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STATISTICAL ANALYSIS PLAN

Efficacy and Safety Study of Acoziborole (SCYX-7158) in Patients with Human African Trypanosomiasis due to *T.b. gambiense*: a Multicentre, Open-label, Prospective Study

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Version 4.0 – 17/03/2021

Written by [redacted]

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1. STATISTICAL ANALYSIS PLAN - APPROVAL FORM

DNDi
Drugs for Neglected Diseases *initiative*

Function	Name	Signature	Date
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Head of HAT Clinical Program	[redacted]	[redacted]	Mar 18, 2021

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Statistician	[redacted]	[redacted]	Mar 22, 2021

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Function	Name	Signature	Date
Head of Interventional Studies Biostatistics	[redacted]	[redacted]	Mar 17, 2021

2. VERSION HISTORY

Version	Date	Author	Comment / changes
0.1	18/10/2016	[redacted]	Initial draft version (based on English draft protocol version 1 dated of 27/04/2016)
0.2	28/02/2017	[redacted]	Add comments from DNDi
0.3	15/03/2017	DNDi	Comments from DNDi
0.4	16/03/2017	[redacted]	Add comments from DNDi
0.5	06/04/2017	[redacted]	Add comments from DNDi
0.6	16/05/2017	[redacted]	Add comments from DNDi
0.7	17/07/2017	[redacted]	Update definition of HAT stages
0.8	08/12/2017	[redacted]	Add comments from DNDi [redacted]
0.9	21/12/2017	[redacted]	Add comments from [redacted]
1.0	17/04/2018	[redacted]	First approved and signed version
2.0	24/10/2018	[redacted]	Clarifications for the 3rd futility analysis: definition of outcome at M6 and definition of the analysis set (cf. Section 8.7).
2.1	20/03/2019	[redacted]	Update based on the first amendment of the protocol. Based on the protocol version 2.0 dated of 17/12/2018. Removal of the protocol reminders. Clarifications for the AEs analysis.
2.2	06/06/2019	[redacted]	Add comments from DNDi.
2.3	29/01/2020	[redacted]	Update based on the second amendment of the protocol. Based on the protocol version 3.0 dated of 07/01/2020. Add sensitivity analyses for the primary endpoint
3.0	11/05/2020	[redacted]	Third approved and signed version.
3.1	11/01/2021	[redacted]	Add analysis of changes in body weight from baseline. Update list of outputs and templates.
3.2	03/02/2021	[redacted]	Add comments from [redacted]
3.3	04/03/2021	[redacted]	Add comments from DNDi.
3.4	09/03/2021	[redacted]	Add comments from DNDi.
3.5	17/03/2021	[redacted]	Add comments from DNDi.
4.0	09/03/2021	[redacted]	Fourth approved and signed version.

3. ABBREVIATIONS

Abbreviation	Description
AE	Adverse event
AUC	Area under the curve
CHMP	Committee for Medicinal Products for Human Use
CRF	Case report form
CSF	Cerebrospinal fluid
DNDi	Drugs for Neglected Diseases *initiative*
DSMB	Data and Safety Monitoring Board
e.g.	For example
ECG	Electrocardiogram
EoH	End of Hospitalisation visit
g-HAT	Human African Trypanosomiasis due to *T.b. gambiense*
HAT	Human African Trypanosomiasis
i.e.	id est
MedDRA	Medical Dictionary for Regulatory Activities
MSF	"Médecins Sans Frontières"
NECT	Nifurtimox-eflornithine combined therapy
PK	Pharmacokinetics
SAE	Serious adverse event
SAWP	Scientific Advice Working Party
WBC	White blood cell

4. PROTOCOL

This Statistical Analysis Plan is based on the Protocol version 4.0 dated of 11/08/2020.

Sections 4.1 to 4.6 below are a reminder of the Protocol.

4.1. Study Design

Cf. Section 3 of the Protocol:

"This is a multicentre, prospective, open-label, non-randomised, phase II/III study to assess the efficacy and safety of acoziborole in two cohorts of patients with g-HAT. The first cohort will be composed of patients with late-stage HAT, and the second cohort will be composed of patients with early- or intermediate-stage HAT".

"Early- and intermediate-stage patients will be enrolled in the same centres as late-stage patients, however enrolment of early- and intermediate-stage patients will begin approximately 6 months later, once the Data and Safety Monitoring Board (DSMB) has examined the PK and safety data at 3 months for the first 20 patients with late-stage HAT and once it has been informed of the results of the first futility analysis".

4.2. Investigational Product

Cf. Section 5.1 of the Protocol:

"The investigational product (IP) is acoziborole, in 320-mg tablets, administered by the oral route to patients in the fasting state according to the following dosing regimen: 960 mg (3 tablets) in a single intake on Day 1".

4.3. General Objective

Cf. Section 2.1.1 of the Protocol:

"The aim of the study is to assess the efficacy and safety of a single oral dose of acoziborole administered to patients in the fasting state with g-HAT".

4.4. Primary Objective

Cf. Section 2.1.2 of the Protocol:

"The primary objective is to estimate the success rate at 18 months of follow-up with acoziborole, administered as a single 960-mg oral dose to patients in the fasting state with late-stage g-HAT. An estimate of the success rate observed with NECT in patients with late-stage g-HAT, based on historical data, will be provided as a yardstick".

4.5. Secondary Objectives

Cf. Section 2.1.3 of the Protocol:

- "To estimate the success rate at 12 months in patients with late-stage g-HAT".
- "To estimate the time course of the failure rate in patients with late-stage g-HAT".
- "To assess the safety profile of a single dose of acoziborole in patients with g-HAT using historical data on NECT as a yardstick".
- "To establish the relationship between, on the one hand, concentrations of acoziborole in the blood and the CSF and, on the other hand, the efficacy and safety of acoziborole".

"A cohort of patients 15 years of age or older with early- or intermediate-stage g-HAT will be enrolled following the futility analysis, provided that the latter does not show futility and that the safety review shows no concerns. The overall objective will be to assess the efficacy of acoziborole in this cohort and to enrich the safety database at the time of regulatory filing".

- "To estimate the success rate with acoziborole in this cohort, using pentamidine as a yardstick, in order to verify the underlying hypothesis according to which, in HAT, a treatment able to clear the parasite from the CSF also clears it from the other compartments (i.e. the blood and lymph)".
- "To assess the safety profile in this cohort and in the overall population".
- "To assess the safety of acoziborole in patients with early- and intermediate-stage HAT to determine whether its safety profile is comparable to the historical safety profile of pentamidine".

4.6. Sample Size Determination

Cf. Section 9.1 of the Protocol:

"The sample size is based on the largest number of patients who can be enrolled within a reasonable timeframe. It is expected that 155 late-stage patients should be enrolled within approximately 2 years. A provision of 5% (7 patients) is planned in order to allow for replacement of patients lost to follow-up who fled the region due to armed conflict or natural disaster. Approximately 50 early- and intermediate-stage patients could be enrolled within this timeframe. As a reminder, enrolment of early- and intermediate-stage patients will begin approximately 6 months after the start of enrolment of late-stage patients and will end at the same time".

"If the observed success rate is around 89% (the same as the expected rate for fexinidazole and the observed rate with eflornithine) then the width of the 95% Jeffreys confidence interval will be 9.8% (83.4%–93.2%). The width decreases with an increase in the success rate to reach 7.4% (89.7%–97.1%) for a 94% success rate. In contrast, the precision is not highly sensitive to the sample size. With 200 patients, the width of the confidence interval is 8.7% (84.1%–92.8%) for an 89% success rate. Indeed, the sample size must increase by 50%, i.e. 300 patients instead of 200, to reduce the width of the lower arm of the 95% confidence interval by one percentage point".

"In early- and intermediate-stage patients, the expected success rate is around 91%, i.e. the same as for pentamidine. The width of the confidence interval with 50 patients will be around 17%".

5. ANALYSIS SETS AND SUBGROUPS

The analysis sets are defined below:

- **Set of screened HAT positive patients**: All HAT positive patients who signed the informed consent. To be noted that after the 1st DSMB meeting, recruitment of stage 1 and intermediate stage HAT patients was authorized. That will trigger a modification of the initial screened set.
- **Treated set**: all patients who received at least one tablet of acoziborole.
- **Modified Intention-To-Treat (mITT):** All patients who received at least one tablet of acoziborole, excluding patients (*) who fled the region due to armed conflict or natural disaster or due to force majeure (**) and for whom no failure was detected early (parasite, needs for rescue medication, death or more than 50 WBC/µL in CSF at M6) and no data are available at M12 and M18 due to armed conflict, natural disaster or force majeure affecting the site.
- **Evaluable patients**: Modified Intent-to-treat patients (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), patients lost to follow-up at 6 months (for secondary efficacy outcome at 6 month), except those who were a failure before being lost to follow-up (cf. Section 7.7 for programming rules).
    - Patients with no post-treatment lumbar puncture (i.e. patients who refused all lumbar puncture after treatment and who were not a failure)
    - Patients who died for reasons clearly unrelated to efficacy or safety or disease evolution (**).
    - Early consent withdrawal (before M6, i.e. no planned visit attended after 3-month visit).
- **Per Protocol Set (PPS)**: Modified Intent-to-treat patients (mITT) with no major protocol deviations (***). Major deviations will be described by patient, and exclusion will be decided during the data review (cf. Section 8.2).

Notes:

(*) These patients will be included in the Treated set population as failures.

(**) This will be reviewed during data review meeting (e.g. review of comments and reasons of early discontinuation in end-of-study form).

Patients who fled the region because of armed conflict or natural disaster will be replaced by new patients from another site in order to maintain the planned sample size. In order to allow for replacement of some patients lost to follow-up due to armed conflict and to maintain the planned sample size of 155 patients, 7 additional patients will be enrolled in the study.

(***) Major protocol deviations are any protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being (cf. ICH E3. Questions and answers (R1). January 2013).

Two cohorts of patients will be studied: patients with stage 1 HAT or intermediate-stage HAT and patients with stage 2 HAT (cf. protocol Section 4.2 inclusion criteria). For the analysis, HAT stages will be determined according to criteria described in Table 1 and Table 2.

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

Tryps in CSF	**WBC in CSF**		
	≤ 5/µl	**[6-20/µl]**	**> 20/ µl**
Tryps in CSF (positive)	Stage 2 (subgroup C)	Stage 2 (subgroup D)	Stage2 (subgroup E)
No tryps in CSF (negative)	Stage 1 (subgroup A)	Intermediate stage (subgroup B)	Stage 2 (subgroup F)

Table 2 : Derivation rules for stage 1, intermediate and stage 2 HAT

According to: Trial FEX004 Trial FEX005 Trial FEX006	According to: OXA002 Protocol FEX009 Protocol	According to WHO Clinical trials recommend…	**Trypanosomes (blood, lymph)**	**Trypanosomes in CSF**		**WBC in CSF**	**Subgroups used in analyses**	**HAT stage used in analyses**	**HAT cohort used in analyses**
Stage1	Early stage	Stage 1	Positive	Negative	AND	≤ 5/µl	A	Stage 1	Cohort 2
Early stage 2	Intermediate stage	Intermediate stage 2 Not recommended for clinical trials focused on second stage	Positive	Negative	AND	[6-20/µl]	B	Intermediate stage	
Late stage 2	Stage 2	Intermediate stage 1 Not recommended for clinical trials focused on second stage	Positive	Positive	AND	≤ 5 /µl	C	Stage 2	Cohort 1
Late stage 2	Stage 2	Intermediate stage 2 Not recommended for clinical trials focused on second stage	Positive	Positive	AND	[6-20/µl]	D		
Late stage 2	Stage 2	Second stage	Positive	Positive	AND	> 20/ µl	E		
Late stage 2	Stage 2	Second stage	Positive	Negative	AND	> 20/µl	F		

Note: subgroups "A", "B", "C", "D", "E" and "F" will be used for exploratory analyses on the primary endpoint and secondary endpoints (cf. Section 8.6.3 for further details). At the time of writing, one patient (centre 4, patient 31) had missing WBC in CSF at baseline. For the analysis, this patient will be considered as having WBC in CSF > 100 /µl at baseline and will therefore be classified in the analysis subgroup E (cf. final data review minutes for further details).

6. DEFINITION OF ENDPOINTS

6.1. Primary efficacy endpoint

Primary endpoint for patients with Stage 2 HAT

The primary endpoint is the outcome (success or failure) at the 18 months visit according to the adapted WHO criteria:

- Success is defined as a cure or a probable cure (cf. algorithm in Section 10.1).
- Failure is defined as a relapse, probable relapse, death for any reason (up to and including the 18 months visit) or use of rescue medication (up to and including the 18 months visit) or lost to follow-up for any reason (up to and including the 18 months visit) or refusal of all post-treatment lumbar puncture (up to and including the 18 months visit) or had unfavourable outcome earlier than M18 or sign and symptoms evoking a relapse at M18 (cf. algorithm in Section 10.1).

Note: data review committee composed of those involved in the study conduct and data processing will check before database lock the status of patients (success or failure) using the algorithm presented in Section 10.1.

6.2. Secondary efficacy endpoints

Endpoint at 6 months in patients with Stage 2 HAT

The response (success or failure) at 6 months in patients with Stage 2 HAT will be derived from the algorithm presented in Section 10.3.

Endpoint at 12 months for patient with Stage 2 HAT

The response (success or failure) at 12 months in patients with Stage 2 HAT will be derived from the algorithm presented in Section 10.2.

Endpoint at 18 months in Patients with Stage 1 and Intermediate-stage HAT

The response (success or failure) at 18 months in patients with stage 1 and intermediate stage HAT will be derived from the algorithm presented in Section 10.1.

Endpoint at 12 months in Patients with Stage 1 and Intermediate-stage HAT

The response (success or failure) at 12 months in patients with stage 1 and intermediate stage HAT will be derived from the algorithm presented in Section 10.2.

Endpoint at 6 months in Patients with Stage 1 and Intermediate-stage HAT

The response (success or failure) at 6 months in patients with stage 1 and intermediate stage HAT will be derived from the algorithm presented in Section 10.3.

Overall success rate at 18 months:

This endpoint will be derived as follows:

- For patients with stage 2 HAT: same algorithm as for the primary endpoint (cf. Section 10.1).
- For patients with stage 1 and Intermediate-stage HAT: same algorithm as for the secondary endpoint "Endpoint at 18 months" (cf. Section 10.1).

6.3. Other secondary efficacy endpoints

Time to proven and definitive failure in Patients with Stage 2 HAT

The starting point is administration of acoziborole. The time of failure is the time of the first objective evidence of sustainable failure defined as:

- Death for any reason (at any time on or after administration of acoziborole)
- Decision to use rescue medication (at any time on or after administration of acoziborole)
- Observation of trypanosomes in any body fluid at M6, M12 or M18
- a CSF WBC above 50 /µL at 6 months followed by a confirmation of failure defined as:
  - CSF WBC above 20 /µL at 12 months, and/or
  - CSF WBC above 20 /µL at 18 months, and/or
  - Sign and symptoms evoking a relapse at M12, and/or
  - Sign and symptoms evoking a relapse at M18.
- a CSF WBC above 20 /µL at 12 months followed by a confirmation of failure defined as:
  - CSF WBC above 20 /µL at 18 months, or
  - Sign and symptoms evoking a relapse at M18.
- a CSF WBC above 20 /µL at 18 months

This endpoint will be derived as follows:

- Proven and definitive failure patients:
  - Event (cf. definition above)
  - Time = Theoretical time of the follow-up visit (i.e. day 15 for EoH visit, day 91 for M3 visit, day 183 for M6 visit, day 365 for M12 visit, day 548 for M18 visit)
- Non-failure patients (i.e. proven and definitive failure free):
  - If CSF WBC > 20/µL at 12 months and CSF WBC < 20/µL at 18 months:
    - Censoring at M12 visit
    - Time = Theoretical time of M12 visit (i.e. at day 365)
  - Otherwise:
    - Censoring at the last visit free from proven and definitive failure
    - Time = Theoretical time of the follow-up visit (i.e. day 15 for EoH visit, day 91 for M3 visit, day 183 for M6 visit, day 365 for M12 visit, day 548 for M18 visit)

Note: Unlike the preceding endpoints, a patient cannot be a proven and definitive failure at a given time point and a success at a subsequent endpoint. Consequently, a patient with a CSF WBC above 20/µL at 12 months and below 20/µL at 18 months will be censored at 12 months. A patient lost to follow-up is a patient censored at the last available visit if there is no evidence of failure up to the last available visit. A success at 18 months (last assessment) is a patient censored at 18 months, i.e. with no evidence of failure up to 18 months.

6.4. Safety endpoints

6.4.1. Adverse events

The following AE categories will be studied:

- All AEs collected during the study
- All AEs occurring before the intake of the study drug (i.e. from D-15 to D-1)
- Treatment-emergent adverse events (TEAE) occurring:
    - During the follow-up period (i.e. from D1 to 18 months)
    - The day of the intake of the study drug (i.e. D1)
    - During the hospitalization period (i.e. from D2 to D15)
    - Post-hospitalization period (i.e. from D16 to 18 months)
- Mild/moderate TEAE (grade 1, grade 2, mild or moderate)
- Severe TEAE (grade 3, grade 4, grade 5 or severe)
- Drug-related TEAE occurring:
    - During the follow-up period (i.e. from D1 to 18 months)
    - The day of the intake of the study drug (i.e. D1)
    - During the hospitalization period (i.e. from D2 to D15)
    - Post-hospitalization period (i.e. from D16 to 18 months)
- Serious TEAE
- Serious drug-related TEAE
- TEAE of interest

Definition of treatment-emergent AEs:

Treatment-emergent AEs are defined as any AE which occurs on or after the date of study-drug administration or which worsen in intensity on or after the date of study-drug administration.

Definition of TEAE of interest:

If data allow, categories of adverse event of interest may be defined during the data review meeting.

Notes: Any adverse event having been reported during the study for a given patient will be classified by preferred term and corresponding system organ class using the Medical Dictionary for Regulatory Activities (MedDRA) terminology (last available version at the beginning of the coding).

AEs will be graded according to the Common Toxicity Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI), version 4.03 (cf. Protocol reference 15)

As per protocol, serious and non-serious adverse events are collected until M6. Only SAE are collected after M6.

6.4.2. Pharmacokinetics

Concentrations of acoziborole in whole blood and CSF, and population PK parameters, i.e. clearance, AUC and half-life. Statistical analyses of the PK parameters will be performed by [redacted]. A separate statistical analysis plan will be prepared by [redacted] for these analyses.

6.4.3. Electrocardiogram

ECG tracings will be recorded at various time points to assess the QT/QTcF interval and variations over time. Statistical analyses of the ECG will be performed by [redacted]. A separate statistical analysis plan will be prepared by [redacted] for these analyses.

6.5. Other endpoints and variables

6.5.1. Demographic data and other baseline characteristics

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

- Demographic data

  In addition, the following data will be derived:

  - Age (years) will be used as collected in CRF. If not available, then it will be calculated as the exact duration in years between date of birth and date of informed consent, i.e. (date of informed consent - date of birth) / 365.25.

The following data will be derived using data recorded at pre-screening (D-15 to D-4) and screening (D-4 to D-1) visits:

- Vital signs at baseline (cf. Section 7.5 for programming rules of baseline value)

The following data will be used as recorded at screening (D-4 to D-1) visit:

- Clinical signs and symptoms of HAT at baseline (cf. Section 7.5 for programming rules of baseline value)
- Physical examination at baseline (cf. Section 7.5 for programming rules of baseline value)
- Neurological examination at baseline (cf. Section 7.5 for programming rules of baseline value)

The following data will be used as recorded at pre-screening (D-15 to D-4) visit:

- HAT diagnosis (i.e. examination of blood, lymph and CSF samples) at baseline

  In addition, the following data will be derived as follows:

  - At least one blood test or lymph node aspirate test positive:
    - Yes, if Serology (CATT) is positive and/or Lymph node aspirate (LNA) is positive and/or Smear test is positive and/or Thick blood smear (TBS) is positive and/or CTC (WOO) is positive and/or mAECT is positive and/or mAECT-BC is positive and/or Rapid diagnostic test (RDT) is positive
    - Missing, if all tests are missing or not done
    - No, otherwise.
  - WBC in CSF will be categorized as:
    - ≤ 5 /µl
    - >6-20] /µl
    - >20-100] / µl
    - > 100 /µl

Note: at the time of writing, one patient (centre 4, patient 31) had missing WBC in CSF at baseline. For the analysis, this patient will be considered as having WBC in CSF > 100 /µl at baseline (cf. final data review minutes for further details).

6.5.2. Medical history

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

6.5.3. 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 study drug administration.
- Concomitant therapies are therapies which ended on or after the study drug administration or are ongoing at the end of the trial.

6.5.4. Laboratory examination

All laboratory parameters recorded in the CRF forms "Hematology", "Biochemistry" and "Thyroid hormones" will be used. For continuous data, the absolute change from baseline to each time point 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 time point.

6.5.5. Extent of exposure and treatment compliance

Extent of exposure is not applicable as dosing regimen is 960 mg (3 tablets) in a single intake on Day 1. Treatment compliance will be assessed using the number of tablets administered (0, 1, 2, 3) on Day 1. The number of re-administered tablets will be described.

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

For the primary endpoint:

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. 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).

For the overall success rate:

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.

Grouping of centers:

The following rules for grouping small centers will be applied for both analyses described above. If any, small centres (i.e. with less than 5 patients) within the same country will be pooled together to form one centre of size comparable to that of other centres. [redacted]

7.4. Descriptive analyses of quantitative and qualitative variables

Quantitative variables will be described by: N (number of patients with non-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. Jeffrey 95% CI interval will be provided for the primary endpoint (at M18) and secondary endpoint at M12. For other endpoints and variables, 95% CI will be computed using Clopper-Pearson exact method, if required.

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

Baseline:

For vital signs, biochemistry, haematology and thyroid parameters, baseline is defined as the last available value collected before study drug administration.

Note: in this trial, re-test values (if any) are collected in the CRF as 'unscheduled visits'. Re-test values are taken into account in baseline calculation.

Analysis periods:

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

- D-15 to D-1: pre-screening, screening and baseline assessment
- D1: treatment day*
- D1 to D15: observation period at hospital
- D11: initial assessment of treatment effect (lumbar puncture)
- D15: end-of-hospitalisation (EoH) visit

Out-patient follow-up visits at 3 months, 6 months, 12 months and 18 months. The timing of follow-up visits is calculated from D1.

(*) Please note there is no visit 'Day 0' is in this trial.

Time-windows:

The following time-windows will be used for statistical analysis. They are defined according to time midpoint between each theoretical visit time. If 2 visits (scheduled and/or unscheduled) falls into the same time-windows, the following rules will be applied for the analysis: the **latest** visit within the corresponding time-windows will be used for the analysis.

Table 3 : Time-window for statistical analysis

		Time-window	
Visit	**Theoretical time**	**Lower limit**	**Upper limit**
Administration	D1	D1	D1
EoH	Between D13 and D18	D2	D18
3 months	D91	D19	D136
6 months	D183	D137	D273
12 months	D365	D274	D456
18 months	D548	D457	D639

Note: time-windows described in section 6.1 of the protocol were defined for operational and monitoring activities. They will not be used for statistical analysis.

Note: Time-windows will be applied and calculated visits will be used for the analysis of the following data:

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

Time-windows will not be used for calculation of the primary endpoint and secondary endpoints since it is included in the algorithms presented in Sections 10.1 to 10.3. Time-windows will not be used for calculation of the time to proven and definitive failure endpoint since it is included in the algorithm presented in Section 6.3.

7.6. Handling of missing data

7.6.1. Handling of missing data for primary and secondary efficacy endpoints

Method used for primary analysis:

Handling of missing data is included in the derivation algorithms for outcome at 18, 12 and 6 months (cf. Section 10).

Fair case method (for sensitivity analysis):

The algorithm defined in Section 10 will be used to derive the outcome at 18, 12 and 6 months, with the following changes. Responses of the following patients will be replaced using a **resampling approach:**

- Patients lost to follow-up (prior or at visit 18, 12 and 6 months, respectively)
- Patients who refused all post treatment lumbar punctures
- Patients without WBC in CSF data at the corresponding visit (6, 12 or 18 months, respectively) and no proven success according to prior or posterior visit(s) (see algorithm defined in Section 10 for details)

The resampling will be performed with a **hot deck multiple imputation** method as follows:

- Responses will be replaced by simple random sampling (with replacement) among non-missing responses (=donnors selection)
- The initial seed for random number generation used to select donor units will be set to 495.
- This step will be repeated 100 times in order to produce 100 samples (=number of donor units).
- Each sample will be analyzed as described in section 8.6.1 (i.e. the estimate, its 95% Jeffrey CI and corresponding standard error will be computed for each samples).
- The results of each of these analyses (estimates and standard errors) will be combined using Rubin's rules as implemented in the SAS MIANALYZE procedure to provide combined estimate and the 95% Jeffrey CI.

Best case method (for sensitivity analysis):

The algorithm defined in Section 10 will be used to derive the outcome at 18, 12 and 6 months, with the following changes. The following patients will be considered as **success**:

- Patients lost to follow-up (prior or at visit 18, 12 and 6 months, respectively)
- Patients who refused all post treatment lumbar punctures

Observed case method (for sensitivity analysis):

The algorithm defined in Section 10 will be used to derive the outcome at 18, 12 and 6 months, with the following changes. The following patients will be considered as having a **missing** outcome:

- Patients with missing data at visit 18, 12 and 6 months, respectively.

7.6.2. Handling of intercurrent events

The handling of post-treatment intercurrent events such as rescue medication intake, death, early consent withdrawal, lumbar puncture refusal, study discontinuation including war and natural disaster are taken into account in the algorithm for determining the outcome and in population definitions. Concomitant therapies other than rescue medication are not taken into account in the assessment of efficacy.

7.6.3. 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 objective is to maximize the probability the AE is considered as treatment-emergent.

Onset date of AE	Imputed AE onset date
Completely missing	Date of first study drug administration
Day is missing	First day of the month. If imputed date is prior to first study drug administration, then replace with date of first study drug administration.
Day and month are missing	First of January. 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.

7.6.4. Handling of missing stop dates of prior and concomitant therapies

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. For therapy collected in the "D-15 / Hospitalisation" form: if imputed date is later than the end of hospitalisation visit date, then replace with the end of hospitalisation visit date. For therapy collected in the "Follow-up" form: 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 For therapy collected in the "D-15 / Hospitalisation" form: if imputed date is later than the end of hospitalisation visit date, then replace with the end of hospitalisation visit date. For therapy collected in the "Follow-up" form: 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.

7.7. Other programming rules

Lost to follow-up patients at M3, M6, M12 and M18 will be computed as follows.

Lost to follow-up at M18:

- Yes, if 'lost-to-follow-up' is ticked 'yes' in End of Study form
- No, otherwise

Lost to follow-up at M12:

- Yes, if 'lost-to-follow-up' is ticked 'yes' in End of Study form
  - and visit M12 was not performed
  - and visit M18 was not performed
- No, otherwise

Lost to follow-up at M6:

- Yes, if 'lost-to-follow-up' is ticked 'yes' in End of Study form
  - and visit M6 was not performed
  - and visit M12 was not performed
  - and visit M18 was not performed
- No, otherwise

Lost to follow-up at M3:

- Yes, if 'lost-to-follow-up' is ticked 'yes' in End of Study form
  - and visit M3 was not performed
  - and visit M6 was not performed
  - and visit M12 was not performed
  - and visit M18 was not performed
- No, otherwise

Note: at the time of writing, no patient who ticked 'lost-to-follow-up' in End of Study form performed and unscheduled visit.

8. PLANNED STATISTICAL ANALYSES

8.1. Disposition of patients

Disposition of patients and reasons for premature discontinuations of follow-up will be tabulated by cohort (i.e. separating stage 2 patients from stage 1 and intermediate-stage patients), by stage of disease and overall.

- Number of screened HAT positive patients (i.e. patients who gave informed consent)
  - Number and percentage of patients who met all inclusion criteria and no exclusion criteria
  - Number and percentage of patients with at least one inclusion criterion not met and/or exclusion criterion met
- Number of patients not treated, and reasons:
  - Number and percentage of patients with at least one inclusion criterion not met and/or exclusion criterion met
  - Number and percentage of patients not treated due to SAE not related to treatment
  - Number and percentage of patients not treated due to early consent withdrawal or another reason (will be listed)
- Number of patients treated (i.e. who received at least one of the 3 tablets of acoziborole)
- Amongst treated patients:
  - Number and percentage of patients who withdrew from the study prematurely, listed by reason for withdrawal (i.e. death, lost to follow-up, withdrawal of consent, investigator's decision, rescue therapy, other reason)
  - 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 fled the region due to armed conflict or natural disaster or due to force majeure and for whom no post-treatment data are available (i.e. follow-up visits M3, M6, M12 and M18 not performed).
  - 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 deviation
  - Number and percentage of patients who had at least one major protocol deviation (an intercurrent post treatment event is not necessarily a major protocol deviation)
  - Number and percentage of patients who underwent lumbar puncture at the end-of-hospitalisation, at the 6-month visit, the 12-month visit and the 18-month visit
  - Number and percentage of patients who attended the end-of-hospitalisation visit, the 3 months visit, the 6-month visit, the 12-month visit and the 18-month visit

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 deviations will be described separately. Results will be displayed by cohort, by stage of disease and overall, on the mITT.

Protocol deviations will be listed and finalised prior to the data review meeting. The sponsor will be responsible for classifying all deviations as either major or minor. Patients with at least one major protocol deviation will be excluded from the PP dataset. Major protocol deviations will be reviewed during the data review meeting.

8.3. Analysis sets and subgroups

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

Frequency and percentage of patients included in each cohort, in each stage of the disease, and in each subgroup defined in Section 5 will be described on the mITT.

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

Descriptive analyses will be provided by cohort, by stage of disease and overall, on the mITT set.

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

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. Treatment compliance

Descriptive analyses will be provided by cohort, by stage of disease and overall, on the mITT set.

8.6. Efficacy analysis

8.6.1. Analysis of the primary efficacy endpoint

8.6.1.1. Primary analysis

The primary analysis is the estimation of the success rate after 18 months of follow-up with acoziborole (cf. Section 6.1). The primary analysis will be performed on Stage 2 patients included in the mITT set.

An estimate of the success rate at 18 months will be provided. The 95% Jeffreys confidence interval of the estimate will be provided. The Jeffreys confidence interval has a coverage probability that does not exceed 95% by too much and is equal tailed, i.e. the probabilities of the interval lying above or below the upper and lower bounds are both close to 2.5%, which is important when the lower bound of the 95% confidence interval is more meaningful from a clinical standpoint than the upper bound.

8.6.1.2. Sensitivity analyses

Sensitivity analysis #1

The analysis described above (cf. primary analysis) will be repeated on Stage 2 patients included in the PPS.

Sensitivity analysis #2

The analysis described above (cf. primary analysis) will be repeated on Stage 2 patients included in the Evaluable patients set.

Sensitivity analysis #3

The analysis described above (cf. primary analysis) will be repeated on Stage 2 patients included in the Treated set.

Sensitivity analysis #4

The analysis described above (cf. primary analysis) will be performed on Stage 2 patients included in the mITT with the "fair case" method (see Section 7.6.1).

Sensitivity analysis #5

The analysis described above (cf. primary analysis) will be performed on Stage 2 patients included in the mITT with the "best case" method (see Section 7.6.1).

Sensitivity analysis #6

The analysis described above (cf. primary analysis) will be performed on Stage 2 patients included in the mITT with the "observed case" method (see Section 7.6.1).

8.6.1.3. Success Rate for the yardsticks

As per protocol, Section 9.6.1: "The current standard of care for stage 2 patients is NECT, and the success rate with NECT will be used as a yardstick".

"The success rates will be provided study-by-study along with the 95% Jeffreys confidence interval. Studies presented in the following table will be taken into account as well as the overall success rate excluding Nect-field. The NECTField study will not be used because it did not include the same population and the large number of missing lumbar punctures could drastically reduce the success rate, particularly at 12 and 18 months (cf. protocol, ref. 20). All of the results will be presented together in graphic format using a Forest plot".

Table 4: Efficacy of NECT

Study	Success rate at 18 M for NECT ITT and 95% Jeffreys CI	Comments
Mesu (2017) Fexi 004 study	S.R. = 124 / 130 = 95.4% 95% CI = [90.7% - 98.1%]	Pivotal Fexinidazole study. mITT: S.R.= 124 / 127 = 97.6% (RZD trial). 95% Jeffreys CI = [93.8% - 99.3%] Reason : 3 patients fleeing the region due to armed conflict
Priotto (2006)	S.R. = 16 / 17 = 94.1% 95% CI = [75.6% - 99.4%]	RZD trial
Checchi (2007)	S.R. = 29 / 31 = 93.5% 95% CI = [80.9% - 98.6%]	
Priotto (2009)	S.R. = 135 / 143 = 94.4% 95% CI = [89.7% - 97.3%]	S.R. = 138 / 143 = 96.5% 95% Jeffreys CI = [92.5% - 98.7%] Note: exclusion of 3 deaths not related to treatment (RZD trial)
Kansiime (2018)	S.R. = 50 / 55 = 90.9% 95% CI = [81.2% - 96.4%]	RZD trial
Total	S.R. = 354 / 376 = 94.1% 95% CI = [91.4% - 96.2%]	Based on randomized studies only.

Study	Success rate at 18 M for NECT ITT and 95% Jeffreys CI	Comments
NECT field	S.R. = 582 / 613 = 94.9% 95% CI = [93.0% - 96.5%]	Evaluations are not always done at M18 (one arm field study with loose monitoring). 49 lost to follow-up at M18 were not necessarily counted as failure.

Note: percentages and their 95% Jeffrey confidence interval of success rate at 18 months will be used as they are in Table 4 (i.e. no further calculation will be performed) in the forest plot.

Note: results from Priotto 2007 [1] will not be displayed in the forest plot as it is actually a sub-cohort of patients from Priotto 2009.

Note: it could be difficult to get all individual historical data of all available studies using NECT. In other words, it will be difficult to use exactly the same criteria for determining the status of each patient treated with NECT. The figures presented in Table 4 and especially the overall estimate will be used as a yardstick even if they are more liberal (except for the Mesu's study) than what could be obtained from the strict application of algorithm. As an example, in Priotto's study (2009) 129 patients completed the M18 visit and were proven cured (*i.e.* WBC in CSF < 20). This represents a success rate of 88.8%. 138 patients out of 143 were considered as cured by the authors leading to a success rate of 96.5%. All deaths regardless the cause (5), relapses (2) and absence of any post-treatment assessment (1) were considered as failure in Table 4 leading to a failure rate of 5.6% (S.R. = 94.4%). Lost to follow-up due to moved out (2 patients moved out) and absence of assessment (probably lumbar puncture) at M18 (4 patients) are not counted as failures in Table 4 and this sort of decision is a potential source of bias (overestimation of success rate of NECT compared to the strict application of the algorithm). Because the retained result in Table 4 is rather in favour of NECT, the possible bias is in disfavour of acoziborole when the yardstick (NECT) is compared to acoziborole.

8.6.1.4. Other sensitivity analyses

Note: statistical analyses described in this section requires databases from other clinical trials. These statistical analyses **may be** performed **on condition** that these databases from other clinical trials can be recovered and pooled together. At the time of writing, it is unknown whether these analyses could be performed or not.

Further to consultation of Scientific Advice Working Party (SAWP) Committee for Medicinal Products for Human Use (CHMP) for sample size decrease, the following advice was provided: "*Although the trial is uncontrolled, it is still considered important to attempt to place the results into context by comparison with the reported efficacy of NECT in a broadly similar HAT patient population. With completion of the primary analysis of the pivotal trial for fexinidazole vs. NECT there are recent data in late stage 2 HAT that could be used to place the data obtained with acoziborole into some context. The cure rate in late stage 2 HAT in the fexinidazole pivotal study was 97.6% and DNDi is aware of the result since the trial was conducted under DNDi's auspices even though the MAH will be Sanofi. Although acoziborole will be a single dose oral treatment, the results of the acoziborole study will need to be discussed in light of the results that were obtained with NECT in late stage 2 patients. Matching on selection criteria or adjustments to account for differences between the study population and the historical/external control should be considered*".

Data presented in Table 4 concerned patients in late stage 2 (WBC in CSF > 20) and are not matched on other inclusion criteria that could affect efficacy. During the discussion meeting on November 5 in 2015 the following points were presented:

Stratification on confounding factors:

- Epicentre company used "Médecins Sans Frontières" (MSF) data to detect variables that are predictive of the response at 18 months (Priotto G et al. PLoS Negl Trop 2012).
- Five available variables significantly explained the outcome at 18 months:
  - Age

- Gender
- WBC count in CSF at baseline
- WBC at 6 months
- WBC at 12 months

- The first 3 factors: age according to 3 terciles (<T1, T1-T2, >T2), gender and WBC at baseline (≤100 /µL, > 100/µL) could be used to create 12 strata. The stratification factor could then be included as a covariate in a CMH test or a log binomial model to get a within strata (blocks) comparison of treatments. This approach would be used as a sensitivity analysis.

The following advice was provided "*Data concerned late stage 2 patients treated with melarsoprol (n = 1469), eflornithine (n = 578) or a combination (n = 143). Moreover, death during treatment and follow-up were not included in the 2190 patients analyzed. At the time of submission of fexinidazole compound, a similar meta-analysis base on all patients treated with fexinidazole was performed using only baseline data as predictors of the outcome at month 18. A series of logistics models were fitted and the model reaching the lowest AIC (Akaike information criterion) was based on only one variable: the natural logarithm of the number of WBC in CSF at entry (p < 0.0001). Other predictors (presence of trypanosome, age or other) had a larger AIC and consequently no interest or added value. Categorization of the number of WBC showed two pertinent thresholds: WBC ≤ 100 /µL and WBC > 400 /µL*".

To meet SAWP (CHMP) request, it is planned:

- To keep the primary analysis as planned in the protocol.
- To use studies presented in Table 4 for the yardstick. One estimate would exclude NECT field (not randomized study and many dropouts) and another one would include NECT field.
- The natural logarithm of WBC in CSF at baseline could be used as covariate in a binary logistic model, i.e. outcome at 18 months (success vs. failure) according to treatment (NECT field versus Acoziborole) and natural logarithm of baseline WBC in CSF.
- The analysis set could be split in 3 strata according to the following threshold: baseline WBC in CSF ≤ 100 /µL and > 400 /µL. A CMH test could then be performed for the comparison, i.e. outcome at 18 months (success vs. failure) according to treatment (NECT field versus Acoziborole), adjusted for the 3 strata.
- The natural logarithm of WBC in CSF at baseline and other available baseline data (presence of trypanosomes in CSF, age, gender, and possibly other available covariates) could be used as covariates in a binary logistic model to obtain a propensity score. The analysis of the outcome at 18 months could then be adjusted using propensity score.
- The last 3 analyses would be considered as sensitivity analyses.

8.6.2. Analysis of the secondary efficacy endpoints

Efficacy analysis in stage 1 and intermediate-stage patients

The efficacy analysis for stage 1 and intermediate-stage patients is a secondary analysis. It concerns the success rate at 6 months, 12 months and at 18 months in stage 1 and intermediate-stage patients. The same analyses as described for the primary endpoint will be provided (cf. Section 8.6.1 "Primary analysis" and "Sensitivity analyses").

Note: the yardstick for this cohort will be pentamidine and possibly newly registered treatment.

Secondary efficacy analysis in stage 2 patients

The success rate at 6 months and 12 months in stage 2 patients will be analyzed as described for the primary endpoint (cf. Section 8.6.1 "Primary analysis" and "Sensitivity analyses").

Analysis of the overall success rate at 18 months

The overall success rate at 18 months (i.e. whatever the stage of HAT) will be calculated, along with the 95% Jeffreys confidence interval.

Three estimates will be provided:

- **(1)** On all patients included in the mITT set, excluding patients with stage 1 and intermediate stage HAT screened before the 20JUN2017, i.e. before recruitment of stage 1 and intermediate stage HAT patients has been authorized by the 1st DSMB meeting; corresponding to date of email from DNDi sent to the sites to allow inclusion of patients with stage 1 and intermediate stage HAT). In that case cohorts are self-weighted.
- **(2)** On all patients included in the mITT set, weighted by the duration of inclusion of each cohort. If the recruitment rate is far to be constant over time, i.e. if the cumulated number of recruited patients in each cohort taken separately is far to be linear, a piecewise estimate of the weight will be done.
- **(3)** On all patients included in the mITT set (*)

(*) Note: for the third estimate, the success rate after 18 months will be compared between "stage 1 + intermediate-stage patients" and "stage 2 patients" using a Fisher test. If there is no statistically significant difference, the estimate of the overall success rate will be provided. Otherwise, the third estimate will not be provided.

In case of a clinically significant difference between the 3 estimates, the second estimate will be used as it is the only one which takes into account all patients and is weighted by the estimated proportion of patients belonging to each sub-population.

Note: the yardstick for this endpoint will be fexinidazole and possibly newly registered treatment.

Analysis of the overall success rate at 18 months, giving equal weight to each centre:

This analysis will be provided on the mITT (cf. section 7.3 for further details).

8.6.3. Analysis of other secondary endpoints

Correlation analyses between concentrations in the blood (AUC) and CSF and the success rate

These analyses will be performed by [redacted]. A separate statistical analysis plan will be prepared by [redacted] for these analyses. Cf. protocol, Section 9.6.3 for further details.

Correlation between concentrations in the blood (AUC) and CSF and the occurrence of AEs

These analyses will be performed by [redacted]. A separate statistical analysis plan will be prepared by [redacted] for these analyses. Cf. protocol, Section 9.6.3 for further details.

Changes in the rate of favourable outcomes over time

Changes in the success rate over time (at 6, 12 and 18 months) for stage 2 patients on one hand, and for stage 1 and intermediate-stage patients on the other hand, will be studied using a logistic mixed model for repeated measures, based on the GLIMMIX SAS procedure, using the following specifications:

- estimation method = Pseudo-Likelihood (METHOD=RSPL)
- binary endpoint = success rate (with events coded as '1' and failures coded as '0')
- distribution = binary
- link = logit
- unique patient id defined as class variable
- visit defined as class variable, with reference value = 6-month visit
- unstructured covariance structure

Odds ratio, their 95% CI and the corresponding p-value will be displayed for the following comparisons of success rate: 12 months versus 6 months, 18 months versus 6 months, and 18 months versus 12 months. This analysis will be provided on the mITT. Algorithms used to derive success rates at 6, 12 and 18 months are described in Section 10.

Time to proven and definitive failure in Patients with Stage 2 HAT

This endpoint will be analysed using the Kaplan-Meier approach in order to estimate, at each follow-up visit (EoH, 3, 6, 12 and 18 months) the cumulative rate of proven failures. The Kaplan-Meier curve will be presented. The number of events and censoring will be provided at each visit (EoH, 3, 6, 12 and 18 months). Survival probability at each visit (EoH, 3, 6, 12 and 18 months) will be calculated with its 95% CIs using the log-log transformation. This analysis will be provided on the mITT.

[redacted]

A trend test (Cochran-Armitage test) will be used to assess the relationship between success rate at 18 months (as well as 12 months) and ordered class of disease progress (see Table 1): stage 1 versus intermediate stage versus stage 2.

Exploratory subgroups analysis:

Descriptive analysis of the success rates at 18 months (i.e. primary and secondary endpoint at 18 months) and at 12 months will be provided on the following subgroup:

- "A" versus "B+C+D+E+F"
- "A" versus "B+C+D" versus "E+F"
- "A" vs "B" vs "C" vs "D" vs "E" vs "F" (i.e. on each subgroup).

A trend test (Cochran-Armitage test) will be used to assess the relationship between success rate at 18 months (as well as 12 months) and each subgroup (i.e. "A" vs "B" **vs "F"** vs "C" vs "D" vs "E", in this order).

By-center analysis of the success rates at 18 months:

Descriptive analysis of the success rate at 18 months on Stage 2 patients will be provided by centre. A test of homogeneity (likelihood-ratio test) will be performed. 95% Jeffreys CI will be provided. This analysis will be provided on the mITT (cf. section 7.3 for further details). 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).

The same analysis will be provided for the success rate at 18 months on Cohort 2 (Stage 1 + intermediate-stage patients).

8.7. Futility Analyses

As per protocol, Section 9.6.2: an independent DSMB will be appointed, among other things, to supervise and review the futility, as well as the safety data. The DSMB will make recommendations on study continuation based on all available information.

Note 1: all analyses, tables, figures and listings to be provided for futility analyses are described in the **DSMB charter**.

Note 2: futility analyses will be performed on the raw database (i.e. not on the CDISC compliant database).

First futility analysis:

The first futility analysis will be performed once the first 20 stage 2 patients reach the 3-month visit. If the failure rate at Day 11 is significantly higher than the failure rate for melarsoprol (cf. Protocol, Reference 18) the study should be stopped for futility and for ethical reasons. The failure rate for melarsoprol at the end of treatment was 5% (4.8% for n = 6840). If 4 patients out of 20 are failures at Day 11 (p = 0.0159 one-sided), then the DSMB should recommend stopping the study, unless the rate can be explained by exceptional circumstances.

Failure rate at Day 11 will be computed as described in the table below.

Table 5 : Derivation rules for failure rate at Day 11 in patients with stage 2 HAT

Outcome at D11 for the 1st and 2nd futility analysis	Patient is ⇒ Dead (any reason) ⇒ *Failure* (stop) ⇓ Alive ⇓ Patient requires rescue medication for HAT ⇒ YES ⇒ *Failure* (stop) ⇓ NO rescue medication ⇓ Evidence of trypanosomes in any body fluid at Day 11 ⇒ YES ⇒ *Failure* (stop) ⇓ NO observed trypanosomes in any body fluid ⇒YES ⇒ *Success* (Stop)

Second futility analysis:

The second futility analysis will be performed once 70 stage 2 patients reach the 3-month visit. The recommendation to stop the study should be made if 8 patients or more out of 70 are failures at the end of hospitalisation (p = 0.023 one-sided).

Third futility analysis:

The last futility analysis will be performed once 70 stage 2 patients reach the 6-month visit. The proven failure rate will be compared to the failure rate with melarsoprol at 6 months, which is around 20%. If the rate is significantly higher than 20%, i.e. ≥ 22 out of 70 patients (p = 0.016, one-sided), the DSMB should recommend stopping the study.

This analysis will be performed on the following analysis set: "**first 70 stage 2 treated patients"** (note: "first" is defined according to the date of treatment administration on D1).

Failure rate at 6 months will be computed as described in the table below.

Table 6: Derivation rules for failure rate at 6 months in patients with stage 2 HAT

Outcome at M6 for the 3rd futility analysis	Patient is dead (any reason) before M6 ⇒ ***Failure*** **(stop)** ⇓ Alive ⇓ Patient requires rescue medication for HAT ⇒ YES ⇒ ***Failure*** **(stop)** ⇓ NO rescue medication up-to M6 ⇓ Evidence of trypanosomes in any body fluid at M6 or between drug intake and M6 visit ⇒ YES ⇒ ***Failure*** **(stop)** ⇓ NO ⇓ Patient Lost to follow-up before M6 ⇒ YES ⇒ ***Failure*** **(stop)** ⇓ NO ⇓ WBC in CSF at M6 ≤ 20 cells and no signs and symptoms related to HAT at M6 ⇒ YES ⇒ ***Success*** **(stop)** ⇓ NO ⇓ WBC in CSF at M6 > 50 cells ⇒ YES ⇒ ***Failure*** **(stop)** ⇓ NO ⇓ Evidence of trypanosomes at M12 ⇒ YES ⇒ ***Failure*** **(stop)** ⇓ NO ⇓ WBC in CSF at M12 ≤ 20 and no signs and symptoms related to HAT at M12: ⇒ ***Success*** **(stop)** ⇓ WBC in CSF at M12 > 50 ⇒ ***Failure*** **(stop)** ⇓ WBC in CSF at M12 between 20 and 50: ⇒WBC in CSF at M12 ≥ M6 (i.e. increase) ⇒ YES ⇒ ***Failure*** **(stop)** ⇒WBC in CSF at M12 < M6 (i.e. decrease): ⇒WBC in CSF at M18 ≤ 20 and no trypanosomes at M18 and no signs/symptoms at M18 ⇒ ***Success*** **(stop)** ⇒WBC in CSF at M18 > 20 or trypanosomes at M18 ⇒ ***Failure*** **(stop)** ⇓ **Otherwise: Not evaluable**

Additional futility analyses:

Additional futility analyses may be performed if deemed necessary during the course of the study.

Rules for Success of the Study:

There are no objective rules for the success of the study. As recommended by the EMA Scientific Advice Working Party, the observed success rate and lower bound of the 95% CI will be interpreted in light of those obtained in the literature and historical data, taking into account the obvious advantage of having a single oral dose for patients living in remote areas.

8.8. Safety analysis

All safety analyses will be performed on the Treated set.

8.8.1. 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 cohort, by stage of disease and overall. The following information will be tabulated (the number, percentage of patient and 95% CI):

- At least one AE
- At least one TEAE
- 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 drug-related TEAE

For the following descriptions the number and percentage of patients and the number of occurrences of TEAE will be presented by cohort, by period of occurrence, by stage of disease and overall, and by MedDRA SOC and PT (descending order of SOC and PT):

- TEAE
- Drug-related TEAE
- Serious TEAE
- Serious drug-related TEAE
- TEAE of interest

All AEs and SAEs will be listed.

8.8.2. Laboratory examination

Descriptive analysis at baseline, at each time points and changes from baseline:

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 cohort, by stage of disease and overall.

Shift tables according to lower and upper limits of normal range:

For all laboratory parameters (except ASAT, ALAT and TSH), shift tables according to lower and upper limits of normal range (<LLN, Normal, >ULN) between baseline and each time point (i.e. D5, D11, M3, M6, M12, M18) for each laboratory parameters will be provided by cohort, by stage of disease and overall. On exploratory purpose, Bowker's symmetry test will be performed.

The same analysis will be provided for ASAT and ALAT using the following classes: <0.5*LLN, [0.5*LLN to <LLN, Normal, >ULN to 2*ULN], >2*ULN to 3*ULN], >3*ULN).

The same analysis will be provided for TSH using the following classes: <0.5*LLN, [0.5*LLN to <LLN, Normal, >ULN to 2*ULN], >2*ULN).

Scatterplots:

Scatterplots between baseline value and value at each of the following time point: D5, D11, M3, M18) for the following laboratory parameters: ASAT, ALAT, Potassium, Bicarbonates, Albumin and TSH will be provided by cohort.

8.8.3. Pharmacokinetics

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

8.8.4. Electrocardiogram

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

8.9. Analysis of other endpoints and variables

Analyses of other endpoints will be performed on the Treated set. Results will be displayed by cohort, by stage of disease and overall.

8.9.1. Vital signs

Descriptive statistics will be provided by visit.

In addition, descriptive statistics of changes in weight (kg) from baseline and relative change from baseline in body weight (%) 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.

8.10. Unscheduled visit

As described in Section 7.5, data from unscheduled visits will be used in the calculation of time-windows and calculated visits.

Data from unscheduled visits will be tabulated in data listings

8.11. Data and Safety Monitoring Board (DSMB)

As per protocol, Section 10: a DSMB, composed of at least 3 members independent of the Investigators and the Sponsor, will be set up prior to the start of the study. The DSMB will monitor the study in order to minimise any risk of harm to the patients included in the study.

At each of its meetings, the DSMB will examine safety data 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 results of the futility analyses will be presented to the DSMB, who will decide whether or not the study can continue and whether the enrolment period should be extended.

The organisation 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.

8.12. Analysis of potential biases

In order to assess a potential selection bias, descriptive statistics will be provided on all patients treated and on all patients NOT treated (but with a confirmation of the presence of trypanosomes in any body fluid) for:

- Demographic data
- 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)

This analysis will be performed if at least 5 % of screened patients are not included in the study.

9. DISPLAY PLAN

9.1. List of Tables, Figures and Listings

Note: outputs listed below should be numbered as described. Sections 14.1, 14.2 and 14.3 may be provided in separate documents, if required. Sections 16.2.1 to 16.2.10 will be provided in separate documents.

9.1.1. List of outputs for ICH Section 14.1 (Study patients)

14. STATISTICAL ANALYSIS

14.1 Study patients

14.1.1 Disposition of patients

14.1.1.1: Disposition of patients by cohort, stage of disease and overall (all patients)

Cf. section 9.2.1, template 1.

14.1.1.2: Disposition of patients: study key dates and study duration (all patients)

Cf. section 9.2.1, template 2.

14.1.2 Protocol deviations

14.1.2.1: Protocol deviations by cohort, stage of disease and overall (mITT)

14.1.3 Analysis sets and subgroups

14.1.3.1: Analysis sets by cohort, stage of disease and overall (all patients)

14.1.3.2: Analysis subgroups (mITT)

14.1.4 Demographic data and other baseline characteristics

14.1.4.1: Demographic data by cohort, stage of disease and overall (mITT)

14.1.4.2: Vital signs at baseline by cohort, stage of disease and overall (mITT)

14.1.4.3: Clinical signs and symptoms of HAT at baseline by cohort, stage of disease and overall (mITT)

14.1.4.4: Physical examination at baseline

- 14.1.4.4.1 Head and neck by cohort, stage of disease and overall (mITT)
- 14.1.4.4.2 Thorax by cohort, stage of disease and overall (mITT)
- 14.1.4.4.3 Abdomen by cohort, stage of disease and overall (mITT)
- 14.1.4.4.4 Lower limbs by cohort, stage of disease and overall (mITT)
- 14.1.4.4.5 Skin by cohort, stage of disease and overall (mITT)

14.1.4.5: Neurological examination at baseline

- 14.1.4.5.1. Psychiatric observation by cohort, stage of disease and overall (mITT)
- 14.1.4.5.2. Higher functions by cohort, stage of disease and overall (mITT)
- 14.1.4.5.3. Cranial nerves by cohort, stage of disease and overall (mITT)

14.1.4.5.4. Mobility by cohort, stage of disease and overall (mITT)

14.1.4.5.5. Motor coordination and balance by cohort, stage of disease and overall (mITT)

14.1.4.5.6. Primitive reflex by cohort, stage of disease and overall (mITT)

14.1.4.5.7. Sensitivity by cohort, stage of disease and overall (mITT)

14.1.4.5.8. Other neurological abnormalities by cohort, stage of disease and overall (mITT)

14.1.4.6: HAT diagnosis (examination of blood, lymph and CSF samples) at baseline

14.1.4.6.1. Blood tests and lymph node aspirate examination by cohort, stage of disease and overall (mITT)

14.1.4.6.2. Examination of cerebrospinal fluid by cohort, stage of disease and overall (mITT)

14.1.5 Medical history

14.1.5.1: Medical history by MedDRA SOC and PT, by stage of disease and overall (mITT)

14.1.5.2: Medical history by MedDRA SOC and PT, by cohort and overall (mITT)

14.1.6 Prior and concomitant therapies

14.1.6.1: Prior therapies by therapeutic class (ATC2) and WHO-DD preferred name, by stage of disease and overall (mITT)

14.1.6.2: Prior therapies by therapeutic class (ATC2) and WHO-DD preferred name, by cohort and overall (mITT)

14.1.6.3: Concomitant therapies by therapeutic class (ATC2) and WHO-DD preferred name, by stage of disease and overall (mITT)

14.1.6.4: Concomitant therapies by therapeutic class (ATC2) and WHO-DD preferred name, by cohort and overall (mITT)

14.1.7 Extent of exposure and treatment compliance

14.1.7.1: Treatment compliance by cohort, stage of disease and overall (mITT)

14.1.8 Analysis of potential biases

14.1.8.1: Demographic data by cohort, stage of disease and overall

Same outputs as above on Treated set

Same outputs as above on Set of patients not treated but with least one blood test or lymph node aspirate test positive

14.1.8.2: Vital signs at baseline by cohort, stage of disease and overall

Same outputs as above on Treated set

Same outputs as above on Set of patients not treated but with least one blood test or lymph node aspirate test positive

14.1.8.3: Clinical signs and symptoms of HAT at baseline by cohort, stage of disease and overall

Same outputs as above on Treated set

Same outputs as above on Set of patients not treated but with least one blood test or lymph node aspirate test positive

14.1.8.4: Physical examination at baseline

Same outputs as above on Treated set

Same outputs as above on Set of patients not treated but with least one blood test or lymph node aspirate test positive

14.1.8.5: Neurological examination at baseline

Same outputs as above on Treated set

Same outputs as above on Set of patients not treated but with least one blood test or lymph node aspirate test positive

14.1.8.6: HAT diagnosis (examination of blood, lymph and CSF samples) at baseline

Same outputs as above on Treated set

Same outputs as above on Set of patients not treated but with least one blood test or lymph node aspirate test positive

9.1.2. List of outputs for ICH Section 14.2.1 (Primary efficacy endpoint)

14.2. Efficacy evaluation

14.2.1 Primary efficacy endpoint: outcome at 18 months in stage 2 patients

14.2.1.1 Primary analysis

14.2.1.1.1: Success rate at 18 months – Stage 2 patients (mITT)

14.2.1.2 Sensitivity analyses

14.2.1.2.1: Success rate at 18 months – Stage 2 patients (PPS)

14.2.1.2.2: Success rate at 18 months – Stage 2 patients (Evaluable patients set)

14.2.1.2.3: Success rate at 18 months – Stage 2 patients (Treated set)

14.2.1.2.4: Success rate at 18 months – Stage 2 patients (mITT / fair case method)

14.2.1.2.5: Success rate at 18 months – Stage 2 patients (mITT / best case method)

14.2.1.2.6: Success rate at 18 months – Stage 2 patients (mITT / observed case method)

14.2.1.3 Forest plot of success rate at 18 months for the yardstick - Stage 2 patients (mITT)

9.1.3. List of outputs for ICH Section 14.2.2 (Secondary efficacy endpoints)

14.2.2 Secondary efficacy endpoints

14.2.2.1 Outcome at 12 months in stage 2 patients

14.2.2.1.1 Primary analyses

14.2.2.1.1.1: Success rate at 12 months – Stage 2 patients (mITT)

14.2.2.1.2 Sensitivity analyses

14.2.2.1.2.1: Success rate at 12 months – Stage 2 patients (PPS)

14.2.2.1.2.2: Success rate at 12 months – Stage 2 patients (Evaluable patients set)

14.2.2.1.2.3: Success rate at 12 months – Stage 2 patients (Treated set)

14.2.1.2.4: Success rate at 18 months – Stage 2 patients (mITT / fair case method)

14.2.1.2.5: Success rate at 18 months – Stage 2 patients (mITT / best case method)

14.2.1.2.6: Success rate at 18 months – Stage 2 patients (mITT / observed case method)

14.2.2.2.2 Outcome at 6 months in stage 2 patients

Same outputs as above.

14.2.2.2.3 Outcome at 18 months in stage 1 and intermediate-stage patients

Same outputs as above.

14.2.2.2.4 Outcome at 12 months in stage 1 and intermediate-stage patients

Same outputs as above.

14.2.2.2.5 Outcome at 6 months in stage 1 and intermediate-stage patients

Same outputs as above.

14.2.2.2.6 Outcome at 18 months in intermediate-stage patients

Same outputs as above.

14.2.2.2.7 Outcome at 12 months in intermediate-stage patients

Same outputs as above.

14.2.2.2.8 Outcome at 6 months in intermediate-stage patients

Same outputs as above.

14.2.2.2.9 Outcome at 18 months in stage 1 patients

Same outputs as above.

14.2.2.2.10 Outcome at 12 months in stage 1 patients

Same outputs as above.

14.2.2.2.11 Outcome at 6 months in stage 1 patients

Same outputs as above.

14.2.2.2.12 Overall success rate at 18 months (whatever the stage of HAT)

14.2.2.2.12.1: Overall success rate at 18 months (mITT, excluding patients with stage 1 and intermediate stage HAT screened before the 20JUN2017)

14.2.2.2.12.2: Overall success rate at 18 months (mITT, weighted by the duration of inclusion of each cohort)

14.2.2.2.12.3: Comparison in success rate at 18-months between stage 1 and intermediate-stage patients versus stage-2 patients (mITT)

14.2.2.2.12.4: Overall success rate at 18 months (mITT)

Note: as written in section 8.6.2, this table will not be provided if the previous comparison is statistically significant.

14.2.2.2.12.5: Overall success rate at 18 months giving equal weight to each centre (mITT)

9.1.4. List of outputs for ICH Section 14.2.3 (Other efficacy endpoints)

14.2.3 Other efficacy endpoints

14.2.3.1: Changes in the rate of favorable outcomes over time in patients with stage 2 HAT (mITT)

14.2.3.2: Changes in the rate of favorable outcomes over time in stage 1 and intermediate-stage patients (mITT)

14.2.3.3: Kaplan-Meier analysis of time to proven and definitive failure in Patients with Stage 2 HAT (mITT)

14.2.3.3.1: Figure: Kaplan-Meier curve

14.2.3.3.2: Table: Survival probabilities

14.2.3.4: Descriptive analysis and trend test of success rates at 18 months: stage 1 versus intermediate stage versus stage 2 (mITT)

14.2.3.5: Descriptive analysis and trend test of success rates at 12 months: stage 1 versus intermediate stage versus stage 2 (mITT)

14.2.3.6: Descriptive analysis and test of homogeneity of success rates at 18 months by center - Stage 2 patients (mITT)

14.2.3.7 Forest plot of success rate at 18 months by center - Stage 2 patients (mITT)

14.2.3.8: Descriptive analysis and test of homogeneity of success rates at 18 months by center - Stage 1 and intermediate-stage patients (mITT)

14.2.3.9 Forest plot of success rate at 18 months by center - Stage 1 and intermediate-stage patients (mITT)

9.1.5. List of outputs for ICH Section 14.2.4 (Exploratory subgroups analysis)

14.2.4: Exploratory subgroups analysis

14.2.4.1: Descriptive analysis of success rates at 18 months: subgroups A versus B+C+D+E+F (mITT)

14.2.4.2: Descriptive analysis of success rates at 18 months: subgroups A versus B+C+D versus E+F (mITT)

14.2.4.3: Descriptive analysis and trend test of success rates at 18 months: subgroups A vs B vs C vs D vs E vs F (mITT)

14.2.4.1: Descriptive analysis of success rates at 12 months: subgroups A versus B+C+D+E+F (mITT)

14.2.4.2: Descriptive analysis of success rates at 12 months: subgroups A versus B+C+D versus E+F (mITT)

14.2.4.3: Descriptive analysis and trend test of success rates at 12 months: subgroups A vs B vs C vs D vs E vs F (mITT)

9.1.6. List of outputs for ICH Section 14.3.1 (Adverse events)

14.3. Safety evaluation

14.3.1 Adverse events

14.3.1.1 Overall summary of Adverse events

14.3.1.1: Overall summary of AEs (Treated set)

14.3.1.2 Adverse events by MedDRA SOC and PT

14.3.1.2.1: All AEs by MedDRA SOC and PT (Treated set)

14.3.1.2.2: TEAE by MedDRA SOC and PT (Treated set)

14.3.1.2.3: Drug-related TEAE by MedDRA SOC and PT (Treated set)

14.3.1.2.4: Serious TEAE by MedDRA SOC and PT (Treated set)

14.3.1.2.5: Serious drug-related TEAE by MedDRA SOC and PT (Treated set)

14.3.1.2.6: TEAE of interest by MedDRA SOC and PT (Treated set)

14.3.1.3 Adverse events by period of occurrence and by MedDRA SOC and PT

14.3.1.3.1: AE occurred before intake of the study drug by MedDRA SOC and PT (Treated set)

14.3.1.3.2: TEAE occurred on Day 1 by MedDRA SOC and PT (Treated set)

14.3.1.3.3: TEAE occurred during hospitalization period by MedDRA SOC and PT (Treated set)

14.3.1.3.4: TEAE occurred during post-hospitalization period by MedDRA SOC and PT (Treated set)

14.3.1.4 Drug-related TEAE by period of occurrence and by MedDRA SOC and PT

14.3.1.4.1: Drug-related TEAE occurred on Day 1 by MedDRA SOC and PT (Treated set)

14.3.1.4.2: Drug-related TEAE occurred during hospitalization period by MedDRA SOC and PT (Treated set)

14.3.1.4.3: Drug-related TEAE occurred during post-hospitalization period by MedDRA SOC and PT (Treated set)

14.3.1.5 Serious TEAE by period of occurrence and by MedDRA SOC and PT

Same outputs as above.

14.3.1.6 Serious drug-related TEAE by period of occurrence and by MedDRA SOC and PT

Same outputs as above.

14.3.1.7 TEAE of interest by period of occurrence and by MedDRA SOC and PT

Same outputs as above.

9.1.7. List of outputs for ICH Section 14.3.2 (Laboratory examination)

14.3.2 Laboratory examination

14.3.2.1: Descriptive analysis of Haematology parameters at baseline, at each time points and changes from baseline

14.3.2.1.1 Basophils

14.3.2.1.1.1: Descriptive analysis of Basophils at baseline, at each time points and changes from baseline (Treated set, Stage 1)

14.3.2.1.1.1: Descriptive analysis of Basophils at baseline, at each time points and changes from baseline (Treated set, Stage Intermediate)

14.3.2.1.1.1: Descriptive analysis of Basophils at baseline, at each time points and changes from baseline (Treated set, Stage 2)

14.3.2.1.1.1: Descriptive analysis of Basophils at baseline, at each time points and changes from baseline (Treated set, Stage 1 and Intermediate)

14.3.2.1.1.1: Descriptive analysis of Basophils at baseline, at each time points and changes from baseline (Treated set, all stages)

14.3.2.1.2 Eosinophils

Same outputs as above.

14.3.2.1.3 Haemoglobin

Same outputs as above.

14.3.2.1.4 Lymphocytes

Same outputs as above.

14.3.2.1.5 Monocytes

Same outputs as above.

14.3.2.1.6 Neutrophils

Same outputs as above.

14.3.2.1.7 Platelets

Same outputs as above.

14.3.2.1.8 White blood cells

Same outputs as above.

14.3.2.2: Descriptive analysis of Biochemistry parameters at baseline, at each time points and changes from baseline

14.3.2.2.1 Albumin

Same outputs as above.

14.3.2.2.2 Alkaline phosphatase

Same outputs as above.

14.3.2.2.3 ALT

Same outputs as above.

14.3.2.2.4 AST

Same outputs as above.

14.3.2.2.5 Bicarbonates

Same outputs as above.

14.3.2.2.6 Blood urea nitrogen

Same outputs as above.

14.3.2.2.7 Calcium

Same outputs as above.

14.3.2.2.8 Chloride

Same outputs as above.

14.3.2.2.9 Creatinine

Same outputs as above.

14.3.2.2.10 Glucose

Same outputs as above.

14.3.2.2.11 Potassium

Same outputs as above.

14.3.2.2.12 Sodium

Same outputs as above.

14.3.2.2.13 Total bilirubin

Same outputs as above.

14.3.2.2.14 Total protein

Same outputs as above.

14.3.2.3: Descriptive analysis of Thyroid function parameters at baseline, at each time points and changes from baseline

14.3.2.3.1 fT3 - result

Same outputs as above.

14.3.2.3.2 fT4 - result

Same outputs as above.

14.3.2.3.3 TSH - result

Same outputs as above.

14.3.2.4: Shift tables according to lower and upper limits of normal range of Haematology parameters between baseline and each time points

14.3.2.4.1 Basophils

14.3.2.4.1.1: Shift tables according to lower and upper limits of normal range of Basophils between baseline and each time points (Treated set, Stage 1)

14.3.2.4.1.2: Shift tables according to lower and upper limits of normal range of Basophils between baseline and each time points (Treated set, Stage Intermediate)

14.3.2.4.1.3: Shift tables according to lower and upper limits of normal range of Basophils between baseline and each time points (Treated set, Stage 2)

14.3.2.4.1.4: Shift tables according to lower and upper limits of normal range of Basophils between baseline and each time points (Treated set, Stage 1 and Intermediate)

14.3.2.4.1.5: Shift tables according to lower and upper limits of normal range of Basophils between baseline and each time points (Treated set, all stages)

Idem for all Haematology parameters.

14.3.2.5: Shift tables according to lower and upper limits of normal range of Biochemistry parameters between baseline and each time points

Idem for all Biochemistry parameters.

Note: for ASAT and ALAT, use the following classes: <0.5*LLN, [0.5*LLN to <LLN, Normal, >ULN to 2*ULN], >2*ULN to 3*ULN], >3*ULN).

14.3.2.6: Shift tables according to lower and upper limits of normal range of Thyroid function parameters between baseline and each time points

Idem for all Thyroid function parameters.

Note: for TSH, use the following classes: <0.5*LLN, [0.5*LLN to <LLN, Normal, >ULN to 2*ULN], >2*ULN).

14.3.2.7: Scatter plots of Haematology parameters between baseline and each time points

14.3.2.7.1. Scatter plots for Basophils - Treated set (Stage 1)

14.3.2.7.1.1 Basophils - Baseline * D5

14.3.2.7.1.2 Basophils - Baseline * D11

14.3.2.7.1.3 Basophils - Baseline * M3

14.3.2.7.1.4 Basophils - Baseline * M6

14.3.2.7.1.5 Basophils - Baseline * M12

14.3.2.7.1.6 Basophils - Baseline * M18

14.3.2.7.1. Scatter plots for Basophils - Treated set (Stage intermediate)

Same outputs as above.

14.3.2.7.2. Scatter plots for Basophils - Treated set (Stage 1 + intermediate)

Same outputs as above.

14.3.2.7.3. Scatter plots for Basophils - Treated set (Stage 2)

Same outputs as above.

14.3.2.7.4. Scatter plots for Basophils - Treated set (Total)

Same outputs as above.

Idem for all Haematology parameters.

14.3.2.8: Scatter plots of Biochemistry parameters between baseline and each time points

Idem for all Biochemistry parameters.

14.3.2.9: Scatter plots of Thyroid function parameters between baseline and each time points

Idem for all Thyroid function parameters.

9.1.8. List of outputs for ICH Section 14.3.3 (Vital signs, physical findings and other observations related to safety)

14.3.3 Vital signs, physical findings and other observations related to safety

14.3.3.1 Vital signs

14.3.3.1.1: Vital signs at baseline, by cohort, stage of disease and overall (Treated set)

14.3.3.1.2: Vital signs at D5, by cohort, stage of disease and overall (Treated set)

14.3.3.1.3: Vital signs at D11, by cohort, stage of disease and overall (Treated set)

14.3.3.1.3: Vital signs at D15, by cohort, stage of disease and overall (Treated set)

14.3.3.1.4: Vital signs at M3, by cohort, stage of disease and overall (Treated set)

14.3.3.1.5: Vital signs at M6, by cohort, stage of disease and overall (Treated set)

14.3.3.1.6: Vital signs at M12, by cohort, stage of disease and overall (Treated set)

14.3.3.1.7: Vital signs at M18, by cohort, stage of disease and overall (Treated set)

14.3.3.1.8: Descriptive analysis of body weight(kg) at baseline, at each time points and changes from baseline (Treated set, Stage 1)

14.3.3.1.9: Descriptive analysis of body weight(kg) at baseline, at each time points and changes from baseline (Treated set, Stage Intermediate)

14.3.3.1.10: Descriptive analysis of body weight(kg) at baseline, at each time points and changes from baseline (Treated set, Stage 2)

14.3.3.1.11: Descriptive analysis of body weight(kg) at baseline, at each time points and changes from baseline (Treated set, Stage 1 and Intermediate)

14.3.3.1.12: Descriptive analysis of body weight(kg) at baseline, at each time points and changes from baseline (Treated set, all stages)

14.3.3.1.13: Descriptive analysis of relative change from baseline in body weight (%) at each time points (Treated set)

14.3.3.2 Clinical signs and symptoms of HAT

14.3.3.2.1 Clinical signs and symptoms of HAT at baseline by cohort, stage of disease and overall (Treated set)

Same output for D5, D11, D15, M3, M6, M12, M18.

14.3.3.3 Physical examination

14.3.3.3.1: Physical examination at baseline

14.3.3.3.1.1 Head and neck at baseline by cohort, stage of disease and overall (Treated set)

14.3.3.3.1.2 Thorax at baseline by cohort, stage of disease and overall (Treated set)

14.3.3.3.1.3 Abdomen at baseline by cohort, stage of disease and overall (Treated set)

14.3.3.3.1.4 Lower limbs at baseline by cohort, stage of disease and overall (Treated set)

14.3.3.3.1.5 Skin at baseline by cohort, stage of disease and overall (Treated set)

Same outputs for D5, D11, D15, M3, M6, M12, M18.

14.3.3.4 Neurological examination

14.3.3.4.1: Neurological examination at baseline

14.3.3.4.1.1. Psychiatric observation at baseline by cohort, stage of disease and overall (Treated set)

14.3.3.4.1.2. Higher functions at baseline by cohort, stage of disease and overall (Treated set)

14.3.3.4.1.3. Cranial nerves at baseline by cohort, stage of disease and overall (Treated set)

14.3.3.4.1.4. Mobility at baseline by cohort, stage of disease and overall (Treated set)

14.3.3.4.1.5. Motor coordination and balance at baseline by cohort, stage of disease and overall (Treated set)

14.3.3.4.1.6. Primitive reflex at baseline by cohort, stage of disease and overall (Treated set)

14.3.3.4.1.7. Sensitivity at baseline by cohort, stage of disease and overall (Treated set)

14.3.3.4.1.8. Other neurological abnormalities at baseline by cohort, stage of disease and overall (Treated set)

Same outputs for D5, D11, D15, M3, M6, M12, M18.

14.3.3.5 HAT diagnosis (examination of blood, lymph and CSF samples)

14.3.3.5.1: HAT diagnosis (examination of blood, lymph and CSF samples) at baseline

14.3.3.5.1.1. Blood tests and lymph node aspirate examination at baseline by cohort, stage of disease and overall (Treated set)

14.3.3.5.1.2. Examination of cerebrospinal fluid at baseline by cohort, stage of disease and overall (Treated set)

Same outputs for D11, M6, M12, M18.

9.1.9. List of outputs for ICH Section 16.2 (Individual data listings)

16.2 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).

16.2.1 Discontinued patients

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

16.2.2 Protocol deviations

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

16.2.3 Patients excluded from the efficacy analysis

- Patients excluded from Treated set
- Patients excluded from mITT
- Patients excluded from Evaluable patients set
- Patients excluded from PPS

16.2.4 Demographic data

- Patients characteristics

- Diagnosis-parasite in blood and/or lymph at baseline
- Lumbar puncture (parasite and WBC) at baseline

16.2.5 Medical history, prior and concomitant therapies

- Medical history
- Pre-treatment of helminthiasis
- Pre-treatment of malaria
- Prior therapies
- Concomitant therapies

16.2.6 Compliance and/or drug concentration data

- Treatment administration
- Compliance

16.2.7 Individual efficacy response data

- Diagnosis-parasite in blood and/or lymph
- Lumbar puncture (parasite and WBC in CSF)
- Efficacy outcomes at 18, 12 and 6 months

16.2.8 Adverse event listings

- All Adverse Events
- Serious Adverse Events
- Drug-related TEAE which occurred during the hospitalization period

16.2.9 Individual laboratory measurements

- Note: listing of individual laboratory measurements (i.e. Haematology, Biochemistry, Thyroid function) will be provided in an excel file.

16.2.10 Other endpoints

- Vital Signs
- Clinical signs and symptoms of HAT
- Physical examination
- Neurological examination

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.

Please note that these are only templates; the final statistical outputs that will be provided may be slightly different (in terms of style, font size, column size, etc.). These templates have been designed using labels of variables from blank CRF. Since the final statistical outputs will be programmed on SDTM/ADaM database (i.e. after CDISC mapping), label of variables in final statistical outputs may be slightly different from those presented here.

9.2.1. Disposition of patients

Template 1:

	Stage 1 (N=XX)	Stage Intermediate (N=XX)	Stage 1 and Intermediate (N=XX)	Stage 2 (N=XX)	Total (N=XX)
Screened HAT positive (=informed consent signed)	xxx	xxx	xxx	xxx	xxx
All inclusion criteria met and no exclusion criteria met	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
At least one inclusion criteria not met or exclusion criteria met	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Not treated	xxx	xxx	xxx	xxx	xxx
Among patients not treated:					
At least one inclusion criteria not met or exclusion criteria met	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Due to SAE not related to treatment	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Due to early consent withdrawal or another reason	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Treated	xxx	xxx	xxx	xxx	xxx
Among patients treated:					
Study completed according to protocol (1)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Premature study 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%)
Rescue therapy	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%)
Among patients treated:					
Fled the region (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%)
At least one minor protocol deviation	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
At least one major protocol deviation	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 M6	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Lumbar puncture performed at M12	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Lumbar puncture performed at M18	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note:
(1) Patient 703-034 completed the trial but took rescue therapy after M18 visit, due to failure.
(2) Patients who fled the region due to armed conflict or natural disaster, or due to force majeure and for whom no post-treatment data are available (i.e. follow-up visits M3, M6, M12 and M18 not performed).

Template 2:

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)
dd/mm/yyyy	dd/mm/yyyy	dd/mm/yyyy	dd/mm/yyyy	xxx

9.2.2. Protocol deviations

	Stage 1 (N=XX)	Stage Intermediate (N=XX)	Stage 1 and Intermediate (N=XX)	Stage 2 (N=XX)	Total (N=XX)
Minor protocol deviation	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Type 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Type 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Type …	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Type n	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Major protocol deviation	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Type 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Type 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Type …	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Type n	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

9.2.3. Analysis sets and subgroups

Template for analysis sets:

	Stage 1 (N=XX)	Stage Intermediate (N=XX)	Stage 1 and Intermediate (N=XX)	Stage 2 (N=XX)	Total (N=XX)
Screened HAT positive - N (%)	XX (100.0%)	XX (100.0%)	XX (100.0%)	XX (100.0%)	XX (100.0%)
Treated set - N (%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
mITT set - N (%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Evaluable patients set - N (%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Per Protocol set - N (%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Template for analysis subgroups:

	Total (N=XX)
Among patients included in the mITT:	
Stage 1	XX (XX.X%)
Stage intermediate	XX (XX.X%)
Stage 1 and intermediate	XX (XX.X%)
Stage 2	XX (XX.X%)
Subgroup A: trypanosomes in CSF negative and WBC in CSF ≤ 5/µl	XX (XX.X%)
Subgroup B: trypanosomes in CSF negative and WBC in CSF [6-20/µl]	XX (XX.X%)

	Total (N=XX)
Subgroup C: trypanosomes in CSF positive and WBC in CSF ≤ 5 /µl	XX (XX.X%)
Subgroup D: trypanosomes in CSF positive and WBC in CSF [6-20/µl]	XX (XX.X%)
Subgroup E: trypanosomes in CSF positive and WBC in CSF > 20/ µl	XX (XX.X%)
Subgroup F: trypanosomes in CSF negative and WBC in CSF > 20/µl	XX (XX.X%)

9.2.4. General template for Continuous and categorical variables

	Stage 1 (N=XX)	Stage Intermediate (N=XX)	Stage 1 and Intermediate (N=XX)	Stage 2 (N=XX)	Total (N=XX)
Continuous data					
Non-missing	XX	XX	XX	XX	XX
Missing	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]

	Stage 1 (N=XX)	Stage Intermediate (N=XX)	Stage 1 and Intermediate (N=XX)	Stage 2 (N=XX)	Total (N=XX)
Categorical variable					
Non-missing	XX	XX	XX	XX	XX
Missing	XX	XX	XX	XX	XX
Modality 1 - N (%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Modality 2 - N (%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Modality … - N (%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Modality n - N (%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

9.2.5. Demographic data

	Stage 1 (N=XX)	Stage Intermediate (N=XX)	Stage 1 and Intermediate (N=XX)	Stage 2 (N=XX)	Total (N=XX)
Sex					
Non-missing	XX	XX	XX	XX	XX
Missing	XX	XX	XX	XX	XX
Male - N (%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Female - N (%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Age (years)					
Non-missing	XX	XX	XX	XX	XX
Missing	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]
Country					
Non-missing	XX	XX	XX	XX	XX

Missing	XX	XX	XX	XX	XX
Country A - N (%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Country B - N (%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Etc. - N (%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

9.2.6. Vital signs at baseline

	Stage 1 (N=XX)	Stage Intermediate (N=XX)	Stage 1 and Intermediate (N=XX)	Stage 2 (N=XX)	Total (N=XX)
Systolic BP (mmHg)					
<continuous>					
Diastolic BP (mmHg)					
<continuous>					
Heart rate (beats/min)					
<continuous>					
Respiratory rate (cycles/min)					
<continuous>					
Temperature (°C)					
<continuous>					
Karnofsky performance status (%)					
<continuous>					
Weight (kg)					
<continuous>					
Height (cm)					
<continuous>					
BMI (kg/m²)					
<continuous>					
General health status					
<categorical>					

9.2.7. Clinical signs and symptoms of HAT at baseline

	Stage 1 (N=XX)	Stage Intermediate (N=XX)	Stage 1 and Intermediate (N=XX)	Stage 2 (N=XX)	Total (N=XX)
Headaches					
Non-missing	XX	XX	XX	XX	XX
Missing	XX	XX	XX	XX	XX
Yes - N (%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
No - N (%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

	Stage 1 (N=XX)	Stage Intermediate (N=XX)	Stage 1 and Intermediate (N=XX)	Stage 2 (N=XX)	Total (N=XX)
If yes: time since start of symptoms					
1 Less than 1 week	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
2 Between 1 week and 1 month	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
3 Between 1 and 3 months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
4 Between 3 et 6 months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
5 More than 6 months	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
6 Not known	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Missing	XX	XX	XX	XX	XX
If yes: frequency					
Continuous	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Intermittent	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Missing	XX	XX	XX	XX	XX
Drowsiness					
<idem>					
Asthenia					
<idem>					
Etc.					
Were there any other signs or symptoms?					
Non-missing	XX	XX	XX	XX	XX
Missing	XX	XX	XX	XX	XX
Yes - N (%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
No - N (%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Note: please refer to individual data listings for details on other signs and symptoms.

9.2.8. Physical examination at baseline

9.2.8.1. Head and neck

	Stage 1 (N=XX)	Stage Intermediate (N=XX)	Stage 1 and Intermediate (N=XX)	Stage 2 (N=XX)	Total (N=XX)
Eye ball					
Non-missing	XX	XX	XX	XX	XX
Missing	XX	XX	XX	XX	XX
Normal	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Enophthalmos	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Exophthalmos	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Other, specify	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Palpebral conjunctiva					
Non-missing	XX	XX	XX	XX	XX
Missing	XX	XX	XX	XX	XX
Normal	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Pale	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Bulbar conjunctiva					
Non-missing	XX	XX	XX	XX	XX
Missing	XX	XX	XX	XX	XX
Normal	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Icteric	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Haemorrhagic	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Facial oedema					
Non-missing	XX	XX	XX	XX	XX
Missing	XX	XX	XX	XX	XX
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%)
Swollen cervical lymph nodes					
Non-missing	XX	XX	XX	XX	XX
Missing	XX	XX	XX	XX	XX
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%)
Nape					
Non-missing	XX	XX	XX	XX	XX
Missing	XX	XX	XX	XX	XX
Supple	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Stiff	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Note: please refer to individual data listings for further details.

9.2.8.2. Thorax

	Stage 1 (N=XX)	Stage Intermediate (N=XX)	Stage 1 and Intermediate (N=XX)	Stage 2 (N=XX)	Total (N=XX)
Inspiratory chest wall retraction					
Non-missing	XX	XX	XX	XX	XX
Missing	XX	XX	XX	XX	XX
Normal	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

	Stage 1 (N=XX)	Stage Intermediate (N=XX)	Stage 1 and Intermediate (N=XX)	Stage 2 (N=XX)	Total (N=XX)
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%)
Cardiac auscultation					
Non-missing	XX	XX	XX	XX	XX
Missing	XX	XX	XX	XX	XX
Normal	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Reduced heart sounds	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Abnormal sound					
If abnormal sound:					
Non-missing	XX	XX	XX	XX	XX
Missing	XX	XX	XX	XX	XX
Murmur	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Friction rub	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Click	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Other	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Pulmonary auscultation					
Non-missing	XX	XX	XX	XX	XX
Missing	XX	XX	XX	XX	XX
Normal	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Bronchial murmur	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Pleuritic murmur	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Amphoric murmur	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Wheeze	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Rhonchi	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Sibilant rales	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Bullous rales	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Crepitant rales	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Subcrepitant rales	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Sonorous rales	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Pleural rub	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Other	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Swollen cervical lymph nodes					
Non-missing	XX	XX	XX	XX	XX
Missing	XX	XX	XX	XX	XX
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%)
Chest percussion					
Non-missing	XX	XX	XX	XX	XX
Missing	XX	XX	XX	XX	XX
Normal	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Dullness	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Tympany	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Note: please refer to individual data listings for further details.

9.2.8.3. Abdomen

	Stage 1 (N=XX)	Stage Intermediate (N=XX)	Stage 1 and Intermediate (N=XX)	Stage 2 (N=XX)	Total (N=XX)
Palpation and Percussion					
Non-missing	XX	XX	XX	XX	XX
Missing	XX	XX	XX	XX	XX
Normal	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Abnormal	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
If abnormal:					
Non-missing	XX	XX	XX	XX	XX
Missing	XX	XX	XX	XX	XX
Tenderness	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Splenomegaly	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Hepatomegaly	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
If Splenomegaly, nb of cm: <continuous>					
If Hepatomegaly, nb of cm: <continuous>					
Hepatojugular reflux					
Non-missing	XX	XX	XX	XX	XX
Missing	XX	XX	XX	XX	XX
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%)

9.2.8.4. Lower limbs

	Stage 1 (N=XX)	Stage Intermediate (N=XX)	Stage 1 and Intermediate (N=XX)	Stage 2 (N=XX)	Total (N=XX)
Lower limbs					
Non-missing	XX	XX	XX	XX	XX
Missing	XX	XX	XX	XX	XX
Normal	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Lower limb oedema	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Other	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Note: please refer to individual data listings for further details.					

9.2.8.5. Skin

	Stage 1 (N=XX)	Stage Intermediate (N=XX)	Stage 1 and Intermediate (N=XX)	Stage 2 (N=XX)	Total (N=XX)
Skin normal					
Non-missing	XX	XX	XX	XX	XX
Missing	XX	XX	XX	XX	XX
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%)
If no:					
Scratch marks	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

	Stage 1 (N=XX)	Stage Intermediate (N=XX)	Stage 1 and Intermediate (N=XX)	Stage 2 (N=XX)	Total (N=XX)
Scabies	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Other abnormality	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
If Scratch marks, location:					
Thorax	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Upper limbs	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Lower limbs	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Other	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
If Other abnormality, location:					
Thorax	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Upper limbs	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Lower limbs	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Other	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Note: please refer to individual data listings for further details.

9.2.9. Neurological examination at baseline

9.2.9.1. Psychiatric observation

Same kind of templates as for Physical examination.

9.2.9.2. Higher functions

Same kind of templates as for Physical examination.

9.2.9.3. Cranial nerves

Same kind of templates as for Physical examination.

9.2.9.4. Mobility

Same kind of templates as for Physical examination.

9.2.9.5. Motor coordination and balance

Same kind of templates as for Physical examination.

9.2.9.6. Primitive reflex

Same kind of templates as for Physical examination.

9.2.9.7. Sensitivity

Same kind of templates as for Physical examination.

9.2.9.8. Other neurological abnormalities

Same kind of templates as for Physical examination.

9.2.10. HAT diagnosis (examination of blood, lymph and CSF samples) at baseline

9.2.10.1. Blood tests and lymph node aspirate examination

	Stage 1 (N=XX)	Stage Intermediate (N=XX)	Stage 1 and Intermediate (N=XX)	Stage 2 (N=XX)	Total (N=XX)
At least one test positive					
Non-missing	XX	XX	XX	XX	XX
Missing	XX	XX	XX	XX	XX
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%)
Serology (CATT)					
Non-missing	XX	XX	XX	XX	XX
Missing	XX	XX	XX	XX	XX
Positive	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Negative	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Not done	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
CATT dilution					
Non-missing	XX	XX	XX	XX	XX
Missing	XX	XX	XX	XX	XX
Factor 1/2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Factor 1/4	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Factor 1/8	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Factor >=1/16	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Lymph node aspirate (LNA)					
<same as for Serology (CATT)>					
Smear test					
<same as for Serology (CATT)>					
Thick blood smear (TBS)					
<same as for Serology (CATT)>					
CTC (WOO)					
<same as for Serology (CATT)>					
mAECT					
<same as for Serology (CATT)>					
mAECT-BC					
<same as for Serology (CATT)>					
Rapid diagnostic test (RDT)					
<same as for Serology (CATT)>					

9.2.10.2. Examination of cerebrospinal fluid

	Stage 1 (N=XX)	Stage Intermediate (N=XX)	Stage 1 and Intermediate (N=XX)	Stage 2 (N=XX)	Total (N=XX)
Trypanosomes					
Non-missing	XX	XX	XX	XX	XX
Missing	XX	XX	XX	XX	XX
Positive	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Negative	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Not done	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Method used					
Non-missing	XX	XX	XX	XX	XX
Missing	XX	XX	XX	XX	XX
Direct	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Modified single centrifugation	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Direct + Modified single centrifugation	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
WBC / mm3					
Non-missing	XX	XX	XX	XX	XX
Missing	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]
≤ 5 /µl	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
>6-20] /µl	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
>20-100] / µl	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
>100 /µl	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

9.2.11. Medical history

Template by stage of disease and overall:

	Stage 1 (N=XX)			Stage 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
At least 1 MH	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X
System Organ Class 1	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X
Preferred Term 1	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
Preferred Term 3	X	X	XX.X	X	X	X.X	X	X	X.X	X	X	X.X
System Organ Class 2	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
Preferred Term 2	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

Template by cohort and overall:

	Stage 1 and 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
At least 1 MH	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X
System Organ Class 1	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X
Preferred Term 1	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
Preferred Term 3	X	X	X.X	X	X	X.X	X	X	X.X
System Organ Class 2	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
Preferred Term 2	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

9.2.12. Prior and concomitant therapies

Template by stage of disease and overall:

	Stage 1 (N=XX)			Stage 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
At least 1 TRT	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X
Therapeutic Class 1	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X
Preferred name 1	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
Preferred name 3	X	X	XX.X	X	X	X.X	X	X	X.X	X	X	X.X
Therapeutic Class 2	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
Preferred name 2	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

Template by cohort and overall:

	Stage 1 and 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
At least 1 TRT	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X
Therapeutic Class 1	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X
Preferred name 1	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
Preferred name 3	X	X	XX.X	X	X	X.X	X	X	X.X
Therapeutic Class 2	X	X	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
Preferred name 2	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

9.2.13. Extent of exposure and treatment compliance

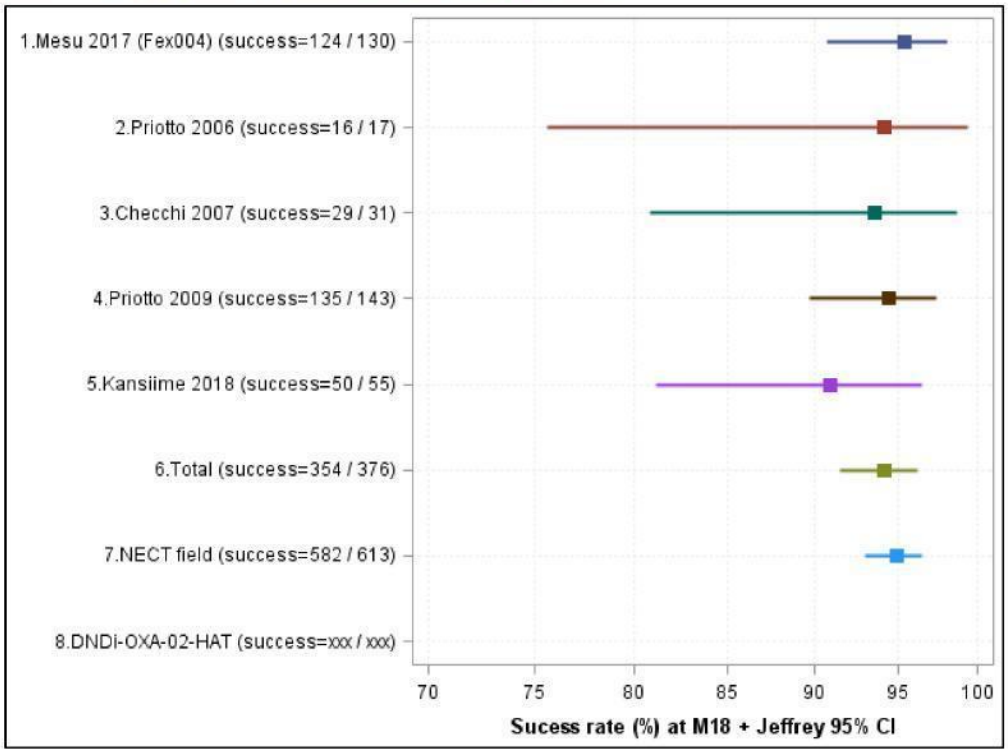
	Stage 1 (N=XX)	Stage Intermediate (N=XX)	Stage 1 and Intermediate (N=XX)	Stage 2 (N=XX)	Total (N=XX)
Number of tablets administered on Day 1					
Non-missing	XX	XX	XX	XX	XX
Missing	XX	XX	XX	XX	XX
0	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of re-administered tablets on Day 1					
Non-missing	XX	XX	XX	XX	XX
Missing	XX	XX	XX	XX	XX
0	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Note: Extent of exposure is not applicable as dosing regimen is 960 mg (3 tablets) in a single intake on Day 1. Please refer to individual data listings for further details on treatment administration.

9.2.14. Analysis of the primary endpoint

	Total (N=XXX)
Success rate at 18 months	
Non-missing	XX
Missing	XX
Yes [n (%)]	XX (XX.X%)
[95% Jeffreys CI]	[XX.X ; XX.X]
No [n (%)]	XX (XX.X%)
[95% Jeffreys CI]	[XX.X ; XX.X]

9.2.15. Forest plot of success rate for the yardsticks



Study	Success rate (%) at M18	Jeffrey 95% CL
1.Mesu 2017 (Fex004) (success=124 / 130)	95.4	90.7-98.1
2.Priotto 2006 (success=16 / 17)	94.1	75.6-99.4
3.Checchi 2007 (success=29 / 31)	93.5	80.9-98.6
4.Priotto 2009 (success=135 / 143)	94.4	89.7-97.3
5.Kansiime 2018 (success=50 / 55)	90.9	81.2-96.4
6.Total (success=354 / 376)	94.1	91.4-96.2
7.NECT field (success=582 / 613)	94.9	93.0-96.5
8. DNDi-OXA-02-HAT (success=xxx / xxx)	xx.x	xx.x–xx.x

9.2.16. Comparison in success rate at 18-months between stage 1 and intermediate-stage patients versus stage-2 patients

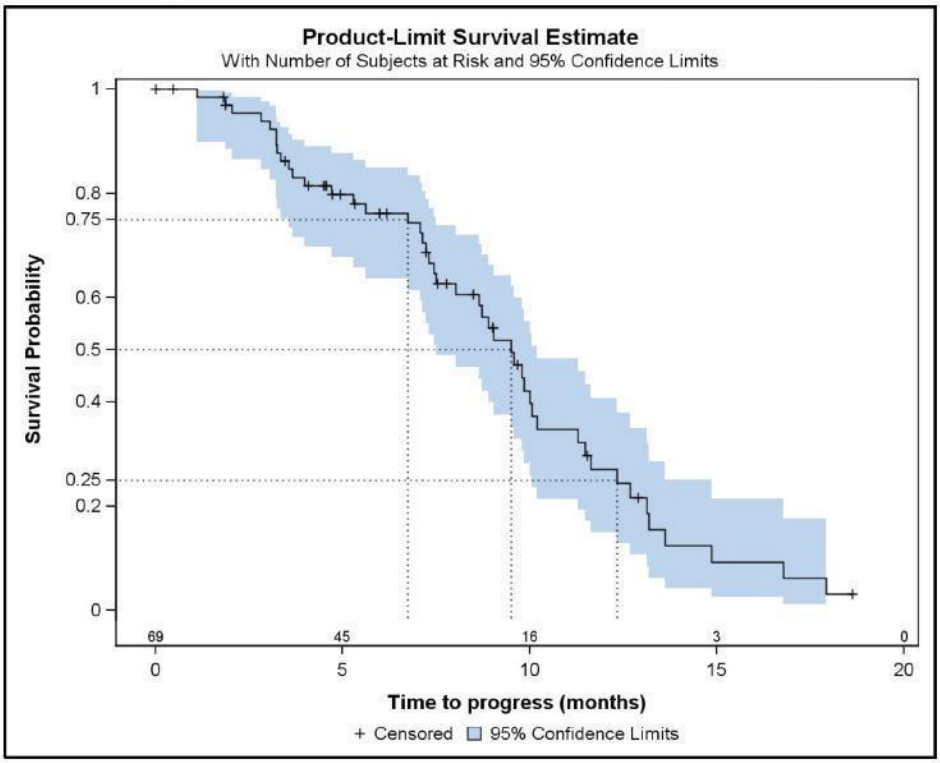
	Statistical test	Stage 1 and Intermediate (N=XX)	Stage 2 (N=XX)
Success rate at 18 months			
Non-missing		XX	XX
Missing		XX	XX
Yes [n (%)]	exact Fisher	XX (XX.X%)	XX (XX.X%)
[95% Jeffreys CI]	p=x.xxx	[XX.X ; XX.X]	[XX.X ; XX.X]
No [n (%)]		XX (XX.X%)	XX (XX.X%)
[95% Jeffreys CI]		[XX.X ; XX.X]	[XX.X ; XX.X]

9.2.17. Changes in the rate of favorable outcomes over time

	Stage 2
Success rate at 12 months versus 6 months	
Odds ratio	x.xx
95% CI	x.xx ; x.x
p-value	x.xxx
Success rate at 18 months versus 6 months	
Odds ratio	x.xx
95% CI	x.xx ; x.x
p-value	x.xxx
Success rate at 18 months versus 12 months	
Odds ratio	x.xx
95% CI	x.xx ; x.x
p-value	x.xxx

From a logistic mixed model for repeated measures.

9.2.18. Kaplan-Meier curve



9.2.19. Kaplan-Meier table for survival probabilities

Visit	Survival probability [95% CI]
EoH (day 15)	x.xx [x.xx ; x.xx]]
3 months (day 91)	x.xx [x.xx ; x.xx]]
6 months (day 183)	x.xx [x.xx ; x.xx]]
12 months (day 365)	x.xx [x.xx ; x.xx]]
18 months (day 548)	x.xx [x.xx ; x.xx]]

9.2.20. Descriptive analysis and trend test of success rates at <xx> months: stage 1 versus intermediaite stage versus stage 2

	Statistical test	Stage 1 (N=XX)	Stage Intermediate (N=XX)	Stage 2 (N=XX)
Success rate at <xx> months				
Non-missing		XX	XX	XX
Missing		XX	XX	XX
Yes [n (%)]	Cochran-Armitage	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
[95% Jeffreys CI]	p=x.xxx	[XX.X ; XX.X]	[XX.X ; XX.X]	[XX.X ; XX.X]
No [n (%)]		XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
[95% Jeffreys CI]		[XX.X ; XX.X]	[XX.X ; XX.X]	[XX.X ; XX.X]

9.2.21. Descriptive analysis and trend test of success rates at <xx> months: subgroups A vs B vs F vs C vs D vs E

	Statistical test	A	B	(...)	E
Success rate at <xx> months					
Non-missing		XX	XX		XX
Missing		XX	XX		XX
Yes [n (%)]	Cochran-Armitage	XX (XX.X%)	XX (XX.X%)		XX (XX.X%)
[95% Jeffreys CI]	p=x.xxx	[XX.X ; XX.X]	[XX.X ; XX.X]		[XX.X ; XX.X]
No [n (%)]		XX (XX.X%)	XX (XX.X%)		XX (XX.X%)
[95% Jeffreys CI]		[XX.X ; XX.X]	[XX.X ; XX.X]		[XX.X ; XX.X]

Note:
Subgroup A = trypanosomes in CSF negative and WBC in CSF ≤ 5/µl
Subgroup B = trypanosomes in CSF negative and WBC in CSF [6-20/µl]
Subgroup F = trypanosomes in CSF negative and WBC in CSF > 20/µl
Subgroup C = trypanosomes in CSF positive and WBC in CSF ≤ 5 /µl
Subgroup D = trypanosomes in CSF positive and WBC in CSF [6-20/µl]
Subgroup E = trypanosomes in CSF positive and WBC in CSF > 20/ µl

9.2.22. Descriptive analysis and test of homogeneity of success rates at 18 months by center

	Statistical test	Centre 1	Centre 2	(...)	Centre 20
Success rate at <xx> months					
Non-missing		XX	XX		XX
Missing		XX	XX		XX
Yes [n (%)]	test of homogeneity	XX (XX.X%)	XX (XX.X%)		XX (XX.X%)
[95% Jeffreys CI]	p=x.xxx	[XX.X ; XX.X]	[XX.X ; XX.X]		[XX.X ; XX.X]
No [n (%)]		XX (XX.X%)	XX (XX.X%)		XX (XX.X%)
[95% Jeffreys CI]		[XX.X ; XX.X]	[XX.X ; XX.X]		[XX.X ; XX.X]

9.2.23. Overall summary of adverse event

	Stage 1 (N=XX)	Stage Intermediate (N=XX)	Stage 1 and Intermediate (N=XX)	Stage 2 (N=XX)	Total (N=XX)
At least one AE - [n (%)]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
[95% Jeffreys CI]	[xx.x ; xx.x]	[xx.x ; xx.x]	[xx.x ; xx.x]	[xx.x ; xx.x]	[xx.x ; xx.x]
At least one TEAE - [n (%)]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
[95% Jeffreys CI]	[xx.x ; xx.x]	[xx.x ; xx.x]	[xx.x ; xx.x]	[xx.x ; xx.x]	[xx.x ; xx.x]
At least one mild or moderate TEAE - [n (%)]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
[95% Jeffreys CI]	[xx.x ; xx.x]	[xx.x ; xx.x]	[xx.x ; xx.x]	[xx.x ; xx.x]	[xx.x ; xx.x]
At least one severe TEAE - [n (%)]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
[95% Jeffreys CI]	[xx.x ; xx.x]	[xx.x ; xx.x]	[xx.x ; xx.x]	[xx.x ; xx.x]	[xx.x ; xx.x]
At least one drug-related TEAE - [n (%)]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
[95% Jeffreys CI]	[xx.x ; xx.x]	[xx.x ; xx.x]	[xx.x ; xx.x]	[xx.x ; xx.x]	[xx.x ; xx.x]
At least one serious TEAE - [n (%)]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
[95% Jeffreys CI]	[xx.x ; xx.x]	[xx.x ; xx.x]	[xx.x ; xx.x]	[xx.x ; xx.x]	[xx.x ; xx.x]
At least one serious drug-related TEAE - [n (%)]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
[95% Jeffreys CI]	[xx.x ; xx.x]	[xx.x ; xx.x]	[xx.x ; xx.x]	[xx.x ; xx.x]	[xx.x ; xx.x]

9.2.24. Adverse event by MedDRA SOC and PT

Template by stage of disease and overall:

	Stage 1 (N=XX)			Stage 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
At least 1 AE	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X
System Organ Class 1	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X

	Stage 1 (N=XX)			Stage 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
Preferred Term 1	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
Preferred Term 3	X	X	XX.X	X	X	X.X	X	X	X.X	X	X	X.X
System Organ Class 2	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
Preferred Term 2	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

Template by cohort and overall:

	Stage 1 and 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
At least 1 AE	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X
System Organ Class 1	XX	XX	XX.X	XX	XX	XX.X	XX	XX	XX.X
Preferred Term 1	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
Preferred Term 3	X	X	X.X	X	X	X.X	X	X	X.X
System Organ Class 2	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
Preferred Term 2	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

9.2.25. Descriptive analysis for laboratory parameters at baseline, at each time points and changes from baseline at each time point

For Stage 1:

	Value at visit								Change from baseline						
	Missing	N	Mean	SD	Median	Q1	Q3	Min	Max	Mean	SD	Median	Q1	Q3	Min	Max
Baseline	0	208	11.7	1.8	11.7	10.6	12.9	7	17	.	.	.	.	.	.	.
D5	1	207	11.3	1.7	11.5	10.2	12.4	6	16	-0.5	1.0	-0.4	-1.0	0.1	-4	4
D11	1	207	11.4	1.8	11.6	10.3	12.5	5	17	-0.3	1.1	-0.2	-0.9	0.3	-4	3
D15	197	11	10.8	2.1	10.1	9.8	12.5	7	14	0.6	0.7	0.5	-0.2	1.2	-1	2
M3	4	204	12.9	1.4	12.9	12.0	13.9	8	17	1.2	1.5	1.1	0.3	2.1	-4	6
M6	3	205	13.1	1.6	13.2	12.1	14.3	8	18	1.5	1.7	1.5	0.5	2.5	-5	7
M12	34	174	13.2	1.5	13.4	12.1	14.3	9	17	1.5	1.8	1.6	0.5	2.7	-4	6
M18	81	127	13.3	1.4	13.3	12.5	14.4	10	18	1.6	1.9	1.6	0.3	3.0	-4	6

For Stage Intermediate: same template as above.

For Stage 2: same template as above.

For Stage 1 and Intermediate: same template as above.

For all stages (total): same template as above.

9.2.26. Shift table by multiple of normal range for laboratory parameters

For Stage 1:

Haemoglobin (g/dL)		Baseline						
		<0.5*LLN	>0.5*LLN - <LLN	Normal	>ULN - <2*ULN	>2*ULN - <3*ULN	3*ULN	Missing
D5	<0.5*LLN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>0.5*LLN - <LLN	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Normal	0 (0.0%)	0 (0.0%)	117 (56.3%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>ULN - <2*ULN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>2*ULN - <3*ULN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>3*ULN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Bowker's symmetry test: p=x.xxx								

<Same template for D11, D15,M3, M6, M12, M18.>

For Stage Intermediate: same templates as above.

For Stage 2: same templates as above.

For Stage 1 and Intermediate: same templates as above.

For all stages (total): same templates as above.

Note: the same template will be provided for TSH using the following classes: <0.5*LLN, [0.5*LLN to <LLN, Normal, >ULN to 2*ULN], >2*ULN).

9.2.27. Shift table according to lower and upper limits of normal range for laboratory parameters

For Stage 1:

		Baseline			
Haemoglobin (g/dL)		<LLN	Normal	>ULN	Missing
D5	<LLN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Normal	0 (0.0%)	117 (56.3%)	0 (0.0%)	0 (0.0%)
	>ULN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Bowker's symmetry test: p=x.xxx					

		Baseline			
Haemoglobin (g/dL)		<LLN	Normal	>ULN	Missing
D11	<LLN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Normal	0 (0.0%)	117 (56.3%)	0 (0.0%)	0 (0.0%)
	>ULN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Bowker's symmetry test: p=x.xxx					

		Baseline			
Haemoglobin (g/dL)		<LLN	Normal	>ULN	Missing
D15	<LLN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Normal	0 (0.0%)	117 (56.3%)	0 (0.0%)	0 (0.0%)
	>ULN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Bowker's symmetry test: p=x.xxx					

		Baseline			
Haemoglobin (g/dL)		<LLN	Normal	>ULN	Missing
M3	<LLN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Normal	0 (0.0%)	117 (56.3%)	0 (0.0%)	0 (0.0%)
	>ULN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Bowker's symmetry test: p=x.xxx					

		Baseline			
Haemoglobin (g/dL)		<LLN	Normal	>ULN	Missing
M6	<LLN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Normal	0 (0.0%)	117 (56.3%)	0 (0.0%)	0 (0.0%)
	>ULN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Bowker's symmetry test: p=x.xxx					

		Baseline			
Haemoglobin (g/dL)		<LLN	Normal	>ULN	Missing
M12	<LLN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Normal	0 (0.0%)	117 (56.3%)	0 (0.0%)	0 (0.0%)
	>ULN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Bowker's symmetry test: p=x.xxx					

		Baseline			
Haemoglobin (g/dL)		<LLN	Normal	>ULN	Missing
M18	<LLN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Normal	0 (0.0%)	117 (56.3%)	0 (0.0%)	0 (0.0%)
	>ULN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Bowker's symmetry test: p=x.xxx					

		Baseline			
Haemoglobin (g/dL)		<LLN	Normal	>ULN	Missing
D5	<LLN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Normal	0 (0.0%)	117 (56.3%)	0 (0.0%)	0 (0.0%)
	>ULN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Bowker's symmetry test: p=x.xxx

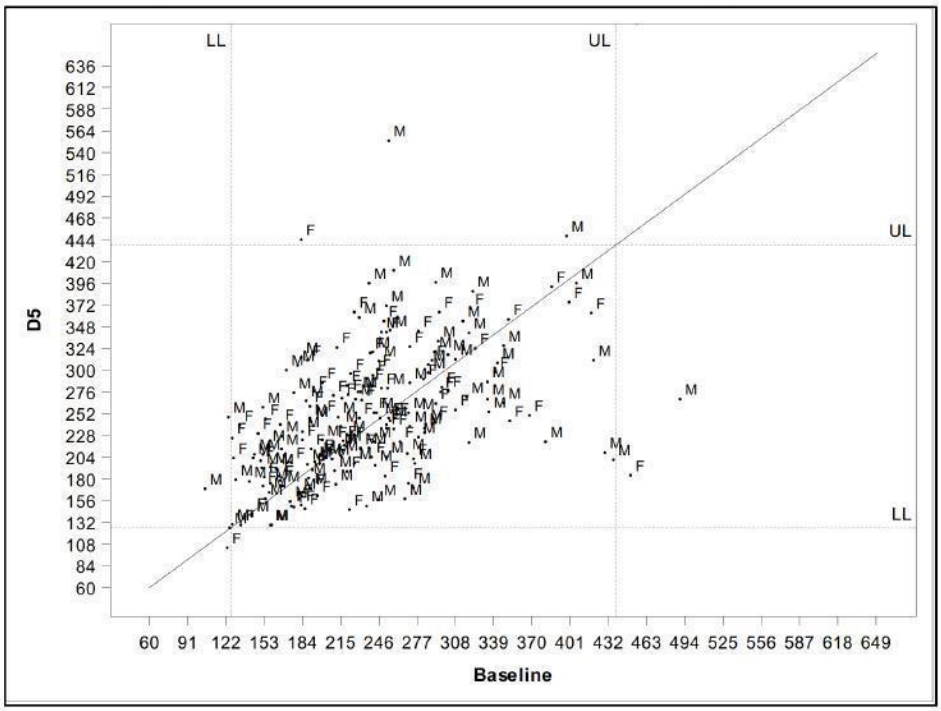
For Stage Intermediate: same template as above.

For Stage 2: same template as above.

For Stage 1 and Intermediate: same template as above.

For all stages (total): same template as above.

9.2.28. Scatterplot between baseline and visit X for laboratory parameters



9.2.29. Descriptive analysis for body weight (kg) at baseline, at each time points and changes from baseline at each time point

For Stage 1:

	Value at visit									Change from baseline						
	Missing	N	Mean	SD	Median	Q1	Q3	Min	Max	Mean	SD	Median	Q1	Q3	Min	Max
Baseline	xx	xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	.	.	.	.	.	.	.
D5	xx	xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
D11	xx	xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
D15	xx	xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
M3	xx	xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
M6	xx	xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
M12	xx	xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
M18	xx	xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x

For Stage Intermediate: same template as above.

For Stage 2: same template as above.

For Stage 1 and Intermediate: same template as above.

For all stages (total): same template as above.

9.2.30. Descriptive analysis of relative change from baseline in body weight (%) at each time points

	Stage 1 (N=XX)	Stage Intermediate (N=XX)	Stage 1 and Intermediate (N=XX)	Stage 2 (N=XX)	Total (N=XX)
Relative changes from baseline in body weight (%) at D5					
Non-mising	xx	xx	xx	xx	xx
Missing	xx	xx	xx	xx	xx
<= -10%	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
> -10% and <= -5%	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
> -5% and < 5%	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>= 5% and < 10%	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>= 10%	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<same statistics for relative changes from baseline in body weight (%) at D11, D15, M3, M6, M12, M18>					

10. KEY DERIVED VARIABLES

10.1. Outcome at 18 months

Derivation algorithm for stage 1 and intermediate stage (month 18)	Derivation algorithm for stage 2 (Month 18)
Patient is ⇒ 1: Dead (any reason of death and any time between drug intake and M18) ⇒ ***Failure (stop)***	**Patient is ⇒ 1:** Dead (any reason of death and any time between drug intake and M18) ⇒ ***Failure*** **(stop)**
⇓	⇓
Alive	Alive
⇓	⇓
Patient requires rescue medication for HAT at M18 or required it before (between drug intake and M18)	**Patient requires rescue medication for HAT at M18 or required it before** (between drug intake and M18)
⇒ YES ⇒2: *(definitive)* ***Failure*** **(stop)**	⇒ YES ⇒ 2: *(definitive)* ***Failure*** **(stop)**
⇓	⇓
NO rescue medication so far	NO rescue medication so far
⇓	⇓
Evidence of trypanosomes in any body fluid between drug intake and M18 visit ⇒ YES ⇒ 3: *(definitive)* ***Failure*** **(stop)**	**Evidence of trypanosomes in any body fluid between drug intake and M18 visit** ⇒ YES ⇒ 3: *(definitive)* ***Failure*** **(stop)**
⇓	⇓
NO observed trypanosomes	NO observed trypanosomes
⇓	⇓
Patient Lost to follow-up at M18 (no survival information at M18 and later)	**Patient Lost to follow-up at M18** (no survival information at M18 and later)
⇒ YES ⇒ 4: ***Failure*** **(Stop) [a,b]**	⇒ YES ⇒ 4: ***Failure*** **(Stop) [a,b]**
⇓	⇓
NO (the patient is not lost to foillow-up)	NO (The patient is not lost to follow-up)
⇓	⇓
Non-hemorrhagic lumbar puncture at M18 and WBC in CSF at M18 > 20 cells	**Non-hemorrhagic lumbar puncture at M18 and WBC in CSF at M18 > 20 cells**
⇒ YES ⇒ 5: ***Failure*** **(stop)**	⇒ YES ⇒ **5:** ***Failure*** **(stop)**
⇓	⇓
NO (WBC in CSF at M18 ≤ 20 cells or no reliable data concerning WBC in CSF at M18)	NO (WBC in CSF at M18 ≤ 20 cells or no reliable data concerning WBC in CSF at M18)
⇓	⇓
Non-hemorrhagic lumbar puncture at M18 and WBC in CSF ≤ 20 cells	**Non-hemorrhagic lumbar puncture at M18 and WBC in CSF ≤ 20 cells**
⇒YES ⇒ 6: ***Success*** **(stop)**	⇒YES ⇒ 6: ***Success*** **(stop)**
⇓	⇓
NO (hemorrhagic CSF sample or no lumbar puncture at M18 for any reason)	NO (hemorrhagic CSF sample or no lumbar puncture at M18 for any reason)
⇓	⇓
No lumbar puncture at M18 or no reliable count of WBC in CSF at M18 but reliable number of WBC in CSF reported later (M24 or other additional visit)	**No lumbar puncture at M18 or no reliable count of WBC in CSF at M18 but reliable number of WBC in CSF reported later** (M24 or other additional visit)
⇒ YES ⇒ **WBC in CSF > 20** ⇒ 7: ***Failure*** **(Stop)**	⇒ YES ⇒ **WBC in CSF > 20** ⇒ 7: ***Failure*** **(Stop)**
⇒ YES ⇒ **WBC in CSF ≤ 20** ⇒ 8: ***Success*** **(Stop)**	⇒ YES ⇒ **WBC in CSF ≤ 20** ⇒ 8: ***Success*** **(Stop)**
⇓	⇓
NO (No lumbar puncture at M18 and no later reliable count of WBC in CSF)	NO (No lumbar puncture at M18 and no later reliable count of WBC in CSF)
⇓	⇓

Derivation algorithm for stage 1 and intermediate stage (month 18)	**Derivation algorithm for stage 2 (Month 18)**
Earlier (before M18) unfavorable outcome: increase of WBC in CSF at M6 or M12 with respect to EOH ⇒ YES ⇒ 9: ***Failure*** **(stop)** ⇓ NO (no information or no earlier unfavorable assessment) ⇓ **Patient has clinical signs or symptoms at M18 evoking a failure** ⇒ YES ⇒ 10: ***Failure*** **(stop)** ⇓ NO (no clinical signs or symptoms evoking a relapse at M18) ⇓ **WBC in CSF ≤ 20 at M12 or absence of LP at M12 and for both cases no increase WBC in CSF at M6 with respect to EOH and no sign and symptoms at M18 evoking a relapse:** ⇒ YES ⇒ 11: ***Success*** (stop) **[b]** ⇓ NO (at least one criterion not met) ⇓ **Patient refused all post treatment lumbar punctures** ⇒ YES ⇒ 12: ***Failure*** **(stop) [a,b]** ⇓ All other cases ⇒ 13. Failure	**Earlier (before M18) unfavorable outcome: WBC in CSF > 50 at M6 or WBC in CSF > 20 at M12 or increasing between M6 and M12** ⇒ YES ⇒ 9: ***Failure*** **(stop)** ⇓ NO (no information or no earlier unfavorable assessment) ⇓ **Patient has clinical signs or symptoms at M18 evoking a failure** ⇒ YES ⇒ 10: ***Failure*** **(stop)** ⇓ NO (no clinical signs or symptoms evoking a relapse at M18) ⇓ **WBC in CSF ≤ 20 at M12 or in absence of LP at M12 and for both cases WBC in CSF ≤ 50 at M6 and no signs and symptoms at M18 evoking a relapse:** ⇒ YES ⇒ 11: ***Success*** (Stop) **[b]** ⇓ NO (at least one criterion not met) ⇓ **Patient refused all post treatment lumbar punctures** ⇒ YES ⇒ 12: ***Failure*** **(Stop) [a,b]** ⇓ All other cases ⇒ 13. Failure

For sensitivity analyses:

[a] will be considered as a success with the best case method (see Section 7.6.1).

[b] re-sampling will be applied with the fair case method (see Section 7.6.1).

10.2. Outcome at 12 months

Note: this algorithm will be used in the time course of the response: status at M12.

Derivation algorithm at 12 months for stage 1 and intermediate stage	**Derivation algorithm at 12 months for stage 2**
Patient is ⇒ 1: Dead (any reason of death and any time between drug intake and M12) ⇒ *(definitive)* ***Failure*** **(stop)** ⇓ Alive ⇓ **Patient requires rescue medication for HAT at M12 or before** ⇒ YES ⇒ 2: ***Failure*** **(stop)** ⇓ NO rescue medication so far ⇓ **Evidence of trypanosomes in any body fluid at M12 or between drug intake and M12 visit** ⇒ YES ⇒ 3: (*definitive*) ***Failure*** **(stop)** ⇓ NO observed trypanosomes so far ⇓ **Patient Lost to follow-up at 12M** (no survival information at M12 and later) ⇒ YES ⇒ 4: ***Failure*** **(Stop) [a,b]** ⇓ NO (the patient is not lost to follow-up) ⇓ **Non-hemorrhagic lumbar puncture at M12 and WBC in CSF >20 cells** ⇒YES ⇒ 5: ***Failure*** **(stop)** ⇓ NO (WBC in CSF at M12 ≤ 20 cells or no reliable count of WBC in CSF at M12) ⇓ **Non-hemorrhagic lumbar puncture at M12 and WBC in CSF at M12 ≤ 20 cells** ⇒ YES ⇒ 6: ***Success*** **(Stop)** ⇓ NO (no reliable count of WBC in CSF at M12) ⇓ ⇓ ⇓ ⇓ ⇓	**Patient is ⇒ 1:** Dead (any reason of death and any time between drug intake and M12) ⇒ *(definitive)* ***Failure*** **(stop)** ⇓ Alive ⇓ **Patient requires rescue medication for HAT at M12 or before** ⇒ YES ⇒ 2: ***Failure*** **(stop)** ⇓ NO rescue medication so far ⇓ **Evidence of trypanosomes in any body fluid at M12 or between drug intake and M12 visit** ⇒ YES ⇒ 3: (*definitive*) ***Failure*** **(stop)** ⇓ NO observed trypanosomes so far ⇓ **Patient Lost to follow-up at 12M** (no survival information at M12 and later) ⇒ YES ⇒ 4: ***Failure*** **(Stop) [a,b]** ⇓ NO (the patient is not lost to follow-up) ⇓ **Non-hemorrhagic lumbar puncture at M12 and WBC in CSF at M12 ≥ 50 cells** ⇒ YES ⇒ **5:** ***Failure*****(stop)** ⇓ NO (WBC in CSF at M12 < 50 cells or no reliable count of WBC in CSF at M12) ⇓ **Non-hemorrhagic 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 ⇒ **6:** ***Failure*** **(stop)** ⇓ NO (patient did not meet at least one of the previous criteria at M12) ⇓ **Non-hemorrhagic 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 ⇒ 7: **Success (stop)** ⇓ NO (patient did not meet at least one of the previous criteria) ⇓

Derivation algorithm at 12 months for stage 1 and intermediate stage	**Derivation algorithm at 12 months for stage 2**
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** ⇒ 7: ***Failure*** **(Stop)** ⇒ YES ⇒ **WBC in CSF ≤ 20 and no signs or symptoms evoking a relapse** ⇒ 8: ***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 ⇒ **9: *Failure*** at M12 **(Stop)** ⇓ NO ⇓ **No reliable count of WBC in CSF at M18 and M12 but WBC counts at M6 available and no signs and symptoms evoking a failure at M12 or M18** ⇒YES ⇒ **WBC in CSF at M6 ≤ 5 and smaller than WBC in CSF at EOH** ⇒ 10: ***Success*** **(stop) [b]** ⇒ NO ⇒ **WBC in CSF at M6 > 5 or larger than WBC in CSF at EOH** ⇒ *11:* ***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 ⇒ 12: *Success*** at M12 **[b]** ⇓ NO (Patient not met at M24 or later) ⇓ **Patient refused all post treatment lumbar punctures** ⇒ YES ⇒ 13: ***Failure*** **(Stop) [a,b]**	**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** ⇒ 8: ***Failure*** **(Stop)** ⇒ YES ⇒ **WBC in CSF ≤ 20** ⇒ 9: ***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 ⇒ 10: ***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** ⇒ ***11: Success (stop)*** **[b]** NO ⇒ **WBC in CSF at M6 > 20 cells ⇒ 12: *Failure*** ⇓ 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 ⇒ 13: *Success*** at M12 **[b]** ⇓ NO (Patient not met at M24 or later) ⇓ **Patient refused all post treatment lumbar punctures** ⇒ YES ⇒ 14: ***Failure*** **(Stop) [a,b]**

For sensitivity analyses:

[a] will be considered as a success with the best case method (see Section 7.6.1).

[b] re-sampling will be applied with the fair case method (see Section 7.6.1).

10.3. Outcome at 6 months

Derivation algorithm at 6 months for stage 1 and intermediate stage	Derivation algorithm at 6 months for stage 2
Patient is ⇒ **1:** Dead (any reason of death and any time between drug intake and M6) ⇒ (*definitive*) ***Failure*** **(stop)** ⇓ Alive ⇓ **Patient requires rescue medication for HAT at M6 or before** ⇒ YES ⇒ 2: (*definitive*) ***Failure*** **(stop)** ⇓ NO rescue medication so far ⇓ **Evidence of trypanosomes in any body fluid at M6 or between drug intake and M6 visit** ⇒ YES ⇒ 3: (*definitive*) ***Failure*** **(stop)** ⇓ NO observed trypanosomes so far ⇓ **Patient Lost to follow-up** ⇒ YES ⇒ 4: ***Failure*** **(Stop) [a,b]** ⇓ NO (no survival information at M6 and later) ⇓ **Non-hemorrhagic lumbar puncture and WBC in CSF at M6 ≤ 20 cells and smaller than that counted at EOH and no signs and symptoms evoking a relapse** ⇒ YES ⇒ **5:** ***Success*** **(stop) [b]** ⇓ NO (at least one criterion is not met) ⇓ **No reliable count of WBC in CSF at M6 or WBC in CSF at M6 > 20 cells or signs and symptoms evoking a relapse** ⇒ YES ⇒ 6: ***Failure*** ⇓ Otherwise ⇒ ***7: Failure***	**Patient is** ⇒ **1:** Dead (any reason of death and any time between drug intake and M6) ⇒ (*definitive*) ***Failure*** **(stop)** ⇓ Alive ⇓ **Patient requires rescue medication for HAT at M6 or before** ⇒ YES ⇒ 2: (*definitive*) ***Failure*** **(stop)** ⇓ NO rescue medication so far ⇓ **Evidence of trypanosomes in any body fluid at M6 or between drug intake and M6 visit** ⇒ YES ⇒ 3: (*definitive*) ***Failure*** **(stop)** ⇓ NO observed trypanosomes so far ⇓ **Patient Lost to follow-up** ⇒ YES ⇒ 4: ***Failure*** **(Stop) [a,b]** ⇓ NO (no survival information at M6 and later) ⇓ **Non-hemorrhagic lumbar puncture and WBC in CSF at M6 ≤ 20 cells and no signs and symptoms evoking a relapse** ⇒ YES ⇒ **5:** ***Success*** **(stop) [b]** ⇓ NO (no reliable count of WBC in CSF at M6 or WBC in CSF at M6 > 20 cells) ⇓ **Non-hemorrhagic lumbar puncture and WBC in CSF at M6 > 50 cells** ⇒ YES ⇒ **6:** ***Failure*** **(stop)** ⇓ NO (no reliable count of WBC in CSF at M6 or WBC in CSF at M6 ≤ 50 cells) ⇓ **Non-hemorrhagic lumbar puncture and WBC in CSF at M6 > 20 but ≤ 50 cells and no further lumbar puncture or increase of WBC in CSF at M12 or failure at M12 or M18** ⇒ YES ⇒ **7:** ***Failure*** **(stop)** ⇓ NO (no reliable count of WBC in CSF at M6, or patient did not meet the previous criterion) ⇓ **Non-hemorrhagic lumbar puncture and WBC in CSF at M6 > 20 but ≤ 50 cells and decrease of WBC in CSF between M6 and M12 and no signs and symptoms evoking relapse at M6 and Success at M12 (if status available)** ⇒ YES ⇒ **8:** ***Success*** **(stop) [b]** ⇓

Derivation algorithm at 6 months for stage 1 and intermediate stage	Derivation algorithm at 6 months for stage 2
	NO (no reliable count of WBC in CSF at M6, or patient did not meet at least one of the previous criteria) ⇓ **Patient refused all post treatment lumbar punctures** ⇒ YES ⇒ 9: ***Failure*** **(Stop)** **[a,b]** ⇓ **Otherwise ⇒ 10: *Failure***

For sensitivity analyses:

[a] will be considered as a success with the best case method (see Section 7.6.1).

[b] re-sampling will be applied with the fair case method (see Section 7.6.1).

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

Changes in the analysis of adverse events:

The part below of Section 9.7 of the Protocol version 4.0 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 patient, 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.

Wording for HAT stage:

In this Statistical Analysis Plan, "stage 1" and "stage 2" are used instead of "early stage" and "late stage", respectively.

Success Rate for the Yardsticks:

Section 9.6.1 of the Protocol version 4.0 has been modified in this SAP version as follows. Revised text is written in bold and red.

"Success Rate for the Yardstick: The current standard of care for stage 2 patients is NECT, and the success rate with NECT will be used as a yardstick. The success rates will be provided study-by-study along with the 95% Jeffreys confidence interval. ~~**Three studies will be taken into account: the study by Priotto et al. (cf. protocol, ref. 17) involving 143 patients exposed to NECT; the WHO-TDR study involving 55 patients exposed to NECT; and the DNDiHATFEX004 study involving approximately 130 patients exposed to NECT. Data from**~~ **Studies presented in the following table will be taken into account as well as the overall success rate excluding Nect-field.** The NECTField study will not be used because it did not include the same population and the large number of missing lumbar punctures could drastically reduce the success rate, particularly at 12 **and 18** months (cf. protocol, ref. 20). All of the results will be presented together in graphic format using a Forest plot (except for NECTfield).

Table 4: Efficacy of NECT

Study	Success rate at 18 M for NECT ITT and 95% Jeffreys CI	Comments
Mesu (2017) Fexi 004 study	S.R. = 124 / 130 = 95.4% 95% CI = [90.7% - 98.1%]	Pivotal Fexinidazole study. mITT: S.R.= 124 / 127 = 97.6% (RZD trial). 95% Jeffreys CI = [93.8% - 99.3%] Reason : 3 patients fleeing the region due to armed conflict
Priotto (2006)	S.R. = 16 / 17 = 94.1% 95% CI = [75.6% - 99.4%]	RZD trial
Checchi 2007	S.R. = 29 / 31 = 93.5% 95% CI = [80.9% - 98.6%]	
Priotto (2009)	S.R. = 135 / 143 = 94.4% 95% CI = [89.7% - 97.3%]	S.R. = 138 / 143 = 96.5% 95% Jeffreys CI = [92.5% - 98.7%] Note: exclusion of 3 deaths not related to treatment (RZD trial)
Kansiime (2018)	S.R. = 50 / 55 = 90.9% 95% CI = [81.2% - 96.4%]	RZD trial
Total	S.R. = 354 / 376 = 94.1% 95% CI = [91.4% - 96.2%]	Based on randomized studies only.

Study	Success rate at 18 M for NECT ITT and 95% Jeffreys CI	Comments
NECT field	S.R. = 582 / 613 = 94.9% 95% CI = [93.0% - 96.5%]	Evaluations are not always done at M18 (one arm field study with loose monitoring). 49 lost to follow-up at M18 were not necessarily counted as failure.

12. QUALITY CONTROL

A self-validation will be performed by the statistician in charge of the analysis as follows: each derived variables will be validated exhaustively (i.e. on all patients) whenever possible. Exhaustive controls can be performed using either contingency tables (i.e. displaying all qualitative variables and minimum/maximum values of quantitative variables involved in the derivation rules) or individual data listings that are considered as not too large (i.e. no more than 50 rows). An exhaustive control is considered possible when the corresponding output contains up to 50 rows. For validation outputs considered as too large (i.e. more than 50 rows), the validation can be performed on a minimum of 5% patients randomly drawn. If the validation output is still too large (i.e. more than 50 rows), the validation will be performed on a subset of 50 rows (minimum).

Validation outputs will be review by a third party (i.e. head of biostatistics or another statistician).

In addition, derivation of the primary endpoint will be double-programmed by a third party (i.e. head of biostatistics or another statistician).

13. REFERENCES

1. Gerardo Priotto, Serena Kasparian, Daniel Ngouama, Sara Ghorashian, Ute Arnold, Salah Ghabri, Unni Karunakara. Nifurtimox-eflornithine combination therapy for second-stage Trypanosoma brucei gambiense sleeping sickness: a randomized clinical trial in Congo. Clin Infect Dis. 2007 Dec 1;45(11):1435-42. doi: 10.1086/522982. Epub 2007 Oct 22.