DNDi
Drugs for Neglected Diseases *initiative*

CLINICAL STUDY PROTOCOL

Efficacy and safety of fexinidazole in patients with Human African Trypanosomiasis (HAT) due to *Trypanosoma brucei rhodesiense*: a multicentre, open-label clinical trial

Registration number NCT03974178

Version 6.0 – 19 August 2022

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CLINICAL TRIAL PROTOCOL

Efficacy and safety of fexinidazole in patients with Human African Trypanosomiasis (HAT) due to *Trypanosoma brucei rhodesiense*: a multicentre, open-label clinical trial

Short title	FEX007
Name of product(s)	Fexinidazole
Drug Class	Antiprotozoal
Phase	II-III
Indication	*Trypanosoma brucei rhodesiense* (*T.b.rhodesiense*) Human African Trypanosomiasis (HAT)
Clinical Trial Protocol Number	DNDi-FEX-07-HAT
EudraCT Number	NA
Sponsor	Drugs for Neglected Diseases initiative (DNDi) 15 Chemin Camille-Vidart 1202 Geneva, Switzerland Phone: +41 22 906 92 30
Principal Investigator and Global/National Coordinating Investigator	Principal Investigator: Prof. Enock Matovu Makerere University, College of Veterinary Medicine, Animal Resources and Biosecurity- Main Campus P.O. Box 7062, Kampala, Uganda Coordinating Investigators: **Coordinating Investigator for Uganda:** [redacted] **Coordinating Investigator for Malawi:** [redacted]
Clinical Trial Protocol Version / Date	6.0_19 Aug 2022
Protocol Amendment Number / Date	4.0_19 Aug 2022

Site Principal Investigator's Signature Page

- I have read this protocol and agree that it contains all necessary details for carrying out this trial.
- I will conduct the trial according to the protocol, any subsequent approved protocol amendments, International Council for Harmonization (ICH) for Good Clinical Practice (GCP) and all applicable regulatory authority requirements and national laws.
- I will not deviate from the protocol without prior written permission from the Sponsor and prior review and written approval from the Institutional Review Board/Independent Ethics Committee (IRB/IEC), except where necessary to prevent any immediate danger to the patient.
- I have sufficient time to properly conduct and complete the trial within the time designated and I have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct it properly and safely.
- I have read and understand fully the Investigator Brochure (IB) for fexinidazole, and I am familiar with the Investigational Medicinal Product(s) and its/their use according to this protocol.
- I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this trial. I will discuss this material with them to ensure they are fully informed regarding the drug and the conduct of the trial.
- I will use only the informed consent form approved by the sponsor or its representative and will fulfill all responsibilities for submitting pertinent information to the IRB/IEC responsible for this trial if required by national law.
- I agree that the sponsor or its representatives shall have access to any source documents from which case report form information may have been generated.

Principal Investigator at each trial site

Investigator Signature _____ Date of Signature (DD/MMM/YY) _____

Name
Title
Institution
Address

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Abbreviations – Glossary of terms

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALB	Albumin
ALT	Alanine aminotransferase (SGPT)
AP	Alkaline Phosphatase
AST	Aspartate aminotransferase (SGOT)
BP	Blood Pressure
BUN	Blood Urea Nitrogen
Ca^{2+}	Calcium
cDNA	Complementary DNA
CIOMS	Council for International Organizations of Medical Sciences
Cl^-	Chloride
CLN	Cervical Lymph Node
CNS	Central nervous system
CRE	Creatinine
CRF	Case Report Form
CSF	Cerebrospinal Fluid
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome
D	Day
DBS	Dry-Blood-Spot
DNA	Deoxyribonucleic acid
DND*i*	Drugs for Neglected Diseases *initiative*
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
e.g.	*Exempli gratia*, “for example”
EMA	European Medicines Agency
EoH	End of Hospitalization
EoT	End of Treatment
EoS	End of Study
g-HAT	Gambiense Human African Trypanosomiasis
GCP	Good Clinical Practice
GLU	Glucose
GMP	Good Manufacturing Practice
H	Hour
HAT	Human African Trypanosomiasis
ICF	Informed Consent Form
ICH	International Council for Harmonization
i.e.	id est, “that is to say”

IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intent to treat
IV	Intravenous
K+	Potassium
LMP	Last Menstrual Period
LP	Lumbar Puncture
M	Month
M1	Sulfoxide Metabolite of fexinidazole
M2	Sulfone Metabolite of fexinidazole
mITT	Modified intention to treat
mAECT	Mini Anion Exchange Centrifugation Technique
mAECT-BC	Mini Anion Exchange Centrifugation Technique on Buffy Coat
MedDRA	Medical Dictionary for Regulatory Activities
MHCT	Microhematocrit centrifugation test
mRNA	Messenger RNA
MSF	*Médecins Sans Frontières*
Na^+	Sodium
NCI	National Cancer Institute
NDA	National Drug Authority
qPCR	Quantitative Polymerase Chain Reaction
PK	Pharmacokinetics
PV	Pharmacovigilance
QT	QT Interval on the ECG (time interval between electrical depolarization and repolarization of the left and right heart ventricles)
QTcF	QT Interval Corrected for Heart Rate by the Fridericia's formula
r-HAT	Rhodesiense Human African Trypanosomiasis
RDT	Rapid Diagnostic Test
RNA	Ribonucleic Acid
RR	Respiratory Rate
RT	Reverse Transcription
SAC	Scientific Advisory Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SSL	Secure Sockets Layer
SUSAR	Suspected Unexpected Serious Adverse Reaction
T.b.	*Trypanosoma brucei*

T.b.r.	*Trypanosoma brucei rhodesiense*
TBIL	Total Bilirubin
tCO_2	Total CO2 - bicarbonate
TEAE	Treatment-Emergent Adverse Event
ToC	Test of Cure
TP	Total Protein
Tryps	Trypanosomes
ULN	Upper limit of normal
vs.	*versus*
W	Week
WBC	White blood cell
WHO	World Health Organization
y.o.	Years old

PROTOCOL SYNOPSIS

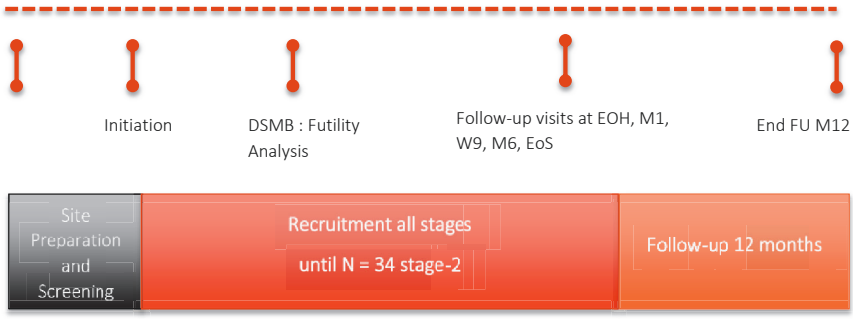
Background Information and Trial Rationale	Rhodesiense human African trypanosomiasis (r-HAT) is the zoonotic, acute form of sleeping sickness in Eastern Africa. The disease is rapidly lethal if untreated and has caused large epidemics in the past century. Over the past 15 years, efforts by the national HAT control programmes in all disease-endemic countries and key stakeholders have brought down the patient number to less than 100 per year. Even though these numbers are encouraging, approximately 1.5 million people live in areas still with moderate to high risk of contracting r-HAT[1,2]. East Africa is affected by sleeping sickness in different foci, which tend to remain spatially stable over time, although the transmission intensity waxes and wanes over the years[3]. To date, Uganda and Malawi reported the highest number of cases worldwide. Latest WHO available data for the 6 years between 2012 and 2017 showed 235 cases in Uganda (50% of all) and 157 in Malawi (34%)[4]. Disease severity appears to be very different across East African countries. In a cohort of patients treated in Lwala, Uganda between 2004-12; 42.8% were identified as 1st stage (306/715)[5] In Zambia, *T.b. rhodesiense* infection has shown two different patterns of progression (acute and chronic)[6], whereas an acute disease with rapid progression to late-stage infection is observed in Uganda and more chronic seems to be prevalent in Malawi[7]. Variation in HAT disease severity could be explained by a genetic variation in trypanosome virulence and/or differences in host response to trypanosomes infection[8]. Indeed, two genetically distinct strains of parasite (*T.b.r. busoga* and *T.b.r. zambezi*) have been associated with separate geographical locations: the strain group *busoga* appears to be associated with infections in northern areas, while the *zambezi* group is associated with the southern semi-acute form of the disease[9]. To date, only one drug, melarsoprol, is available for late-stage (meningoencephalitic stage) r-HAT. The use of this arsenic-based drug is associated with severe adverse drug reactions, the most important being an encephalopathic syndrome, which occurs in an average 8.0% of *T.b. rhodesiense* patients, with a case fatality rate of 57%[10]. Patients treated with melarsoprol need to be hospitalized. Furthermore, melarsoprol-monotherapy could be prone to the development of parasite resistance to the drug in the long term, as already observed in the *T. b. gambiense* endemic region of northwestern Uganda[11]. Suramin, a sulphated naphtylamide, remains the treatment of choice for early haemolymphatic stage of Tb rhodesiense infection as it does not penetrate the CSF. Its half-life in Plasma can be between 44-54 days. Its relapse levels have been described between 6.9 -31% of 1st

	stage *Tb rhodesiense* patients, increasing up to 64% in patients with borderline CSF anomalies (WBC count between 7-10/µL). It has sometimes been recommended as pre-treatment before giving melarsoprol, but its effect in improving the outcome has not been demonstrated[10] In a declaration for the elimination of HAT due to *T.b. rhodesiense*, WHO stakeholders urged for a safe, effective and preferably oral treatment[2]. Fexinidazole was identified by DND*i* out of hundreds of nitroimidazole compounds as a promising anti-protozoal drug candidate for the treatment of sleeping sickness. The ultimate goal of this study is to provide evidence for the safety and efficacy of fexinidazole for *Tb rhodesiense* HAT. Fexinidazole is a 2-substituted 5-nitroimidazole, formulated for oral administration. It has been shown to possess *in vitro* and *in vivo* activity against both *T.b. rhodesiense* and *T.b. gambiense* parasites[12]. Fexinidazole was shown to be safe in healthy volunteers given single or repeated doses for 14 days. Study participants administered with fexinidazole have shown mild to moderate headache, vomiting and/or other gastrointestinal symptoms. Some reversible elevations in liver enzymes and plasma creatinine levels have been observed in few volunteers after receiving fexinidazole. Changes in ECG parameters consisting of an increased heart rate and prolongation of the QT interval have been observed across several dose levels, with no clear dose effect seen. None of these changes are considered clinically relevant. Predicted CSF concentrations reached target levels after repeated dosing[13]. Fexinidazole efficacy and safety in patients with early- and late-stage HAT due to *T.b. gambiense* has been tested in three clinical trials (DNDiFEX004[14], DNDiHATFEX005, DNDiHATFEX006). Overall tolerance in all three studies is similar to healthy volunteers' studies (see section IB for Phase I clinical data). Patients presented nausea/vomiting, CNS/psychiatric AEs (dizziness, headache, tremor, anxiety, depression including suicidal ideation or insomnia), decreased appetite and asthenia. The majority of AEs were mild or moderate in severity and only two led to permanent treatment discontinuation. Also, a mild and reversible increase in creatinine levels was observed in some patients without any clinical consequence. Variations in ECG parameters were observed within normal ranges including asymptomatic QTc prolongation (see IB section for Phase II/III and cohort studies in HAT). The trial DNDi-FEX-09-HAT testing fexinidazole for *Tb gambiense* has been recently completed in additional population groups, including pregnant and breastfeeding women, as well as outpatients taking the treatment at home. Preclinical testing has shown that fexinidazole has no genotoxicity in mammalian

	cells. It is present in breast milk, in similar concentration as in blood, but no relevant toxicity has been predicted for breastfed children[15] Efficacy and safety of fexinidazole as a treatment in other kinetoplastid diseases has been tested. The dose finding, 7-arm placebo-controlled trial for American trypanosomiasis (Chagas disease) DNDi-CH-FEXI-001 was interrupted for safety and tolerability after including 47 patients, using higher dosages than the one used for HAT. The key safety events are described in the IB (section DNDi-CH-FEXI-001 study results). This led to a second clinical trial DNDi-FEX-12-CH, a proof-of-concept evaluation of low doses (600 and 1200 mg) and short treatment duration (at 3, 7 and 10 days) to determine the minimal efficacious and safe dose for the treatment of adult patients with chronic indeterminate Chagas disease. This trial is ongoing. The proof-of-concept trial DNDiFEXIVL001 for visceral leishmaniasis, which used the same dose as for HAT, was suspended for lack of efficacy. Overall, fexinidazole was well tolerated by the 14 visceral leishmaniasis patients enrolled in the trial. No SAEs have been reported during this clinical trial. Refer to IB for details in section possible risks, adverse drug reactions and contraindications
Risks and benefits of study intervention	First-in-man studies showed that fexinidazole is safe and well tolerated when given in the same doses used in this study[13]. The drug is well absorbed when administered in tablet form and its bioavailability depends on concomitant food intake. Drug-related adverse events are generally mild to moderate, and include headaches, nausea, vomiting, reversible rise in markers of the liver function and psychological problems (anxiety) with high doses[13]. Data in patients with HAT due to *T.b. gambiense* confirmed that fexinidazole is overall well tolerated[14]. Higher doses studied in Chagas disease patients showed transient neutropenia and raised transaminases. This trial will be conducted in hospitals experienced in the treatment of HAT patients, where qualified staff, equipment and other agents will be available in case of severe adverse reactions to fexinidazole or lack of efficacy. Patients will be followed up to 12 months after hospital discharge to detect potential relapses. If proven to be safe and effective, fexinidazole could replace the toxic melarsoprol for late-stage and suramin for early-stage HAT caused by *T.b rhodesiense.* Furthermore, fexinidazole could be used even in community health centres because it is easy to administer. If proven to be safe and effective in both stages of HAT, fexinidazole could then overcome the need for staging the disease. This would not only save patients from a painful lumbar puncture but also reduce the overall costs of equipment, infrastructure and trained personnel. If an early failure is observed, the DSMB may propose to continue the

	study until 34 stage-2 patients or until further decision whichever comes first, assuming that no statistical conclusion will be drawn. Fexinidazole has received a positive opinion from the European Medicines Agency (EMA) on 15th November 2018 and has been registered in Democratic Republic of the Congo on 24th December 2018 for the use in HAT due to *T.b gambiense.* It has been submitted for registration in Uganda and is currently under review by the National Drug Authority (NDA).
Trial Objectives	**Ultimate Objective** To show that fexinidazole offers an alternative over melarsoprol in stage-2 r-HAT patients and over suramin in stage-1 r-HAT patients **Primary objective** To show that the fatality rate (r-HAT or treatment related death) at the end of hospitalisation in stage-2 patients treated with fexinidazole is smaller than a threshold of unacceptable rate of 8.5% *Rationale: The major issue with melarsoprol is not the cure rate if the patient survives at EoH, but the fatality rate due to toxicity* **Secondary Objectives** 1. To show that the failure rate (r-HAT or treatment related death according to DSMB or presence of trypanosomes) at the end of hospitalisation in stage-2 patients treated with fexinidazole is smaller than a threshold of an unacceptable rate of 9% *Rationale: A new compound can show low mortality rate but still be not efficacious.* 2. To show that the proven failure rate (r-HAT related death according to DSMB or relapse) at 12 months (or before) in stage-2 patients treated with fexinidazole is below an unacceptable rate of 12% *Rationale: A new compound can be non-toxic and initially efficacious (trypanosomes no longer observed at EoH), but the sustainability of effect can be poor (i.e. no complete elimination of trypanosomes or persistence of high WBC in CSF during follow-up).* 3. To estimate the failure rate at EoH and at 12 months in stage-1 r-HAT patients treated with fexinidazole and to verify whether the estimates are smaller than that of suramin 4. To estimate the fatality rate and success rate at 12 months in the overall population (late- and early-stage r-HAT patients) treated with fexinidazole *Rationale: 1) It is the same parasite; the same population of patients and the ultimate objective is to yield one treatment*

	regardless of the stage of advancement of the disease. 2) Stage-1 patients are rare hence the estimates for stage 1 alone will not be very informative. 5. To evaluate the safety profile of fexinidazole in late- and early-stage r-HAT patients and to compare it to the one of melarsoprol and suramin as reported in the literature[16]. **Exploratory Objective** 1. To estimate the time course of relapse of fexinidazole from EoT to 12 months after the end of treatment 2. To assess the PK of fexinidazole and its main metabolites in the blood 3. To assess the reduction in the number of trypanosomes in the blood until the end of study visit
Trial Endpoints	**Primary Endpoint** Possibly Related fatality rate at the end of hospitalisation in stage 2 r-HAT patients treated with fexinidazole (death possibly related to r-HAT or treatment according to DSMB; since at the study sites anatomopathological techniques are not available, the completion of the WHO verbal autopsy questionnaire will be requested in case of death) **Secondary endpoints** 1. Success rate at the end of treatment in stage 1 and stage 2 r-HAT patients, where success is defined as: no trypanosomes at EoT and patient alive at EoH. Failure is defined as presence of trypanosomes in any body fluid at EoT or death at EoH. Deaths to be considered are defined as possibly related to r-HAT or treatment according to DSMB. Unrelated deaths are neither success nor failure. 2. Success and failure outcomes at the test-of-cure (ToC) visit 12 months after the end of treatment (EOT). A modification of the WHO recommendations [15] is used to determine success and failure for stage-1 and stage-2 r-HAT patients (Appendix 2 - Evaluation criteria of efficacy endpoints) 3. Occurrence of adverse events, including abnormal laboratory or ECG findings, during the observation period (until the end of hospitalisation scheduled up to 7 days after EOT) and those considered as possibly related to r-HAT or treatment, among those detected until the end of the follow-up period (12-month visit). All serious adverse events (SAE) whether they are considered as possibly related to r-HAT treatment or not. 4. Unsatisfactory clinical and parasitological response, defined as the compound analysis of the evolution of signs and symptoms

	as well as laboratory tests during the observation period and at the end of treatment visit. **<u>Exploratory Endpoints</u>** 5. Earliest time to detect a relapse from EOT to 12 months after the end of treatment 6. PK parameters for fexinidazole and its metabolites in whole blood 7. Semi quantification of trypanosomes in blood until end of study and trypanosomes genetic analysis until EoT
Trial Design	Multicentre, open-label, non-randomized, clinical trial of patients with r-HAT on efficacy/ tolerability of fexinidazole  From 2012 to 2017, the annual number of patients treated for Tb rhodesiense in all endemic countries was decreasing almost every year: 110, 86, 118, 71, 54 and 27[4]. This rare occurrence/incidence of disease raises the issue of the best use of available patients. A positive control randomized trial is not applicable because a randomized study based on the failure rate at EoH requires 124 patients per arm to get a power of 80%. A randomized study based on fatality rate at EoH would require a similar number of patients. With 20 patients per group and using the same expectations (failure rate of 9% and mortality rate of 1%), the exact power is equal to 2.39% This is actually equal to the type I error. In this case, the working hypothesis (smaller fatality rate with fexinidazole) cannot be validated through a frequentist statistical test. In order to retain a null hypothesis that can be rejected by data with a small and realistic sample size, a benchmark study comparing the observed fatality rate to an unacceptable rate (that of melarsoprol in the recent years) was designed. Moreover, a non-inferiority trial is not applicable because the non-inferiority margin is a possible difference in fatality rate in favour of the positive control (melarsoprol) and the goal of the trial is to verify whether fexinidazole could decrease the mortality rate at EOH. For this reason, this trial was designed as a single-arm trial treating patients with fexinidazole only.

Main Entry Criteria Inclusion/Exclusion	Patients must meet all the inclusion criteria and none of the exclusion criteria. **<u>Inclusion criteria</u>** • Signed Informed Consent Form (plus assent for children) • ≥ 6 years old • ≥ 20 kg body weight • Ability to ingest at least one complete meal per day (or at least one Plumpy'Nut® sachet) • Karnofsky index ≥ 40 • Parasitological confirmed of *T.b. rhodesiense* infection • Having a permanent address or being traceable by others and willing and able to comply with follow-up visit schedule • Agreement to be hospitalised for a minimum of 13ays and to receive the study treatment **<u>Exclusion criteria</u>** • Active clinically relevant medical conditions other than HAT that may jeopardize subject safety or at the investigator discretion may interfere with participation in the study (e.g. Patients at risk of QT interval prolongations, cf. details listed in IB section Possible Risk), • Compromised general health or severely deteriorated general condition, such as severe malnutrition, cardiovascular shock, respiratory distress, or terminal illness • Known hypersensitivity to fexinidazole, to any nitroimidazole drugs (e.g. metronidazole, tinidazole) or to any of the excipients • Patients previously enrolled in the study or having already received fexinidazole • Patients with severe hepatic impairment (ex: clinical signs of cirrhosis or jaundice)

Study Duration	The entire study should last about 36 months.
	The enrolment period should be at least 24 months. The participation of each patient will last 12-13 months, and will include:
	• Hospitalisation period:
	  ○ Pre-treatment: up to 7 days
	  ○ Treatment: 10 days
	  ○ Observation: 2 to 8 days
	• Follow-up period: 12 months after the first dose of treatment.
	If the recruitment of 34 evaluable stage-2 patients is shorter than 2 years, the duration of the study can be shortened.

Study	Fexinidazole, 600 mg tablets, given orally, once daily for 10 days, right

Treatments	after the main meal and preferably at the same time every day and only during hospitalisation. The daily doses are adjusted based on body weight and day of treatment, as follows: • Patients with a body weight ≥ 35 kg: – 1800 mg (3 tablets) from day 1 to 4 – 1200 mg (2 tablets) from day 5 to 10 • Patients with a body weight ≥ 20 and < 35 kg: – 1200 mg (2 tablets) from day 1 to 4 – 600 mg (1 tablet) from day 5 to 10 **Allocation of treatment** All consenting individuals will be assigned to treatment with fexinidazole.
Sample size	A scientific hypothesis is a hypothesis that can be rejected in an experimentation through a statistical test or a given observed fact. If the sample size is too small, the null hypothesis is not rejected even if no deaths are observed (whatever the observed death rate, H_0 is not rejected). **The minimal sample size** to get a possible rejection of H_0 (fatality rate at EOH = 8.5% or more) in favour of H_1 (fatality rate < 8.5%) **is 34 <u>evaluable</u> stage-2 patients** for alpha = 0.05 one-sided. In that case if no patients died during treatment the exact one-sided test becomes significant (p = 0.0488). Consequently, the sample size is not set according a minimal power of 80%, but according to the possible rejection of the null hypothesis. The second consequence of such an approach is: as soon as one death is observed at EOH, the study may be stopped for futility and failure (inconclusive result). To accept one failure and get a rejection of the null hypothesis once one failure is observed, the minimal sample size becomes 53 patients (p = 0.04967, for 1/53 deaths). Because this sample size cannot be reached within two years, the study is unfeasible if this hypothesis is applied. Even if the minimal sample size (n= 34) was retained to get a working hypothesis that can be rejected statistically, the power of the study remains quite reasonable. Fexinidazole was administered to 361 stage 2 patients suffering from HAT T.*b gambiense*. Two deaths were observed before the end of hospitalisation, considered unrelated to the treatment or disease. The fatality rate for any cause was therefore equal to 0.554%. These deaths were probably not due to treatment but considering the case of deaths regardless the cause, the power of the study in patients infected by T.*b gambiense* would be 82.79%. Using MSF data [17], the fatality rate in r-HAT stage 2 patients treated with

	melarsoprol was twice (exactly 1.98) larger in *T.b rhodesiense* than in T.*b gambiense* stage 2 patients. If we consider it is due to the fragility of patients infected by rhodesiense trypanosomes, then the expected fatality rate for any cause with fexinidazole could reach 1.097%. Using the corrected estimate (1.097%) as true then the exact power of the study is 68.73 %. Considering deaths possibly related to treatment or disease, the power should be larger than 70% that is a reasonable power in a rare and neglected disease. If one death attributable to the treatment or disease–may occur, the DSMB will rule whether or not the use of fexinidazole shall continue until the sample size of 34 patients is reached but no statistical inference will be made with regards to the unacceptable limit of 8.5%. **N.B. In case of non-evaluable patients, the sample size will be increased to reach 34 evaluable patients that are required to get a testable hypothesis in the primary analysis** (see primary analysis)**.** The recruitment will be stopped once 34 evaluable stage-2 patients are recruited
Statistics Randomization Planned Analyses	**Unacceptable Thresholds:** <u>Unacceptable fatality rate at end of hospitalisation</u> Annual fatality rates reported in the four most endemic countries together (Malawi, Uganda, Zambia and Zimbabwe) for stage-2 patients treated with melarsoprol are the following: 12.5% (12/96) in 2010, 12.4% (11/89) in 2011, 20% (14/70) in 2012, 12.1% (8/66) in 2013, 10.4% (10/96) in 2014 and 14.3% (6/42) in 2015. On average, the fatality rate in these 6 years in those 4 countries was 13.3% (61/459). The average (13%) cannot be retained as a threshold because the fatality rate is clearly dependent upon the site and the rate is probably lower in clinical studies. For example, in 2014, the observed fatality rate was 23.3% at the Rumphi site (Malawi) and 6.7% at the Lwala site (Uganda). Moreover, in the Impamel III clinical study the observed death rate was 8.4% (9/107)[16]. The retained threshold for the unacceptable fatality rate is therefore 8.5%. <u>Unacceptable failure rate at end of hospitalisation</u> The rate of failure at the end of hospitalisation due to presence of trypanosome is quite infrequent. In the Impamel III study, all failures at end of hospitalisation were due to death. The unacceptable rate of failure (death or presence of trypanosomes) at the end of hospitalisation for stage-2 patients is therefore set at 9%. This threshold was proposed by HAT experts and WHO

representatives in a meeting held in December 2016[18].

Unacceptable failure rate at 12 months follow-up

The rate of failure at 12 months in the IMPAMEL III study for stage-2 patients was 10.3% (9 deaths at EOH + 1 death and 1 relapse during FU). The unacceptable rate of failure set by HAT experts and WHO representatives in December 2016 was 12% and this threshold was retained in this study[18]. The slightly higher failure rate is justified by the fact that a relapse with a new drug can be treated with melarsoprol as a rescue medication

Populations

The population of evaluable patients is composed of patients who took at least one dose of fexinidazole excluding those whose death (if any) is documented and clearly attributable to other causes than r-HAT or treatment according to the DSMB and those who escape from the hospital and were not retrieved later to know their status on the primary outcome. This is the primary population. The choice of this set as the primary one is justified by the fact that the study is inconclusive if only one death occurred. If a death is, according to the DSMB, clearly unrelated to r-HAT or treatment such as poisoning, it is not reasonable to stop the trial for failure due to such an unrelated event. The secondary population is the modified intent to treat (mITT) set of patients consisting of all patients who took at least one dose of the study drug. This set will also be the safety set of patients.

The intent to treat population (ITT set of patients: all recruited patients who signed the inform consent and were eligible for treatment) will be used to describe the disposition of patient.

The fexinidazole treatment completer set of patients will consist of all patients who terminate the 10 days of treatment with fexinidazole.

Primary analysis

The primary population is the evaluable set of stage-2 patients.

The primary outcome is survival (alive or dead) at EoH.

The primary parameter of interest is death rate at the EoH.

In case of escape of a patient from the hospital and if the patient is not retrieved, the patient will be excluded from the population of evaluable patients and will be considered as a failure, but not a proven death.

A one-sided exact test with respect to 8.5% (unacceptable fatality rate under H_0) will be performed (alpha = 0.05 one-sided).

The one-sided test is justified by the very small number of available patients.

Sensitivity analyses

The same analysis will be performed on the mITT set of patients and

	on the set of treatment completers if at least 34 patients belong to these sets. **Sample size** Recruitment of both stages will stop once 34 evaluable stage-2 patients are reached. **Futility analysis** Because it is a one arm design and because only one death will lead to a failure of the trial (inconclusive results), the DSMB will meet as soon as one death occurs and the study can be stopped depending on the DSMB recommendations (the DSMB can recommend continuing the trial for exploratory purposes). Presence of trypanosomes or persistence of high WBC in CSF at any time from the end of hospitalisation until the end of follow up will also be considered as failure and could also help the DSMB in their recommendation to stop the trial. In case of unsatisfactory clinical and/or parasitological response during the treatment period and if the patient's survival is at risk for an assumed lack of efficacy of the study treatment, the investigator may introduce rescue treatment with suramin for stage 1 and melarsoprol for stage 2 patients. These cases may also be taken into consideration by the DSMB in their recommendation. **Secondary analyses** The first secondary analysis will consist of calculating the failure rate at end of hospitalisation in stage-2 patients and to compare it with the threshold of unacceptable failure rate 9%) through a one-sided exact test (alpha = 0.05 one-sided). The second secondary analysis will consist of estimating the failure rate at 12 months in stage-2 patients and comparing it with the unacceptable threshold of 12%. A one-sided exact test of comparison will be performed if the observed rate is below 12%. The fatality rate at EOH, failure rate at EOH and failure rate at 12 months will be estimated. Because the sample size will be very small, no null hypotheses will be testable. The estimate of fatality rate at EOH, failure rate at EOH and failure rate at 12 months for stage-1 and stage-2 combined will be calculated and tested against the unacceptable limit of 8.5%, 9% and 12%, respectively. **Stopping rules** The study can be stopped prematurely after recommendation by the DSMB if the DSMB considers that the tolerance to treatment or efficacy is insufficient.

1 Background and Trial Rationale

Rhodesiense human African trypanosomiasis (r-HAT) is the zoonotic, acute form of sleeping sickness in Eastern Africa. The disease is rapidly lethal if untreated and has caused large epidemics in the past century. Over the past 15 years, efforts by the national HAT control programmes in all disease-endemic countries and key stakeholders have brought down the patient number to less than 100 per year. Even though these numbers are encouraging, approximately 1.5 million people live in areas still with moderate to high risk of contracting r-HAT[1,2]. East Africa is affected by sleeping sickness in different foci, which tend to remain spatially stable over time, although the transmission intensity waxes and wanes over the years[3]. To date, Uganda and Malawi reported the highest number of cases worldwide. Latest WHO available data for the 6 years between 2012 and 2017 showed 235 cases in Uganda (50% of all) and 157 in Malawi (34%)[4]. Disease severity appears to be very different across East African countries. In a cohort of patients treated in Lwala, Uganda between 2004-12; 42.8% were identified as 1st stage (306/715)[5]
In Zambia, *T.b. rhodesiense* infection has shown two different patterns of progression (acute and chronic)[6], whereas an acute disease with rapid progression to late-stage infection is observed in Uganda and more chronic seems to be prevalent in Malawi[7]. Variation in HAT disease severity could be explained by a genetic variation in trypanosome virulence and/or differences in host response to trypanosomes infection[8]. Indeed, two genetically distinct strains of parasite (*T.b.r. busoga* and *T.b.r. zambezi*) have been associated with separate geographical locations: the strain group *busoga* rather appears to be associated with infections in northern areas, while the *zambezi* group is associated with the southern semi-acute form of the disease[9].

To date, only one drug, melarsoprol, is available for late-stage (meningoencephalitic stage) r-HAT. The use of this arsenic-based drug is associated with severe adverse drug reactions, the most important being an encephalopathic syndrome, which occurs in an average 8.0% of *T.b. rhodesiense* patients, with a case fatality rate of 57%[10]. Patients treated with melarsoprol need to be hospitalized. Furthermore, melarsoprol-monotherapy could be prone to the development of parasite resistance to the drug in the long term, as already observed in the *T. b. gambiense* endemic region of north-western Uganda[11].

Suramin, a sulphated naphtylamide, remains the treatment of choice for early haemolymphatic stage of Tb rhodesiense infection as it does not penetrate the CSF. Its half-life in Plasma can be between 44-54 days[10]. Its relapse levels have been described between 6.9 -31% of 1sts stage *Tb rhodesiense* patients, increasing up to 64% in patients with borderline CSF anomalies (WBC count between 7-10/µL). It has sometimes been recommended as pre-treatment before giving melarsoprol, but its effect in improving the outcome has not been demonstrated[10].

In a declaration for the elimination of HAT due to *T.b. rhodesiense*, World Health Organization (WHO) stakeholders urged for a safe, effective and preferably oral treatment[2]. Fexinidazole was identified by DND*i* out of hundreds of nitroimidazole compounds as a promising anti-protozoal drug candidate for the treatment of sleeping sickness. The ultimate goal of this study is to provide evidence for the safety and efficacy of fexinidazole for *Tb rhodesiense* HAT.

Fexinidazole is a 2-substituted 5-nitroimidazole, formulated for oral administration. It has

been shown to possess *in vitro* and *in vivo* activity against both *T.b. rhodesiense* and *T.b. gambiense* parasites[12].

Fexinidazole was shown to be safe in healthy volunteers given single or repeated doses for 14 days. Study participants administered with fexinidazole have shown mild to moderate headache, vomiting and/or other gastrointestinal symptoms. Some reversible elevations in liver enzymes and plasma creatinine levels have been observed in few volunteers after receiving fexinidazole. Changes in ECG (Electrocardiogram) parameters consisting of an increased heart rate and prolongation of the QT interval have been observed across several dose levels, with no clear dose effect seen. None of these changes are considered clinically relevant. Predicted CSF (Cerebrospinal Fluid) concentrations reached target levels after repeated dosing[13].

Fexinidazole efficacy and safety in patients with early- and late-stage HAT due to *T.b. gambiense* has been tested in three clinical trials (DNDiFEX004[14], DNDiHATFEX005, DNDiHATFEX006). Overall tolerance in all three studies is similar to healthy volunteers' studies (see IB section for Phase I clinical data). Patients presented nausea/vomiting, CNS (Central Nervous System)/psychiatric AEs (dizziness, headache, tremor, anxiety depression including suicidal ideation or insomnia), decreased appetite and asthenia. The majority of AEs were mild or moderate in severity and only two led to permanent treatment discontinuation. Also, a mild and reversible increase in creatinine levels was observed in some patients without any clinical consequence. Variations in ECG parameters were observed within normal ranges including asymptomatic QTc prolongation (see IB section for Phase II/III and cohort studies in HAT). The trial DNDi-FEX-09-HAT testing fexinidazole for *T.b. gambiense* has been recently completed in additional population groups, including pregnant and breastfeeding women, as well as outpatients taking the treatment at home without new safety issues.

Preclinical testing has shown that fexinidazole has no genotoxicity in mammalian cells. It is present in breast milk, in similar concentration as in blood, but no relevant toxicity has been predicted for breastfed children[15].

Efficacy and safety of fexinidazole as a treatment in other kinetoplastid diseases has been tested. The dose finding, 7-arm placebo-controlled trial for American trypanosomiasis (Chagas disease) DNDi-CH-FEXI-001 was interrupted for safety and tolerability after including 47 patients, using higher dosages than the one used for HAT. The key safety events are described in the IB (section DNDi-CH-FEXI-001 study results). This led to a second clinical trial DNDi-FEX-12-CH, a proof-of-concept evaluation of low doses (600 and 1200 mg) and short treatment duration (at 3, 7 and 10 days) to determine the minimal efficacious and safe dose for the treatment of adult patients with chronic indeterminate Chagas Disease. This trial is ongoing.

The proof-of-concept trial DNDiFEXIVL001 for visceral leishmaniasis, which used the same dose as for HAT, was suspended for lack of efficacy. Overall, fexinidazole was well tolerated by the 14 visceral leishmaniasis patients enrolled in the trial. No SAEs have been reported during this clinical trial.

Refer to IB section for details on possible risks, adverse drug reactions and contraindications.

Fexinidazole has received a positive opinion from the European Medicines Agency (EMA) on 15th November 2018 and has been registered in Democratic Republic of the Congo

on 24th December 2018 for the use in HAT due to *T.b gambiense.* It has been submitted for registration in Uganda and is currently under review by the National Drug Authority (NDA).

2 Trial Objectives and Endpoints

2.1 Objectives

2.1.1 Ultimate Objective

To show that fexinidazole offers an alternative over melarsoprol in stage-2 r-HAT patients and over suramin in stage-1 r-HAT patients

2.1.2 Primary Objective

To show that the fatality rate (r-HAT or treatment related death) at the end of hospitalisation in stage-2 patients treated with fexinidazole is smaller than a threshold of unacceptable rate of 8.5%
Rationale: The major issue with melarsoprol is not the cure rate if the patient survives at EoH, but the fatality rate due to toxicity.

2.1.3 Secondary Objectives

1. To show that the failure rate (r-HAT or treatment related death according to DSMB (Data Safety Monitoring Board) or presence of trypanosomes) at the end of hospitalisation in stage-2 patients treated with fexinidazole is smaller than a threshold of an unacceptable rate of 9%
   Rationale: A new compound can show low mortality rate but still be not efficacious.
2. To show that the proven failure rate (r-HAT or treatment related death according to DSMB or relapse) at 12 months (or before) in stage-2 patients treated with fexinidazole is below an unacceptable rate of 12%
   Rationale: A new compound can be non-toxic and initially efficacious (trypanosomes no longer observed at EoH (End of Hospitalisation)), but the sustainability of effect can be poor (i.e. no complete elimination of trypanosomes or persistence of high WBC in CSF during follow up).
3. To estimate the failure rate at EoH and at 12 months in stage-1 r-HAT patients treated with fexinidazole and to verify whether the estimates are smaller than that of suramin
4. To estimate the fatality rate and success rate at 12 months in the overall population (late- and early-stage r-HAT patients) treated with fexinidazole
   Rationale: 1) It is the same parasite; the same population of patients and the ultimate objective is to yield one treatment regardless of the stage of advancement of the disease. 2) Stage-1 patients are rare hence the estimates for stage 1 alone will not be very informative.
5. To evaluate the safety profile of fexinidazole in late- and early-stage r-HAT patients and to compare it to the one of melarsoprol and suramin as reported in the literature[16].

2.1.4 Exploratory Objectives

1. To estimate the time course of relapse of fexinidazole from EoT to 12 months after the end of treatment
2. To assess the PK (pharmacokinetics) of fexinidazole and its main metabolites in the blood
3. To assess the reduction in the number of trypanosomes in the blood until the end of study visit

2.2 Trial Endpoints

2.2.1 Primary Endpoint

Possibly related fatality rate at the end of hospitalisation in stage 2 r-HAT patients treated with fexinidazole (death possibly related to r-HAT or treatment according to DSMB; since at the study sites anatomopathological techniques are not available, the completion of the WHO verbal autopsy questionnaire will be requested in case of death).

2.2.2 Secondary Endpoint(s)

1. Success rate at the end of treatment in stage 1 and stage 2 r-HAT patients, where success is defined as: no trypanosomes at EoT and patient alive at EoH. Failure is defined as: presence of trypanosomes in any body fluid at EoT or death at EoH. Deaths to be considered are defined as possibly related to r-HAT or treatment according to DSMB. Unrelated deaths are neither success nor failure.
2. Success and failure outcomes at the test-of-cure (ToC) visit 12 months after the start of treatment. A modification of the WHO recommendations [15] is used to determine success and failure for stage-1 and stage-2 r-HAT patients (Appendix 2 - Evaluation criteria of efficacy endpoints)
3. Occurrence of adverse events, including abnormal laboratory or ECG findings, during the observation period (until the EoH scheduled up to 7 days after EoT) and those considered as possibly related to r-HAT or treatment among those detected until the end of the follow-up period (12-month visit). All serious adverse events (SAE) whether they are considered as possibly related to r-HAT treatment or not.
4. Unsatisfactory clinical and parasitological response, defined as the analysis of the evolution of signs and symptoms as well as laboratory tests during the observation period and at the end of treatment visit.

2.2.3 Exploratory Endpoints

1. Earliest time to detect a relapse from EoT to 12 months after the end of treatment
2. PK parameters for fexinidazole and its metabolites in whole blood
3. Semi quantification of trypanosomes in blood and trypanosome nucleid acids detection until end of study

3 Trial design and Trial design rationale

3.1 Trial design

This is a multicentre, phase II/III, open-label, non-randomized clinical trial of r-HAT patients on efficacy and safety of fexinidazole.

3.2 Trial duration and duration of patient participation

The entire study should last about 36 months.

- Hospitalisation period:
  - Pre-treatment: up to 7 days
  - Treatment: 10 days
  - Observation: 2 to 8 days
- Follow-up period: 12 months after the first dose of treatment

If the recruitment of 34 evaluable stage-2 patients is shorter than 2 years, the duration of the study can be shortened.
Patients will be hospitalized from their arrival at the hospital/study centre until D18. They will be able to leave the hospital starting from D12 if their clinical status allows it.

Additional unscheduled visits could occur and will be recorded as such in the Case Report Form (CRF).

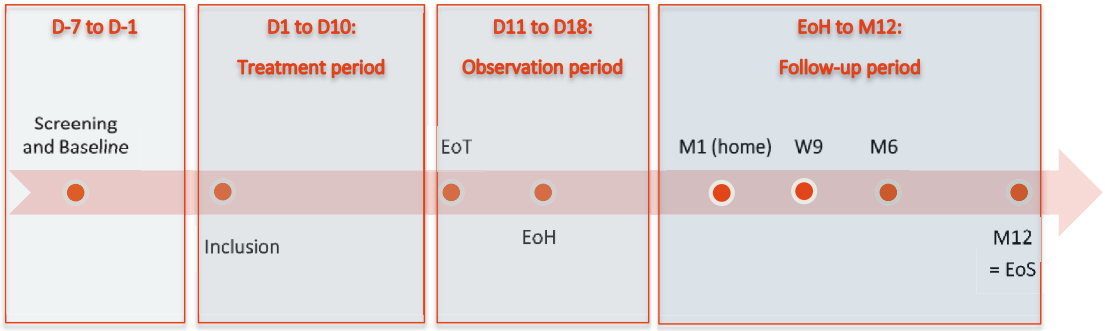
3.3 Definition of the end of trial

The end of the trial is defined as the last visit of the last patient undergoing the trial (Last Patient Last Visit (LPLV)).

3.4 Rationale of trial design

From 2012 to 2017, the annual number of patients treated for *T.b rhodesiense* in all endemic countries was decreasing almost every year: 110, 86, 118, 71, 54 and 27[4]. This rare occurrence/incidence of disease raises the issue of the best use of available patients. A positive control randomized trial is not applicable because a randomized study based on the failure rate at EoH requires 124 patients per arm to get a power of 80%. A randomized study based on fatality rate at EoH would require a similar number of patients. With 20 patients per group and using the same expectations (failure rate of 9% and mortality rate of 1%) the exact power is equal to 2.39%. This is actually equal to the type I error. In this case the working hypothesis (smaller fatality rate with fexinidazole) cannot be validated through a frequentist statistical test. In order to retain a null hypothesis that can be rejected by data with a small and realistic sample size, a benchmark study comparing the observed fatality rate to an unacceptable rate (that of melarsoprol in the recent years) was designed[18]. Moreover, a non-inferiority trial is not applicable because the non-inferiority margin is a possible difference in fatality rate in favour of the positive control (melarsoprol) and the goal of the trial is to verify whether fexinidazole could decrease the mortality rate at EoH. For this reason, this trial was designed as a single-arm trial treating patients with fexinidazole only.
The overall trial design is presented in the Figure 1- Overall trial design below:

Figure 1- Overall trial design



4 Selection of Patients

34 stage-2 patients have to be enrolled and the recruitment of both stages will stop once 34 evaluable stage-2 patients are reached.
The following eligibility criteria were designed to select patients for whom the protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient. Any questions regarding a patient's eligibility should be discussed with DNDi Medical responsible person prior to patient's enrolment. No waiver will be allowed to include a patient who do not fulfil all eligibility criteria.

4.1 Inclusion criteria

Patients must meet **all** the following inclusion criteria to be eligible for enrollment into the trial:

- Signed Informed Consent Form (plus assent for children)
- ≥ 6 years old
- ≥ 20 kg body weight
- Ability to ingest at least one complete meal per day (or at least one Plumpy'Nut® sachet)
- Karnofsky index ≥ 40
- Parasitological confirmed *T.b. rhodesiense* infection
- Having a permanent address or being traceable by others and willing and able to comply with follow-up visit schedule
- Agreement to be hospitalised for a minimum of 13 days and to receive the study treatment

4.2 Exclusion criteria

The presence of any of the following will exclude a patient from trial enrolment:

- Active clinically relevant medical conditions other than HAT that may jeopardize subject safety or at the investigator discretion may interfere with participation in the study (e.g. Patients at risk of QT interval prolongations, cf details listed in IB section Possible Risk).

- Compromised general health or severely deteriorated general condition, such as severe malnutrition, cardiovascular shock, respiratory distress, or terminal illness
- Patients with severe hepatic impairment (ex. Clinical signs of cirrhosis or jaundice)
- Known hypersensitivity to fexinidazole, to any nitroimidazole drugs (e.g. metronidazole, tinidazole) or to any of the excipients
- Patients previously enrolled in the study or having already received fexinidazole

5 Schedule of events

Cf Appendix 5 – Schedule of events

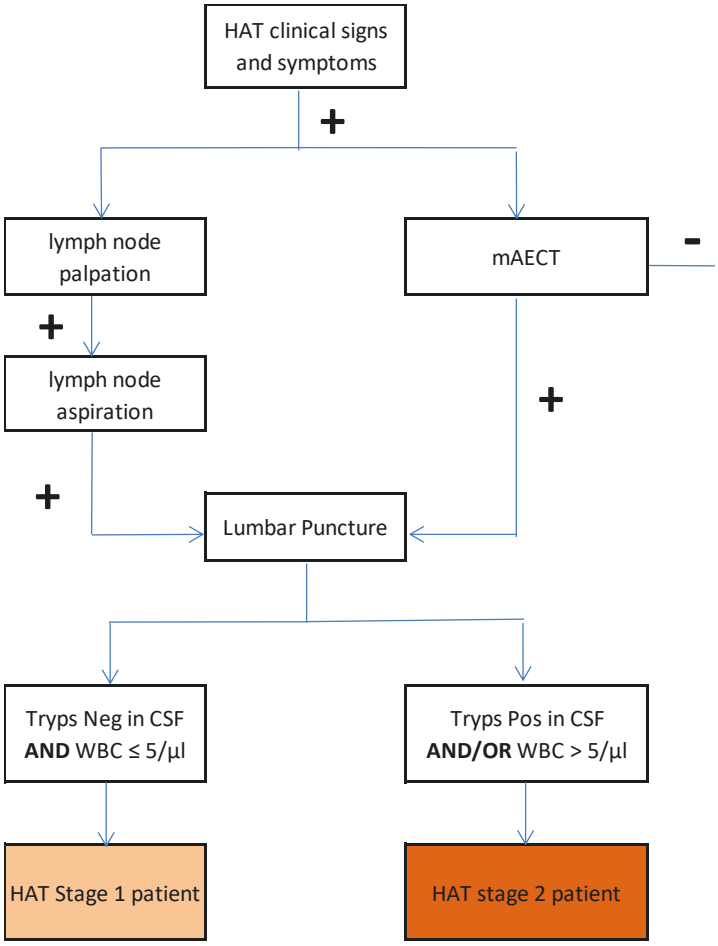
6 Enrolment procedures

This clinical trial will be conducted in 2 centres in Uganda (Lwala Hospital) and Malawi (Rumphi District Hospital). Eligible HAT patients from other hospitals and centres in Kaberamaido/Dokolo Districts (Uganda) and Rumphi/Mzimba North Districts (Malawi) and possibly from Chama province in Zambia will be referred to Lwala and Rumphi Hospitals, respectively, for treatment.

According to the standard medical procedures for HAT, patients presenting at the study site will undergo blood sampling and/or lymph node aspirate collection, followed by microscopic examination, to detect trypanosomes. In case of a positive result, a diagnostic lumbar puncture will be performed to evaluate the disease stage (Figure 2 – Diagnostic tree)
Prior to any clinical trial specific procedures and evaluations, written signed informed consent must be obtained (as per ICF process detailed in Section 0). A patient number will be assigned to the patient.

After signing the Informed Consent Form, HAT patients will be subjected to further evaluations/tests, including complete medical history, physical and neurological examination, haematology and biochemistry to assess their eligibility to the study (see Section 8.1.2). All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient based on inclusion and exclusion criteria (refer to section 4).
Patients who are not eligible or who decide not to participate in the trial for any reason will be treated with melarsoprol or suramin according to the National guidelines.

Figure 2 – Diagnostic tree



If mAECT is not available, Woo test, also named micro Haematocrit Centrifugation Technique (mHCT) to be done or thin/thick blood smear (only for initial diagnosis at screening)

mAECT = Mini Anion Exchange Centrifugation Technique

Tryps= Trypanosomes

WBC = White Blood Cells

The clinical sites should complete a Patient Screening/Enrolment Log to reflect patient number, enrolment status, date of enrolment, study enrolment number, date of non-enrolment, and reason for not enrolling. Subjects older than 6 years old who fulfil the inclusion / exclusion criteria will be included in the study and will receive study medication. There is no randomization in this study.
A note describing how the ICF (Informed Consent Form) was presented and the signature obtained, and a confirmation of eligibility to treat the patient will also be made in the patient's file.

7 Trial treatments

7.1 DNDi trial treatment

Fexinidazole, a 2-substituted 5-nitroimidazole drug, is presented as pale yellow, round biconvex tablets packaged into aluminium/aluminium foil blisters. Each blister will contain one fexinidazole 600 mg tablet and the number of blisters per strip will be determined by the clinical trial protocol. The Investigational Medicinal Product (IMP) will be manufactured and packaged by [redacted].

7.2 Comparator trial treatment

Not applicable

7.3 Non-IMP(s)

Not applicable

7.4 Doses and treatment regimens

Fexinidazole will be given orally, once daily after the main meal under direct observation of an authorized staff member, and preferably at the same time every day, and only during hospitalization.
The daily doses are adjusted based on body weight and day of treatment, as follows:

- Patients with a body weight ≥ 35 kg:
  - 1800 mg (3 tablets) from day 1 to 4
  - 1200 mg (2 tablets) from day 5 to 10
- Patients with a body weight ≥ 20 and < 35 kg:
  - 1200 mg (2 tablets) from day 1 to 4
  - 600 mg (1 tablet) from day 5 to 10

The tablets must not be broken nor crushed.
The total treatment duration will be 10 days. Treatment compliance will be guaranteed by the direct observed administration of the drug exclusively by the assigned staff.

Allocation of treatment

All consenting individuals will be assigned to treatment with fexinidazole.

Dose modification

Patients who vomit shortly after dosing (within 2 hours of drug administration) will receive the daily dose of fexinidazole again. If vomiting occurs more than 2 hours after drug administration, fexinidazole will not be re-administered, as drug absorption is considered to be complete.
The treatment might be discontinued for a maximum of one day (i.e. one dose of fexinidazole is missed), and end of treatment will therefore be delayed. Treatment can be resumed, if the Investigator in charge of the patient considers it to be appropriate. One day of treatment will be added to compensate for the missed dose. The patient should continue with the study visits and procedures as planned, taking into account the delay. The reason for the temporary treatment discontinuation should be recorded in the appropriate source documentation and CRF. More details on treatment interruption(s) are presented in Section 0 Rules for temporary interrupting the trial treatment

7.5 Trial treatments labelling, packaging

Fexinidazole tablets will be packaged into aluminium/aluminium foil blisters containing the number of tablets for one day of treatment (i.e. for adult and children patients with a body weight ≥ 35 kg: 3 tablets/blister strip for the first 4 days, and then 2 tablets/blister strip for the following 6 days). Every patient is attributed a treatment kit in a cardboard box containing 10 foil blister strips for a total of 14 or 24 tablets depending on their body weight.
All study drug supplies will be prepared and labelled according to the requirements of local law and legislation and applicable Good Manufacturing Practice (GMP) guidelines. Detailed information of study medication secondary packaging and labelling will be included in the Pharmacy Manual.

Minimum information to be included at study medication primary package (wallet card):

- Name address and phone number of sponsor (DNDi)
- Name of investigator
- Drug name, dosage form, strength and quantity
- Route of administration
- Batch number
- Clinical protocol number
- Directions for use – refer to study protocol
- “For clinical trial use only”
- Storage conditions
- Expiry date

7.6 Accountability

Responsibility for drug accountability at the study site rests with the Investigator; however, the Investigator may assign some of the drug accountability duties to an appropriate qualified pharmacist or designee. Inventory and accountability records must be maintained and must be readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities. The Investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug until the end of the study.
The Investigator or designee must maintain records that document:

- investigational product delivery to the study site
- the inventory at the site
- use by each subject
- return to the Investigator or designee.

These records should include dates, quantities, batch/serial numbers (if available), and the unique code numbers (if available) assigned to the investigational product and trial subjects.

The investigational product must be used only in accordance with the protocol. The Investigator will also maintain records adequately documenting that the trial subjects were provided the study drug specified. Completed accountability records will be archived by the site.

At the completion of the study, the Investigator or designee will oversee shipment of any remaining study drug/empty kits back to the Sponsor or Sponsor's designee according to institutional standard operating procedures. All unused medications will be carefully recorded and documented before destruction.
If local procedures allow for site destruction of investigational supply, prior written approval must be obtained from DNDi before disposing of the study drug. If the study drug is destroyed locally, a destruction record will be provided to DNDi.

Fexinidazole must not be used for purposes other than this protocol. Under no circumstances may the Investigator or site staff supply study fexinidazole to other Investigators or healthcare services or allow the drug to be used other than as directed by this protocol, without prior written authorisation from DNDi.

7.7 Compliance

All participants will receive their treatment under hospitalisation. Fexinidazole will be administered within 30 minutes from a meal. A study nurse will oversee patient's food intake to make sure that the patient has eaten sufficiently (a meal equivalent to a dose of Plumpy'Nut®; if not, the patient will be provided with a bag of Plumpy'Nut®). Drug intake will be monitored by a study nurse to make sure that fexinidazole is swallowed. The compliance is assessed and reported in the CRF, as well as the timing of administration.

7.8 Storage

Fexinidazole can be shipped at room temperature. Storage at a temperature not exceeding 30°C is recommended. Fexinidazole must be stored protected from the light, a condition which is provided by the alu-alu foil blisters packaging. The stability of the tablets in the alu-alu foil blisters will be monitored as part of the regulatory stability studies. Study drugs must be kept in a locked cabinet and/or in a room with restricted access, under the control of the Investigator or a delegated person i.e. the study pharmacist Site storage conditions and temperature should be monitored and recorded daily by the site personnel in a temperature log. Temperature excursions below or above the allowable range should be reported to the study monitor.

7.9 Blinding and procedures for unblinding

Not applicable. This is an open-labelled study

7.10 Concomitant treatments

7.10.1 Concomitant Medications/measures

Patients may receive concomitant therapy for medical occurrences during the course of the study. The investigator shall refrain from giving comfort drugs and use concomitant treatment only in case of need, choosing drugs included in the National Essential Medicines Lists of their own country.

- Anti-malaria drugs: All patients will have a diagnostic test for malaria. All patients with positive thick smear and/or Rapid Diagnostic Test (RDT) should be treated.
- All existing ACT (Artemisinin-based Combination Therapy) against malaria have

effects on QT. In case malaria is diagnosed, the Artemisinin-based combination of Artemether and Lumefantrine should be used for treatment as it is known to have only a moderate and well quantified effect on QT prolongation[19]. The choice was made to minimize confounding factors regarding the evaluation of QT prolongation due to fexinidazole treatment. In case of contraindication to Coartem®, the Investigator will be allowed to choose another antimalarial treatment, which should be documented. This treatment will be provided free of charge by the Sponsor.

- Anti-helminthics: The treatment of helminthiasis with mebendazole or albendazole will be provided in compliance with the site's routine practice. Costs for participants will be covered by the Sponsor.
- Other medications: Only the medications or treatments needed for the welfare of a subject and not expected to interfere with the study drug may be administered at the discretion of the Investigator.

All concomitant medications taken by the patient during the study, from the date of signature of the informed consent until the end of hospitalization, will be recorded in the appropriate section of the patients' charts and in the appropriate sections of the CRF, with reason for use and dates of administration.

All concomitant medications are to be entered under the International Non-proprietary Name (NNI) and will be reviewed for harmonization and coded at data management level. Any essential medication that is required during the trial period (until the 12-month follow-up visit) will be provided free of charge to the patient, see Section 0 below. The WHO Model Lists of Essential Medicines for adults[20] and children [21], the National Essential Medicines lists and the MSF (*Médecins sans Frontières*) essential drugs practical guidelines[22] will serve as reference for treatment of any concurrent condition. For any chronic disease which develops or worsens during treatment, the study team will take all necessary measures to have the patient referred to the most appropriate medical centre of the area.

7.10.2 Prohibited treatments

Since the pathways involved in the formation, metabolism and elimination of the active M2 metabolite are unknown and as no drug-drug interaction studies have been performed, it is recommended not to administer any other concomitant medications with fexinidazole

Due to pharmacodynamics interactions, the following concomitant uses is contra-indicated:

	Rational
Anti-arrhythmics class IA (e.g. quinidine, hydroquinidine, disopyramide)	May prolonge the QT interval
Anti-arrhythmics class III (e.g. amiodarone, sotalol, dofetilide, ibutilide)	
Tricyclic antidepressive agents (e.g. imipramine, amitriptyline)	
Certain antimicrobials including some antituberculosis agents (saquinavir, atazanavir, erythromycin IV, sparfloxacin, moxifloxacin, ofloxacin, levofloxacin, clofazimine, delamanid,	

pentamidine, certain antimalarials particularly halofantrine)	
Certains antihistaminics (terfenadine, astemizole, mizolastine)	
Others (cisapride, vincamine IV, diphemanil, lithium,)	
loop and thiazide diuretics, laxatives and enemas at high doses, corticosteroids, amphothericin B	May lead to proarrhythmic events
beta-blockers, calcium channel blockers	
Alcohol (until 48hrs after the last dose)	Risk of a disulfiram-like reaction (antabuse effect) characterized by flushing, rash, peripheral oedema, nausea and headache

In case of medical emergency, these drugs may be administered under the responsibility of the investigator as needed. Close supervision will be required

If patients are, or need to be treated with drugs known to prolong QT interval or to induce bradycardia or hypokalaemia, fexinidazole should not be initiated until such drugs are eliminated from the body (allow a washout period of 5 half-lives), or treatment with such drugs should not be started until fexinidazole and its active metabolites are eliminated from the body (allow a washout period of 7 days).

Due to potential pharmacodynamic interactions, the following concomitant uses are not recommended:

	Rational
Drugs metabolized by CYP1A2 (such as caffeine, duloxetine, melatonin, tacrine, tizanidine, theophylline) or CYP2C19 (such as omeprazole, mephenytoin, diazepam),	Fexinidazole could potentially increase the exposures to these drugs
Disulfiram	Possible psychotic reactions
Propylene glycol	5-Nitroimidazoles interfere with its metabolism
Traditional medicine: traditional or herbal medicine	Potential interactions are unknown

Some medications can be used with caution:
Antipsychotics (in context of treatment of psychiatric events) could be used if required in hospitalised patients under close monitoring.

7.10.3 Contraception Methods

Women of childbearing potential will be advised not to become pregnant and will be encouraged to use contraception or practice abstinence from sexual intercourse during the treatment period and at least until 48hrs after the last dose of fexinidazole. Medically proven means of contraception (hormonal contraception and condoms) may be made available free of charge to study participants during the 12 months of the individual study follow-up.

7.11 Rescue treatment

Patients with trypanosomes detectable at EOT visit, as well as patients with evidence of relapse (i.e. presence of *T.b. rhodesiense* in any body fluid) or probable relapse at any time during follow-up, will receive alternative HAT treatment according to the study site's medical standards and recommendation from the National Sleeping Sickness Control Program. The rescue treatment will be provided by the Sponsor free of charge for the patient.
Probable relapse at 1-month, 9-week, 6- and 12-month follow-up visit is defined as shown in Appendix 2 – Evaluation criteria of efficacy endpoints.

8 Trial Assessments

8.1 Timing of Assessments

Ideal and acceptable timing for visits is indicated in the below table and are calculated based on D1.

Visit type	Ideal timing for visits	Acceptable timing for visits
End of Treatment (EoT)	D11 (D1 + 10 days)	D11 to D12
End of Hospitalization (EoH)	Between D12 and D18	D18 at the latest
M1	D31 (D1 + 30d) +/- 7 days	D24 to D38
W9	D64 (D1 + 63d) +/- 7 days	D39 to D120
M6	D181 (D1 + 180d) +/- 30 days	D121 to D300
M12	D361 (D1 + 360d) +/- 30 days	D301 to D421

Details on the schedule of assessments can be found in Appendix 5 – Schedule of events

8.1.1 Diagnosis of HAT

As part of routine diagnostics, the following tests will be performed before signature of the informed consent, within 7 days of ICF signature.
Diagnosis of a trypanosome infection will be based on the following parasitological methods:

- Capillary or venous blood sampling and microscopic examination for parasite detection – blood samples should be processed according to the mini Anion Exchange Centrifugation Technique (mAECT). If mAECT is not available, the Micro-haematocrit Centrifugation Technique (Woo Test) or the thick or thin blood smear may be used for initial diagnosis.
- If enlarged lymph node is detected in the cervical area, aspirate sampling and microscopic examination for parasite detection can be done, if routinely performed at the centre.

- Lumbar puncture and CSF collection followed by WBC count, modified single centrifugation and microscopic examination for parasite detection.
- For details on these tests, please refer to the Study Lab Manual.

Note:

- If the subject is parasite-negative in the blood and/or lymph node aspirate and lumbar puncture has not been performed, the subject will not be proposed the study. If signs strongly suggestive for HAT are present, a lumbar puncture may be performed at discretion of the Investigator, and if trypanosomes are detected in CSF, a patient may be proposed for the study if compliant with all inclusion and exclusion criteria.

Parasite-positive subjects will be informed about the study according to the process presented in Section 6. Enrolment procedures of this protocol and be offered to sign the Informed Consent Form before undergoing any further testing. Microscopic videos of the trypanosomes in the CSF and in the blood can be taken but will be transmitted to the Sponsor only after the patient signs the Informed Consent Form.

8.1.2 Screening and Baseline Assessments

The screening visit should occur within 7 days before starting the treatment and after obtaining the informed consent and will include the following procedures, to evaluate:

At the screening visit, the following procedures are to be completed in order to evaluate patient eligibility for the study:

- Demographic information
- Body weight and height
- Complete medical history and observation
- Record of concomitant diseases and concomitant medications taken for the 7 days-period prior to dosing with fexinidazole
- Pregnancy test for women of reproductive age (≥12 years old) on the first day of screening
- Karnofsky index
- Pre-treatment of helminthiasis
- Malaria rapid diagnostic test and/or thick blood smear and treatment if positive.

The following assessments will be performed within 4 days before the first dose of medication is administered, in order to obtain baseline safety data and data for further comparative analyses and multiple parameter correlations:

- Vital signs including blood pressure, heart rate, respiratory rate and body temperature
- Physical and neurological examination
- HAT signs and symptoms questionnaire
- mAECT baseline examination for semi-quantitative evaluation of trypanosomes in blood if not done previously. Video to be recorded if trypanosomes are observed.
- Clinical safety laboratory evaluations: haematology and biochemistry
- Blood sampling for qPCR analysis.

- ECG digital recording (CarTouch®): a simple ECG will be recorded. Each screening ECG download will be sent to the centralised cardiologist for interpretation. All ECGs will be analysed by the cardiologist for rhythm and conduction abnormalities to help the Investigator with the subject inclusion
- ECG digital recording (CarTouch®): a triplicate ECG at 2 min intervals will be recorded for QT evaluationPatients fulfilling all the inclusion criteria and none of the exclusion criteria will be eligible for fexinidazole treatment.

Note: subjects who are not eligible for fexinidazole treatment or who decide not to participate in the trial for any reason will be treated with melarsoprol or suramin according to the national guidelines.

8.1.3 Treatment period assessments

All participants will receive fexinidazole treatment for 10 days.
The following tests will be performed along the treatment period or at the specified time points:

- Vital signs, every day from D1 to D10
- Clinical status, including physical and neurological examination, on **D5**
- Karnofsky index on **D5**
- HAT signs and symptoms questionnaire on **D5**
- ECG digital recording (CarTouch®): A single ECG will be recorded on **D2 pre-dose**, **D3** and **D4 pre-dose**.
- Triplicate ECGs at 2 min intervals will be recorded on **D4**, 3h, **and 12 hours after drug intake.**
- During treatment, other ECGs can be recorded at the Investigator's discretion
- mAECT on **D5** for semi-quantitative evaluation of trypanosomes (If parasites are not seen, mAECT-BC may also be performed). Video to be recorded if trypanosomes are observed.
- Blood sampling for PK and qPCR analysis on **D1** and **D4**.
- Biochemistry and haematology tests on **D5**.
- During treatment, additional biochemistry and haematology tests can be recorded at the Investigator's discretion

8.1.4 Post-treatment period assessments

The following tests will be performed at the end of treatment visit (EoT) on **D11**:

- If enlarged cervical lymph node is present, then aspirate sampling followed by microscopic examination for parasite detection
- mAECT for semi-quantitative evaluation of trypanosomes (If parasites are not seen, mAECT-BC will also be performed). Video to be recorded if trypanosomes are observed
- Lumbar puncture and CSF collection followed by WBC count, modified single centrifugation and microscopic examination for parasite detection
- Clinical status, including vital signs and physical and neurological examination
- Karnofsky index
- Haematology and biochemistry
- Triplicate ECG at 2 min interval recorded **23 hours after last dose**

- Blood sampling for PK analysis on **D10H24 (D11)** and on **D10H48 (D12)** and for qPCR analysis on **D10H24.**

Before final discharge, between D12 and D18, patients will undergo the following exams:

- Clinical status, including vital signs, physical and neurological examination, HAT signs and symptoms, Karnofsky index
- Pregnancy test for women of reproductive age (≥12 years old)

8.1.5 Follow-up period assessments

All efforts should be made to follow-up the patients for 12 months.

8.1.5.1 M1

The 1-month follow-up visit will consist of a home visit of the patient by the physician, it should take place 30 days after D1 (+/- 7 days). He will check the clinical status, HAT signs and symptoms, Karnofsky index and make a physical and neurological examination. In case of suspected relapse, or bad clinical status, the patient will be transferred to the hospital for additional examinations.

8.1.5.2 W9

The following tests will be performed at the hospital 9 weeks after D1 on D64 (+/- 7 days):

- If cervical lymph node is enlarged, then aspirate sampling followed by microscopic examination
- mAECT and/or mAECT-BC and video if trypanosomes are observed
- Lumbar puncture and CSF collection followed by WBC count, single modified centrifugation and microscopic examination for parasite detection and video if trypanosomes are observed
- Blood sampling for qPCR analysis**.**
- Clinical status, including vital signs (i.e. blood pressure, heart rate, respiratory rate and body temperature), physical and neurological examination, HAT signs and symptoms and Karnofsky index.
- Body weight and height, the latter only in children ≤ 16 y.o.
- Haematology and biochemistry
- ECG digital recording (CarTouch®): triplicate ECGs at 2 min intervals will be recorded
- Pregnancy test for women of reproductive age (≥12 years old)

8.1.5.3 M6 and M12 (Test of Cure)

6 months and 12 months after D1 (+/- 30 days), patients will undergo the following exams at the hospital:

- If cervical lymph node is enlarged, then aspirate sampling followed by microscopic examination
- mAECT and/or mAECT-BC and video if trypanosomes are observed
- Lumbar puncture and CSF collection followed by WBC count, modified single centrifugation and microscopic examination for parasite detection and video if trypanosomes are observed
- Blood sampling for qPCR analysis

- Clinical status, including vital signs (i.e. blood pressure, heart rate, respiratory rate and body temperature), physical and neurological examination, HAT signs and symptoms and Karnofsky index.
- Body weight and height, only in children ≤ 16 years
- Additional safety examinations such as biochemistry, haematology and ECG can be performed at Investigator's discretion

If the patient is unable or unwilling to attend the 12-month follow-up visit, direct evidence of a satisfactory patient's clinical condition by the Investigator or a delegated staff from the trial team will be acceptable to assess the success for this patient. If the clinical condition is unclear, patient should be brought back to the hospital for clarification, including parasitological exams.

8.1.6 Unscheduled visits

If uncertain evolution is diagnosed (based on clinical examination or on WBC count in the CSF) at any visit, patients will be asked to come back after one to three months (at the Investigator's discretion). The patient will also be invited to come back anytime if s/he feels sick, even if there is no clear relationship to treatment and/or to HAT.
The following parameters will be measured:

- Clinical status, including vital signs (i.e. blood pressure, heart rate, respiratory rate and body temperature), physical and neurological examination, HAT signs and symptoms
- Diagnosis of concomitant disease which triggered the visit
- Blood and/or lymph node aspirate sampling followed by microscopic examination for parasite detection (mAECT and/or mAECT-BC) if the patient presents clinical signs of HAT.
- Lumbar puncture and CSF collection followed by WBC count, modified single centrifugation and microscopic examination for parasite detection, if disease progression is suspected
- Karnofsky index
- Additional safety examinations such as biochemistry, haematology and ECG can be performed at Investigator's discretion

8.2 Assessment of efficacy

8.2.1 HAT diagnosis and staging

HAT diagnostic tests will consist of blood and lymph node examination followed by CSF examination.
These will be done at screening, EoT visit (D11) and during follow-up visits (W9, M6 and M12)
Refer to the diagnostic tree presented in Figure 2 – Diagnostic tree for more details.

8.2.1.1 Lymph node examination

Cervical lymph nodes (CLN) will be palpated to detect any enlarged node. Enlarged CLNs will be punctured and aspirates examined under the microscope to verify the presence of trypanosomes.[23]
Depending on the result of this test, further tests will be performed, according to the

diagnostic tree presented in Figure 2 – Diagnostic tree

8.2.1.2 Blood examination

Blood examination will consist of performing one or more of the below parasitological tests, listed in preference order:

- mAECT, on 500 µl heparinized venous blood [23]
- Micro-hematocrit centrifugation technique or Woo test. Can be used for initial diagnosis only if mAECT are not available at the peripheral testing site.

All these examinations will be done via capillary or venous blood sampling and videos and images will be collected if the parasite is detected. These deidentified images and videos will be sent to the Sponsor only after the patient signs the ICF.
Parasites in blood examination will be done at screening, D5, EoT visit (D11) and during follow-up visits (W9, M6 and M12).

8.2.1.3 CSF examination

Lumbar puncture will be done on patients with trypanosomes in blood and/or lymph to verify the presence of trypanosomes in the CSF for disease staging and to count the number of WBC.
4 mL of CSF will be withdrawn and if trypanosomes are detected, videos will be taken and sent to the Sponsor (only after ICF signature, during screening, at D11, W9, M6 and M12).

8.2.2 Medical History with emphasis on HAT signs and symptoms questionnaire

The Medical History will be collected up to the first dose of study drug and should be reported in standard medical terminology and will be coded according to the most recent version of Medical Dictionary for Regulatory Activities (MedDRA).
Signs and symptoms specific to HAT disease will be collected at baseline and at further visits (including unscheduled visits), using a specific questionnaire.

8.2.3 Karnofsky Index

The Karnofsky index[24] will be calculated using the scale presented in Appendix 3 – Karnofsky Index at screening, D5, EoT, EoH, and during all follow-up visits, and during unscheduled visits.

8.2.4 Physical and Neurological Examinations

A comprehensive physical and neurological examination will be performed at Screening, D5, EoT visit, EoH visit, all follow-up visits and during unscheduled visits.

- The comprehensive physical examination will include height and body weight, all relevant body systems including circulatory, respiratory, digestive, excretory (renal), integumentary (skin), and lymphatic systems.
- The neurological assessment will include a psychiatric observation (verbal flow, psychomotricity, behavioral disturbances, mood, etc.), higher function, cranial nerves, mobility, motor coordination and balance, primitive reflexes, and sensitivity.

8.3 Other assessments

8.3.1 PK sampling

2mL of venous blood will be collected for PK analyses on **D1**, **D4**, **D11** and **D12** at the time points shown in the below table.

Visit	Timing after treatment administration
D1	30 min 3h30 6h
D4	3h30 6h 12h
D10	24h (D11) 48h (D12)

A small amount of blood will be placed on a DBS (Dried Blood Spot) card and shipped to the Central Laboratory for analyses.

8.3.2 qPCR to detect trypanosome nucleic acids in patient blood

In order to monitor treatment success, quantitative PCR (qPCR) will be carried out both on DNA and cDNA obtained after reverse transcription (RT) of ribonucleic acid (RNA) isolated from patient blood. The advantage of RT-qPCR is that it could be a finer way to describe this disappearance since presence of RNA implies that of live trypanosomes, while signals from DNA might persist even long after parasite clearance[25].
2 mL of venous blood will be collected for trypanosome genetic analyses at the following time points:

Visit	Timing after treatment administration
D-4 to D-1	Baseline
D1	6h
D4	12h
D10	24h (D11)
W9	anytime
M6	anytime
M12	anytime

The blood will be injected into PAXgene tubes to stabilize RNA for downstream extraction; we shall also make dry blood spots from which DNA will be extracted. Samples will be transported at ambient conditions to the [redacted] laboratories.

8.4 Assessment of Safety

8.4.1 Vital Signs

Vital sign measurements including body temperature, blood pressure (BP), heart rate (HR), and respiratory rate will be taken at screening, along the treatment period, at EoT

and EoH visits and during W9, M6 and M12 follow-up visits and during unscheduled visits. Vital signs will be performed with the subject in sitting position after at least 10 minutes of rest.

8.4.2 Laboratory examinations

Capillary or venous blood collection for biochemistry and haematology tests on D5. Blood samples will be analysed at each centre's laboratory using standardised chemistry equipment provided by the Sponsor. Blood collection should be performed in fasting status, as much as possible. If the patient is not fasting, this shall be reported together with the test results.
Refer to Lab Manual for further details.

Any abnormal finding (after retesting) will be assessed for clinical significance.

- Haematology: haemoglobin, total WBC count, differential WBC count, platelet count
- Biochemistry: albumin (ALB), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), chloride (Cl-), creatinine (CRE), glucose (GLU), potassium (K+), sodium (Na+), calcium (Ca2+), total bilirubin (TBIL), bicarbonates (tCO2), total protein (TP)

8.4.3 Pregnancy test

Three urine pregnancy tests are planned during the study: on the first day of screening at discharge from hospital and at the 9-week visit.

8.4.4 ECG

ECG digital recording (CarTouch®) will be measured at the following time points:

	Single ECG	Triplicate ECG
D-4 to D-1	X	X
D2	X (Pre-dose)	
D3	X (Pre-dose)	
D4	X (Pre-dose)	X (D4H3, D4H12)
D11		X (D10H23)
W9		X
M6		At investigator's discretion
M12		At investigator's discretion

- A single ECG: a simple recording will be analysed by the Investigator to check the QTcF value (corrected QT interval using the Fridericia's formula – calculated automatically). If QTcF value is equal or over 500 ms, another ECG should be performed after 10-20 minutes rest. If the value is confirmed, the patient should be withdrawn from the study and no additional fexinidazole should be administered.
- Triplicate ECGs at 2 min intervals will be recorded (the latest ECGs should be used

to evaluate patient's safety before administration)

- During treatment, other ECGs can be recorded at the Investigator's discretion

8.5 Adverse event definitions and reporting

Safety of the study treatment will be assessed through routine monitoring of adverse events, which will be done daily from screening to EoH and then during scheduled follow-up visits. At each study visit, the patients will be enquired about current adverse events or any events observed during the period before the visit. During the follow-up period, patients will be advised to return to the clinic at any moment for additional AE (Adverse Event) assessment, in case they present any medical occurrence.
In addition, evaluation of laboratory parameters, ECG recordings, regular measurement of vital signs and physical examinations will be made at scheduled follow-up visit, as detailed in Section 8.1.5. A pregnancy test for women ≥ 12y.o will be done at screening, EoH and W9 visits.

8.5.1 Adverse Event definition

An AE is defined as:

"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 that treatment.

It can therefore be any unfavourable and unintended sign (for e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product."

Definition of an AE includes worsening (in severity and frequency) of pre-existing conditions ("Medical history") before first IMP administration and abnormalities of procedures (i.e., ECG, X-ray, ophthalmologic or neurological examination etc.) or laboratory results which are assessed as "clinically significant".

What is not an AE

- Medical conditions present at the initial study visit that do not worsen in severity or frequency during the study are NOT considered as AEs.
- Symptoms, exacerbation or worsening of the studied disease will NOT be considered as AE nor captured on the AE page of the CRF if consistent with the anticipated natural progression of the disease (overall and for this given subject).
- Lack of efficacy of the IMP is not considered as AE.

8.5.2 Assessment of Laboratory/Procedures Abnormalities

For every laboratory/procedure assessment, the investigator will evaluate if the laboratory/procedure test is normal or abnormal. If abnormal (after repeat testing), the investigator will assess if this finding is "clinically significant" or not.

An abnormal lab test must be compared with the previous value taking into account normal values in the studied population/country.

If a laboratory/procedure parameter is **abnormal AND** the abnormality assessed **clinically significant**, it should be reported as an AE.

An AE is a new event appearing after the signature of the ICF or a worsening in the condition (in the case of laboratory/procedure tests, it is an increase in severity (clinical intensity) of the abnormality which is judged clinically significant by the investigator.

Laboratory/procedures (i.e. ECG...) abnormalities (or worsening in severity or frequency of pre-existing abnormalities) should be assessed as "clinically significant" (and therefore have to be reported as an AE) if they meet **at least one** of the following conditions:

- The abnormality suggests a disease and/or organ toxicity **AND** this abnormality was not present at the screening visit or is assessed as having evolved since the screening visit
- The abnormality results in discontinuation of the study drug
- The abnormality requires medical intervention or concomitant therapy

When reporting an abnormal lab/procedure as an adverse event, an etiologic or syndromic **clinical diagnosis should be recorded** rather than the abnormal value itself, if available (*eg:* acute hepatitis instead of high levels of AST/ALT, TBIL, abdominal pain, vomiting, icterus.; eg: "hypokalemia" rather than "decreased potassium levels"; "anaemia" rather than "decreased red blood cell count").

8.5.3 Serious Adverse Event (SAE)

An adverse event will be defined as serious if it:

- **results in death**

i.e. causes or contributes to the death.

A possibly related death is a death for which there are facts (some evidence) that suggest a toxicity of treatment or an insufficiency of efficacy of treatment to stop the progress of the disease and prevent death.

An unrelated death is a death for which there are facts (evidence) that excludes the toxicity of the drug or lack of efficacy or the contribution of the drug and is generally due to an external event (accident, homicide, snake bite, …) or a pre-existing disease such as a cancer.

- **is life-threatening**

in this context refers to an AE in which the subject is at risk of death at the time of the AE; it does not refer to an AE that hypothetically might have caused death if more severe.

- **requires in-patient hospitalisation or prolongation of existing hospitalisation**

i.e. the AE requires at least an overnight admission or prolongs a hospitalisation beyond the expected length of stay. Hospital admissions for surgery planned before study entry, for social reasons, for any elective surgery (i.e. plastic surgery) or per protocol or for normal disease management (including treatment adjustment) are NOT to be considered as SAE according to this criterion (i.e. if the patient needs to stay overnight in order to get the follow up visit exams the morning after).

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

- **results in persistent or significant disability or incapacity**

i.e. the AE resulted in a substantial disruption of the subject's ability to conduct normal activities overtime.

- **is a congenital anomaly / birth defect**

i.e. an AE outcome in a child or foetus of a subject exposed to the Investigational Medicinal Product before conception or during pregnancy.

- **is an important medical event, i.e. is medically significant**

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious events/reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the subject or might require intervention to prevent one of the other outcomes listed above.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious AE.

In the study, ALT or AST levels above 3 times the upper limits of normal (ULN) associated with total bilirubin above 2 ULN will be considered SAEs.

SAE onset/start date:

Start date of SAE or date when the AE becomes serious (see seriousness criteria of an SAE).

SAE end/stop date:

SAE end date is the date of AE recovery.

8.5.4 Adverse Event of Special Interest (AESI):

AESI is defined as an adverse event (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the Sponsor may be appropriate. Such an event may require further investigation to characterize and understand it.

AESI, are not all SAEs from a regulatory point of view but the Sponsor shall be informed in an expedited manner within same timelines (irrespective of the grade of the AESI) as required for SAEs but using the "***AESI form***". Shall they meet any seriousness criteria (see Serious Adverse Event (SAE) 8.1.19) they should then comply for associated safety reporting requirements and be reported on BOTH the AE CRF and SAE form.

In this study, we will consider as AESI **any neuropsychiatric signs and symptoms** (excluding headaches and insomnia, that will be reported as AE) **requiring specialized therapeutic intervention** (such as specific pharmacotherapy or psychotherapy (including psychological counseling).

8.5.5 Eliciting Adverse Event information

The investigator is required to report all directly observed adverse events and all adverse events spontaneously reported by the trial patient using concise medical terminology.

In addition, to avoid bias in eliciting AEs, each trial patient will be questioned about the occurrence of adverse events at scheduled visits (every day during hospitalization and 1 month, 9 weeks, 6 months and then 12 months after D1), with general, non-leading questions such a*s: "Since the last visit have you had any health problem?" or "How are you feeling?".*

In this study, all AEs (serious and non-serious) must be recorded on the source documents and case report forms (CRFs) regardless of the assumption of a causal relationship with the study drug until the EoH visit. During the follow-up period only SAEs and AEs considered related to the study drug will be recorded in the CRF. The definition, reporting, and recording requirements for AEs are described in sections 8.1.17 and 8.1.22.

Information on adverse events must be evaluated by a physician.

Each AE is to be classified by the investigator as serious or non-serious (see definition of a SAE in section 8.1.19). This classification will determine the reporting procedure for the event.

In addition, the frequency, seriousness (see section 8.1.19), severity (see section 8.1.23), and causality (see section 8.1.24) assessment of AEs will be described. The frequency of AEs and AEs/SAEs leading to treatment discontinuation will be reported.

Non-serious AEs are to be reported on the CRF, including description of the event, onset date, duration, severity, seriousness, relationship to all study drugs, actions taken and outcome.

In the CRF, a given AE will be recorded only one time per subject, and the severity recorded will be the maximum level reached. If several distinct episodes of the same condition occur, their number will be recorded in the CRF.

SAEs will be reported both on the AE CRF and the SAE forms.

8.5.6 Adverse Event reporting period

The AE reporting period begins upon patient enrolment in the trial (after signature of informed consent) and ends at the EoH visit.
All AEs that occur during the adverse event reporting period specified in the protocol must be reported to DNDi, whether the event is considered study medication related or not.
In addition, any serious AE that occurs subsequent to the adverse event reporting period and that the investigator assesses as related to the investigational medication should also be reported as an AE.
After EoH until EoS (M12), only AEs considered as related to fexinidazole and SAEs will be reported.

Screening failure: beyond the date of screening failure (to be recorded), only serious study-related events will be followed-up.

8.5.7 Grading of Adverse Event severity

For each serious and non-serious AEs, the investigator is required to assess the severity.

Please note the distinction between severity and seriousness of adverse events. A severe AE is not necessarily a SAE.

The severity for an AE should be graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE, version 5.0[26] and a modified version of it, presented in Appendix 4 – modified CTCAE 5.0) as a guide in the grading of the severity of AEs.

In case of AEs that are not described in the CTCAE v 5.0 AE severity grading system, the Investigator will use the terminology MILD, MODERATE, SEVERE, LIFE-THREATENING or DEATH to describe the maximum severity of the adverse event as follows:

Mild:	The subject is aware of the event or symptom, but the event or symptom is easily tolerated (e.g. no reduction in daily activities is required).
Moderate:	The subject experiences sufficient discomfort to interfere with or reduces his or her usual level of activity.
Severe:	Significant impairment of functioning: the subject is unable to carry out usual activities and/or the subject's life is at risk due to the event.
Life-Threatening:	The subject is at significant risk of life; it does not refer to an event which hypothetically might have caused death if it were more severe (life-threatening consequences, urgent intervention required).
Death:	Death related to an event.

This information will be entered in the AE case report forms.

When the intensity of an AE changes over time, each change in intensity will be recorded in the source documents until the event resolves. However, only one AE and the maximum intensity will be recorded in the CRF for each separate event. If the AE resolves but then recurs, each will be recorded as a separate AE, with the appropriate start and stop times.

8.5.8 Adverse Event causality assessment

For each serious and non-serious AEs, the investigator is required to assess the possible relationship between the adverse event and the trial drug, i.e. to determine whether there exists a **reasonable possibility** that the trial drug caused or contributed to the **AE(s)**.

The following categories for relationship to treatment will be used during AE reporting:

Related	There is at least a reasonable possibility of a causal relationship between an AE and an investigational medicinal product. This means that there are **facts (evidence) or arguments** to suggest a causal relationship

Not related There is no reasonable possibility of causal relationship.

To help investigators with the decision binary tree (Related/Not related) in the evaluation of causality, the CIOMS (Council for International Organizations of Medical Sciences) VI group recommends that investigators be asked to consider the following before reaching a decision:

- Medical history (including presence of risk factors)
- Lack of efficacy/worsening of existing condition
- Trial medications
- Other medications (concomitant or previous)
- Withdrawal of trial medication, especially following trial discontinuation / end of trial medication
- Erroneous treatment with trial medication (or concomitant)
- Protocol related procedure

8.5.9 Adverse Event reporting requirements

Information on AEs must be evaluated by a physician.

Each AE is to be classified by the investigator as serious or non-serious. This classification will determine the reporting procedure for the event.

All serious adverse events (SAE) and adverse events of special interest (AESI) are to be reported immediately (**within 24 hours of awareness of SAE by the investigator) to** [redacted] using the SAE report form or AESI report form, respectively. This includes a description of the event, onset date and type, duration, severity, relationship to trial drug, outcome, measures taken and all other relevant clinical and laboratory data.

The initial report is to be followed by submission of additional information (follow-up SAE/AESI form) as it becomes available. Any follow-up reports should be submitted as soon as possible, and if possible within 5 working days.

SAE/AESIs should also be reported on the clinical trial adverse event case report form (CRF). It should be noted that the form for reporting of SAE/AESI (SAE or AESI form) is not the same as the AE section of the CRF. Where the same data are collected, the two forms must be completed in a consistent manner, and the same medical terminology should be used.

In addition to immediately reporting SAE/AESIs to DNDi, **the Investigator will immediately notify the Ethics Committee/Health Authorities of SAEs (not AESIs)** that occur during this trial, if applicable, in accordance with the standard operating procedures/guidance/regulations issued by the Ethics Committees/Health Authorities.

A **Suspected Unexpected Serious Adverse Reaction (SUSAR)** is a suspected AE **related** to an investigational medicinal product that is **both unexpected and serious**.

DNDi, the Sponsor is responsible for determining the expectedness of the event, using the reference safety information (described in the fexinidazole Investigator Brochure) defined for this trial.

DNDi or the investigator will notify the Ethics Committee/Regulatory Authorities of all SUSARs/other types of SAEs (If applicable) in compliance with local safety reporting requirements).

8.5.10 Exposure *in utero*

Pregnant women can be included into the trial. This lies within the anticipated lower toxicity of fexinidazole as compared to the standard treatment with melarsoprol or suramin, resulting in a lower risk of developing severe secondary effects in patients undergoing study treatment.

There are no data from the use of fexinidazole in pregnant women.

In animals, effects of fexinidazole on embryo-fetal development were observed only at doses harmful to the dams. These effects were considered as secondary to maternal toxicity. Plasma concentrations of fexinidazole and of its metabolites at these dose levels were low as compared to clinical exposures.

As a precautionary measure, it is preferable to avoid the use of fexinidazole during the 1st trimester of pregnancy, that's why the decision to include pregnant women in the study lies with the investigator after assessing the benefit/risk for the patient and women will be encouraged to use a contraceptive method at least during the hospitalization period.

Nevertheless, women exposed during pregnancy will be closely monitored for safety during the entire duration of the study.

If any trial subject becomes or is found to be pregnant (based on date start last menstruation period (LMP)) while receiving an investigational drug or is found pregnant at the EoH or at W9 visit, the investigator must report the event on a "***Pregnancy Surveillance form*"**.

This must be done irrespective of whether an AE has occurred. The information submitted should include the anticipated date of delivery.

The investigator will follow the subject until completion of the pregnancy or until pregnancy termination (i.e., abortion). The investigator will provide pregnancy follow-up or outcome information on a "***Pregnancy Surveillance Form***".

In the case of a live birth, a medically qualified person should examine the infant at the time of birth and submit a "***Child Surveillance form*"**. The Investigator will offer the parents follow-up on infants exposed to the study treatment *in utero* until they reach 24 months of age. As far as possible, stillborn infants should be examined by a physician to assess the cause of death.

A pregnancy is not an SAE.

Any unfavorable outcome meeting at least one seriousness criteria i.e. in the case of unfavorable pregnancy outcome (abortion, stillbirth) or congenital abnormality shall be reported using the "***SAE form***" (in addition to the ***Pregnancy/Child Surveillance Form***).

Follow-up of such newborns should be proposed up to the age of 2 years.

8.5.11 Exposure during breastfeeding

Children breastfed whilst their mother was on treatment will also be closely followed-up until 2 years of age or until the mother's last follow-up visit (12-month visit) whichever comes last, using the "Child-Surveillance Form"

8.5.12 Adverse event follow-up

All AEs should be followed until

- they are resolved; or
- the investigator assesses them as 'chronic' or 'stable'; or
- the patient's participation in the trial ends (i.e., until a final report is completed for that patient, or otherwise the last contact with the subject).

The following categories will be used to document outcome of each AE:

Action taken: None, drug treatment, subject withdrawn, other (specified).
Outcome: Completely recovered; recovered with sequelae; ongoing; death; unknown.

The decision to suspend, and resume treatment or to permanently interrupt treatment due to an adverse event will be left to the clinician in charge.

In addition, all SAEs (related or not) and those non-serious events assessed by the investigator as related to the investigational drug must continue to be followed even after the patient's participation in the trial is over. Such events should be followed until they resolve or until the investigator assesses them as "chronic" or "stable." Resolution of such events is to be documented on the AE page of the CRF and SAE form (if applicable).

Note: The recording of such events in the CRF/clinical database is not possible after the end of the trial (after LPLV). In that case, the follow-up information should be reported to the organisation in charge of the pharmacovigilance of the trial and recorded in the safety database.

9 Withdrawal criteria

A subject may withdraw from the trial at any time at their own request, or they may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety, behavioural, or administrative reasons.

If a subject does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome, if possible.

If the subject withdraws consent, no further evaluations should be performed, and no attempts should be made to collect additional data, with the exception of safety data, which should be collected if possible and in accordance with patient consent. The Sponsor may retain and continue to use any data collected before any withdrawal of consent. However, if the subject consents to follow-up but asks the Investigator to destroy all identifiable samples taken from the subject and/or not enter into the CRF results of the follow-up examinations, the Investigator will comply with the subject's requests.

9.1 Rules for temporary interrupting the trial treatment

In the event that treatment is interrupted (e.g. due to an AE), the decision to resume treatment will be taken by the site Principal Investigator.

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 completion will therefore be delayed. Treatment can be reintroduced at the discretion of the Investigator according to his assessment of the clinical status of the patient. 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

9.2 Rules for permanently interrupting trial treatment

A subject can be withdrawn from the treatment for the following reasons:

- In the Investigator's medical judgment, further participation would be injurious to the subject's health or well-being.
- AE or laboratory abnormalities occurring that in the opinion of the Investigator may constitute a potential risk for continued participation by the subject. These patients will continue to be followed up within the study.
- Clinically significant intercurrent illness which could compromise the safety of the subject or the scientific value of the trial
- Need for, or use of, contraindicated medication which could compromise the safety of the subject or the scientific value of the trial.
- Decision of the patient to stop the treatment

A participant **must** be discontinued from the treatment if at least one of the following medical conditions occurs:

- Severe skin reactions
- ALT or AST > 8x ULN
- ALT or AST > 3x ULN and total bilirubin > 2x ULN
- ALT or AST > 3x ULN and onset of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)
- Confirmed QTcF measurement ≥ 500 msec pre-dose (D2, D3, D4), i.e. after second ECG recording at a 10-20 minutes interval in resting position
- Any other condition which, in the eyes of the Investigator, requires treatment interruption due to medical reasons

The Investigator will make all necessary arrangements to ensure that the subject receives the appropriate treatment for HAT, if necessary and for any other relevant medical condition. Patients will be advised and offered the standard course of melarsoprol for stage-2 patients and suramin for stage-1 patients.
The date the subject discontinued the trial medication, and the specific reason for discontinuation will be recorded in the CRF

9.3 Patient withdrawal from the trial and patient replacement

9.3.1 Rules in case of withdrawal from trial

A subject can be withdrawn from the study for the following reasons:

- Withdrawal of consent

- Significant non-compliance of the subject with the requirements of the trial. If a subject is non-compliant in the opinion of the Investigator, the Sponsor's Medical Monitor should be consulted for instruction on handling the patient
- Major protocol violation as discussed and agreed upon between the Sponsor and Investigator.
- Termination of the study by the Sponsor.
- Termination of the study by the local health or regulatory authority or IRB/IEC.

If a subject discontinues the trial prior to completion, regardless of the reason:

- The site must notify DNDi within 48 hours.
- The reason(s) for withdrawal must be documented in the subject's medical record and CRF (End of Study form and other appropriate CRF pages to be completed).
- If the withdrawal is due to a SAE, the patient will be followed up according to the process detailed in section 8.1.28 Adverse events follow-up).
- If the withdrawal is due to a treatment limiting AE, thorough efforts should be made to clearly document the outcome of that AE.
- Reasonable efforts should be made to have the subject return for an early termination visit, with evaluations corresponding to those stipulated for the M12 end-of-study visit described in the schedule, to the extent feasible.
- All trial subjects must be followed for safety until M12 end-of-study visit described in the schedule of events or until study drug related AEs resolve or stabilize, or are deemed irreversible, whichever is later.

9.3.2 Patient replacement:

Patients who die for unrelated causes or withdraw from the trial before the end of hospitalization will be replaced in order to reach the 34-evaluable stage-2 patients required for the study.

10 Data Analysis and Statistical Methods

10.1 Sample size determination

A scientific hypothesis is a hypothesis that can be rejected in an experimentation through a statistical test or a given observed fact. If the sample size is too small, the null hypothesis is not rejected even if no deaths are observed (whatever the observed death rate, H_0 is not rejected). **The minimal sample size** to get a possible rejection of H_0 (fatality rate at EoH = 8.5% or more) in favour of H_1 (fatality rate < 8.5%) **is 34 evaluable stage-2 patients** for alpha = 0.05 one-sided. In that case if no patients died during treatment the exact one-sided test becomes significant (p = 0.0488).
Consequently, the sample size is not set according to a minimal power of 80%, but according to the possible rejection of the null hypothesis. The second consequence of such an approach is: as soon as one death is observed at EoH, the study may be stopped for futility and failure (inconclusive result). To accept one failure and get a rejection of the null hypothesis once one failure is observed, the minimal sample size becomes 53

patients (p = 0.04967, for 1/53 deaths). Because this sample size cannot be reached within two years, the study is unfeasible if this hypothesis is applied.
Even if the minimal sample size (n= 34) was retained to get a working hypothesis that can be rejected statistically, the power of the study remains quite reasonable. Fexinidazole was administered to 361 stage 2 patients suffering from HAT *T.b gambiense*. Two deaths were observed before the end of hospitalisation, considered unrelated to the treatment or disease. The fatality rate for any cause was therefore equal to 0.554%. These deaths were probably not due to treatment but considering the case of deaths regardless the cause, the power of the study in patients infected by *T.b gambiense* would be 82.79%. Using MSF data[17], the fatality rate in r-HAT stage 2 patients treated with melarsoprol was twice (exactly 1.98) larger in *T.b rhodesiense* than in T*.b gambiense* stage 2 patients. If we consider it is due to the fragility of patients infected by rhodesiense trypanosomes, then the expected fatality rate for any cause with fexinidazole could reach 1.097%. Using the corrected estimate (1.097%) as true then the exact power of the study is 68.73 %. Considering deaths possibly related to treatment or disease, the power should be larger than 70% that is a reasonable power in a rare and neglected disease.
If one death attributable to the treatment or disease–may occur, the DSMB will rule whether or not the use of fexinidazole shall continue until the sample size of 34 patients is reached but no statistical inference will be made with regards to the unacceptable limit of 8.5%.
N.B. In case of non-evaluable patients, the sample size will be increased to reach 34 evaluable patients that are required to get a testable hypothesis in the primary analysis (see primary analysis)**.**
The recruitment will be stopped once 34 evaluable stage-2 patients are recruited.

10.2 Definition of trial populations included in the analysis

The population of evaluable patients is composed of patients who took at least one dose of fexinidazole excluding those whose death during hospitalization (if any) is documented and clearly attributable to other causes than r-HAT or treatment according to the DSMB and those who escape from the hospital and were not retrieved later to know their status on the primary outcome. This is the primary population used in the primary analysis. The choice of this set as the primary one is justified by the fact that the study is inconclusive if only one death occurred. If a death is, according to the DSMB, clearly unrelated to r-HAT or treatment such as poisoning, it is not reasonable to stop the trial for failure due to such an unrelated event.
The secondary population is the modified intent to treat (mITT) set of patients consisting of all patients who took at least one dose of the study drug. This set will also be the safety set of patients.
The intent to treat population (ITT set of patients: all recruited patients, who signed the informed consent and were eligible for treatment) will be used to describe the disposition of patients.
The fexinidazole treatment completer set of patients will consist of all patients who terminate the 10 days of treatment with fexinidazole

10.3 Analyses

10.3.1 Primary analysis

The primary population is the evaluable set of stage-2 patients.

The primary outcome is survival (alive or dead) at EoH.

The primary parameter of interest is death rate at the EoH.

In case of escape of a patient from the hospital and if the patient is not retrieved, the patient will be excluded from the population of evaluable patients and will be considered as a failure, but not a proven death.

A one-sided exact test with respect to 8.5% (unacceptable fatality rate under H_0) will be performed (alpha = 0.05 one-sided).

The one-sided test is justified by the very small number of available patients.

An algorithm will be presented in the Statistical Analysis Plan (SAP).

Sensitivity analyses

The same analysis will be performed on the mITT set of patients and on the set of treatment completers if at least 34 patients belong to these sets.

10.3.2 Secondary analysis

The first secondary analysis will consist of calculating the failure rate at end of hospitalisation in stage-2 patients and to compare it with the threshold of unacceptable failure rate (9%) through a one-sided exact test (alpha = 0.05 one-sided).

The second secondary analysis will consist of estimating the failure rate at 12 months in stage-2 patients and comparing it with the unacceptable threshold of 12%. A one-sided exact test of comparison will be performed if the observed rate is below 12%.

The fatality rate at EoH, failure rate at EoH and failure rate at 12 months will be estimated. Because the sample size will be very small, no null hypotheses will be testable.

The estimate of fatality rate at EoH, failure rate at EoH and failure rate at 12 months for stage-1 and stage-2 combined will be calculated and tested against the unacceptable limit of 8.5%, 9% and 12%, respectively.

10.4 Safety Analysis

The safety analyses will be performed on the mITT population, i.e. all patients (stage-1 and stage-2) 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 provided by system-organ class using MedDRA terms and/or NCI (National Cancer Institute) CTCAE, version 5.0[26] and, for certain laboratory parameters, the modified CTCAE version 5.0 will be used (see Appendix 4 – modified CTCAE 5.0).

The proportion and number of patients who experienced at least one AE will be provided. 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 magnitude of the increase in relation to the ULN for liver function tests (< 1 ULN, 1–2 ULN, 2–3 ULN etc.). Scatter grams 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 until D11 will be described.

10.5 Analysis of other endpoints

10.5.1 PK analyses

Analyses on PK samples will be performed on all patients who took at least one tablet of fexinidazole.

The DBS concentrations of fexinidazole and its metabolites data of DNDi-FEX-07-HAT study will be pooled with those obtained from the DNDiFEX004 and DNDiFEX006 studies, in order to compare the exposure and the PK parameters of g-HAT and r-HAT patients through a population PK approach. Different and complementary timepoints will be looked at to complete the analysis of existing data.

The structural model previously developed on these studies will be used, the model considered one compartment for fexinidazole, M1 and M2 assuming that fexinidazole was metabolized in metabolite M1, which was in turn metabolized in metabolite M2 (Sulfone Metabolite of fexinidazole), the model will be refined with study specifications. Covariates will also be investigated as HAT type, concomitant medications, HAT stage, and demographics characteristics.

PK parameters in patients considered to be treatment failures or who experienced intolerance to fexinidazole will be described individually.

NONMEM software will be used for the population PK analysis.

All methods to be applied for the population modelling will be fully detailed in a dedicated analysis plan.

10.5.2 ECG analysis

The following study will investigate cardiovascular safety of fexinidazole on QTc interval, including all patients for whom matching ECG evaluations and PK samplings were obtained.

QTc interval will be calculated from single or triplicate ECG using RR (Respiratory Rate) and QT intervals. In the case of triplicate ECG, the values for HR and QT will be average before to compute the QTc:

- Fridericia's cube-root corrected QT[1]: QTcF (ms) = QT (ms) / RR(s)1/3
- Bazett's square-root corrected QT[2]: QTcB (ms) = QT (ms) / RR(s)1/2

Note: for all correction methods the RR is converted in second (RR (ms)/1000).

Individual ECG parameters will be listed.
Continuous ECG variables will be summarized on observed values and changes from baseline, by time points, using the number of observations (N), mean, Standard Deviation (SD), min, median and max. The 90% confidence interval of the mean will be added on changes from baseline statistics.
A Categorical analysis will be performed consisting on number and percentage of subjects, presenting at least one value on treatment above a pre-defined threshold (e.g. QTcF>450 ms, QTcF>480 ms, QTcF>500 ms, etc.).
Incidence of subjects presenting at least one treatment emergent morphological finding will also be presented.
To match PK-ECG data, a concentration-QTc analysis will be performed on change from baseline between QTcF and fexinidazole, M1 and M2.

10.5.3 Trypanosome nucleid acids detection analysis.

Standard protocols for extracting DNA and RNA will be applied, followed by Reverse transcription of the latter to obtain cDNA. Both templates will be used alongside each other to determine trypanosome nucleic acid presence in samples from the same patient at different time points. qPCR will be carried out as previously described[25], only including primers and probes specific for *T. brucei* that will consequently amplify *T. b. rhodesiense*. Outputs will be stored in electronic form for future reference.

10.6 Futility analysis

Because it is a one arm design and because only one death can lead to a failure of the trial (inconclusive results), the DSMB will meet as soon as one death occurs and the study can be stopped depending on the DSMB recommendations (the DSMB can decide to continue the trial for exploratory purposes).

Presence of trypanosomes or persistence of high white blood cells (WBC) in CSF at any time from the end of hospitalisation until the end of follow up will also be considered as failure and could also help the DSMB in their recommendation to stop the trial.

In case of unsatisfactory clinical and/or parasitological response during the treatment period and if the patient's survival is at risk for an assumed lack of efficacy of the study treatment, the investigator may introduce rescue treatment with suramin for stage 1 and melarsoprol for stage 2 patients according to the national treatment guidelines. These cases may also be taken into consideration by the DSMB in their recommendation.

11 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB), composed of at least 3 members independent of the investigator and sponsor, will be set up prior to trial initiation. The DSMB monitors the trial in order to ensure that harm is minimised, and benefits maximised for the trial patients. They will review the trial data at pre-determined intervals and issue recommendations about the trial. The data and intervals will be agreed prior to or soon after the trial initiation and documented in the DSMB Charter.

Stopping rules

The study can be stopped prematurely after recommendation by the DSMB if the DSMB considers that the tolerance to treatment or efficacy is insufficient.

12 Quality Assurance and Quality Control Procedures

12.1 Investigator's file

The investigator must maintain adequate and accurate records to enable the conduct of the trial to be fully documented and the trial data to be subsequently verified. These documents include Investigator's Site File, patient clinical source documents and screening / enrolment logs. The Investigator's Site File will contain the protocol/protocol amendments, CRF/SAE/AESI/pregnancy/Child Surveillance Forms and query forms, IEC and regulatory approval with correspondence, sample informed consent, drug accountability records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence etc.

12.2 Case report forms (CRFs)

Data will be collected by laboratory technicians, medical doctors, clinical officers and nurses authorized by the investigator. It will be supervised by the Investigator and signed by the investigator or by an authorised staff member. Trial-specific information will be entered into the Case Report Form (CRF) and forms/documents sent to data management and PV (Pharmacovigilance) (SAE/AESI/pregnancy/Child Surveillance Forms). Data that are derived should be consistent with the source documents or the discrepancies should be explained. All CRF data will be de-identified, i.e. identified by trial patient number only.

The investigator at each trial site should ensure the accuracy, completeness, legibility, consistency, and timelines of all data reported to the sponsor in the CRFs and any other additional information (including SAE/AESI/pregnancy/Child Surveillance Forms and queries) that is required. The investigator is responsible for keeping all consent forms, screening forms, CRF and PV forms and the completed patient identification code list in a secure location.

12.3 Source documents

The verification of the CRF data must be by direct inspection of source documents. Source documents include patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, signed informed consent forms, consultant letters, and patient screening and enrolment logs. Specific pages from the CRF, including HAT sign and symptoms, neurological and physical examination will be used directly as source documents.
The investigator must maintain source documents such as laboratory and consultation reports, history and physical examination reports, etc., for possible review and/or audit by DNDi and/or Regulatory Authorities. The Investigator / designee will record the date of each patient's visit together with a summary of their status and progress in the trial.

12.4 Record Retention

The investigator must keep all trial documents on file for at least 25 years after completion or discontinuation of the trial. After that period of time the documents may be destroyed

with prior permission from DNDi, in compliance with local regulations.

Should the investigator wish to assign the trial records to another party or move them to another location, DNDi must be notified in advance.

12.5 Monitoring, audits and inspections

Monitoring visits to the trial site will be made periodically by DNDi representatives or designated clinical monitors to ensure that GCP and all aspects of the protocol are followed. Source documents will be reviewed for verification of consistency with data on CRFs. The investigator will ensure direct access to source documents by DNDi or designated representatives. It is important that the investigators and their relevant personnel are available during the monitoring visits.
The investigators will permit representatives of DNDi and/or designated clinical monitors to inspect all CRFs, medical records, laboratory work sheets and to assess the status of drug storage, dispensing and retrieval at any time during the trial. The corresponding source documents for each patient will be made available provided that patient confidentiality is maintained in accord with local regulations. The inspections are for the purpose of verifying the adherence to the protocol and to ensure the trial is conducted according to GCP. It is important that the investigators and other trial site staff are available at these visits.
The monitoring visits provide DNDi with the opportunity to evaluate the progress of the trial, verify the accuracy and completeness of CRFs/SAE/AESI/pregnancy/Child Surveillance Forms and queries, resolve any inconsistencies in the trial records, as well as to ensure that all protocol requirements, applicable regulations, and investigator's obligations are being fulfilled. Four visit types are planned: pre-trial, trial start, during the trial, and trial end. Visits may also be performed by regulatory authorities. All monitoring activities are detailed in the study clinical monitoring plan.
The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

12.6 Audits and inspections

The trial site may also be subject to quality assurance audits by DNDi or designated representatives and/or to inspection by regulatory authorities or Independent Ethics Committees (IEC).

It is important that the investigators and their relevant personnel are available for possible audits or inspections.

12.7 Data Management

After the CRF visit has been completed, reviewed, signed by the investigator (or delegate) and monitored by the clinical monitor on the study site, CRFs will be scanned and uploaded on a platform or sent by email to [redacted] for a centralized double data-entry in the electronic data capture system REDCap software system (www.project-redcap.org). The REDCap server will be kept in a locked server room at [redacted] and will only be accessible to authorized personnel.

All data entered into the CRFs will be transferred to the database using Secure Sockets

Layer (SSL) encryption and a multi-level back-up system will be implemented.
Data clarification will be issued at data entry level and afterwards in order to ensure data quality; queries will be issued and sent on site for resolution.

Procedures to ensure good quality data will be detailed in the Data Management Plan, including details of the following:

- CRFs versions and completion guidelines
- Database structure, dictionary, data entry system and validation of the database
- Methods of data collection
- Type of data entry
- Data preparation before entry onto electronic system
- Data entry validation, data cleaning, data validation plan and data clarification form generation
- Data flow
- Database audit trail
- Database lock
- Data review checks to support monitoring
- SAE reconciliation
- Security/backup
- Electronic data transfer rules
- Archiving and security arrangements
- Coding conventions

12.8 Confidentiality of trial documents and patients' records

The investigator must assure that patients' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents submitted to the sponsor, patients should not be identified by their names, but exclusively by an identification code. The investigator should keep a patient enrolment list showing codes, names, and addresses. The investigator should maintain documents for submission to sponsor authorized representatives, and patients signed written consent forms, in strict confidence.

13 Protocol Amendments

The Principal investigator will ensure that the trial protocol is strictly adhered to throughout, and that all data are collected and recorded correctly on the CRF. In case one or more laboratory or clinical assessments cannot be performed, the investigator will contact and discuss with the medical responsible person for the trial, to qualify whether the deviation is minor, or the patient has to do this assessment at an additional visit.

All protocol modifications must be documented in writing. Any protocol amendment must be approved and signed by the sponsor and the Principal investigator and is to be submitted to the appropriate IEC for information and approval in accordance with local requirements, and to regulatory agencies if required.

Approval by IEC (and Regulatory Authority, if applicable) must be awaited before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial patients, or when the change involves only logistical or administrative aspects of the trial [e.g. change in clinical monitor[s], change of telephone number[s].

The protocol amendment can be initiated by either sponsor or by any Principal investigator.

The investigator will provide in writing the reasons for the proposed amendment and will discuss with the medical coordinator and sponsor.

14 Early Termination of the Trial

Both the sponsor and the investigator reserve the right to terminate the trial at any time prior to inclusion of the intended number of patients, but they intend to exercise this right only for valid scientific or administrative reasons. Should this be necessary, both parties will arrange the procedures on an individual trial basis after review and consultation. In terminating the trial, the sponsor and the investigator will assure that adequate consideration is given to the protection of the patient's interest.
Reasons for early termination by the sponsor(s) may include but not be limited to:

- Too low enrolment rate.
- Protocol violations.
- Inaccurate or incomplete data.
- Unsafe or unethical practices.
- Questionable safety of the test article.
- Suspected lack of efficacy of the test article.
- Following the recommendation of the DSMB or IEC
- Administrative decision.

Reasons for early termination by the investigator may be:

- Insufficient time or resource to conduct the trial
- Lack of eligible patients

In the event that a trial is early terminated either by the sponsor or by the investigator, the investigator has to:

- Complete all CRFs to the greater extent possible
- Return all test articles, CRF, and related trial materials to the sponsor who provided them
- Answer all questions of the sponsors or their representatives related to data of patients enrolled at the site prior to trial termination
- Ensure that patients enrolled in the trial who had not yet reached a follow up time point are followed up with the necessary medical care.
- Provide in writing the reasons for his decision to the national health authority and the sponsor.

15 Ethics

The experimental protocol for this trial has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki and ICH guidelines for GCP (ICH-GCP E6 (R2)).

DNDi assures that it will comply with all applicable state, local and foreign laws for protecting the rights and welfare of human patients.

This protocol and any protocol amendments will be reviewed / approved by all applicable

IECs before its implementation.

It is the responsibility of the National Coordinating Investigator to apply for review to the IEC of the country where the trial takes place regarding local rules and regulations. Written approval from all involved IECs must be obtained before implementation of any protocol-specified intervention /investigation provided to the patient [such as patient information sheets or descriptions of the trial].

Any modifications made to the protocol after receipt of the IEC approval must also be submitted by the investigator in writing to the IEC in accordance with local procedures and regulatory requirements. (see section 13 Protocol Amendments).

The protocol will be submitted for an opinion from the “Direction Générale de la Santé Commission Cantonale d'Ethique de la Recherche (CCER) “ in Geneva, Switzerland.

15.1 Informed consent process

Inclusion in the trial will occur only if the patient (for adults) or the parent/guardian (for children or incapacitated adult) gives written informed consent. It is the responsibility of the investigator / designee to obtain written informed consent from each individual participating in this trial, after adequate presentation of aims, methods, anticipated benefits, and potential hazards of the trial. The written informed consent document will be translated into the local language or a language understood by the patient(s). If needed, the person will be given time to discuss the information received with members of the community or family before deciding to consent. The patient or parent/guardian will be asked to provide written and signed consent.

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 and an impartial witness has to be present during the whole consent process. 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 provided during the consent process and to that end may call upon a “translator/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 (drawings) 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.

If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All patients (including those already being treated) should be informed of the new information, given a copy of the revised form and give their consent to continue in the trial.

15.1.1 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 15.1.2 Illiterate Patients; 15.1.3 Patients Unable to Give Consent; and 15.1.4 Collection of Assent from Children (patients below 18 years old)).

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 study team, 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.

15.1.2 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.

15.1.3 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 the patient's legally acceptable 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.

15.1.4 Collection of Assent from Children (patients below 18 years old)

Children who are eight (8) years old or above must give their assent after the parent or legal representative's and/or guardian's consent is obtained. Exceptions are made for emancipated young adults, as described in the last paragraph.

Children who are between 6 and 8 years old will be asked to give their assent. It is difficult to obtain assent from children under 14 years of age as children have difficulty weighing up benefits and risks. 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. 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.

If the parent or the legal representative is illiterate, a fingerprint should replace the signature and an impartial witness must attend the assent process and the consent process for the parent or legal representative (see 15.1.1 Section Impartial Witness).

For young adults considered as emancipated because they are already married or having a child, according to specific local regulations, the consent can be obtained without requiring the signature from a legal representative or guardian. If the emancipated minor is illiterate, a fingerprint should replace the signature an impartial witness must attend the consent process.

15.2 Ethical aspects of patient inclusion and trial procedures

Blood 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 total volume of blood drawn up to the end of the study would be about 30mL.The maximal quantity during 1 visit is 5mL. 5 mL of blood is about the volume of a small tea spoon.

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, in France and then to Belgium. The samples collected in tubes and on filter paper for qPCR analyses will be sent to a Central Laboratory in [redacted]. 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.

The number of lumbar punctures will be kept to a minimum and the amount of CSF to be drawn will be 4mL per LP (Lumbar Puncture), i.e. 20ml in total up to the end of study.

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 once all the expected results are obtained and the destruction procedure will be recorded in a certificate of destruction.

15.3 Patient costs

Patients will be reimbursed for travel costs to and from the trial site but will not receive any payment for trial participation. Any medication that is required during the trial period will be provided free of charge to the patient. Food during the in-patient treatment phase will also be provided free of charge to the patient and to the caregiver, irrespective of whether the patient is included in the study or not. This is seen as an essential part of the patient care plan bearing in mind the high prevalence of malnutrition and the poverty of these patients.

15.4 Insurance and Liability

DNDi is insured to indemnify the investigator against any claim for damages brought by a research patient who suffers from a research related injury during the performance of the trial according to the protocol.

16 Reporting and Publication of Trial results

All clinical trials will be registered with a recognised clinical trial registry such as **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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18 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 – Evaluation criteria of efficacy endpoints

Category / Visit	Death	Relapse	Probable Relapse	Lost to Follow up	Uncertain Evolution	Favourable Evolution	Probable Cure	Cure
EoH	All deaths during hospitalisation, after the start of treatment or resulting from an event that started within that period, which cannot be clearly attributed to reasons other than HAT or the treatment itself	Trypanosomes detected in any body fluid	Tryps-negative patient who refuses lumbar puncture OR whose CSF is haemorrhagic AND who requires rescue treatment		Tryps-negative patient whose clinical condition requires, in the opinion of the Investigator, a close follow-up	Patient alive with no evidence of trypanosomes in any body fluid		
Intermediate follow up visits	All deaths with a clinical picture certainly or possibly compatible with HAT, with the treatment or unknown, to which no alternative cause can be clearly attributed	Trypanosomes detected in any body fluid	Tryps-negative patient with increased WBC/µl in CSF from previous values, whose WBC count is unlikely due to causes other than HAT OR who refuses lumbar puncture OR whose CSF is haemorrhagic AND who requires rescue treatment		Tryps-negative patient who, in the opinion of the Investigator, requires a close follow-up exam because of a rising CSF WBC count OR a deterioration of clinical condition that might be due to HAT	Tryps-negative patient with ≤5 WBC/µl in CSF in a not haemorrhagic sample OR decreased from previous values AND for whom there is direct evidence of satisfactory clinical condition OR whose clinical status is unlikely due to HAT		
12-month	All deaths with a clinical picture certainly or possibly compatible with HAT, with the treatment or unknown, to which no alternative cause can be clearly attributed	Trypanosomes detected in any body fluid	• Tryps-negative patient with >20 WBC/µl in CSF in a non-haemorrhagic sample, whose WBC count is unlikely due to causes other than HAT • Tryps-negative patient who refuses lumbar puncture OR whose CSF is haemorrhagic AND who requires rescue treatment	Patient who did not attend the 6 and the 12 months visits AND for whom there is no direct evidence of satisfactory clinical condition OR there is direct evidence of a clinical status likely due to HAT			• Tryps-negative patient who refuses lumbar puncture OR whose CSF sample is haemorrhagic AND whose clinical condition is satisfactory OR whose clinical status is unlikely due to HAT • Patient who did not attend the 6 and the 12 months visit AND for whom there is direct evidence of satisfactory clinical condition OR whose clinical status is unlikely due to HAT	Tryps-negative patient whose CSF sample is not haemorrhagic with ≤20 WBC/µl
Analysis	**Failure**	**Failure**	**Failure**	**Failure**	**To be assessed by an Independent evaluation committee**	**To be assessed by an Independent evaluation committee**	**Success**	**Success**

Appendix 3 – Karnofsky Index

KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA

The Karnofsky Performance Scale Index allows patients to be classified as to their functional impairment [24]. This can be used to compare effectiveness of different therapies and to assess the prognosis in individual patients. The lower the Karnofsky score, the more serious the impairment is.

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

Appendix 4 – modified CTCAE 5.0

	CTCAE v5.0 SOC	CTCAE v5.0 Term	units	LLN	ULN	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v5.0 AE Term Definition
Hematology											
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	-	
Biochemistry											

	CTCAE v5.0 SOC	CTCAE v5.0 Term	units	LLN	ULN	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v5.0 AE Term Definition
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; intervention indicated	>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	125-129 and asymptomatic	<125 - 129 symptomatic; 120-124 regardless of symptoms	<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	<LLN - 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			>ULN - 5.5	>5.5 - 6.0; intervention initiated	>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)"					

	CTCAE v5.0 SOC	CTCAE v5.0 Term	units	LLN	ULN	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v5.0 AE Term Definition
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			<LLN - 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			Abnormal glucose above baseline with no medical intervention	Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes	Insulin therapy initiated; hospitalization indicated	life-threatening consequences; urgent intervention indicated	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			>ULN - 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.

	CTCAE v5.0 SOC	CTCAE v5.0 Term	units	LLN	ULN	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v5.0 AE Term Definition
	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	
Blood Urea Nitrogen			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)"					
Creatinine	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			>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		Navigational Note: Also consider Renal and Urinary disorders: Acute Kidney Injury
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 if baseline was normal; 2.0-2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal;	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal;	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal		
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 if baseline was normal; 1.5-3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal;	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal;	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal		Navigational Note: Also consider Hepatobiliary disorders: Hepatic Failure

	CTCAE v5.0 SOC	CTCAE v5.0 Term	units	LLN	ULN	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v5.0 AE Term Definition
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 if baseline was normal; 1.5-3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal;	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal;	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal		Navigational Note: Also consider Hepatobiliary disorders: Hepatic Failure
Total Bilirubin	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 if baseline was normal; >1.0-1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal;	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal;	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal		Navigational Note: Also consider Hepatobiliary disorders: Hepatic Failure
Albumin	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	
Total Protein			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 new biological values									

Appendix 5 – Schedule of events

Protocol Procedures and Forms to be completed	Screening and Baseline	Treatment Period										EoT Visit	EoH Visit	Follow-up Visits				Unschedu-led Visit[1]
Time	**D-7 to D-1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11[2]**	**D12-D18[2]**	**M1[3]**	**W9**	**M6**	**M12**	
Thick/thin blood smear	x																	
mAECT[4]	x					x						x			x	x	(x)[5]	
Lymph node aspirate microscopic examination	x											x			x	x	(x)[5]	
Lumbar Puncture	x											x			x	x	(x)[5]	
Patient informed consent	x																	
Inclusion/Exclusion criteria review	x																	
Demographics	x														x[6]	x[6]	(x)[5,6]	
Medical history	x																	
Concomitant medications record	x	x	x	x	x	x	x	x	x	x	x	x	x					x
Karnofsky index	x					x						x	x	x	x	x	x	x
Treatment of helminthiasis	x																	
Malaria rapid test and/or thick blood smear	x																	
Pre-treatment of malaria[7]	x																	

[1] Additional tests can be performed at investigator's discretion, if medically needed

[2] EoT could be at D12 and EoH from D13 and D19 if there was a temporary interruption of treatment (max 24hours)

[3] M1 consists of a home visit to the patient by the investigator. In case of clinical concerns, the investigator could request parasitological test

[4] If parasites show negative, mAECT-BC will also be performed. mAECT-BC to be used as as back-up method if mAECT not available

[5] If patient is unable or unwilling to attend M12 visit, direct evidence of a satisfactory patient's clinical condition by the Investigator or a delegated staff from the trial team is sufficient. If the clinical condition is unclear, patient should be brought back to the hospital for parasitological exams

[6] Applied only to children

[7] Only if malaria test is positive

Protocol Procedures and Forms to be completed	Screening and Baseline	Treatment Period										EoT Visit	EoH Visit	Follow-up Visits				Unschedu-led Visit[1]
Time	**D-7 to D-1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11[2]**	**D12-D18[2]**	**M1[3]**	**W9**	**M6**	**M12**	
Vital signs	x[8]	x	x	x	x	x	x	x	x	x	x	x	x		x	x	(x)[5]	x
Biochemistry	x[8]					x						x			x			
Haematology	x[8]					x						x			x			
PK sampling		H0.5 H3.5 H6			H3.5 H6 H12							D10 H24	D10 H48					
Blood sampling for qPCR	x[8]	H6			H12							D10H 24			x	x	x	
ECG recording (safety)	x[8]		x[9]	x[9]	x[9]													
ECG recording (triplicate)	x[8]				H3 H12							D10 H23			x			
HAT signs and symptoms questionnaire	x[8]					x							x	x	x	x	(x)[5]	x
Physical examination	x[8]					x						x	x	x	x	x	(x)[5]	x
Neurological examination	x[8]					x						x	x	x	x	x	(x)[5]	x
Pregnancy test	x[8][10]												x		x			
Fexinidazole administration		x	x	x	x	x	x	x	x	x	x							
Adverse events record	x	x	x	x	x	x	x	x	x	x	x	x	x	x[11]	x[11]	x[11]	(x)[5,11]	x
Serious adverse events (SAEs) record	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	(x)[5]	x

8 Tests to be performed at baseline (D -4 to D -1)

9 Pre-dose

10 Test to be done on the first day of screening

11 From M1 to M12: only AEs considered related to fexinidazole are to be reported