, 12 and 18 months (per visit)

	Type of test	Specific test	Number of samples	Quantity per sample (approx.)	Total volume 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 (M3 and M6)	Haemoglobin	1	20 µL	170 µL (capillary blood[1)])
		WBC	1	20 µL	
		Platelet count	1	10 µL	
		Differential WBC	1	20 µL	
	Biochemistry (M3 and M6)	14 parameters	1	100 µL	
Lymph	Parasitology	If lymph nodes detectable			
CSF	Parasitology	Modified Single Centrifugation	1	4 mL	4 mL
Urine	Pregnancy (M3 and M6)		1	5 mL	5 mL

Quantity of blood required for PK analyses

Entire study

	Type of test	Number of samples	Quantity per sample (approx.)	Total volume
Blood	PK	6	2mL	12 mL

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

Appendix 4 - Study Schedule

Final protocol available	August 2016
IMP available	October 2016
First patient first visit	November 2016
Duration of recruitment period	36 months
Duration of follow-up period	18 months
Last patient last visit	1st quarter 2021
Final clinical study report	3rd quarter 2021

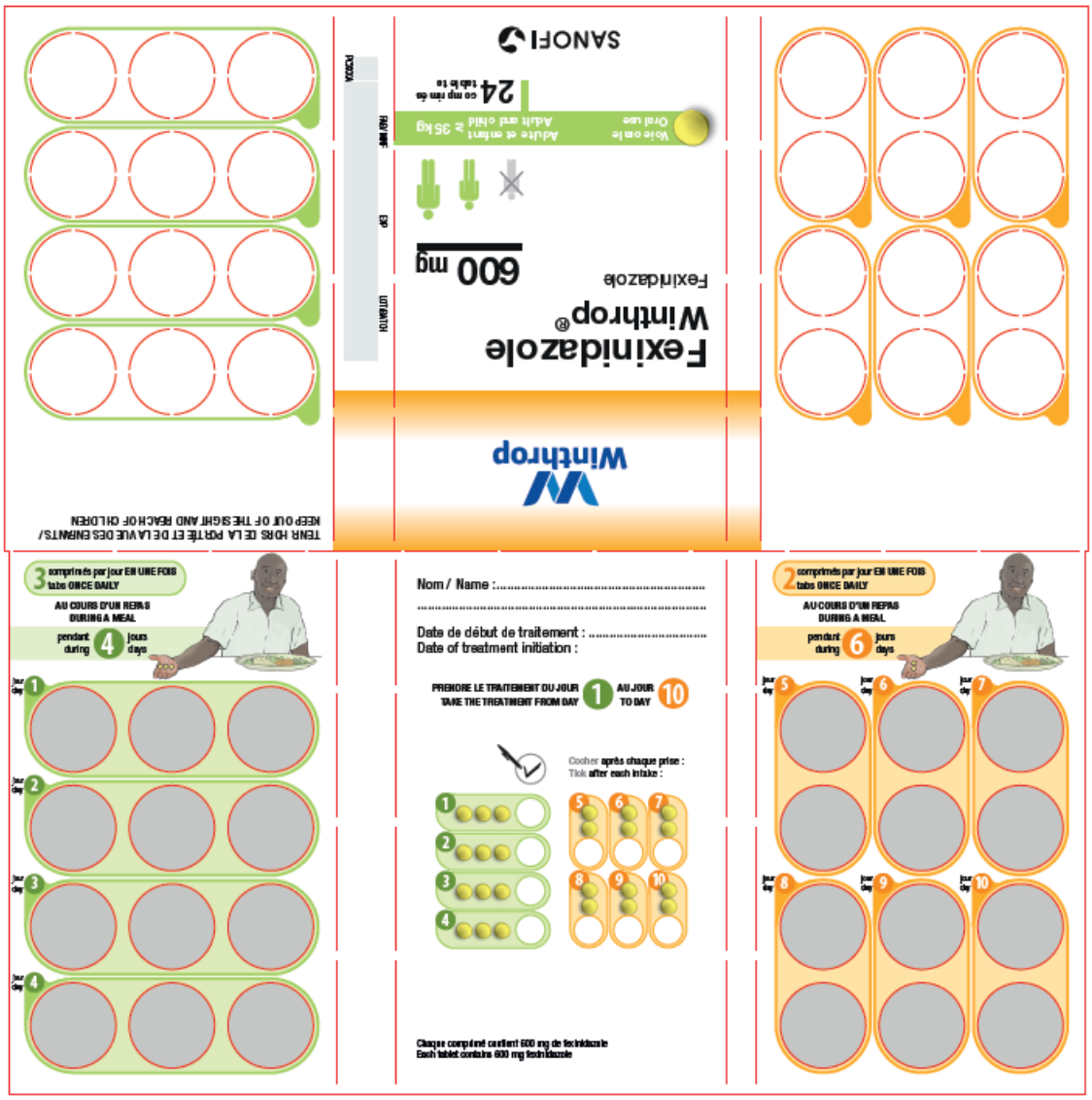
Organisation of Study

Country	DRC and Guinea
Planned number of patients	174 patients
Number of sites	At least 4 sites
Number of patients per site	Between 20 and 50
Role of DSMB	A DSMB will be appointed, in charge of safety issues in the same way as for study DNDiFEX004.
Role of partners	Ministry of Health, Kinshasa, DRC • Principal Investigator PNLTHA, Kinshasa, DRC • Supervision of investigational site teams • Coordination of supplies and active screening teams IRD and PNLTHA in Guinea • Supervision of investigational site teams • Coordination of supplies and active screening teams
Other particular needs	Mobile teams for active case screening Equipment and supplies for biochemical and haematological analyses Telecommunication facilities and computing equipment

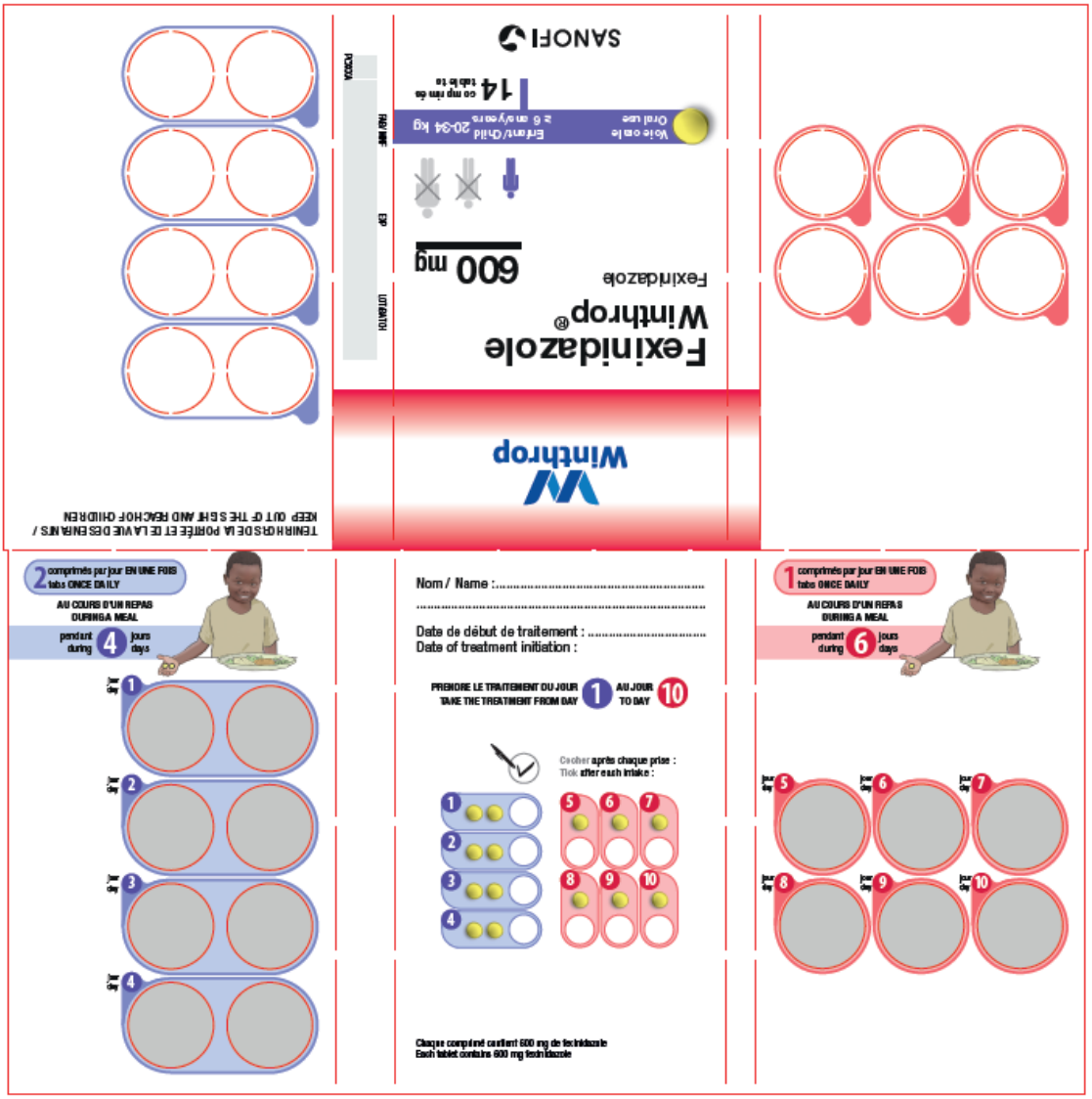
Appendix 5 - Packaging of IMP

Mock-up of Packaging

a. Adults and children with body weight 35 kg or more



b. Children with body weight less than 35 kg



Appendix 6 – CTCAE version 4.03 adapted

	CTCAE v4.0 SOC	CTCAE v4.0 Term	units	LLN	ULN	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Hematologie											
Hemoglobin	Blood and lymphatic system disorders	Anemia - Man	g/dL	12.2	17.7	<12.2 - 10.0	<10.0 - 8.0	<8.0	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by an reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.
	Blood and lymphatic system disorders	Anemia - Woman	g/dL	9.5	15.8	<9.5 - 8.5	<8.5 - 7.5	<7.5	Life-threatening consequences; urgent intervention indicated	Death	
	CTC criteria	Anemia	g/dL			<LLN - 10.0 g/dL	<10.0 - 8.0	<8.0 g/dL transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death	
Platelets	Investigations	Platelet count decreased	nb/µL	126 000	438 000	<126,000 - 75,000	<75,000 - 50,000	<50,000 - 25,000	<25,000	-	A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.
	CTC criteria	Platelet count decreased	nb/µL			<LLN - 75,000	<75,000 - 50,000	<50,000 - 25,000	<25,000	-	
Leucocytes	Blood and lymphatic system disorders	Leukocytosis	nb/µL	3100	9100	-	-	>100,000	Clinical manifestations of leucostasis; urgent intervention indicated	Death	A disorder characterized by laboratory test results that indicate an increased number of white blood cells in the blood.
	CTC criteria	Leukocytosis	nb/µL					>100,000	Clinical manifestations of leucostasis; urgent intervention indicated	Death	
	Investigations	White blood cell decreased	nb/µL	3100	9100	<3100-2500	<2500 - 2000	<2000 - 1000	<1000/mm3	-	A finding based on laboratory test results that indicate an decrease in number of white blood cells in a blood specimen.
	CTC criteria	White blood cell decreased	nb/µL			<LLN - 3000	<3000 - 2000	<2000 - 1000	<1000	-	
Biochimie											
Na - Sodium	Metabolism and nutrition disorders	Hypernatremia	mmol/L	128	145	>145 - 150	>150 - 155	>155 - 160 ; hospitalization indicated	>160 ; life-threatening consequences	Death	A disorder characterized by laboratory test results that indicate an elevation in the concentration of sodium in the blood.
	CTC criteria	Hypernatremia	mmol/L			<ULN - 150	>150 - 155	>155 - 160 ; hospitalization indicated	>160 ; life-threatening consequences	Death	
	Metabolism and nutrition disorders	Hyponatremia	mmol/L	128	145	-	<128 - 125	<125 - 120	<120 ; life-threatening consequences	Death	A disorder characterized by laboratory test results that indicate a low concentration of sodium in the blood.
	CTC criteria	Hyponatremia	mmol/L			<LLN - 130	-	<130 - 120	<120 ; life-threatening consequences	Death	
K - Potassium	Metabolism and nutrition disorders	Hypokalemia	mmol/L	3.6	5.1	<3.6 - 3.0	<3.6 - 3.0 ; symptomatic; intervention indicated	<3.0 - 2.5 ; hospitalization indicated	<2.5 ; life-threatening consequences	Death	A disorder characterized by laboratory test results that indicate a low concentration of potassium in the blood.
	CTC criteria	Hypokalemia	mmol/L			<LLN - 3.0	<3.6 - 3.0 ; symptomatic; intervention indicated	<3.0 - 2.5 ; hospitalization indicated	<2.5 ; life-threatening consequences	Death	
	Metabolism and nutrition disorders	Hyperkalemia	mmol/L	3.6	5.1	>5.1 - 5.5	>5.5 - 6.0	>6.0 - 7.0 ; hospitalization indicated	>7.0 ; life-threatening consequences	Death	A disorder characterized by laboratory test results that indicate an elevation in the concentration of potassium in the blood; associated with kidney failure or sometimes with the use of diuretic drugs.
	CTC criteria	Hyperkalemia	mmol/L			>5.1 - 5.5	>5.5 - 6.0	>6.0 - 7.0 ; hospitalization indicated	>7.0 ; life-threatening consequences	Death	
Bicarbonates			mmol/L	18	33	to be assessed as: • "normal", • "abnormal not clinically significant" or • "abnormal clinically significant (to be graded by the investigator and declared as mild, moderate or severe)"					
Chloride			mmol/L	98	108	to be assessed as: • "normal", • "abnormal not clinically significant" or • "abnormal clinically significant (to be graded by the investigator and declared as mild, moderate or severe)"					
Glucose	Metabolism and nutrition disorders	Hypoglycemia	mg/dL	73	118	<73 - 55	<55 - 40	<40 - 30	<30 ; life-threatening consequences; seizures	Death	A disorder characterized by laboratory test results that indicate a low concentration of glucose in the blood.
	CTC criteria	Hypoglycemia	mg/dL			<73 - 55	<55 - 40	<40 - 30	<30 ; life-threatening consequences; seizures	Death	
	Metabolism and nutrition disorders	Hyperglycemia	mg/dL	73	118	Fasting glucose value >118 - 160	Fasting glucose value >160 - 250	>250 - 500 ; hospitalization indicated	>500 ; life-threatening consequences	Death	A disorder characterized by laboratory test results that indicate an elevation in the concentration of blood sugar. It is usually an indication of diabetes mellitus or glucose intolerance.
	CTC criteria	Hyperglycemia	mg/dL			Fasting glucose value >118 - 160	Fasting glucose value >160 - 250	>250 - 500 ; hospitalization indicated	>500 ; life-threatening consequences	Death	
Ca - Calcium	Metabolism and nutrition disorders	Hypercalcemia	mg/dL	8.0	10.3	>10.3 - 11.5	>11.5 - 12.5 ; symptomatic	>12.5 - 13.5 ; hospitalization indicated	>13.5 ; life-threatening consequences	Death	A disorder characterized by laboratory test results that indicate an elevation in the concentration of calcium (corrected for albumin) in blood.
	CTC criteria	Hypercalcemia	mg/dL			>10.3 - 11.5	>11.5 - 12.5 ; symptomatic	>12.5 - 13.5 ; hospitalization indicated	>13.5 ; life-threatening consequences	Death	
	Metabolism and nutrition disorders	Hypocalcemia	mg/dL	8.0	10.3	-	<8.0 - 7.0 ; symptomatic	<7.0 - 6.0 ; hospitalization indicated	<6.0 ; life-threatening consequences	Death	A disorder characterized by laboratory test results that indicate a low concentration of calcium (corrected for albumin) in the blood.
	CTC criteria	Hypocalcemia	mg/dL			<LLN - 8.0	<8.0 - 7.0 ; symptomatic	<7.0 - 6.0 ; hospitalization indicated	<6.0 ; life-threatening consequences	Death	
Azote uréique sanguin			mg/dL	7	22	to be assessed as: • "normal", • "abnormal not clinically significant" or • "abnormal clinically significant (to be graded by the investigator and declared as mild, moderate or severe)"					
Créatinine	Investigations	Creatinine increased	mg/dL	0.5	1.2	>1.2 - 1.8	>1.8 - 3.6	>3.6 - 7.2	>7.2	-	A finding based on laboratory test results that indicate increased levels of creatinine in a biological specimen.
	CTC criteria	Creatinine increased	mg/dL			>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN		
Alkaline phosphatase	Investigations	Alkaline phosphatase increased	U/L	48	164	>164 - 410	>410 - 820	>820 - 3280	>3280	-	A finding based on laboratory test results that indicate an increase in the level of alkaline phosphatase in a blood specimen.
	CTC criteria	Alkaline phosphatase increased	U/L			>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN		
ALT (SGPT)	Investigations	Alanine aminotransferase increased	U/L	8	61	>61 - 183	>183 - 305	>305 - 1220	>1220	-	A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.
	CTC criteria	Alanine aminotransferase increased	U/L			>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN		
AST (SGOT)	Investigations	Aspartate aminotransferase increased	U/L	14	60	>60 - 180	>180 - 300	>300 - 1200	>1200	-	A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.
	CTC criteria	Aspartate aminotransferase increased	U/L			>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN		
Bilirubine totale	Investigations	Blood bilirubin increased	mg/dL	0.2	2.2	>2.2 - 3.3	>3.3 - 6.6	>6.6 - 22.0	>22.0	-	A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.
	CTC criteria	Blood bilirubin increased	mg/dL			>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN		
Albumine	Metabolism and nutrition disorders	Hypoalbuminemia	g/dL	3.5	5.2	<3.5 - 3	<3 - 2	<2	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by laboratory test results that indicate a low concentration of albumin in the blood.
	CTC criteria	Hypoalbuminemia	g/dL			<LLN - 3	<3 - 2	<2	Life-threatening consequences; urgent intervention indicated	Death	
Protéine Totale			g/dL	5.8	8.8	to be assessed as: • "normal", • "abnormal not clinically significant" or • "abnormal clinically significant (to be graded by the investigator and declared as mild, moderate or severe)"					
	CTC criteria	CTC differs from nouvelles valeurs bio									

Appendix 7 - Schedule of Study Events

Table 5 – Schedule of Events - Patients treated in hospital

Protocol-planned procedures and forms to be completed	Screening	Treatment period										In-hospital Follow-up			Follow-up period
Timepoint →	D-15 to D-1	*D1*	*D2*	*D3*	*D4*	*D5*	*D6*	*D7*	*D8*	*D9*	*D10*	*D11 (EoT)*	*D12*	*D13-D18 (EoH)*	3 – 6 – 12 – 18 months
Rapid Diagnostic Test or CATT	x														
Detection of parasite in blood and/or lymph	x											x			x
Informed consent (before any additional medicines or study-specific procedures)	x														
Lumbar puncture (parasite and white blood cells in CSF)	x														x[1]
Pretreatment of helminthiasis[2]	x														
Rapid Diagnostic Test and/or thick blood smear for diagnosis of malaria and, if necessary, treatment[2]	x														
Karnofsky Performance Status	x											x			x
Inclusion and exclusion criteria	x														
Demographic data	x														
Medical history	x														
Signs and symptoms of HAT	x											x			x
Vital signs[3]	x								x[4]			x		x	x
Physical and neurological examinations	x								x[4]			x		x	x
Haematology and biochemistry	x											x			x[5]
Urine analysis	x											x			
Urine pregnancy test	x (D-1)											x			x (3 and 6 months only)
Triplicate ECG	x (D-1)				x D4 H4	x D4 H23						x			
Administration of fexinidazole		x	x	x	x	x	x	x	x	x	x				
Blood sampling for PK analyses (specific patient groups)									x H3.15	x H3	x H3 H7.15	x D10H24	x D10H48		
Adverse event (AE) collection	x (if considered related to study participation)	x	x	x	x	x	x	x	x	x	x	x	x	x	x (If reasonable possibility of relation to treatment)
Serious adverse event (SAE) collection from signature of consent form to last study visit	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Collection of concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	

[1] At 3 months, only if indicated by patient's clinical status.
[2] Treatment according to national guidelines.
[3] Temperature, blood pressure, heart rate and respiratory frequency.
[4] Only if indicated by patient's clinical status.
[5] At 3 and 6 months. At 12 and 18 months only if indicated by patient's clinical status.

Table 6 – Schedule of Events - Patients treated on an out-patient basis

Protocol-planned procedures and forms to be completed	**Screening**	**Dispensing**	**Treatment period**										**Follow-up period**	
Timepoint →	D-15 to D-1	*D0*	*D1*	*D2*	*D3*	*D4*	*D5*	*D6*	*D7*	*D8*	*D9*	*D10*	*D11 (EoT)*	3 – 6 – 12 – 18 months
Rapid Diagnostic Test or CATT	x													
Detection of parasite in blood and/or lymph	x												x	x
Informed consent (before any additional medicines or study-specific procedures)	x													
Lumbar puncture (parasite and white blood cells in CSF)	x													x[1]
Pretreatment of helminthiasis[2]	x													
Rapid Diagnostic Test and/or thick blood smear for diagnosis of malaria and, if necessary, treatment[2]	x													
Karnofsky Performance Status	x												x	x
Inclusion and exclusion criteria	x													
Demographic data	x													
Medical history	x													
Signs and symptoms of HAT	x												x	x
Vital signs[3]	x												x	x
Physical and neurological examinations	x												x	x
Haematology and biochemistry	x												x	x[4]
Urine analysis	x												x	
Urine pregnancy test	x (D-1)												x	x (3 and 6 months only)
Triplicate ECG	x (D-1)												x	
IMP dispensing / Discharge from hospital		x												
Administration of fexinidazole			x	x	x	x	x	x	x	x	x	x		
Blood sampling for PK analyses													x D10H24[5]	
Assessment of understanding of instructions for treatment (questionnaire)		x												
Treatment compliance (interview)													x	
Acceptability of packaging (questionnaire)													x	
Adverse event (AE) collection	x (if considered related to study participation)												x (interview)	x (If reasonable possibility of relation to treatment)
Serious adverse event (SAE) collection from signature of consent form to last study visit	←													→
Collection of concomitant medication	x												x (interview)	

[1] At 3 months, only if indicated by patient's clinical status.

[2] Treatment according to national guidelines.

[3] Temperature, blood pressure, heart rate and respiratory frequency.

[4] Only if indicated by patient's clinical status.

[5] Additional sampling for PK may be performed between Day 1 and Day 11 if the patient returns to the centre for an unscheduled visit