DNDi
Drugs for Neglected Diseases *initiative*

STATISTICAL ANALYSIS PLAN

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 1.0 – 25 August 2020

Study Title:

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

Statistical Analysis Plan

SAP		**Effective Date**: 31Aug2020
Version Number and Date: 1.0, 25 Aug 2020		
Revision		
List of changes:		
Name and function	**Date** (DD-MMM-YYYY)	**Signature**
Author		
[redacted] Biostatistician	Sep 1, 2020	[redacted]
Reviewed by		
[redacted] Director of Research department	Sep 2, 2020	[redacted]
[redacted]. Statistician	Sep 10, 2020	[redacted]
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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
BMI	Body Mass Index
CI	Confidence Interval
CRF	Case Report Form
CSF	Cerebrospinal Fluid
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
DND*i*	Drugs for Neglected Diseases *initiative*
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EoH	End of Hospitalization
EoT	End of Treatment
EoS	End of Study
GCP	Good Clinical Practice
H	Hour
ITT	Intent to Treat
M	Month
mAECT	Mini Anion Exchange Centrifugation Technique
mAECT-BC	Mini Anion Exchange Centrifugation Technique on Buffy Coat
MHCT	Microhematocrit centrifugation test
MSF	Médecins sans Frontières
PK	Pharmacokinetics
PP	Per Protocol
PV	Pharmacovigilance
REDCap	Research Electronic Data Capture
r-HAT	*Rhodesiense* Human African Trypanosomiasis
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
WBC	White Blood Cell
W	Week

WHO	World Health Organization

1. Introduction

This standard methodology document, the statistical analysis plan, explains the rules and conventions to be used in the presentation and analysis of efficacy and safety data for the study "Efficacy and safety of fexinidazole in patients with Human African Trypanosomiasis (HAT) due to *Trypanosoma brucei rhodesiense*: a multicentre, open-label clinical trial ".

It describes the data and endpoints to be summarized and analysed, including specifics of the statistical analyses to be performed and is based on protocol "DNDi-FEX-07-HAT protocol_v4.0_23JAN2020". Any ad hoc analyses not described in this SAP may be performed and will be detailed in the appropriate section of the clinical study report.

2. Study objectives

The primary objective is to show that the fatality rate (r-HAT or treatment related death) at the end of hospitalization in stage-2 patients treated with fexinidazole is smaller than a threshold of unacceptable rate of 8.5%.

The secondary objectives are the followings:

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%
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%
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
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].

And the 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

The analyses on the PK component will be detailed in another document.

3. Study design

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

4. Sample size calculation

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[1], 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%.

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.

The recruitment will be stopped once 34 evaluable stage-2 patients are recruited.

5. Interventions

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.

6. Study plan

The following time and events schedule provides all the assessments performed during the study up to the M12 visit.

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																	
Vital signs	x[8]	X	x	x	x	x	x	x	x	x	x	x	x		x	x	(x)[5]	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

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

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**	
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

[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

7. Analysis sets and presentation of data

7.1. Analysis variables

7.1.1 Demographic and baseline characteristics

The following variables will be described for demographic and baseline characteristics.

Demographics characteristics:

- Age (derived from the date of birth or as reported in years, if date of birth unknown), sex

Laboratory characteristics for diagnosis of HAT

- Results of blood and lymph tests (including the mAECT test and the number of trypanosomes observed (Semi-quantification), the mAECT-BC test, the lymph node aspirate test, mHCT (Woo test), Thin/Thick blood smear
- Results of Cerebrospinal fluid test including the presence of trypanosome, the used method and the value of WBC/µl
- HAT stage (stage 1 is defined as at least one test for trypanosomes detected in blood and/or lymph is positive, and absent in the CSF and WBC≤5/µl of CSF, and stage 2 is defined as the presence of trypanosome in the CSF with any number of WBC in CSF and/or any positive trypanosome test in blood, lymph and/or CSF with WBC>5/µl of CSF.

Clinical and other baseline characteristics:

- History of HAT (stage and treatment received during the last episode of HAT if any)
- Medical history (including allergies, psychiatric disorders, metabolic disturbances, active malignancy, drug abuse, seizure disorders, cardiovascular disease, HIV and others if any)
- Results of malaria test (including malaria rapid diagnostic test and thick smear test)
- Vital signs (including temperature, Heart Rate, Respiratory rate, blood pressure), weight, height, BMI and a general health status
- Signs and symptoms of trypanosomiasis (presence of the sign/symptom, time from the first sign/symptom, continuous or intermittent and grade)
- Physical and neurological examinations (presence of any abnormality)
- Hematology and biochemistry results (result, presence of abnormality and CTCAE grade if clinically significant)
- Pregnancy status for women and trimester for pregnant women

7.1.2 Dosing and adherence to the treatment

The total dose of Fexinidazole to which the participant was exposed will be calculated, taking into account the need to replace vomited doses within 2 hours after administration, considering the re-administered doses following vomiting (if any). The total dose will be compared to the theoretical dose the patient should have received following the posology:

For patients with a body weight ≥35kg), the theoretical total dose is:

- 1800 mg (3 tablets) from day 1 to 4
- 1200 mg (2 tablets) from day 5 to 10

Leading to a total dose of 14400 mg.

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

Leading to a total dose of 8400 mg.

Adherence (in %) to Fexinidazole as described in the protocol, i.e. not taken into account the vomited doses within two hours after administration, will be calculated following the formula: [(Total dose (mg) intake-vomited doses)/Total theoretical dose (mg)] x100. The total dose will include re administered doses after vomiting but not the vomited doses.

Duration of the treatment will be also stated in number of days, and the reasons for longer or shorter duration that 10 days will be shown in a table.

Additionally, the following will be displayed:

- Patients who completed the full course of treatment (i.e. at least 10 days) (yes/no)
- Patients fully compliant (i.e. children with body weight less than 35 kg who took exactly 14 tablets or children with body weight who took exactly 24 tablets or adults who took exactly 24 tablets) (yes/no)
- Patients who always took their treatment during a meal (yes/no)
- Patients who had at least one re-administration (yes/no)
- Patients who had at least one re-administration due to vomiting (yes/no)
- Patients who had at least one re-administration due to other reason (yes/no)
- Number of re-administration(s) by patient (0, 1, 2, …)

7.1.3 Efficacy variables

The primary efficacy variable is the death possibly related to r-HAT or to Fexinidazole, according to DSMB, up to the end of hospitalisation in stage 2 r-HAT patients.
Any death not related to r-HAT nor to the treatment during the hospitalisation will not be taken into account and the patient will be considered as not evaluable. Any patient leaving the hospital on his own will before the planned end of hospitalisation period and for whom no outcome could be retrieved will also be considered as non-evaluable.

The secondary efficacy variables are:

1. The success and failure at the end of hospitalisation in stage 1 and stage 2 r-HAT patients. The success is defined by:
    - the absence of trypanosome at the end of treatment visit
    - and the patient alive at the EoH visit

The failure is defined as:

- the presence of trypanosome in any fluid at the end of treatment visit
- or the death of the patient possibly related to r-HAT or treatment, according to DSMB.
- or absence of clinical improvement leading to the use of rescue treatment

Any death not related to r-HAT nor to the treatment, during the hospitalisation will not be taken into account and the patient will be considered as not evaluable for this efficacy variable. In the absence of lumbar puncture at EoT visit, the patient will be considered as non-evaluable for this specific variable, unless a lumbar puncture is done before the EoH visit.

2. The success and failure at the M12 visit. A modification of the WHO recommendations is used to determine success and failure for stage-1 and stage-2 r-HAT patients (Appendix 1 - Evaluation criteria of efficacy endpoints).
   The success is defined as:
    - any patient with a success at EoH,
      and
    - absence of trypanosomes in any body fluid, with WBC in the CSF ≤20 /µl at the M12 visit, OR
    - absence of trypanosomes in blood but without lumbar puncture results and presence of a satisfactory clinical condition according to the investigator (ability

to have an active life without relevant symptoms of disease) or a clinical status unlikely due to HAT at the M12 visit, OR

- any patient who did not attend the M6 and the M12 visits but with reports of either a satisfactory clinical condition or a clinical status unlikely due to HAT at the M12, according to the investigator or delegated staff from the trial team.
- any patient fitting to one of the definitions above and not qualifying as failure according to the definitions below.

A patient is considered as a failure at the M12 visit, in case of any of the following condition:

- patient with a failure at EoH, or
- any death with a clinical picture certainly or possibly compatible with HAT, with the treatment or unknown, to which no alternative cause can be clearly attributed, between the EoH visit and the theoretical date of M12 visit (D1 +306 days), or
- presence of trypanosomes at any visit after EoH up to the M12 visit, or
- result of the cerebrospinal fluid test negative for the presence of trypanosome and with WBC in the CSF >20 /µl at any visit after EoH visit in CSF in a non-hemorrhagic sample, whose WBC count is unlikely due to causes other than HAT, or
- result of the blood or lymph node aspiration (if done) tests negative for the presence of trypanosome but without lumbar puncture OR whose CSF is haemorrhagic AND who requires rescue treatment at any visit after EoH visit
- patient who did not attend M6 and M12 visits and for whom there is no direct evidence of satisfactory clinical condition or there is a direct evidence of a clinical status likely due to HAT

3. Unsatisfactory clinical and parasitological response during the observation period and at the EoT visit. In order to evaluate this unsatisfactory response, the following will be be displayed:
    - Persistence of any initially reported signs and symptoms with the same grade as compared to baseline or occurrence of new sign(s) of HAT at the end of hospitalisation visit,
    - Persistence of abnormal laboratory test results as compared to baseline or occurrence of new abnormalities at the end of hospitalization,

- Persistence of positive result in parasitological tests as compared to baseline at the end of treatment visit

The exploratory efficacy variables to assess the efficacy are:

- The earliest time to detect a relapse defined as:
  - presence of trypanosomes in any body fluid from the EoT visit to 12 months after D1, or
  - The date of death if attributable to r-HAT or treatment administration according to the DSMB or
  - The administration of rescue medication
- The quantification of trypanosomes in blood at all visits
- Trypanosome nucleid acids detection until the end of study (analyses described elsewhere)

7.1.4 Safety variables

The safety analysis will be based on the reported adverse events (AEs)/adverse events of special interest (AESIs)/Serious Adverse Events (SAEs) in the case report forms, and other safety information, such as vital signs, laboratory examinations, ECG, physical and neurological examinations during the hospitalization and the follow-up of the study.

7.1.4.1 Adverse events

An adverse event refers to 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". In this study, will be considered 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).

Adverse events will be collected all along the study duration, following as detailed below:

- during the screening period, with potential AE that may be linked to study procedure;
- during the hospitalization period, any worsening pre-existing condition of the medical history (not HAT signs/symptoms) or any new event occurring after treatment initiation
- during the follow-up visits, only AE(s) related to Fexinidazole, or SAE or AESI

7.1.4.2 Clinical signs

Vital sign measurements including body temperature, blood pressure (BP), heart rate (HR), and respiratory rate will be taken at screening, during the treatment period, at EoT, at EoH visits and during W9, M6 and M12 follow-up visits and can be reported also during unscheduled visits.

Physical and neurological assessments will be performed at screening, during the treatment period, at EoT, at EoH visits and during W9, M6 and M12 follow-up visits and can be reported also during unscheduled visits.

7.1.4.3 Laboratory assessments

Biochemistry and haematology tests will be performed at screening, D5, EoT, at W9 visit and at unscheduled visit if needed.

The following parameters will be measured:

- 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 (CI-), creatinine (CRE), glucose (GLU), potassium (K+) sodium (Na+), calcium (Ca2+), total bilirubin (TBIL), total carbon dioxyde (tCO2), total protein (TP)

Any abnormal finding will be assessed for clinical significance and graded when appropriate.

7.1.4.4 Other data

Single ECG will be performed at screening, D2, D3, D4 and during unscheduled visits if needed. A centralized reading will be performed by [redacted] and results will be reported

separately.

Triplicates ECG will be performed at screening, D4, EoT, W9 and during unscheduled visits if needed. A centralized reading will be performed by [redacted] and results will be reported separately..

Pregnancy tests will be performed at screening, EoH and W9 visit. Any woman exposed during pregnancy will be monitored for safety up to the outcome of the pregnancy, and the child followed up until 2 years of age as feasible (information reported in the DNDi PV database).

7.2. Analysis populations

The intent to treat (ITT) population, including all recruited patients who signed the informed consent and included in the study will be used for the disposition of patients.

7.2.1 Safety population

The safety population includes all patients who took at least one dose of the study drug, regardless of study deviations/violations and stage of r-HAT. This corresponds also to the modified intent to treat population (mITT) defined in the efficacy population section.

7.2.2 Efficacy population

The modified intent to treat (mITT) population, consisting of all patients from the ITT who took at least one dose of fexinidazole, will be used for sensitivity analyses . This set will also be the safety population.

The primary population for efficacy analyses is the population of evaluable patients, excluding from the mITT population, patients whose death during hospitalization (if any) is documented and clearly attributable to other causes than r-HAT or treatment according to the DSMB and patients who escaped from the hospital and were not retrieved later to know their status on the primary outcome.

Another population for efficacy is composed of patients from the mITT who completed the treatment with fexinidazole, either in 10 days or in 11 days if one dose of fexinidazole is missed.

7.2.3 Participant disposition

The total number of participants for each of the following categories will be presented:

- Screened participants and reason for non-inclusion
- ITT population
- mITT population
- Evaluable population
- Treatment Completer population
- Participants who discontinued the treatment and reason for discontinuation
- Participants who completed the follow-up
- Participants who discontinued the follow-up and reason for discontinuation

7.3. Statistical methods

Continuous variables will be summarized using the number of observations available (N), median and IQR (interquartile range) or mean and standard deviation (SD) and min/max when more appropriate; categorical data will be summarized for each category using counts of non-missing data and percentages. 95% confidence intervals (CIs) for binomial proportions will be estimated using the Clopper-Person exact method. Nevertheless, comparisons to pre-specified thresholds will be done using a one-sided exact test at the significance level of 5%.

7.3.1 Demographic and baseline characteristics

Descriptive statistics will be displayed to summarize the demographic and baseline characteristics data on the safety population.

7.3.2 Analysis of efficacy data

7.3.2.1 Analysis of the primary endpoint

The primary analysis of the primary endpoint is the comparison of the proportion (pdeath) of deaths possibly related to r-HAT or to Fexinidazole at the end of the hospitalization (as defined in section 7.1.3) to the threshold of 8.5%.

The hypotheses of test will be under H_0: pdeath≥8.5% vs H_1 pdeath<8.5%. The hypothesis will be tested using a one-sided exact test for proportions, at the 0.05 significance level.

This comparison will be performed on the stage 2 patients from the evaluable population which must be composed of at least 34 patients.

Sensitivity analyses will be performed by repeated this comparison on stage-2 patients from the mITT and completers if those populations contain at least 34 patients.

7.3.2.2 Analysis of the secondary endpoints

The proportion of failure at the end of hospitalisation will be compared to the thresholds of 9% on stage 2 patients from the mITT and completer populations.

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.

The failure rate at the M12 visit will be compared to the threshold of 12% on the stage-2 r-HAT patients from the mITT and treatment completer populations, using a one-sided test if the observed rate if below 12%.

The fatality rate at EoH, failure rate at EoH and failure rate at 12 months will be estimated and presented with a 95%CI, on the stage-2 r-HAT patients from the mITT and treatment completer populations. No comparison to pre specified thresholds will be performed.

The fatality rate at EoH, failure rate at EoT, and failure rate at the month12 visit will then be estimated in the entire (stage-1 and stage 2-patients) evaluable population and compared respectively to the pre specified threshold of 8.5%, 9% and 12%. The comparisons will be repeated on the mITT and completers.

All comparisons will be done using a one-sided exact test for proportions, at the 0.05 significance level (one sided).

Time to failure (as defined previously) and time to reduction in the number of trypanosomes in the blood will be estimated using survival analysis.

7.3.3 Analysis of safety data

The analyses of safety data will be performed on the safety population (mITT). AE(s) will be tabulated overall and by grade, and by period of reporting as appropriate:

- During the screening period (AE(s) potentially linked to study procedure)
- During hospitalization (all AE(s), including AESI(s) and SAE(s))
- Follow up (AE(s) related to Fexinidazole, SAE(s) and AESI(s))

If a patient experiences several events described with the same term, the event with the maximal severity will be included in the analysis.
The SAE(s) and AESI(s) will be tabulated overall during the entire follow-up including the hospitalization and by period.

7.3.3.1 Analyses of adverse events

Each AE will be coded to a "Preferred Term" (PT) and primary associated "System-Organ Class" (SOC) according to the MedDRA dictionary (Medical Dictionary for Regulatory Activities, version 22.0 or higher). Counts will be provided overall and for each PT within each SOC. The coding will be updated to the latest available version of MedDRA at the time of the database lock.

The summaries of AE will include:

- The number and percentage of participants with at least one AE
- The number and percentage of participants with at least one AE in a specific PT/SOC

Number and percentage of participants with at least one AE of the following categories will also be provided, by SOC and PT:

- AEs related to the IP
- AEs leading to follow-up discontinuation
- Serious AEs
- AESI
- AEs leading to death

7.3.3.2 Analyses of clinical signs

Descriptive statistics of vital signs, weight and BMI parameter at baseline and change from baseline will be presented at each visit whenever applicable. Summaries will be displayed for participants having at least one baseline and one post baseline values.

For the physical examination, findings and changes from baseline will be summarized at each visit it was planned to be assessed.

7.3.3.3 Analyses of laboratory data

Haematology and biochemistry parameters will be described with the number and % of abnormal results clinically significant by visit, and quantitative description at each visit.

Shift plots will be provided comparing baseline with values collected at EoT and W9.

7.3.4 Data handling convention

The baseline value is defined as the latest measured value of a parameter before the first drug intake of Fexinidazole. A post baseline value is a value obtained after the first drug intake.

The BMI will be calculated at each visit the weight is collected using the height collected at screening for adults, and using the height for less than 15 yo at its latest measure.

8. Interim analysis

A Data Safety Monitoring Board (DSMB) is implemented and will conduct review of data following the developed charter in use for this study.

9. Software conventions

All analyses will be performed using STATA version 15.0 or higher for the final analysis.

Appendix 1 – 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**