DNDi
Drugs for Neglected Diseases *initiative*

STATISTICAL ANALYSIS PLAN

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

Registration number NCT03025789

Version 3.0 – 30 September 2022

DNDi-FEX-09-HAT

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Version 3.0 – 30/09/2022

Written by [redacted]

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1. STATISTICAL ANALYSIS PLAN - APPROVAL FORM

Function	Name	Signature	Date
Clinical Project Manager	[redacted]		
HAT Clinical Program Team Leader	[redacted]		

Function	Name	Signature	Date
Head of Biostatistics	[redacted]		

2. VERSION HISTORY

Version	Date	Author	Comment / changes
0.1	24/10/2016	[redacted]	Initial draft version (based on protocol version 1.0 dated of 10/08/2016 and CRF version 1.0 dated of 27/09/2016)
0.2	21/03/2017	[redacted]	Add comments from DNDi
0.3	12/12/2017	[redacted]	Add comments from [redacted] Version based on protocol version 2.0 dated of 17/03/2017)
0.4	22/03/2018	[redacted]	Add comments from [redacted]
1.0	27/04/2018	[redacted]	First approved and signed version
2.0	23/09/2022	[redacted]	Second approved and signed version. Included changes as requested by DSMB on 03-AUG-2022.
3.0	23/09/2022	[redacted]	third approved and signed version. Included changes on algorithms.

3. ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CATT	Card Agglutination Test for Trypanosomiasis
CI	Confidence Interval
CRF	Case Report Form
CSF	Cerebrospinal Fluid
D	Day
DNDi	Drugs For Neglected Diseases Initiative
DSMB	Data And Safety Monitoring Board
e.g.	Exempli Gratia (For Example)
ECG	Electrocardiogram
EoH	End Of Hospitalisation
EoT	End Of Treatment
g-HAT	Human African Trypanosomiasis due to T.B. Gambiense
H	Hour
HAT	Human African Trypanosomiasis
i.e.	Id Est (That is to say)
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ITT	Intention To Treat
mAECT	Mini-Anion Exchange Column Test
mAECT-BC	Mini-Anion Exchange Column Test - Buffy Coat
MedDRA	Medical Dictionary For Regulatory Affairs
mITT	Modified Intention To Treat
PK	Pharmacokinetic
PP	Per Protocol
QT	QT interval on ECG (time interval between electrical depolarisation and repolarisation of the left and right cardiac ventricles)
RDT	Rapid Diagnostic Test
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
T.b.	Trypanosoma Brucei
ULN	Upper Limit of Normal
WBC	White Blood Cell Or White Blood Cell Count
WHO	World Health Organisation
µL	Microlitre

4. PROTOCOL

The overall study design, plan description, study objectives, inclusion and exclusion criteria and sample size calculation are described in the Protocol version 2.0 dated of 17/03/2017.

5. ANALYSIS SETS AND SUBGROUPS

The analysis sets are the following.

- **Screened HAT positive patients**: all HAT positive patients who signed the informed consent.
- **Intent-to-treat (ITT)** population: all patients included in the study, regardless of whether or not they took the IMP (but the treatment unit was provided to the outpatient);
- **Modified intent-to-treat (mITT)** population: all patients who took at least one tablet of fexinidazole;
- **Evaluable patients:** patients included in the mITT and excluding:
    - Patients lost to follow-up at 18 months (for primary efficacy endpoint and secondary efficacy outcome at 18 month), patients lost to follow-up at 12 months (for secondary efficacy outcome at 12 month), except those who were a failure before being lost to follow-up.
    - Patients with no post-treatment lumbar puncture
    - Patients who died for reasons clearly unrelated to efficacy or safety or disease evolution (**).
- **Per protocol (PP):** all patients who completed the study in accordance with the protocol with no major violations (cf. Section 8.2) that could interfere with the efficacy evaluation. An out-patient who did not take any tablet of the IMP or with a compliance below 75% of the expected number of tablets is not per protocol unless it is due to lack of tolerance. Premature withdrawal from the study due to treatment inefficacy or intolerance will not be considered as a protocol violation.

Two study cohorts are defined:

- **Inpatients**: patients treated in hospital,
- **Outpatients**: patients treated on an outpatient basis. Note that outpatients that would require hospitalization (for any reason) will be analyzed according to their initial cohort (i.e. as “outpatients”).

The following subgroups are defined according to the stage and severity of disease at inclusion:

- Stage 1
- Intermediate stage
- Stage 1 + Intermediate stage
- Stage 2
- WBC in CSF ≤ 100 / µL
- 100 < WBC in CSF ≤ 400 / µL
- WBC in CSF > 400 / µL

For the analysis, these subgroups will be calculated as described in Table 1. Subgroups analyses are specified in Section 8.

Table 1 : Classification of patients according to stage/severity at inclusion

Tryps in CSF	**WBC in CSF**		
	≤ 5/µl	**[6-20/µl]**	**> 20/µl**
Tryps in CSF (positive)	Stage 2	Stage 2	Stage 2
No tryps in CSF (negative)	Stage 1	Intermediate stage	Stage 2

6. ENDPOINTS

6.1. Primary endpoint

The primary endpoint for the assessment of effectiveness will be the outcome (success or failure) at 18 months after the end of treatment. Success is defined as a cure, according to the criteria adapted from the WHO.

The outcome (success or failure) at 18 months will be calculated using the algorithm defined in Section 10.1.

6.2. Secondary endpoints

6.2.1. Intermediate endpoint at 12 months

The endpoint for an early assessment of effectiveness will be the outcome (success or failure) at 12 months after the end of treatment. Success is defined as a cure, according to the criteria adapted from the WHO.

The outcome (success or failure) at 12 months will be calculated using the algorithm defined in Section 10.2.

6.2.2. Compliance

As defined in the protocol, the secondary endpoints for the assessment of compliance with treatment in patients treated on an outpatient basis will be:

- Presence of fexinidazole and/or its main metabolites in the blood sample collected on Day 11 and/or at any unscheduled visit between Day 1 and the end-of-treatment (EoT) visit *(note: this endpoint will be analyzed by* [redacted]*)*
- Patients who had tablets left over at the end of treatment (i.e. number of tablets returned on day 11 > 0) (yes/no)
- Number of tablets left over at the end of treatment (i.e. number of tablets returned on day 11) (0, 1, 2, …)
- Patients' responses to the questionnaire at the compliance interview on Day 11: Questions 5, 5.1, 5.2, 5.3 and 5.4.

In addition, the following endpoints will be assessed on all patients (i.e. inpatients and outpatients):

- 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, …)
- Overall compliance defined as:
  - For patients with body weight < 35 kg (Children):

$$\text{Compliance (\%)} = \frac{100 \times \text{Actual dose taken (mg)}}{8\,400 \text{ mg (i.e. } 1200 \text{ mg } \times \text{ 4 days} + 600 \text{ mg } \times \text{ 6 days)}}$$

  - For patients with body weight ≥ 35 kg (Children) or Adults:

$$\text{Compliance (\%)} = \frac{100 \times \text{Actual dose taken (mg)}}{14\,400 \text{ mg (i.e. } 1800 \text{ mg } \times \text{ 4 days} + 1200 \text{ mg } \times \text{ 6 days)}}$$

Note for overall compliance:

Actual dose taken (mg) = 600 mg X number of tablets taken

Number of tablets taken = (sum of tablets taken from Day 1 to Day 11) + (sum of tablets taken for re-administration from D1 to D11)

Patients with one day delayed treatment (missing dose compensated at the end of treatment) should be considered as treatment completers. In case of death during the treatment, compliance will be calculated according to theoretical dose expected until the death.

6.2.3. Feasibility

As defined in the protocol, the secondary endpoints for assessment of the feasibility of self-management of treatment intake, or with the assistance of the caregiver under recommended conditions are the following for patients treated on an outpatient basis:

- Patients who temporarily discontinued their treatment (yes/no)
- Patients who prematurely (i.e. prior to Day 10) discontinued their treatment (permanent interruption) (yes/no)
- Patients who delayed starting treatment (i.e. date of D1 – date of D0 > 1 day) (yes/no)
- Patients who mislaid treatment units (i.e. number of tablets left over>0) (yes/no)
- Patients who were hospitalized during their treatment period
- Patients with:
  - 1, 2, 3, …, 9, 10 days of treatment administration performed at the hospital.
  - 0 days (=treatment adminstration performed at home only).
- Patients who took treatment regularly, according to the patients themselves (=questionnaire on Day 11: Question 5 “How did you take your treatment?”) (yes/no)
- Patients who understood the instructions concerning the dosing regimen of fexinidazole (=questionnaire on Day 0: patients who correctly answered to the 8 questions) (yes/no)
- Patients who complied with the dosing regimen, including intake of treatment during a meal (=questionnaire on Day 11: patients who correctly answered to the 4 questions 5.1 to 5.4) (yes/no)

In addition, the following data will be listed:

- Reasons of temporary treatment discontinuation
- Reasons of premature and permanent treatment discontinuation
- Reasons of hospitalization during the treatment period

The following data will also be described in patients treated in hospital:

- Patients who temporarily discontinued their treatment (yes/no)

- Patients who prematurely discontinued their treatment (permanent interruption) (yes/no)

The following data will also be listed in patients treated in hospital:

- Reasons of temporary treatment discontinuation
- Reasons of premature and permanent treatment discontinuation

6.2.4. Packaging

As defined in the protocol, the secondary endpoint for assessment of understanding and acceptability of the packaging by outpatients will be:

- Questionnaire on Day 0 (patients and/or caregivers):
  - Questions 1 to 8, separately
- Questionnaire on Day 11 (patients and/or caregivers):
  - Question 3: "Did you need help to take the treatment?"
  - Question 4: "Was the instruction manual (provided with the treatment) useful?"

6.2.5. Pharmacokinetic (PK)

As defined in the protocol, the secondary endpoint for the PK assessment will be:

- PK parameters in whole blood, measured in all patients treated in hospital.

Statistical analyses of the PK parameters will be performed by [redacted]. These analyses will be defined in a separate statistical analysis plan, written by [redacted].

6.3. Safety endpoints

As defined in the protocol (Section 2.2.2), the secondary endpoints for the assessment of the safety of fexinidazole will be:

- Occurrence of grade ≥ 3 adverse events (AEs), including laboratory and haematological abnormalities (if considered clinically significant), between the first intake of fexinidazole and the end of the observation period* or the follow-up period (18 months) for non-serious AEs assessed as related to fexinidazole.
- Occurrence of any serious adverse event (SAE) between the first intake of fexinidazole and the end of the follow-up period (18 months).
- Number of patients who prematurely discontinued treatment (i.e. prior to Day 10) or were hospitalised for reasons related to safety** (e.g. including overdose).

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

*** A patient will be considered as "hospitalised for reasons related to safety" if he/she experienced a SAE during the treatment period and he/she was initially planned to be treated as an outpatient and he/she was hospitalized during the treatment period.*

Clarifications:

Only laboratory and haematological abnormalities reported as AEs by investigators (cf. Section 6.8.1 of the protocol for further details) will be analyzed as AEs.

Additional secondary safety endpoints are defined in this SAP (cf. sections 6.3.1, 6.3.2 and 6.3.4).

6.3.1. Adverse events

The following AE categories will be studied:

- Treatment-emergent adverse events (TEAE)
- TEAE leading to treatment discontinuation (i.e. permanent or temporary)
- TEAE leading to permanent treatment discontinuation
- Mild/moderate TEAE (grade 1, grade 2, mild or moderate)
- Severe TEAE (grade 3, grade 4, grade 5 or severe)
- Drug-related TEAE
- Serious TEAE
- Serious TEAE leading to treatment discontinuation (i.e. permanent or temporary)
- Serious TEAE leading to permanent treatment discontinuation
- Serious drug-related TEAE

Definition of treatment-emergent AEs:

Treatment-emergent AEs are defined as any AE which occurs on or after the date of the first study-drug administration until the end of the follow-up visit (i.e. 18-month visit).

6.3.2. Laboratory examination

All laboratory parameters recorded in the CRF in sections “Hematology”, “Biochemistry” and “Urinalysis” will be used. For continuous data, the absolute change from baseline to each timepoints will be derived. In addition, continuous laboratory values will be compared to their reference ranges and classified as “<LLN”, “Normal” and “>ULN” at baseline and each timepoints.

For the following parameters, CTCAE grades will be derived as defined in Appendix 6 of the protocol:

- Hemoglobin
- Platelets
- Leukocytes
- Sodium
- Potassium
- Calcium
- Bicarbonates
- Chloride
- Glucose
- BUN
- Creatinine
- Alkaline phosphatase
- ALAT
- ASAT
- Total bilirubin
- Albumin
- Total protein

6.3.3. Electrocardiogram

Statistical analyses of ECG parameters will be performed by [redacted]. These analyses will be defined in a separate statistical analysis plan, written by [redacted]

6.3.4. Other safety endpoints

- Number of patients who discontinued treatment for safety reason*,

- Number of patients who were hospitalized for reasons related to safety*, including overdose.

** Reasons collected in the CRF comments will be classified by a medical review as "safety reason" or "other reason".*

6.4. Other endpoints and variables

6.4.1. Demographic and other baseline characteristics

The following standard characteristics (gender, BMI, etc.) will be used as recorded in the CRF:

- Demographic characteristics
- Vital signs at baseline
- Clinical signs and symptoms of HAT at baseline
- Physical examination at baseline
- Neurological examination at baseline
- HAT diagnosis (i.e. examination of blood, lymph and CSF samples)

The following data will be derived:

- Age (years) will be used as collected in eCRF. If not available then it will be calculated as the exact duration in years between date of birth and date of informed consent
- BMI classified according to the World Health Organization (WHO):
  - <18.5 – Underweight
  - 18.5 - <25 – Normal weight
  - 25 - <30 – Overweight
  - ≥30 – Obesity

6.4.2. Medical history

Medical and surgical history will be coded using MedDRA dictionary (last available version at the beginning of the coding).

6.4.3. Prior and concomitant therapies

Prior and concomitant therapies will be coded with WHO-Drug Dictionary September 2013 C-format.

- Prior therapies are therapies which stopped before the first study drug administration.
- Concomitant therapies are therapies which ended on or after the first study drug administration or are ongoing at the end of the trial.

6.4.4. Extent of exposure

Extent of exposure will be derived as follows:

- Extent of exposure (days) = Date of last study drug administration - Date of first study drug administration + 1

7. DATA ANALYSIS CONSIDERATIONS

7.1. Statistical software

The statistical analysis will be performed using SAS® software v9.4 (or a later version).

7.2. Type I error

For all analyses, the type I error (α) is set to 0.05 two-sided.

7.3. Centre effect

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

7.4. Descriptive analyses of quantitative and qualitative variables

Quantitative variables will be described by: N (number of patients with non-missing data), missing (number of patients with missing data), mean, standard deviation (SD), minimum, maximum, median, first quartile (Q1) and third quartile (Q3).

Categorical variables will be described by frequency and percentage of patients in each category. Percentages will be expressed with one decimal place. The Clopper-Pearson (exact) 95% confidence interval will be provided, if required in Section 8.

7.5. Definition of baseline, time-windows and analysis periods

Baseline:

Baseline is defined by data collected during the D-15 to D-1 period before the beginning of the treatment.

Analysis periods:

Study procedures will be performed in accordance with the following schedule:

- Between D-15 to D-1: screening and baseline assessment,
- D0: IMP dispensing visit prior to first intake of IMP (Patients on an outpatient basis only)
- D1 to D10: treatment period,
- D11: End of Treatment (EoT) visit
- Between D13 to D18 : End of Hospitalization (EoH) visit (Patients treated in hospital only)

Follow-up visits for all patients will be performed at 3 months, 6 months, 12 months and 18 months.

Time-windows:

The timing of follow-up visits is calculated from the first day of treatment (D1).

The table below defines the theoretical schedule of follow-up visits and the acceptable Leeway:

Type of visit	Schedule of visit and ideal timing of visits	Acceptable Leeway*
End-of-hospitalisation (EoH) visit, only for patients treated in hospital	Between D13 and D18 after D1	D18 at the latest
3 months	3 months ± 1 week after D1	2 to 4 months, i.e. 60 to 149 days, after Day 1
6 months	6 months ± 1 weeks after D1	5 to 9 months, i.e. 150 to 299 days, after Day 1
12 months	12 months ± 4 weeks after D1	10 to 16 months, i.e. 300 to 509 days, after Day 1
18 months	18 months ± 4 weeks after D1	17 to 21 months, i.e. 510 to 659 days, after Day 1

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

Any additional unscheduled visits that may take place must be recorded in the CRF. Real timing of unscheduled visits will be calculated and they will be analysed in the corresponding time-window (see table above).

7.6. Handling of missing data and outliers

Handling of missing data for primary and secondary efficacy endpoints:

Handling of missing data is described in Section 9.8 of the Protocol and is included in the derivation algorithms for outcome at 18 and 12 months (cf. Section 10).

Handling of missing AE attributes:

Missing relationship, missing seriousness, and/or missing severity will not be replaced and will be analysed as such.

Onset date of AE will be imputed as below. The general rule in the absence of information is to retain a conservative imputation.

Onset date of AE	Imputed AE onset date
Completely missing	For AEs collected in the "Screening" form: Date of informed consent For AEs collected in the "Follow-up" forms: Date of first study drug administration
Day is missing	First day of the month. For AEs collected in the "Screening" form: If imputed date is prior to date of informed consent, then replace with date of informed consent. For AEs collected in the "Follow-up" forms:

Onset date of AE	**Imputed AE onset date**
	If imputed date is prior to date of first study drug administration, then replace with date of first study drug administration.
Day and month are missing	First of January. <u>For AEs collected in the "Screening" form:</u> If imputed date is prior to date of informed consent, then replace with date of informed consent. <u>For AEs collected in the "Follow-up" forms:</u> If imputed date is prior to first study drug administration, then replace with date of first study drug administration.

Note: partially or completely missing end dates of AE will not be imputed.

<u>Handling of missing stop dates of prior and concomitant therapies:</u>

For therapies marked as "ongoing": the stop date will not be imputed.

For therapies marked as "not ongoing", the stop date will be imputed as below.

Stop date of therapy	**Imputed stop date**
Completely missing	No imputation. The therapy will be considered as "ongoing" for the analysis.
Day is missing	Last day of the month. <u>For therapy collected in the "Screening" form:</u> if imputed date is later than the end of hospitalisation visit date, then replace with the end of hospitalisation visit date. <u>For therapy collected in the "Follow-up" form:</u> if imputed date is later than the date of last contact, then replace with the date of last contact.
Day and month are missing	31 December <u>For therapy collected in the "Screening" form:</u> if imputed date is later than the end of hospitalisation visit date, then replace with the end of hospitalisation visit date. <u>For therapy collected in the "Follow-up" form:</u> if imputed date is later than the date of last contact, then replace with the date of last contact.

Note: partially or completely missing start dates of therapies will not be imputed.

8. PLANNED STATISTICAL ANALYSES

8.1. Disposition of patients

Disposition of patients and reasons for premature discontinuations will be tabulated overall, by cohorts (i.e. "inpatients" and "outpatients") and in each subgroups defined in Section 5 (i.e. "Stage 1", "Intermediate stage", "Stage 1 + intermediate stage" and "Stage 2"):

- Number of screened HAT positive patients (i.e. patients who gave informed consent)
- Amongst screened HAT positive patients:
  - Number and percentage of patients who attended the dispensation visit (i.e. Day 0), for "inpatients"
  - Number and percentage of patients who attended visit "Day 1", for "outpatients"
- Number of patients included (i.e. which meets all the criteria for inclusion and has no exclusion criteria)
- Number of patients treated (i.er. who received at least one tablet of fexinidazole)
- Amongst treated patients:
  - Number and percentage of patients who withdrew from the study prematurely, listed by reason for withdrawal
  - Number and percentage of patients who completed the trial according to the protocol
- The following data will also be provided amongst treated patients:
  - Number and percentage of patients who received all of the protocol-planned doses (=treatment completers)
  - Number and percentage of patients who died for reasons clearly unrelated to the IP or HAT
  - Number and percentage of patients who had at least one minor protocol violation
  - Number and percentage of patients who had at least one major protocol violation
  - Number and percentage of patients who underwent lumbar puncture at the end-of-hospitalisation, at the 3-month visit, at the 6-month visit, the 12-month visit and the 18-month
  - Number and percentage of patients who attended visits "Day 1" to "Day 10" (for inpatients only), the end-of-treatment (EoT) visit, the end-of-hospitalisation (EoH) visit (for inpatients only), the 3-month, 6-month, 12-month and 18-month visits.

In addition the following data will be provided:

- Date of first patient screened
- Date of first administration of the first patient
- Date of first administration of the last patient
- Date of last patient last visit (i.e. last visit performed)
- Study duration (days) = date of last patient last visit - date of first administration of the first patient

8.2. Protocol deviations

Minor and major protocol violations will be described separately, by cohort, by subgroups and overall on the mITT.

Protocol violations will be listed and finalised prior to the data review meeting. The sponsor will be responsible for classifying all violations as either major or minor. Patients with at least one major protocol violation will be excluded from the PP set. A specific data review plan will provide a more detailed description on deviation review. All decision taken by the data review members will be reported in the Data review document.

8.3. Analysis sets and subgroups

Frequency and percentage of patients included in each analysis sets defined in Section 5 will be provided by cohorts, subgroups and overall.

8.4. Demographic data and baseline characteristics, including medical history and therapies

Descriptive analyses will be provided by cohorts, subgroups and overall on the mITT.

Number and percentage of patients included in each subgroups defined in Section 5 will be provided by cohorts and overall on the mITT.

Medical and surgical history will be analyzed by MedDRA SOC and PT. Medical and surgical history will be tabulated with number of history, number and percentage of patients with at least one history classified by SOC and PT.

Prior therapies and concomitant treatments will be tabulated with number of treatments, number and percentage of patients with at least one treatment classified by therapeutic class (ATC2) and preferred name.

8.5. Extent of exposure

Descriptive analyses will be provided by cohorts, subgroups and overall on the mITT.

The same analyses will be provided according to expected dose:

- Adult patients and children with body weight equal to or above 35 kg (i.e. who should took 24 tablets)
- Children with body weight of at least 20 kg and below 35 kg (i.e. who should took 12 tablets)

8.6. Analysis of the primary endpoint

Primary analysis

A descriptive analysis of the primary efficacy endpoint with the 95% exact Clopper-Pearson confidence intervals will be provided on the mITT (overall).

Sensitivity analysis

A descriptive analysis of the primary efficacy endpoint with the 95% exact Clopper-Pearson confidence intervals will be provided on the Evaluable patients set and PP set (overall).

Secondary analysis

A descriptive analysis of the primary efficacy endpoint with the 95% exact Clopper-Pearson confidence intervals will be provided by cohorts and by subgroups on the mITT.

8.7. Analysis of the secondary endpoints

8.7.1. Analysis of the endpoint at 12 months

The endpoint at 12 months will be analysed as described for the primary endpoint (see above Section 8.6: "primary", "sensitivity" and "secondary" analyses).

8.7.2. Analysis of failures

Analysis of failures will be provided on the mITT (overall).

Description:

A listing of failures will provide for each failure:

- The time to failure (since the first treatment administration)
- Signs of failure observed: WBC in CSF >20/µL, death (cause if known), presence of trypanosomes in blood or lymph, rescue medication and LTFU
- Number of WBC in CSF at inclusion
- WBC in CSF at inclusion classified as follows: ≤ 100, 100-400 and > 400/µL
- Presence of trypanosomes in CSF
- Presence of the following symptoms at inclusion: sleepiness, prurit, tremor, asthenia and headache
- Number of tablets left over at the end of treatment.

Statistical modeling: logistic regression

- Model 1: the failure rate will be related to the $\log_e$ of the number of WBC in CSF (/µL) at inclusion.
- Model 2: the failure rate will be related to the compliance (number of tablets left over at the end of treatment)
- Model 3: the failure rate will be related to the score equal to the sum of weighted symptoms at inclusion (5 points if sleepiness observed at entry, 4 points for prurit, 3 points for tremor, 2 points for asthenia and 1 point for headache).
- Model 4: the failure rate will be related to the presence of a symptom score of 12 or more (see model 3).

8.7.3. Compliance

Descriptive analyses will be provided on outpatients from the ITT population for the following endpoints:

- Presence of fexinidazole and/or its main metabolites in the blood sample collected on Day 11 and/or at any unscheduled visit between Day 1 and the end-of-treatment (EoT) visit *(note: this endpoint will be analyzed by* [redacted]*)*
- Patients who had tablets left over at the end of treatment (i.e. number of tablets returned on day 11 > 0) (yes/no)
- Number of tablets left over at the end of treatment (i.e. number of tablets returned on day 11) (0, 1, 2, …)
- Patients' responses to the questionnaire at the compliance interview on Day 11: Questions 5, 5.1, 5.2, 5.3 and 5.4.

Descriptive analyses of other endpoints listed in Section 6.2.2 will be provided by cohorts, by subgroups and overall on the ITT.

Patients for whom the number of tablets taken is different from 24 (14 for children <35 kg) or number of treatment day is different from 10 or number of tablets remaining is different from 0 or number of

re-administered tablets is different from 0 or had treatment discontinuation (permanent or temporary) will be listed with all the information concerning their treatment.

The following analysis defined in Section 9.6.2 of the protocol will be provided by [redacted]: "*the number and percentage of patients in whom the presence of fexinidazole or its main metabolites was detected in the blood sample collected on D11 will be presented, as well as the success rate in this sub-group of patients and in the subgroup of patients in whom no trace of fexinidazole or its main metabolites was detected. The distribution of the frequency of the number of tablets remaining at the end of the treatment period will be presented, and the relationship between the success rate and the number of tablets remaining will be determined using a logistic regression or a sub-group analysis. The distribution of the frequencies of responses from patients during the compliance interview will be presented. The information provided by the PK analyses, the number of tablets remaining and the questionnaire will be combined to define perfect compliance and noncompliance. Perfect compliance corresponds to a patient in whom fexinidazole is detected in the blood, who has no remaining tablets and whose report on full compliance with treatment seems unquestionable. The success rate in patients with perfect compliance will be compared to that in non-compliant patients*".

8.7.4. Feasibility

The secondary analyses concerning the feasibility of patient self-management of treatment intake under recommended conditions will be performed on outpatients from the ITT population. The endpoints analysed will be those defined in Section 6.2.3. For each of the endpoints, the proportion of patients will be presented with the 95% CI.

8.7.5. Packaging

Descriptive results of the questionnaires completed at D0 and D11 by the patients and/or caregivers will be presented on an outpatient and/or caregivers basis (sub-group of outpatients from the ITT population).

8.7.6. PK

The statistical analysis of the pharmacokinetic data will be performed by [redacted] and is not covered in the current statistical analysis plan. A separate statistical analysis plan will be prepared by [redacted] for these analyses. Cf. protocol, Section 9.6.5 for further details.

8.8. Safety analysis

Safety analyses will be performed on the mITT.

8.8.1. Secondary endpoints for assessment of safety

Analysis of "occurrence of grade ≥ 3 AEs" and "occurrence of any SAE" is described below in Section 8.8.2.

A descriptive analysis will be provided by cohorts, subgroups and overall for the following endpoint: "number of patients who discontinued treatment or were hospitalized for reasons related to safety, including overdose".

8.8.2. Adverse events

Analysis of adverse events will be based on the concept of treatment-emergent adverse events (TEAE) (cf. definition in Section 6.3.1).

An overall summary of TEAEs occurring during the 18 months follow-up period (i.e. from first drug intake up-to end of follow-up) will be presented by cohorts, subgroups and overall. The following information will be tabulated (the number, percentage of patient and 95% CI):

- At least one TEAE
- At least one TEAE leading to treatment discontinuation (i.e. permanent or temporary)
- At least one TEAE leading to permanent treatment discontinuation
- At least one mild/moderate TEAE (grade 1, grade 2, mild or moderate)
- At least one severe TEAE (grade 3, grade 4, grade 5 or severe)
- At least one drug-related TEAE
- At least one serious TEAE
- At least one serious TEAE leading to treatment discontinuation (i.e. permanent or temporary)
- At least one serious TEAE leading to permanent treatment discontinuation
- At least one serious drug-related TEAE

For the following descriptions the number and percentage of patients and also the number of occurrences of TEAE will be presented by cohorts, subgroups and overall, and by MedDRA SOC and PT:

- TEAE
- Drug-related TEAE
- Serious TEAE
- Serious drug-related TEAE

All AEs and SAEs will be listed. In addition, TEAE leading to permanent or temporary treatment discontinuation and Drug-related TEAE which occurred during the treatment period (i.e. between the first study-drug intake (included) and the last study-drug intake (included)) will be listed (cf. Section 9.1).

8.8.3. Laboratory examination

For continuous data, a descriptive analysis will be provided for baseline, at each time point and for the changes from baseline at each time point, by cohorts, subgroups and overall.

Changes in blood levels over time will be presented in graphs.

Shift tables between baseline severity (normal value, abnormal not clinically significant, abnormal clinically significant) and severity at each timepoint (i.e. D5, D11, M3, M6, M12, M18) for each laboratory parameters will be provided by cohorts, subgroups and overall.

Scattergrams between baseline value and value at each timepoint (i.e. D5, D11, M3, M6, M12, M18), for each laboratory parameters will be provided by cohorts, subgroups and overall.

Proportions of patients by category corresponding to the size of the increase in relation to the ULN for liver function tests (i.e. ALT, AST, total bilirubin and alkaline phosphatase) will be described (< 1 ULN, 1–2 ULN, 2–3 ULN etc.) by cohorts, subgroups and overall.

A listing of patients with clinically significant abnormalities in laboratory parameters will be provided (cf. Section 9.1).

8.8.4. Electrocardiogram

The statistical analysis of ECG data will be performed by [redacted] and is not covered in the current statistical analysis plan. A separate statistical analysis plan will be prepared by [redacted] for these analyses.

8.8.5. Other safety endpoints

Descriptive analyses will be provided by cohorts, subgroups and overall on the mITT.

8.9. Analysis of other endpoints and variables

Analyses of other endpoints will be performed on the mITT. Results will be displayed by cohorts, subgroups and overall.

8.9.1. Vital signs

Descriptive statistics will be provided by visit.

8.9.2. Clinical signs and symptoms of HAT

Descriptive statistics will be provided by visit.

8.9.3. Physical examination

Descriptive statistics will be provided by visit.

8.9.4. Neurological examination

Descriptive statistics will be provided by visit.

8.9.5. HAT diagnosis (i.e. examination of blood, lymph and CSF samples)

Descriptive statistics will be provided by visit.

8.9.6. Pharmacokinetics

The statistical analysis will be performed by [redacted] and will be described in a separate statistical analysis plan.

8.9.7. Electrocardiogram

The statistical analysis will be performed by [redacted] and will be described in a separate statistical analysis plan.

8.10. Interim analyses

No interim analysis is planned. This a change from the analysis planned in the protocol (cf. Section 11 for further details).

8.11. Unscheduled visit

During the data review, any efficacy and safety data from unscheduled visit which must be taken into account in the analysis will be identified.

Other data from unscheduled visits will only be tabulated in listings except for time to event analyses where they will be taken into account.

8.12. Data and Safety Monitoring Board (DSMB)

A DSMB, composed of at least 3 members independent of the Investigators and the Sponsor, will be set up prior to the start of the study. The DSMB will monitor the study in order to minimize any risk of harm to the patients included in the study.

At each of its meetings, the DSMB will examine safety data and all information related to SAEs, and will issue recommendations regarding the study if the benefit-to-risk ratio for patients seems to be in jeopardy. The data and the intervals for review will be decided before, or shortly after the start of the study and will be recorded in the DSMB Charter.

The organization of the DSMB will be described in the DSMB Charter, which will be prepared and approved prior to the first planned futility analysis.

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

9. DISPLAY TEMPLATES

9.1. List of Tables, Figures and Listings

1. TRIAL PATIENTS:

1.1 Disposition of patients

Statistical Table 1.1.1: Disposition of patients

1.2 Important protocol deviations

Statistical Table 1.2.1: Protocol deviations (ITT)

1.3 Analysis sets

Statistical Table 1.3.1: Analysis datasets

1.4 Demographic data and baseline characteristics

Statistical Table 1.4.1: Demographic data (mITT)

Statistical Table 1.4.2: Vital signs at baseline (mITT)

Statistical Table 1.4.3: Clinical signs and symptoms of HAT at baseline (mITT)

Statistical Table 1.4.4: Physical examination at baseline (mITT)

Statistical Table 1.4.5: Neurological examination at baseline (mITT)

Statistical Table 1.4.6: HAT diagnosis (examination of blood, lymph and CSF samples) at screening (mITT)

1.5 Medical history

Statistical Table 1.5.1: Medical history (mITT)

1.6 Prior and concomitant therapies

Statistical Table 1.6.1: Prior therapies (mITT)

Statistical Table 1.6.2: Concomitant treatments (mITT)

1.7 Extent of exposure

Statistical Table 1.7.1: Extent of exposure (mITT)

2. Primary and secondary endpoints

2.1 Primary efficacy endpoint

2.1.1 Primary analysis

Statistical Table 2.1.1.1: Success rate at 18 months (mITT - overall)

2.1.2 Sensitivity analyses

Statistical Table 2.1.2.1: Success rate at 18 months (PP - overall)

Statistical Table 2.1.2.2: Success rate at 18 months (Evaluable set - overall)

2.1.3 Secondary analyses

Statistical Table 2.1.3.1: Success rate at 18 months by cohorts and subgroups (mITT)

2.2 Secondary endpoints

2.2.1 Endpoint at 12 months

Same outputs as in Section 2.1.

2.2.2 Analysis of failures

Statistical Table 2.2.2.1: Logistic regression: Model 1 – all patients (mITT)

Statistical Table 2.2.2.2: Logistic regression: Model 2 – all patients (mITT)

Statistical Table 2.2.2.3: Logistic regression: Model 3 – all patients (mITT)

Statistical Table 2.2.2.4: Logistic regression: Model 4 – all patients (mITT)

Statistical Table 2.2.2.5: Logistic regression: Model 5 – all patients (mITT)

2.2.3 Compliance

Statistical Table 2.2.3.1: Compliance – outpatients (ITT)

Statistical Table 2.2.3.2: Compliance – all patients (ITT)

2.2.4 Feasibility

Statistical Table 2.2.4.1: Feasibility – outpatients (ITT)

2.2.5 Packaging

Statistical Table 2.2.5.1: Packaging – outpatients (ITT)

3. Safety

3.1 Adverse events

Statistical Table 3.1.1: Overall summary of AEs (mITT)

Statistical Table 3.1.2: TEAE by SOC and PT (mITT)

Statistical Table 3.1.4: Drug-related TEAE by SOC and PT (mITT)

Statistical Table 3.1.5: Serious TEAE by SOC and PT (mITT)

Statistical Table 3.1.7: Serious drug-related TEAE by SOC and PT (mITT)

3.2 Laboratory examinations

3.2.1 Haematology:

Statistical Table 3.2.1.1: Descriptive analysis of haematology parameters at baseline, at each time points and changes from baseline at each time points (mITT)

Statistical Figure 3.2.1.2: Changes over time of each haematology parameters (mITT)

Statistical Table 3.2.1.3: Shift tables between baseline and each time points of haematology parameters' severity (mITT)

Statistical Table 3.2.1.4: Shift tables of CTCAE grades between baseline and each time points of haematology parameters (mITT)

Statistical Figure 3.2.1.5: Scattergrams between baseline value and value at each time points of each haematology parameters (mITT)

3.2.2 Biochemistry:

Same outputs as above (except Figure 3.2.1.2).

Statistical Table 3.2.1.6: Liver function tests (mITT)

3.2.3 Urinalysis:

Statistical Table 3.2.3.1: Shift tables between baseline and each time points of urinalysis parameters (mITT)

4. Other endpoints

Statistical Table 4.1: Descriptive analysis of vital signs by visit (mITT)

Statistical Table 4.2: Descriptive analysis of clinical signs and symptoms of HAT by visit (mITT)

Statistical Table 4.3: Descriptive analysis of physical examination by visit (mITT)

Statistical Table 4.4: Descriptive analysis of neurological examination by visit (mITT)

Statistical Table 4.5: Descriptive analysis of HAT diagnosis (examination of blood, lymph and CSF samples) by visit (mITT)

5. Individual data listings:

The following listings will be included in the clinical study report. They will include all patients included in the study and all visit information will be presented chronologically (including unscheduled visits).

5.1 Discontinued patients

- Disposition of patients – all patients
- Study discontinuation – all patients

5.2 Protocol deviations

- Informed consent
- Inclusion/Exclusion criteria
- Eligibility
- Protocol deviation

5.3 Patients excluded from the efficacy analysis

- Patients excluded from ITT
- Patients excluded from Treated set
- Patients excluded from PPS

5.4 Demographic data

- Patients characteristics
- Diagnosis-parasite in blood and/or lymph
- Lumbar puncture (parasite and WBC)

5.5 Medical history, prior and concomitant therapies

- Medical history
- Pre-treatment of helminthiasis

- Pre-treatment of malaria
- Prior medications
- Concomitant treatments

5.6 Compliance and/or drug concentration data

- Treatment administration
- Compliance

5.7 Individual efficacy response data

- Diagnosis-parasite in blood and/or lymph
- Lumbar puncture (parasite and WBC in CSF)
- Efficacy outcomes at 18 and 12 months
- Listing of failures

5.8 Adverse event listings

- All Adverse Events
- Serious Adverse Events
- TEAE leading to permanent or temporary treatment discontinuation
- Drug-related TEAE which occurred during the treatment period

5.9 Individual laboratory measurements

- Haematology
- Biochemistry
- Thyroid function
- Patients with clinically significant abnormalities in laboratory parameters

5.10 Other endpoints

- Vital Signs
- Clinical signs and symptoms of HAT
- Physical examination
- Neurological examination
- HAT diagnosis (examination of blood, lymph and CSF samples)

9.2. Display templates

The display templates in this section are designed for 4 groups. They will be adapted to display 2 groups or 3 groups, when specified in Section 8.

9.2.1. Disposition of patients

Disposition of patients	**Inpatients (N=XX)**	**Outpatients (N=XX)**	**Stage 1 and Intermediate (N=XX)**	**Stage 2 (N=XX)**	**Total (N=XX)**
Screened positive (=informed consent signed)	xxx	xxx	xxx	xxx	xxx
- Visit Day 0 (for outpatients) or Day 1 (for inpatients) performed?	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Included (=all in/ex criteria respected)	xxx	xxx	xxx	xxx	xxx
Treated	xxx	xxx	xxx	xxx	xxx
- Study completed according to protocol	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
- Premature withdrawal:	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
- Death	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
- Lost to follow-up	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
- Withdrawal of consent	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
- Investigator's decision	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
- Adverse event (AE)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
- Rescue treat. prescribed < D11 (1)	NA	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
- Rescue treat. due to relapse	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
- Other reason	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
- Treatment completers (2)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
- Death not related to the IP or HAT	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
- Minor PV	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
- Major PV	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
- Lumbar puncture performed at EoH	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
- Lumbar puncture performed at M3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
- (…)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
- Attended visit D1	xx (xx.x%)	NA	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
- Attended visit (…)	(…)	NA	(…)	(…)	(…)
- Attended visit D10	xx (xx.x%)	NA	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
- Attended visit EoT	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
- Attended visit EoH	xx (xx.x%)	NA	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
- (…)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
- Attended visit M18	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
First patient screened					dd-mmm-yy
First study-drug admin. of the first patient					dd-mmm-yy
First study-drug admin. of the last patient					dd-mmm-yy
Last patient last visit					dd-mmm-yy
Study duration (days)					xxx

(1) Rescue treatment prescribed for outpatients before Day 11.

(2) Patients who received all of the protocol-planned doses.

9.2.2. Protocol deviations

Protocol Deviations		**Inpatients (N=XX)**		**Outpatients (N=XX)**		**Stage 1 and Intermediate (N=XXX)**		**Stage 2 (N=XXX)**		**Total (N=XXX)**	
		n Patients	nDeviations	nPatients	nDeviations	nPatients	nDeviations	nPatients	nDeviations	nPatients	nDeviations
Major protocol deviation	Yes	n (xx.x%)	xx	n (xx.x%)	xx	n (xx.x%)	xx	n (xx.x%)	xx	n (xx.x%)	xx
Type of major protocol deviation	Type 1	n (xx.x%)	xx	n (xx.x%)	xx	n (xx.x%)	xx	n (xx.x%)	xx	n (xx.x%)	xx
	Type 2	n (xx.x%)	xx	n (xx.x%)	xx	n (xx.x%)	xx	n (xx.x%)	xx	n (xx.x%)	xx
	Type …	n (xx.x%)	xx	n (xx.x%)	xx	n (xx.x%)	xx	n (xx.x%)	xx	n (xx.x%)	xx
	Type n	n (xx.x%)	xx	n (xx.x%)	xx	n (xx.x%)	xx	n (xx.x%)	xx	n (xx.x%)	xx
Minor protocol deviation	Yes	n (xx.x%)	xx	n (xx.x%)	xx	n (xx.x%)	xx	n (xx.x%)	xx	n (xx.x%)	xx
Type of minor protocol deviation	Type 1	n (xx.x%)	xx	n (xx.x%)	xx	n (xx.x%)	xx	n (xx.x%)	xx	n (xx.x%)	xx
	Type 2	n (xx.x%)	xx	n (xx.x%)	xx	n (xx.x%)	xx	n (xx.x%)	xx	n (xx.x%)	xx
	Type …	n (xx.x%)	xx	n (xx.x%)	xx	n (xx.x%)	xx	n (xx.x%)	xx	n (xx.x%)	xx
	Type n	n (xx.x%)	xx	n (xx.x%)	xx	n (xx.x%)	xx	n (xx.x%)	xx	n (xx.x%)	xx

9.2.3. Analysis datasets

Analysis datasets	Inpatients (N=XX)	Outpatients (N=XX)	Stage 1 and Intermediate (N=XX)	Stage 2 (N=XX)	Total (N=XX)
Screened positive set - N (%)					
Missing	xxx	xxx	xxx	xxx	xxx
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total	xxx	xxx	xxx	xxx	xxx
ITT set - N (%)					
Missing	xxx	xxx	xxx	xxx	xxx
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total	xxx	xxx	xxx	xxx	xxx
mITT set - N (%)					
Missing	xxx	xxx	xxx	xxx	xxx
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total	xxx	xxx	xxx	xxx	xxx
Evaluable set - N (%)					
Missing	xxx	xxx	xxx	xxx	xxx
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total	xxx	xxx	xxx	xxx	xxx
PP set - N (%)					
Missing	xxx	xxx	xxx	xxx	xxx
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total	xxx	xxx	xxx	xxx	xxx

9.2.4. Continuous variable

Quantitative variable	Inpatients (N=XX)	Outpatients (N=XX)	Stage 1 or intermediate (N=XX)	Stage 2 (N=XX)	Total (N=XX)
Missing	x	x	x	x	x
N	xx	xx	xx	xx	xx
Mean (±SD)	x.x (±x.x)	x.x (±x.x)	x.x (±x.x)	x.x (±x.x)	x.x (±x.x)
Median	x.x	x.x	x.x	x.x	x.x
Q1-Q3	[x.x;x.x]	[x.x;x.x]	[x.x;x.x]	[x.x;x.x]	[x.x;x.x]
Min-Max	[x.x;x.x]	[x.x;x.x]	[x.x;x.x]	[x.x;x.x]	[x.x;x.x]

9.2.5. Categorical variables

Categorical variable	Inpatients (N=XX)	Outpatients (N=XX)	Stage 1 or intermediate (N=XX)	Stage 2 (N=XX)	Total (N=XX)
Categorical variable - N (%)					
Missing	x	x	x	x	x
Class 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Class 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Class (…)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total	xx	xx	xx	xx	xx

9.2.6. Medical history

	Inpatients (N=XX)			Outpatients (N=XX)			Stage 1 or intermediate (N=XX)			Stage 2 (N=XX)			Total (N=XX)		
System Organ Class / Preferred Term	Nb MH	Nb pat	% pat	Nb MH	Nb pat	% pat	Nb MH	Nb pat	% pat	Nb MH	Nb pat	% pat	Nb MH	Nb pat	% pat
At least 1 MH	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X
System Organ Class 1	X	X	XX.X	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X
- Preferred Term 1	X	X	X.X	X	X	XX.X	X	X	XX.X	X	X	XX.X	X	X	XX.X
- Preferred Term 2	X	X	XX.X	X	X	XX.X	X	X	XX.X	X	X	XX.X	X	X	XX.X
- Preferred Term 3	X	X	X.X	X	X	XX.X	X	X	X.X	X	X	X.X	X	X	X.X
System Organ Class 2	X	X	XX.X	X	X	XX.X	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X
- Preferred Term 1	X	X	X.X	X	X	X.X	X	X	X.X	X	X	X.X	X	X	X.X
- Preferred Term 2	X	X	X.X	X	X	X.X	X	X	X.X	X	X	X.X	X	X	X.X
- Preferred Term 3	X	X	X.X	X	X	X.X	X	X	X.X	X	X	X.X	X	X	X.X

9.2.7. Concomitant medication

	Inpatients (N=XX)			Outpatients (N=XX)			Stage 1 or intermediate (N=XX)			Stage 2 (N=XX)			Total (N=XX)		
Therapeutic Class / Preferred name	Nb TRT	Nb pat	% pat	Nb TRT	Nb pat	% pat	Nb TRT	Nb pat	% pat	Nb TRT	Nb pat	% pat	Nb TRT	Nb pat	% pat
At least 1 TRT	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X
Therapeutic Class 1	X	X	XX.X	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X
- Preferred name 1	X	X	X.X	X	X	XX.X	X	X	XX.X	X	X	XX.X	X	X	XX.X
- Preferred name 2	X	X	XX.X	X	X	XX.X	X	X	XX.X	X	X	XX.X	X	X	XX.X
- Preferred name 3	X	X	X.X	X	X	XX.X	X	X	X.X	X	X	X.X	X	X	X.X
Therapeutic Class 2	X	X	XX.X	X	X	XX.X	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X
- Preferred name 1	X	X	X.X	X	X	X.X	X	X	X.X	X	X	X.X	X	X	X.X
- Preferred name 2	X	X	X.X	X	X	X.X	X	X	X.X	X	X	X.X	X	X	X.X
- Preferred name 3	X	X	X.X	X	X	X.X	X	X	X.X	X	X	X.X	X	X	X.X

9.2.8. Analysis of the primary endpoint

Description	Statistics	Total (N=XXX)
Success Rate	N	XXX
	Missing	X
	n (%) – Yes [95CI]	n (XX.X%) [XX.X ; XX.X]
	n (%) – No [95CI]	n (XX.X%) [XX.X ; XX.X]

9.2.9. Overall summary of adverse event

Adverse Event summary	Inpatients (N=XX)	Outpatients (N=XX)	Stage 1 or intermediate (N=XX)	Stage 2 (N=XX)	Total (N=XX)
At least one TEAE - N (%) IC95%					
Yes	xx (xx.x%) [xx.x ; xx.x]	xx (xx.x%) [xx.x ; xx.x]	xx (xx.x%) [xx.x ; xx.x]	xx (xx.x%) [xx.x ; xx.x]	xx (xx.x%) [xx.x ; xx.x]
At least one TEAE leading to treatment discontinuation (temporary or permanent)- N (%) IC95%					
Yes	xx (xx.x%) [xx.x ; xx.x]	xx (xx.x%) [xx.x ; xx.x]	xx (xx.x%) [xx.x ; xx.x]	xx (xx.x%) [xx.x ; xx.x]	xx (xx.x%) [xx.x ; xx.x]
At least one TEAE leading to permanent treatment discontinuation - N (%) IC95%					
Yes	xx (xx.x%) [xx.x ; xx.x]	xx (xx.x%) [xx.x ; xx.x]	xx (xx.x%) [xx.x ; xx.x]	xx (xx.x%) [xx.x ; xx.x]	xx (xx.x%) [xx.x ; xx.x]
(etc.)					
At least one Serious TEAE - N (%) IC95%					
Yes	xx (xx.x%) [xx.x ; xx.x]	xx (xx.x%) [xx.x ; xx.x]	xx (xx.x%) [xx.x ; xx.x]	xx (xx.x%) [xx.x ; xx.x]	xx (xx.x%) [xx.x ; xx.x]
(etc.)					

9.2.10. Adverse event by SOC and PT

	Inpatients (N=XX)			Outpatients (N=XX)			Stage 1 or intermediate (N=XX)			Stage 2 (N=XX)			Total (N=XX)		
System Organ Class / Preferred Term	Nb AE	Nb pat	% pat	Nb AE	Nb pat	% pat	Nb AE	Nb pat	% pat	Nb AE	Nb pat	% pat	Nb AE	Nb pat	% pat
At least 1 AE	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X
System Organ Class 1	X	X	XX.X	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X
- Preferred Term 1	X	X	X.X	X	X	XX.X	X	X	XX.X	X	X	XX.X	X	X	XX.X
- Preferred Term 2	X	X	XX.X	X	X	XX.X	X	X	XX.X	X	X	XX.X	X	X	XX.X
- Preferred Term 3	X	X	X.X	X	X	XX.X	X	X	X.X	X	X	X.X	X	X	X.X
System Organ Class 2	X	X	XX.X	X	X	XX.X	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X
- Preferred Term 1	X	X	X.X	X	X	X.X	X	X	X.X	X	X	X.X	X	X	X.X
- Preferred Term 2	X	X	X.X	X	X	X.X	X	X	X.X	X	X	X.X	X	X	X.X
- Preferred Term 3	X	X	X.X	X	X	X.X	X	X	X.X	X	X	X.X	X	X	X.X

9.2.11. Shift table for laboratory parameters

Template by severity:

	Laboratory parameter – Visit A			
Parameter XXXX	**Normal**	**Abnormal NCS**	**Abnormal CS**	**Missing**
Visit B				
- Normal	X (XX.X%)	XX (XX.X%)	X (XX.X%)	X (XX.X%)
- Abnormal NCS	X (XX.X%)	X (XX.X%)	XX (XX.X%)	XX (XX.X%)
- Abnormal CS	X (XX.X%)	X (XX.X%)	XX (XX.X%)	XX (XX.X%)
- Missing	X (XX.X%)	X (X.X%)	X (XX.X%)	XX (XX.X%)

Template by CTCAE grades:

	Laboratory parameter – Visit A				
Parameter XXXX	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Visit B					
- Grade 1	X (XX.X%)	X (XX.X%)	XX (XX.X%)	X (XX.X%)	X (XX.X%)
- Grade 2	X (XX.X%)	X (XX.X%)	X (XX.X%)	XX (XX.X%)	XX (XX.X%)
- Grade 3	X (XX.X%)	X (XX.X%)	X (XX.X%)	XX (XX.X%)	XX (XX.X%)
- Grade 4	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	XX (XX.X%)
- Grade 5	X (XX.X%)	X (XX.X%)	X (X.X%)	X (XX.X%)	XX (XX.X%)

10. KEY DERIVED VARIABLES

10.1. Outcome at 18 months

<table>
<tr><th>Derivation algorithm for
stage 1 and intermediate stage (Month 18)</th><th>Derivation algorithm for
stage 2 (Month 18)</th></tr>
<tr><td colspan="2"><u>Patient is dead</u> (any reason of death and any time between drug intake and M18)
⇒ YES ⇒ Failure (stop)
⇓
NO (patient alive)
⇓
<u>Patient requires rescue medication for HAT at M18 or required it before</u> (between drug intake and M18)
⇒ YES ⇒ (definitive) Failure (stop)
⇓
NO rescue medication so far
⇓
<u>Evidence of trypanosomes in any body fluid between drug intake and M18 visit</u>
⇒ YES ⇒ (definitive) Failure (stop)
⇓
NO observed trypanosomes
⇓
<u>Patient Lost to follow-up at M18</u> (no survival information at M18 and later)
⇒ YES ⇒ Failure (Stop)
⇓
NO (the patient is not lost to follow-up)
⇓
<u>Non-haemorrhagic lumbar puncture at M18</u> and <u>WBC in CSF at M18 >20 cells</u>
⇒ YES ⇒ Failure (stop)
⇓
NO (WBC in CSF at M18 ≤20 cells or no reliable data concerning WBC in CSF at M18)
⇓
<u>Non-haemorrhagic lumbar puncture at M18 and WBC in CSF ≤20 cells</u>
⇒YES ⇒ Success (stop)
⇓
NO (haemorrhagic CSF sample or no lumbar puncture at M18 for any reason)
⇓
<u>No lumbar puncture at M18 or no reliable count of WBC in CSF at M18 but reliable number of WBC in CSF reported later</u> (M24 or other additional visit)
⇒ YES ⇒ WBC in CSF >20 ⇒ Failure (Stop)
⇒ YES ⇒ WBC in CSF ≤20 ⇒ Success (Stop)
⇓
NO (No lumbar puncture at M18 and no later reliable count of WBC in CSF)</td></tr>
<tr><td>⇓
<u>Patient has clinical signs or symptoms at M18 evoking a failure</u>
⇒ YES ⇒ Failure (stop)
⇓
NO (no clinical signs or symptoms evoking a relapse at M18)
⇓
<u>WBC in CSF ≤20 at M12 or absence of lumbar puncture at M12 and no sign and symptoms</u></td><td>⇓
<u>Earlier (before M18) unfavourable outcome: WBC in CSF >50 at M6 or WBC in CSF >20 at M12 or increasing between M6 and M12</u>
⇒ YES ⇒ Failure (stop)
⇓
NO (no information or no earlier unfavourable assessment)
⇓
<u>Patient has clinical signs or symptoms at M18 evoking a failure</u>
⇒ YES ⇒ Failure (stop)</td></tr>
</table>

Derivation algorithm for stage 1 and intermediate stage (Month 18)	**Derivation algorithm for stage 2 (Month 18)**
at M18 evoking a relapse: ⇒ YES ⇒ ***Success*** (stop) ⇓ NO (at least one criterion not met) ⇓ **Patient refused all post treatment lumbar punctures** ⇒ YES ⇒ ***Failure*** **(stop)** ⇓ All other cases ⇒ Failure	⇓ NO (no clinical signs or symptoms evoking a relapse at M18) ⇓ **WBC in CSF ≤20 at M12 or in absence of lumbar puncture at M12 and for both cases WBC in CSF ≤50 at M6 and no signs and symptoms at M18 evoking a relapse:** ⇒ YES ⇒ ***Success*** (Stop) ⇓ NO (at least one criterion not met) ⇓ **Patient refused all post treatment lumbar punctures** ⇒ YES ⇒ ***Failure*** (Stop) ⇓ All other cases ⇒ Failure

Note :

Modification of the algorithm due to an undetected error, as there was no lumbar puncture at the end of hospitalisation visit foreseen in the protocol.

10.2. Outcome at 12 months

Derivation algorithm for stage 1 and intermediate stage (Month 12)	**Derivation algorithm for stage 2 (Month 12)**
Patient is dead (any reason of death and any time between drug intake and M12) ⇒ YES ⇒ *(definitive)* ***Failure*** **(stop)** ⇓ NO (patient alive) ⇓ **Patient requires rescue medication for HAT at M12 or before** ⇒ YES ⇒ ***Failure*** **(stop)** ⇓ NO rescue medication so far ⇓ **Evidence of trypanosomes in any body fluid at M12 or between drug intake and M12 visit** ⇒ YES ⇒ (*definitive*) ***Failure*** **(stop)** ⇓ NO observed trypanosomes so far ⇓ **Patient Lost to follow-up at 12M** (no survival information at M12 and later) ⇒ YES ⇒ ***Failure*** **(Stop)** ⇓ NO (the patient is not lost to follow-up)	
⇓ **Non-haemorrhagic lumbar puncture at M12 and WBC in CSF >20 cells** ⇒YES ⇒ ***Failure*** **(stop)** ⇓ NO (WBC in CSF at M12 ≤20 cells or no reliable count of WBC in CSF at M12) ⇓ **Non-haemorrhagic lumbar puncture at M12 and WBC in CSF at M12 ≤20 cells** ⇒ YES ⇒ ***Success*** **(Stop)** ⇓ NO (no reliable count of WBC in CSF at M12) ⇓ ⇓ ⇓ ⇓	⇓ **Non-haemorrhagic lumbar puncture at M12 and WBC in CSF at M12 ≥ 50 cells** ⇒ YES ⇒ **Failure (stop)** ⇓ NO (WBC in CSF at M12 <50 cells or no reliable count of WBC in CSF at M12) ⇓ **Non-haemorrhagic lumbar puncture at M12 and WBC in CSF at M12 ≤20 cells** ⇒ YES ⇒ ***Success*** **(Stop)** ⇓ NO (no reliable count of WBC in CSF at M12) ⇓ **Non-haemorrhagic lumbar puncture at M12 with WBC in CSF <50 but >20 and increase of WBC in CSF with respect to M6 or sign and symptoms evoking a failure** ⇒ YES ⇒ ***Failure*** **(stop)** ⇓ NO (patient did not meet at least one of the previous criteria at M12) ⇓ **Non-haemorrhagic lumbar puncture at M12 with WBC in CSF<50 but >20 cells and decrease of WBC in CSF with respect to M6 and no signs and symptoms evoking a failure (success at M18 if status is available)** ⇒ YES ⇒ ***Success*** **(stop)** ⇓ NO (patient did not meet at least one of the previous criteria)

Derivation algorithm for stage 1 and intermediate stage (Month 12)	**Derivation algorithm for stage 2 (Month 12)**
⇓ **No lumbar puncture at M12 or no reliable count of WBC in CSF at M12 but reliable number of WBC in CSF reported later** (M18 or other additional visit) ⇒ YES ⇒ **WBC in CSF >20** ⇒ ***Failure*** **(Stop)** ⇒ YES ⇒ **WBC in CSF ≤20 and no signs or symptoms evoking a relapse** ⇒ ***Success*** **(Stop)** ⇓ NO (no later reliable count of WBC in CSF) ⇓ **No reliable WBC count in CSF at M12 and later and Failure at M18 for any reason** ⇒ YES ⇒ ***Failure*** at M12 **(Stop)** ⇓ NO ⇓ **Patient refused all post-treatment lumbar punctures but was met at M24 or later with no signs and symptoms evoking a relapse (normal activity)** ⇒ YES ⇒ ***Success*** at M12 ⇓ NO (Patient not met at M24 or later) ⇓ **Patient refused all post treatment lumbar punctures** ⇒ YES ⇒ ***Failure*** **(Stop)**	⇓ **No lumbar puncture at M12 or no reliable count of WBC in CSF at M12 but reliable number of WBC in CSF reported later** (M18 or other additional visit) ⇒ YES ⇒ **WBC in CSF >20** ⇒ ***Failure*** **(Stop)** ⇒ YES ⇒ **WBC in CSF ≤20** ⇒ ***Success*** **(Stop)** ⇓ NO (no later reliable count of WBC in CSF) ⇓ **No WBC count in CSF at M12 and later and Failure at M18 for any reason** ⇒ YES ⇒ ***Failure*** at M12 **(Stop)** ⇓ NO ⇓ **No reliable count of WBC in CSF at M18 and M12 but WBC counts at M6 available and no sign and symptoms evoking relapse at M12 or M18** ⇒ YES ⇒ **WBC in CSF at M6 ≤20 cells** ⇒ ***Success (stop)*** ⇓ NO ⇒ **WBC in CSF at M6 >20 cells** ⇒ ***Failure*** **(Stop)** ⇓ NO (no lumbar puncture at M6, M12 and M18) ⇓ **Patient refused all post-treatment lumbar punctures but was met at M24 or later with no signs and symptoms evoking a relapse (normal activity)** ⇒ **YES** ⇒ ***Success*** at M12 ⇓ NO (Patient not met at M24 or later) ⇓ **Patient refused all post treatment lumbar punctures** ⇒ YES ⇒ ***Failure*** **(Stop)**

11. CHANGES IN THE STATISTICAL METHODS FROM THOSE STATED IN THE PROTOCOL

Changes in the analysis of adverse events:

The part below of Section 9.6.1 of the Protocol will not be taken into account: "*Events described with 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.*"
Actually, if several events are described with the same preferred terms for a subject, all events will be included in the analysis. The number of occurrence of events, the number and percentage of patients with at least one event will be calculated by SOC and Preferred term.

Removal of interim analyses:

Interim analyses were planned in Section 9.7 of the protocol in order to supplement the registration file for fexinidazole. These interim analyses are not required anymore and will not be performed.

Post-DBL changes :

Modification of the algorithm by an undetected error, as there was no LP in the end of treatment visit foreseen in the protocol.

12. QUALITY CONTROL

The statistician in charge of the analysis will validate the whole derived variables, using an exhaustive method whenever it is possible. When an exhaustive control is impossible, 10% of patients will be randomly drawn and checked in order to validate derived variables.

The primary endpoint will be exhaustively validated and double-checked (i.e. head of biostatistics or another statistician).