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CLINICAL STUDY PROTOCOL

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

Registration number NCT03087955

Version 4.0 – 11 August 2020

DNDi
Drugs for Neglected Diseases *initiative*

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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

Short title	OXA002
Product name/code	Acoziborole (SCYX-7158)
Therapeutic class	Antiprotozoal
Phase	II/III
Indication	Human African Trypanosomiasis (HAT) due to *Trypanosoma brucei gambiense*
Protocol Number	DNDi-OXA-02-HAT
EudraCT Number	Not applicable
Sponsor	Drugs for Neglected Diseases initiative (DND*i*) 15 chemin Louis Dunant, 1202 Geneva, Switzerland Telephone: +41 22 906 9230
Principal Investigator	[redacted]
Coordinating Investigator	[redacted]
National Coordinator in Guinea	[redacted]

Protocol Version and Date	Version 4.0 / 11 August 2020
Protocol Amendment Number and Date	Amendment 3 dated 11 August 2020

Signatures

Head of HAT Clinical Programme

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Statistician

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Investigator Signature Page

I have read this protocol and agree that it contains all of the information required to conduct the study. I will conduct the study in compliance with the protocol, with Good Clinical Practice (GCP) and with the regulations in effect in my country, and I will complete the study within the specified timeframe.
I will provide copies of the protocol and all relevant information to all individuals participating in the study under my responsibility. I will ensure that they are given all of the necessary information on the study treatment and the procedures of the study.
I will use only the informed consent form approved by the Sponsor or its representative, and I agree to submit all relevant documentation to the Independent Ethics Committee (IEC) responsible for the study.
I also agree that the Sponsor or its representatives shall have access to all source documents from which data entered in the case report forms was generated.

Principal Investigator and National Investigator for the DRC

Date of signature
(DD/MM/YYYY)

Signature of
Investigator

Name
Title
Organisation

Address

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Coordinating Investigator

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(DD/MM/YYYY)

Signature of
Investigator

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Title
Organisation
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Investigator Signature Page

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Investigator

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TABLE OF CONTENTS

List of Tables

List of Figures

Abbreviations – Glossary of Terms

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransférase
AUC	Area under the curve
BMI	Body mass index
BUN	Blood urea nitrogen
CATT	Card agglutination test for trypanosomiasis
CERSAC	Ethics Committee for Health Research in Central Africa (*Comité d'Ethique pour la Recherche en Santé en Afrique Centrale*)
CRF	Case report form
CSF	Cerebrospinal fluid
CTCAE	Common Toxicity Criteria for Adverse Events
D	Day
DBS	Dry blood spot
DNDi	Drugs for Neglected Diseases *initiative*
DRC	Democratic Republic of the Congo
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*
H	Hour
HAT	Human African trypanosomiasis
i.e.	id est
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INRB	*Institut National de Recherche Biomédicale* (Democratic Republic of the Congo)
IV	Intravenous
M	Month
mAECT	Mini-anion exchange column test
mAECT-BC	Mini-anion exchange column test - buffy coat
mITT	Modified Intention to treat (set)
MSC	Modified single centrifugation
NCI	National Cancer Institute
NECT	Nifurtimox-eflornithine combined therapy
PD	Pharmacodynamics
PK	Pharmacokinetics
PNLTHA	*Programme National de Lutte contre la Trypanosomiase Humaine Africaine*

QT	QT interval on ECG (time interval between electrical depolarisation and repolarisation of the left and right cardiac ventricles)
QTcF	QT interval corrected by heart rate, according to the formula proposed by Fridericia
RDT	Rapid diagnostic test
SAE	Serious adverse event
SAP	Statistical analysis plan
SMS	Short message service
T.b.	*Trypanosoma brucei*
T_3	Tri-iodothyronine
T_4	Thyroxine
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal range
WBC	White blood cell / white blood cell count
WHO	World Health Organisation
WHO-TDR	*Tropical Disease Research* programme of the WHO
Y	Year

Protocol Summary

Study Title	Efficacy and safety study of acoziborole (SCYX-7158) in patients with human African trypanosomiasis (HAT) due to *Trypanosoma brucei gambiense:* a multicentre, open-label, prospective study
Study Phase	II/III
Indication	Human African Trypanosomiasis (HAT) due to *Trypanosoma brucei gambiense*
Protocol Number	DNDi-OXA-02-THA Short Number: OXA002
Study Rationale	Human African trypanosomiasis (HAT) is a neglected disease that is usually fatal. Few therapeutic options are currently available to treat HAT in the late (or meningoencephalitic) stage. Nifurtimox-eflornithine combination therapy (NECT), introduced in 2009, has demonstrated efficacy with a success rate between 94% and 97%, and has been chosen as first-line treatment in all endemic countries where cases have been declared in the past 10 years. The need for a hospital infrastructure to administer NECT (2-hour infusions, twice daily for 7 days for eflornithine) and logistical difficulties relating to supply, as well as difficulties relating to access to patients have prompted research into drugs that can be administered orally, including fexinidazole and acoziborole. Acoziborole is an orally active benzoxaborole-6-carboxamide that has been shown to have *in vitro* and *in vivo* activity against the two subspecies of parasites, *T.b. rhodesiense* and *T.b. gambiense*, responsible for HAT. Single oral doses of acoziborole ranging from 20 to 1200 mg have been administered to healthy volunteers with no major toxic effects (6). The dose of 960 mg was chosen as the therapeutic dose because it ensures exposure levels in the cerebrospinal fluid (CSF) 1.5-fold higher than the pharmacologically active levels at which a 100% trypanocidal effect was obtained in infected animals. In healthy volunteers, plasma levels remained above the effective concentration up to 69 days after the administration of acoziborole. The objective of the study is to assess the efficacy and safety of acoziborole administered as a single oral dose in fasting patients with HAT due to *T.b. gambiense*.
Study Objectives	**General Objective** To assess the efficacy and safety of a single oral dose of acoziborole administered to patients in the fasting state with g-HAT. **Primary Objective**

	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. **Secondary Objectives** ▪ To estimate the success rate at 12 months in late-stage patients ▪ 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. As part of the clinical package, a cohort of patients over 15 years of age with early- or intermediate-stage g-HAT will be enrolled following the futility analysis, provided that it does not show futility and that the safety review shows no concerns. The general 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. ▪ 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.
Primary Endpoint	**Efficacy** The rate of success, according to World Health Organisation (WHO) criteria (23), for patients with late-stage HAT 18 months after receiving acoziborole.
Secondary Endpoints	**Efficacy** ▪ Treatment efficacy at each visit between the end of treatment and 18 months, estimated, on the one hand, based on criteria for success specific to each visit and, on the other hand, based on a calculation of the cumulative risk of failure over time. **Safety** ▪ Occurrence of any adverse event during the observation period. Adverse events will be graded according to the

	Common Toxicity Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI), version 4.03. ▪ Occurrence of any serious adverse event during the observation period and until the 18-month follow-up visit. **Pharmacokinetics (PK) / Pharmacodynamics** ▪ PK parameters in the blood and CSF: acoziborole concentrations in whole blood and in the CSF; population PK parameters, i.e. clearance, area under the curve and half-life. **Electrocardiogram** ▪ Categories of QT/QTcF interval and changes at various timepoints.
Futility Analyses	Futility analyses to assess the response rate are planned in order to stop exposure to the investigational product if efficacy is below an acceptable limit.
Study Design	This is a prospective, multicentre, open-label, non-randomised phase II/III study.
Inclusion and Exclusion Criteria	To be included in the study, the patient must fulfil all of the inclusion criteria and none of the exclusion criteria: Inclusion Criteria ▪ Male or female ▪ 15 years of age or older ▪ Signed informed consent form (as well as assent from illiterate and under-age patients, and those unable to give consent) ▪ Karnofsky Performance Status above 50 ▪ Able to ingest oral tablets ▪ Having a permanent address or being traceable by other persons ▪ Able to comply with the schedule of follow-up visits and requirements of the study ▪ Agreement to be hospitalised in order to receive treatment For patients with late-stage HAT: ▪ Confirmation of g-HAT by detection of the parasite in the blood and/or the lymph and/or the CSF, at the investigational centre ▪ If trypanosomes are found in the blood or lymph, but not in the CSF, the CSF white blood cell count, measured at the investigational centre, must be above 20/µL for the patient to be included in the cohort of patients with late-stage HAT For patients with early- or intermediate-stage HAT: ▪ Confirmation of g-HAT by detection of the parasite in the blood and/or the lymph, at the investigational centre

	▪ Absence of parasites in the CSF ▪ The CSF white blood cell count, measured at the investigational centre, must be between 6 and 20/µL for the patient to be included in the cohort of patients with intermediate-stage HAT and equal to or below 5/µL for the patient to be included in the cohort of patients with early-stage HAT <u>Exclusion Criteria</u> ▪ Severe malnourishment, as defined by a body-mass index below 16 ▪ Pregnancy or breastfeeding, (for women of child-bearing potential, confirmed pregnancy on a urine pregnancy test performed within 24 hours prior to administration of acoziborole) ▪ Clinically significant medical condition that could, in the opinion of the Investigator, jeopardise the patient's safety or interfere with participation in the study, including, but not limited to significant liver or cardiovascular disease, suspected or proven active infection, central nervous system trauma or seizure disorder, coma or consciousness disturbances ▪ Severely deteriorated health status, e.g. due to cardiovascular shock, respiratory distress syndrome or end-stage disease ▪ Previously treated for HAT (except prior treatment with pentamidine) ▪ Prior enrolment in the study ▪ Foreseeable difficulty complying with follow-up, including migrant worker, refugee status, itinerant trader etc. ▪ Current alcohol abuse or drug addiction ▪ Not tested for malaria and/or not having received appropriate treatment for malaria ▪ Not having received appropriate treatment for soil-transmitted helminthiasis ▪ Clinically significant abnormal laboratory value including: o AST and/or ALT more than 2 times the upper limit of normal (ULN), o Total bilirubin more than 1.5 ULN, o Severe leukopenia at less than 2000/mm^3, o Potassium below 3.5 mmol/L, o Any other clinically significant abnormal laboratory value.
Investigational Product	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.

Study Duration	The duration of the enrolment period is estimated to be approximately 28 months. Each patient's participation in the study will last approximately 18 months and will include: ▪ pre-treatment period (pre-screening and screening, treatment of concurrent diseases) up to 15 days; ▪ a treatment period of 1 day; ▪ an observation period in hospital of a total of 15 days, including the treatment day (Day 1); ▪ an out-patient follow-up period of 18 months with visits at 3, 6, 12 and 18 months. The total duration of the study is estimated to be 46 months.
Study Schedule	D-15 to D-1: pre-screening and screening • including the baseline assessment: D-4 to D-1 D1: treatment day D1 to D15: observation period at hospital D11: initial assessment of treatment effect (lumbar puncture) D15: end-of-hospitalisation visit Out-patient follow-up visits at 3 months, 6 months, 12 months and 18 months
Sample Size Calculation	The sample size is based on the largest number of patients who can be enrolled within a reasonable timeframe. The sample size will be 155 late-stage patients. Patients lost to follow-up who fled the region due to armed conflict or natural disaster will be replaced. A provision of 5% (7 patients) is planned in order to allow for replacement of patients lost to follow-up. Thus, a total of 162 patients will be included. As a result of the reduction in the number of patients, it is estimated that approximately 50 early- or intermediate-stage patients may be enrolled in the study during the enrolment period.
Statistical Analyses	**<u>Analysis Sets</u>** The population of late-stage patients will be separated from the population of early- and intermediate-stage patients. The primary analysis will be performed on late-stage patients in the modified intention-to-treat (mITT) population and who received at least one tablet of acoziborole. Patients lost to follow-up who fled the region due to armed conflict or natural disaster will not be included in the mITT population and will be replaced by other patients. The analysis of the primary endpoint for early- and intermediate-stage patients, which is considered to be a secondary analysis, will be also performed on the mITT population. The sensitivity analyses will be performed by cohort, separating late-stage patients from early- and intermediate-

	stage patients. **Primary Efficacy Analysis: Success Rate at 18 Months in Late-stage Patients** The primary analysis is based on the mITT set, i.e. patients who received at least one tablet of acoziborole, and will consist in an estimate of the success rate at 18 months of follow-up. The 95% Jeffreys confidence interval of the estimate will be provided. **Analysis of Surrogate Primary Endpoint for Late-stage Patients** Amendment 2 dated 07/01/2020 deletes analysis of the surrogate primary endpoint at 12 months in patients with late-stage g-HAT, as the data set required for early submission at 12 months is not available in its entirety. **Success Rate for the Yardstick** The current standard of care for late-stage 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. (18) involving 143 patients exposed to NECT; the WHO-TDR study (13) involving 55 patients exposed to NECT; and the DNDiHATFEX004 study involving approximately 130 patients exposed to NECT. Data from the NECT-Field 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 months (20). **Secondary Efficacy Analysis at 12 Months in Late-stage Patients** The estimated success rate at 12 months in late-stage patients is a secondary analysis. The 95% Jeffreys confidence interval of the estimate will be provided. **Efficacy Analysis in Early- and Intermediate-stage Patients** The efficacy analysis for early- and intermediate-stage patients is a secondary analysis, similar to the primary analysis for late-stage patients and concerns the success rate at 12 months and at 18 months in early- and intermediate-stage patients. The 95% Jeffreys confidence interval for the estimated rates will be provided. **Other Secondary Analyses** ▪ The correlation between acoziborole concentrations in the blood and CSF and the success rate in late-stage patients will be determined using logistic regression with success or failure as the response (dependent variable) and two covariables (explanatory variables): blood and CSF concentrations. ▪ The correlation between acoziborole concentrations in the blood and CSF and the occurrence of AEs in late-stage patients will be determined using logistic regression with the occurrence of AEs during hospitalisation as the response

(dependent variable) and two covariables (explanatory variables): blood and CSF concentrations.

- Changes in the rate of favourable outcomes over time for late-stage patients on the one hand, and for early- and intermediate-stage patients on the other hand, will be studied using the mixed model for repeated measures (Glimmix).
- Time to proven relapse will be analysed in each cohort using the Kaplan-Meier approach in order to estimate, at each follow-up visit, the cumulative rate of proven failures. Patients lost to follow-up will be censored at the last available visit, unless the outcome at that visit was failure.

Safety Analyses

All patients who received acoziborole will be included in the safety analyses.

The percentage of patients who experienced a serious adverse event (SAE) will be described by system-organ class.

The percentage of patients who experienced at least one adverse event will (AE) be described. Each SAE will be described in a narrative presenting all aspects of the medical event and the causality assessment.

The incidence of AEs and of SAEs and their respective 95% confidence intervals will be presented by category and by frequency. In other cases, only descriptive statistics will be presented.

Laboratory safety parameters, i.e. haematology and biochemistry, will be described individually, indicating the percentages of patients by the size of the increase in relation to the ULN and to baseline values, as well as changes in blood levels over time. Shift tables will be provided. A listing of patients with increases in laboratory parameters will be provided.

Abnormalities on electrocardiogram (ECG) tracings will be described for each timepoint.

Futility Analyses

An independent Data and Safety Monitoring Board (DSMB) will be appointed, among other things, to supervise and review the futility and PK analyses, as well as the safety data. The DSMB will make recommendations on study continuation based on all available information.

The first futility analysis will be performed once the first 20 late-stage patients reach the 3-month visit. If the failure rate at Day 11 is significantly higher than the failure rate for melarsoprol (19), 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), then the DSMB should recommend stopping the study, unless the rate can be explained by exceptional circumstances.

The second futility analysis will be performed once 70 late-stage patients reach the 3-month visit. The recommendation to

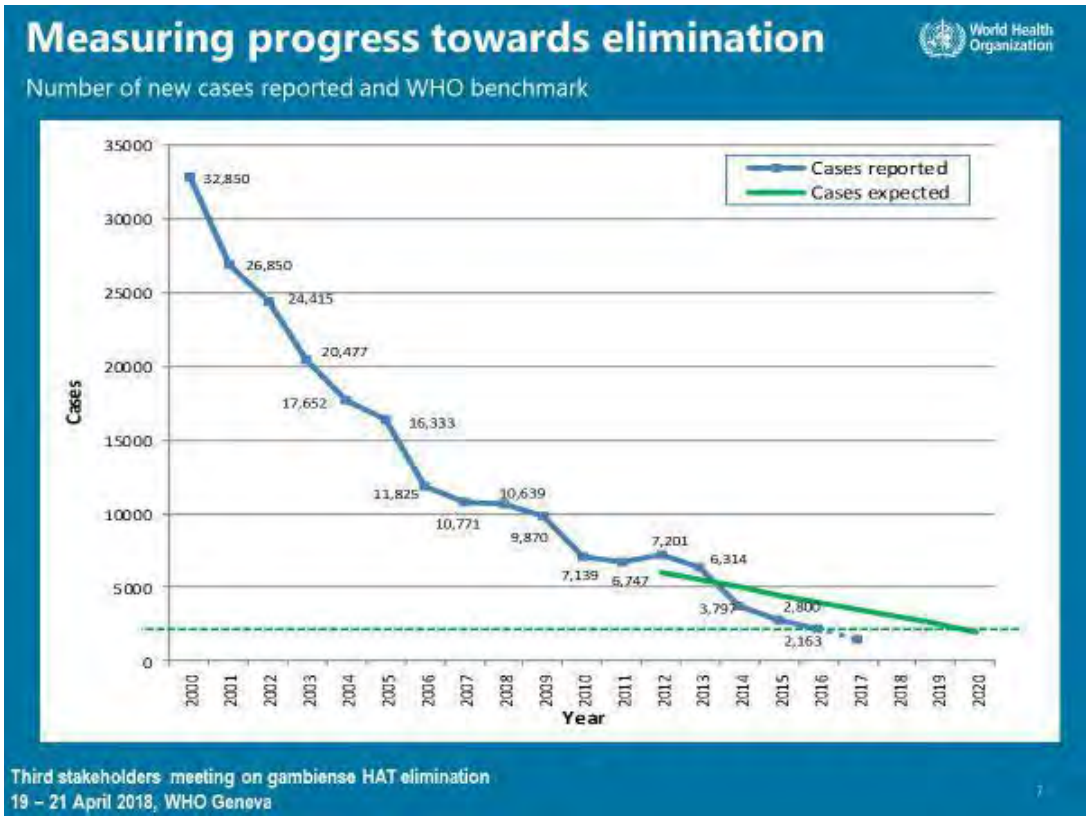
	stop the study should be made if 8 patients or more out of 70 are failures at the end of hospitalisation (p = 0.023 one-sided). The last futility analysis will be performed once 70 late-stage patients reach the 6-month visit. The proven failure rate will be compared to the failure rate with melarsoprol at 6 months, which is 20%. If the failure rate is significantly higher than 20%, i.e. $\geq$ 22 out of 70 patients (p = 0.016, one-sided), the DSMB should recommend stopping the study. 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 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 with the historical data, taking into account the obvious advantage of having a single oral dose for patients living in remote areas.

1. Background and Study Rationale

1.1. Epidemiology

Human African trypanosomiasis (HAT), or sleeping sickness, is a vector-borne parasitic disease that is present in sub-Saharan Africa. It is transmitted by the bite of the tsetse fly (genus *Glossina*) and, if left untreated, it invariably leads to the patient's death. The parasites responsible for HAT are the protozoa, *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*, which are found only in foci in regions of sub-Saharan Africa where the tsetse fly is endemic (2, 15, 22). Twenty-four countries are considered to be endemic for HAT due to *T.b. gambiense* (g-HAT), however, since 2005, cases have been reported in only 14 of these countries. Thirteen countries are considered to be endemic for HAT due to *T.b. rhodesiense*, however cases have been reported in only 6 of the countries. Uganda is the only country where both subspecies of parasite are found. In 2014, the WHO identified 3679 cases of g-HAT worldwide, 87% of which in the Democratic Republic of the Congo (DRC) alone (11, 24, 25). According to the same source, however, the actual number of cases may be as high as 20,000 and as many as 65 million people may actually be exposed to the disease. The number of reported cases steadily declines each year, and the historically lowest level of 2110 cases was reached in 2016 (12). The most recent data presented by WHO in April 2018, i.e. 1420 cases in 2017, confirmed this trend, as shown in Figure 1.

Figure 1. Number of New Cases Reported at End of 2017



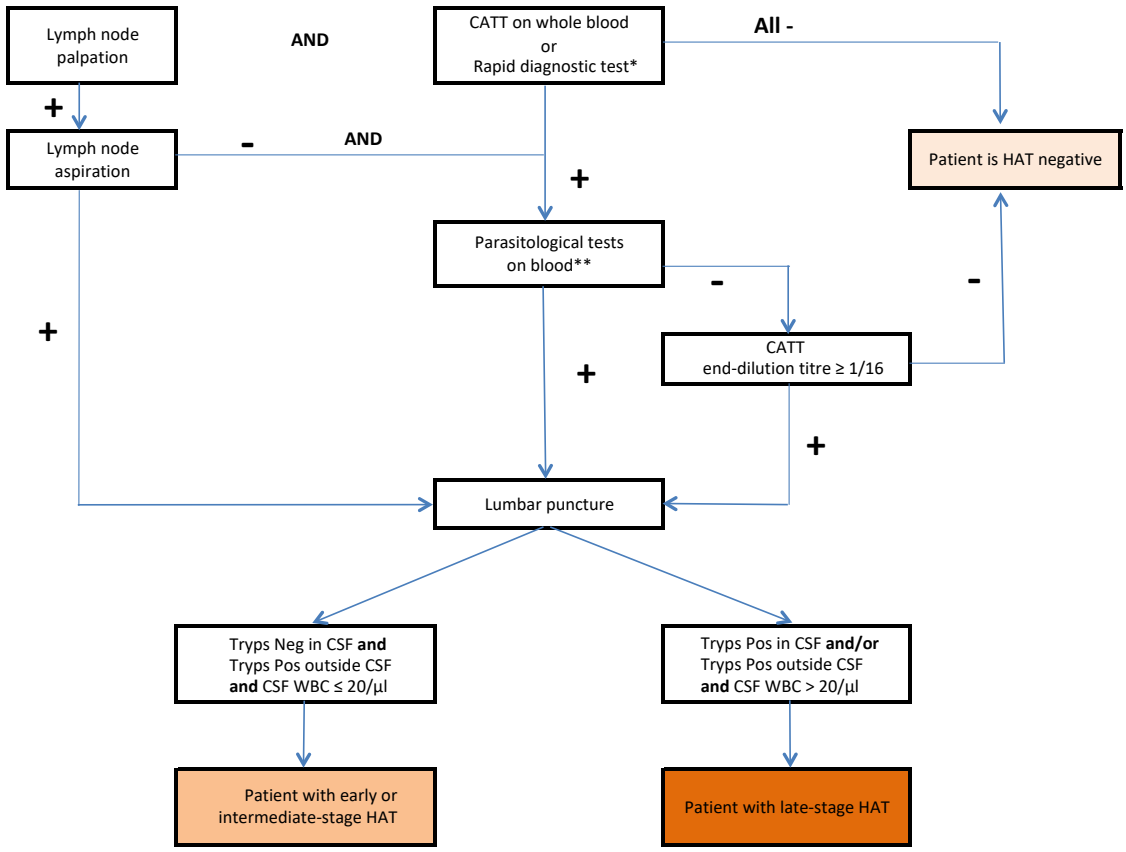
1.2. Clinical Presentation of HAT

There are two successive stages in the clinical course of HAT. In the first stage, called the haemolymphatic or early stage, trypanosomes are present only in the blood and lymphatic system. The clinical signs and symptoms are mild and non-specific, including bouts of fever, headache, joint pain, itching and lymph node enlargement. The signs and symptoms are very similar to those of malaria, which explains why patients with early-stage HAT are often misdiagnosed with malaria. If HAT is not diagnosed and treated, patients progress to the next stage, called the meningoencephalitic stage or late stage, in which parasites invade the central nervous system. At this stage, patients display neurological signs including mental confusion, behavioural changes, sensory disturbances, sleep disturbances and, eventually, coma and death. There is also an intermediate stage in which no parasites are detected in the cerebrospinal fluid (CSF), however the white blood cell count (WBC) in the CSF is between 6 and 20/µL (2, 15, 22, 27).

1.3. Management of Patients in the Study

HAT due to *T.b. gambiense* may be diagnosed either in the context of passive screening in patients who present spontaneously to the hospital or to one of the outlying healthcare centres or in the context of active screening by mobile teams working in the field. In Guinea, the study will be conducted in the HAT treatment centre in Dubreka, with two satellite centres, i.e. the HAT treatment centre in Forecariah and the prefectural hospital in Boffa, for screening and follow-up of patients. Whatever the context, the diagnostic process will consistently include the following three steps: screening for potential infection using clinical and serological assessments, detection of the parasite and staging of the disease (see Figure 2).

Figure 2. Decision Tree for the Diagnosis of HAT in the Context of the Study



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

Screening, which consists in investigation of potential infection, will be performed by assessing clinical signs, including the presence of swollen cervical lymph nodes, and by serological tests. In the community or at hospital, serological screening will be performed using a rapid diagnostic test (RDT) or the card agglutination test for trypanosomiasis (CATT) (9).

For patients with a positive result on serological screening, tests to detect the parasite will be performed, preferably using one of the concentration methods that allow for microscopic detection of motile parasites in fresh centrifugated samples. The testing will be performed on lymph node aspirate collected by needle biopsy and in the blood, using the Woo test (capillary tube centrifugation) or the mini-anion exchange centrifugation test (mAECT) (3) or, if concentration methods are not available, by examination of a thin blood smear or stained thick blood smear.

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

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

Current therapeutic options are not the same for early- and late-stage HAT and, as a result, before initiating treatment, it is necessary to determine the stage of the disease by analysing CSF collected on lumbar puncture. In usual practice, late-stage HAT is confirmed by the presence of parasites and/or of a CSF WBC above 5/µL. However, in clinical studies assessing treatments for late-stage HAT, the WHO recommends that a CSF WBC of 20/µL should be used as the threshold for determination of late-stage HAT (23). A CSF WBC of 20/µL will therefore be used as the threshold in this study.

In current practice, when early-stage HAT is diagnosed, patients can be treated in their village with intramuscular injections of pentamidine for 7 days. Patients diagnosed with late-stage HAT are hospitalised to receive treatment with Nifurtimox-eflornithine combination therapy (NECT) (see Section 1.4, Current Therapeutic Options for g-HAT; p24). In the present study, all patients will receive acoziborole.

In the context of the study, patients diagnosed outside the investigational centre will undergo a second assessment based on the decision tree presented above. Lumbar puncture for disease staging will be performed only at the investigational centre. It is planned to perform lumbar puncture, whenever possible, using a local anaesthetic cream, i.e. Emla®, as well as an atraumatic needle. Parasitological tests will be performed after modified single centrifugation (MSC) of the CSF.

Only patients in whom the presence of parasites is confirmed by at least two team members at the investigational centre and approved by the Investigator, will be included in the study, regardless of the findings reported by the mobile teams.

For quality control purposes, it is planned to record digital images of the parasitological tests and CSF WBC counts at the time of the initial diagnosis, as well as during follow-up visits.

In usual practice, cure is defined as the absence of parasites in any body fluid and by a CSF WBC below 20/µL at 18 months. As a result, lumbar punctures must be performed to confirm the cure in patients treated for HAT. In the past, the recommendations for HAT control programmes were to assess cure every 6 months up to 24 months after the end of treatment (5, 26). However, with the use of highly effective anti-HAT treatments such as pentamidine for the early stage and NECT for the late stage, and given the difficulty of routine post-treatment follow-up, systematic follow-up with CSF examination to confirm cure is no longer recommended, and assessment should be based on clinical features. This recommendation does not apply to clinical studies intended to test new compounds for the treatment of HAT (27). Therefore, in the present study,

parasitological tests on the blood and lymph, as well as lumbar puncture, will be performed at the 6-, 12- and 18-month follow-up visits.

1.4. Current Therapeutic Options for g-HAT

Few therapeutic options are currently available to treat HAT at either stage (1, 14). When early-stage HAT is diagnosed, patients can be treated in their villages with intramuscular injections of pentamidine for 7 days. In patients with late-stage HAT, NECT, a combination of oral nifurtimox for 10 days plus eflornithine, two 2-hour intravenous (IV) infusions daily for 7 days, was found to provide similar cure rates to the standard regimen with eflornithine for 14 days, but with obvious practical advantages, including ease of administration and a shorter duration of treatment.

In May 2009, the WHO Expert Committee added NECT to the 16th edition of the WHO List of Essential Medicines for adults, as an alternative to single-drug therapy with melarsoprol or eflornithine.

In keeping with the WHO recommendation, almost all of the national HAT control programmes have already adopted NECT as first-line treatment for late-stage g-HAT and, in 2014, NECT became the most widely used treatment for late-stage disease (21).

NECT represents a significant improvement over current therapies, however it is far from ideal given the conditions under which patients with HAT generally live, i.e. in poor, remote areas with little or no healthcare infrastructures and problems with logistics. Thus, there is an urgent need to develop easier-to-use products for the treatment of this fatal disease, ideally a simplified, short-course treatment that can be administered orally at a primary healthcare facility or indeed on an out-patient basis.

1.5. Investigational Product and Preclinical Data

Acoziborole (SCYX-7158) is an orally active benzoxaborole-6-carboxamide. Acoziborole, also referred to as [redacted], is the result of a collaboration between DND*i*, [redacted]. Preclinical studies have identified the concentrations of acoziborole that must be achieved in the plasma and brain in order to be effective against late-stage g-HAT. Indeed, reversible *in vitro* assays for acoziborole showed that it is necessary to know the exposure time and area under the curve (AUC) for the minimum inhibitory concentration in order to predict efficacy.

Complete and irreversible inhibition of parasite growth was achieved with an unbound AUC of 5.81 µg•h/mL. This was confirmed in animal models considered to be predictive of HAT in humans in which a 100% trypanocidal effect was obtained with daily administration of 25 mg/kg for 7 days. On the first day of

treatment, plasma concentrations reached 4.98 µg•h/mL, which is close to the critical threshold of 5.81 µg•h/mL for the unbound AUC of the minimum inhibitory concentration. From the second to the seventh day, the threshold was exceeded, and concentrations reached 7.15 µg•h/mL (28).

Preclinical pharmacokinetic (PK) studies showed that acoziborole is well absorbed by the oral route, that it is widely distributed throughout the body and that it crosses the blood-brain barrier. In all of the animal species studied, acoziborole was rapidly metabolised through oxidation, leading to the formation of at least one inactive metabolite, SCYX-3109 (10). Toxicological studies, including safety pharmacology and 4-week repeated-dose toxicity studies (including toxicokinetics) in the rat and dog, have shown that acoziborole is well tolerated up to 40 mg/kg/day in rats, with no major toxicities identified. In both species, 15 mg/kg/day was considered as the no observed adverse effect level in the 4-week repeated-dose studies.

1.6. Pharmacokinetics and Metabolism In Healthy Volunteers

A randomised, double-blind, placebo-controlled Phase-I study (6) was performed in healthy African male volunteers between 18 and 45 years of age in order to assess the safety, PK and pharmacodynamics (PD) of acoziborole after single ascending oral doses. A total of 128 subjects were included, 102 of whom received acoziborole, and 26 received placebo. The doses studied ranged from 20 mg to 1200 mg.

Acoziborole was rapidly absorbed in the healthy volunteers, and the plasma concentrations remained stable for at least 96 hours, indicating that the elimination half-life is relatively long. Analysis of the PK data showed that acoziborole undergoes extensive enterohepatic recycling. Activated charcoal was administered to subjects, generally starting on Day 5, in order to accelerate clearance of the product and shorten the follow-up period for the subjects. The therapeutic dose of 960 mg was also administered without activated charcoal to mimic the future conditions of administration to patients. Clearance of acoziborole from the body was very slow with a half-life of approximately 400 hours. This profile suggests that a single administration of acoziborole may be sufficient for the treatment of HAT. Inter-subject variability was low at approximately 20%.

Contrary to what was observed in animals, metabolism of acoziborole was very limited, which may explain the very long half-life in humans.

The unbound fraction was determined by ultrafiltration. The ultrafiltrate-to-plasma ratio was in the same range as that in the *in-vitro* study. The mean unbound fraction was 2.2% of the plasma concentration.

In addition, concentrations of acoziborole were determined in the CSF of healthy volunteers. In the 240 and 320 mg dose-level groups, mean CSF concentrations corresponded to 2.2% of the plasma concentration with a range of 1.8% to 3.2%.

1.7. Safety in Healthy Volunteers

The safety of acoziborole was assessed in the Phase-I study (6).

The most frequently reported acoziborole-related adverse events (AEs) were gastrointestinal disorders, mainly consisting in abdominal pain, nausea, constipation, vomiting and, more rarely, reduced appetite. The AEs were observed at different doses of acoziborole and were also observed with placebo. It should be noted that the use of activated charcoal promoted the occurrence of some gastrointestinal disorders such as constipation or vomiting. Central nervous system disorders were also reported, mainly consisting in headache, but none were considered to be possibly related to acoziborole. No correlation was found between the dose and the number of AEs observed.

No relevant abnormal findings were observed on clinical monitoring, i.e. physical examination, vital signs and electrocardiograms (ECG). Conversely, laboratory monitoring found a few clinically significant abnormalities with acoziborole, as well as with placebo, primarily consisting in elevated levels of creatine phosphokinase and of transaminases. In addition, thyroid function tests found irregular and incomplete, sub-clinical variations in TSH, free T3 and free T4, in the acoziborole group, as well as with placebo. One case of sub-clinical hyperthyroidism after administration of acoziborole at 240 mg was however reported as a serious adverse event (SAE). The case was mild in severity, sub-clinical, transient and spontaneously resolutive, and was considered to be possibly related to acoziborole. The variations were observed in both the placebo and the acoziborole groups, regardless of the dose, however considerably fewer variations were observed in the higher dose-level groups, including the selected therapeutic dose.

In subjects exposed to acoziborole, no abnormalities were observed in the following parameters: bilirubin, pancreatic function (blood glucose, lipase and amylase) lipid profile (triglycerides, total cholesterol, high-density lipoproteins - cholesterol, low-density lipoproteins - cholesterol), kidney function (creatinine, urea, electrolytes), haematology, coagulation tests (activated partial thromboplastin time, international normalised ratio), reticulocytes, haptoglobin, ferritin and Coombs test.

1.8. Choice of the Dose and Dosing Regimen

The dose of 960 mg was chosen as the therapeutic dose because it ensures exposure levels in the CSF 1.5-fold higher than the pharmacologically active levels at which a 100% trypanocidal effect was obtained in infected animals. In healthy volunteers, plasma levels remained above the effective concentration up to 69 days after the administration of acoziborole.

No safety signals were observed at 1200 mg, which was the highest dose tested in humans. This provides a safety margin approximately 1.5- to 3-fold higher than the no observed adverse effect level in animals.

No studies have been performed on the effect of food on the bioavailability of acoziborole and, for this reason, the single dose of the investigational product must be taken in the fasting state.

1.9. Rationale for the Study Design

The principle of an open-label, non-randomised, prospective study was accepted by the European Medicines Agency, taking into account the difficulty of completing enrolment of late-stage HAT patients in a prospective, randomised, non-inferiority study within a reasonable timeframe.

The European Agency recommended calculating the sample size in the present non-randomised study based on the maximum feasible enrolment within a reasonable timeframe.

Given the drastic decline in prevalence, it was estimated that the sample size that is possibly feasible to attain within a reasonable timeframe, i.e. approximately 28 months, is 155 patients with late-stage g-HAT, with a provision of 5% (7 patients) to allow for possible replacement of patients lost to follow-up who fled the region due to armed conflict or natural disaster, for a total of 162 late-stage patients.

1.10. Target Population

The target population will initially be limited to patients 15 years of age or older with late-stage HAT. After the first futility analysis, a second cohort of patients with early- or intermediate-stage HAT will be enrolled in order to enrich the safety database on acoziborole and to assess its efficacy in this population.

As in the preceding studies on HAT, the inclusion of adolescent patients 15 years of age or older, in addition to adults, will facilitate the enrolment of patients with late-stage HAT.

2. Study Objectives and Endpoints

2.1. Objectives

2.1.1. General Objective

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.

2.1.2. Primary Objective

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.

2.1.3. Secondary Objectives

- To estimate the success rate at 12 months in late-stage patients
- 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.
- 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.

2.2. Endpoints

2.2.1. Primary Endpoint – Efficacy

Primary Endpoint for Patients with Late-stage HAT

A patient will be considered as a success, in accordance with the WHO criteria (23), if the patient is alive with no evidence of trypanosomes in any body fluid and a CSF WBC equal to or below 20/µl 18 months after receiving acoziborole.

A patient with no parasitological evidence of a relapse and a CSF WBC above 20/µL or who, in the Investigator's opinion, requires rescue treatment will be considered as a probable relapse.

A patient who refuses the end-of-study lumbar puncture will be classified as a probable cure (success) in the absence of any clinical signs or symptoms suggestive of THA or with another obvious aetiology, provided that the outcome was favourable, i.e. a CSF WBC equal to or below 20/µl, at the last available assessment at 6 months or later.

Death for any reason, patients lost to follow-up and not retrieved or patients who refuse a lumbar puncture at 18 months and who had an unfavourable outcome earlier (probable relapse) will be considered as failures, with the exception of patients who fled the region due to armed conflict or natural disaster. These patients will be replaced by patients from another centre 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 evaluable patients, 7 additional patients will be enrolled in the study.

Surrogate Primary Endpoint for Patients with Late-stage HAT

Amendment 2 dated 07/01/2020 deletes analysis of the surrogate primary endpoint at 12 months in patients with late-stage g-HAT, as the data set required for early submission at 12 months is not available in its entirety.

2.2.2. Secondary Endpoints - Efficacy

Efficacy in Patients with Late-stage HAT

A patient with late-stage HAT will be considered as a success at 6 months and at 12 months if the CSF WBC is equal to or below 20/µL and in the absence of trypanosomes, rescue treatment and signs or symptoms suggesting a relapse at the visit in question or previously.

If the patient does not have a lumbar puncture at 6 months, the outcome of the lumbar puncture at 12 months will be used. If the patient does not have a lumbar puncture at 12 months and if a lumbar puncture is performed at 18 months, the outcome at 18 months will be used. Otherwise, the outcome at 6 months will be used. If the patient has no post-treatment lumbar puncture, s/he will be considered as a failure. Patients lost to follow-up and deaths, regardless of the cause, will be considered as failures.

Endpoints in Patients with Early- or Intermediate-stage HAT

Two efficacy endpoints will be used for patients with early- and intermediate-stage HAT: the outcome at 12 months and the outcome at 18 months after receiving treatment. A patient will be considered as a success at 12 months if the patient is alive with no evidence of trypanosomes in any body fluid and if the CSF

WBC is equal to or less than 20/µL. A patient with no parasitological evidence of relapse, but with a CSF WBC above 20/µL or who, in the Investigator's opinion, requires rescue treatment, will be considered as a relapse. A patient who refuses the lumbar puncture at 12 months will be classified as a probable cure (success) in the absence of any clinical signs or symptoms suggestive of THA or with another obvious aetiology, provided that the outcome was favourable, i.e. a CSF WBC equal to or less than 5/µL, at 6 months. Death for any reason, patients lost to follow-up and not retrieved or patients with no post-treatment lumbar puncture will be considered as failures, with the exception of patients who fled the region due to armed conflict or natural disaster. For memory, patients who fled the region due to armed conflict or natural disaster will not be included in the mITT population and will therefore not be taken into account in the calculation of the success rate. A patient with early- or intermediate-stage HAT will be considered as a **success** at 18 months if the CSF WBC is equal to or below 20/µL and in the absence of trypanosomes, rescue treatment and signs or symptoms suggestive of a relapse. If the patient does not have a lumbar puncture at 18 months, the outcome at 6 months or at 12 months will be used.

A patient with early- or intermediate-stage HAT will be considered as a success at 6 months and at 12 months if the CSF WBC is equal to or less than 20/µL and in the absence of trypanosomes, rescue treatment and signs or symptoms suggestive of a relapse. If the patient does not have a lumbar puncture at 6 months, the outcome at 12 months and, if necessary, at 18 months will be used. If the patient does not have a lumbar puncture at 12 months, the outcome at 18 months will be used and, if necessary, the outcome at 6 months will be used. If no post-treatment lumbar punctures were performed, the outcome will be considered as unfavourable.

Time to Failure in Patients with Late-stage HAT

The starting point is administration of acoziborole. The time to failure is the time up until the first objective evidence of failure is observed. The first evidence may be the presence of trypanosomes in any body fluid, a CSF WBC above 50/µL at 6 months and above 20/µL at 12 and/or 18 months, clinical signs or symptoms suggestive of a relapse (see Table 1, Clinical Classification of Patients in Section 5.4 Rescue Treatment; p38), the decision to use rescue treatment or death for any reason. Unlike the preceding endpoints, a patient cannot be a failure at a given timepoint and a success at a subsequent timepoint. Consequently, a patient with a CSF WBC above 20/µL at 12 months and below 20/µL at 18 months becomes a success at 6 months and 12 months in the time-to-failure analysis, but not in the time course of the success rate. 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.

2.2.3. Secondary Endpoints - Safety

The secondary endpoints concerning the safety of acoziborole are as follows:

- Occurrence of any AE, including an abnormal laboratory test result, during the observation period. AEs will be graded according to the Common Toxicity Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI), version 4.03 (16).
- Occurrence of any SAE during the observation period and until the end of follow-up (18 months).

2.2.4. Secondary Endpoints - Pharmacokinetics

The following PK parameters will be measured in the blood and CSF:

- Concentrations of acoziborole in whole blood and CSF, and population PK parameters, i.e. clearance, AUC and half-life (see also Section 6.3.3 Pharmacokinetic Analyses; p43)

2.2.5. Secondary Endpoints - Electrocardiogram

ECG tracings will be recorded at various timepoints to assess the QT/QTcF interval and variations over time (see Section 6.3.2 Digital ECG; p42 and the Schedule of Procedures; p89).

3. Study Design

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. Selection of Study Population

The patient must fulfil all of the inclusion criteria and none of the exclusion criteria. The inclusion and exclusion criteria are similar to those in the study published by Priotto et al. (18), and the study design is the same as that in the study conducted by WHO-TDR and in the DNDiHATFEX004 study, as these three studies constitute the basis for the use of NECT as a yardstick in this study. Once the patient has signed the informed consent form, s/he will be assigned a number comprising the 3-digit centre number starting with 7 (7XX- and a 3-digit patient

number, which the Investigator will assign in ascending order of inclusion of the patient in the study.

4.1. Enrolment and Inclusion Procedures

The study is to be conducted in hospitals located in endemic regions and having experience in treating patients with HAT.

In Guinea, the clinical study will be conducted in the HAT treatment centre in Dubreka. The HAT treatment centre in Forecariah and the prefectural hospital in Boffa will be satellite centres whose role will be to screen patients and refer them to the centre in Dubreka. Follow-up visits may take place in the centres in Forecariah and Boffa with the National Investigator and her/his team, who will travel to the centres to ensure better patient follow-up and avoid patients lost to follow-up.

Patients who meet pre-inclusion criteria that do not require any study-specific procedures will be invited to participate in the study, and they will then receive the information necessary to collect their informed consent.

For the patient to be enrolled in the study, s/he must sign the informed consent form after having received explanations from the Investigator or a representative. The patient will then be considered as a “screened patient”.

The enrolment and inclusion procedures are to be performed between 1 and 15 days prior to the planned date of administration of acoziborole. The procedures are described in Section 6, Schedule of Study Procedures and Assessments; p39.

4.2. Inclusion Criteria

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

- Male or female
- 15 years of age or older
- Signed informed consent form (as well as assent from illiterate and under-age patients, and those unable to give consent)
- Karnofsky Performance Status above 50 (see Appendix 2; p83)
- Able to ingest oral tablets
- Having a permanent address or being traceable by other persons
- Able to comply with the schedule of follow-up visits and requirements of the study
- Agreement to be hospitalised in order to receive treatment.

For patients with late-stage HAT:

- Confirmation of g-HAT by detection of the parasite in the blood and/or the lymph and/or the CSF, at the investigational centre
- If trypanosomes are found in the blood or lymph, but not in the CSF, the CSF WBC, measured at the investigational centre, must be above 20/µL for the patient to be included in the cohort of patients with late-stage HAT

For patients with early- or intermediate-stage HAT:

- Confirmation of g-HAT by detection of the parasite in the blood and/or the lymph, at the investigational centre
- Absence of parasites in the CSF
- The CSF WBC, measured at the investigational centre, must be between 6 and 20/µL for the patient to be included in the cohort of patients with intermediate-stage HAT and equal to or below 5/µL for the patient to be included in the cohort of patients with early-stage HAT.

4.3. Exclusion Criteria

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

- Severe malnourishment, defined as body-mass index (BMI) below 16
- Pregnancy or breastfeeding (for women of child-bearing potential, confirmed pregnancy on a urine pregnancy test performed within 24 hours prior to administration of acoziborole – see Section 5.2.3 Contraception; p36)
- Clinically significant medical condition that could, in the opinion of the Investigator, jeopardise the patient's safety or interfere with participation in the study, including, but not limited to significant liver or cardiovascular disease, suspected or proven active infection, central nervous system trauma or seizure disorder, coma or consciousness disturbances
- Severely deteriorated health status, e.g. due to cardiovascular shock, respiratory distress syndrome or end-stage disease
- Previously treated for HAT (except prior treatment with pentamidine)
- Prior enrolment in the study
- Foreseeable difficulty complying with follow-up, including migrant worker, refugee status, itinerant trader etc.
- Current alcohol abuse or drug addiction
- Not tested for malaria and/or not having received appropriate treatment for malaria (see Section 5.2.1 Malaria; p36)

- Not having received appropriate treatment for soil-transmitted helminthiasis (see Section 5.2.2 Helminthiasis; p36)
- Clinically significant abnormal laboratory values including:
  - AST and/or ALT more than 2 times the upper limit of normal (ULN)
  - Total bilirubin more than 1.5 ULN
  - Severe leukopenia at less than 2000/mm^3
  - Potassium below 3.5 mmol/L
  - Any other clinically significant abnormal laboratory value.

5. Study Treatments

5.1. Investigational Product

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.

Acoziborole will be provided by DND*i*, 15 chemin Louis Dunant, 1202 Geneva, Switzerland.

For the course of action in the event of vomiting, see the Investigator Manual.

5.1.1. Treatment Allocation

All patients who give their consent or assent to participate in the study and who fulfil the inclusion and exclusion criteria will be allocated to treatment with acoziborole. In addition, the treatment kits will be numbered, and the number will be recorded in the case report form (CRF).

5.1.2. Labelling and Packaging of IP

The tablets of acoziborole will be packaged in aluminium-aluminium blister packs. Each pack will contain the number of tablets required for one administration, i.e. 3 tablets. The blister pack will be packaged in an individual treatment kit for each patient.

The labelling on the treatment kit will display the following information items:

- Name of Sponsor*, name and contact details for the Coordinating or Principal Investigator
- Study number*
- Name* and dosage strength* of the IP
- Dosage form*, route of administration*, number of dosage units*
- Instructions for use
- Statements “For clinical study use only”* and “Keep out of reach of children”

- Batch number* and number of treatment kit*
- Expiry date and storage conditions

The information items marked with an asterisk (*) will also be displayed on the immediate packaging of the IP.

Information on acoziborole will be provided in the Investigator Brochure attached to the protocol submitted to the National Authorities.

5.1.3. Accountability of IP

Study-specific forms must be used for accountability of acoziborole. Appropriate records concerning receipt, use, return, loss or any other disposition of acoziborole must be maintained by the Investigators at the investigational centre, or by their delegates, under the supervision of the Principal Investigator. In addition, the study monitors must check accountability of acoziborole during their on-site monitoring visits.

In the investigational centres, acoziborole must be stored in a locked room, or a locked cabinet if no specific room is available, with access limited to the nurse in charge of the pharmacy or to authorised study personnel.

The IP, acoziborole, must not be used for purposes other than the present protocol. The Investigator and the study personnel may not under any circumstances provide other investigators or healthcare services with the acoziborole attributed to their centre, or allow acoziborole to be used other than as described in this protocol without prior written approval from DND*i*.

5.1.4. Storage of IP

The IP, acoziborole, must be transported and stored at a temperature not exceeding 30°C. It is recommended to store acoziborole at room temperature. Long-term stability studies showed that the 320-mg tablets of acoziborole, packaged in aluminium-aluminium blister packs, were stable for at least 24 months at 30°C under very humid conditions (75%) and for 6 months at 40°C.

The storage conditions, including the temperature, at the investigational centres must be monitored by the study personnel, and appropriate records must be available.

5.1.5. Blinding and Procedure for Unblinding

This is an open-label study. Thus, the patients and the Investigators will necessarily know which treatment is administered.

5.2. Concomitant Treatment

5.2.1. Malaria

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

Prior to administration of acoziborole, malaria will be treated with Coartem® unless the patient has personal contraindications, such as severe malaria or hypersensitivity to one of the components, i.e. artemether or lumefantrine. All of the existing artemisinin-based combination therapies used against malaria have effects on the QT interval. Coartem® was chosen because its effects on QT-interval prolongation are known to be moderate and well quantified (8).

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

Treatment will be followed by a recovery period of at least 3 days between the last dose of the antimalarial agent and the administration of acoziborole.

5.2.2. Helminthiasis

Treatment for helminthiasis, with mebendazole or albendazole, will be provided free of charge by the Sponsor.

This prophylactic treatment will be given to all patients in the study and will be followed by a recovery period of at least 3 days between the last dose of the anthelminthic agent and the administration of acoziborole.

5.2.3. Contraception

Preclinical studies showed that acoziborole has no effect on fertility or on post-natal development (cf. Investigator Brochure). However, because acoziborole has never been administered to women of child-bearing potential, women, as well as men, of reproductive age will be advised to have protected sexual relations during the observation period and up to the 3-month visit. Contraceptive methods, i.e. hormonal contraception and/or condoms, will be available to patients free of charge throughout the duration of their participation in the study.

5.3. Other Medication

If the patient requires treatment during the first 6 months after administration of acoziborole, the Investigator should be informed and approve the proposed medication. Any medication used after inclusion in the study and/or during the first 6 months of the follow-up period must be recorded in the CRF, specifying the reason for use.

Any medication used to treat an SAE during the follow-up period must be recorded in the CRF (see Section 6.5 Safety Assessments, Definitions and Collection of Adverse Events; p48) and on the SAE reporting form. Any

medication used to treat other non-serious medical events will be recorded only in the patient's medical file.

Any essential medicine required during the 18-month follow-up period will be provided to the patient free of charge. The WHO List of Essential Medicines will be used as a reference guide for the treatment of any concomitant condition (see Investigator Manual). For any chronic condition, the study team will take all necessary measures to ensure that the patient is referred to the most appropriate healthcare facility in the region.

5.4. Rescue Treatment

In the event of a relapse and after discussion with the Principal Investigator, the patient will receive first-line rescue treatment with NECT or pentamidine, depending on the stage of the disease.

Rescue treatment for HAT will be recorded as rescue treatment in the CRF on the end-of-study page.

Probable relapse at the 6-month, 12-month or 18-month follow-up visit is defined as shown in Table 1.

Table 1 - Clinical Classification of Patients

Visit	*Ideal timing of visit after end of treatment*	*Favourable outcome*	*Uncertain outcome*	*Probable relapse*	*Proven relapse*
D11	*± 1 day*	• Patient alive with no evidence of trypanosomes in any body fluid (23)			• Evidence of trypanosomes in any body fluid
3 months	*3 months* *± 1 week*	• Patient alive with no evidence of trypanosomes in any body fluid (no lumbar puncture at 3 months unless Investigator suspects a relapse)	• Any reason prompting the Investigator to request an additional follow-up visit	• Neurological signs or symptoms leading to use of rescue treatment	• Evidence of trypanosomes in any body fluid
6 months	*6 months* *± 2 weeks*	• Patient alive with no evidence of trypanosomes in any body fluid and CSF WBC ≤ 20/µL	• CSF WBC between 20 and 50/µL and additional visit requested within 1-3 months • Any reason prompting the Investigator to request an additional follow-up visit	• CSF WBC ≥ 50/µL • Neurological signs or symptoms leading to use of rescue treatment	• Evidence of trypanosomes in any body fluid
12 months	*12 months* *± 4 weeks*	• Patient alive with no evidence of trypanosomes in any body fluid and CSF WBC ≤ 20/µL • CSF WBC between 20 and 50/µL, and lower as compared to prior value(s)	• CSF WBC > 20/µL and non-significant increase from a clinical standpoint in relation to prior value(s) • Any reason prompting the Investigator to request an additional follow-up visit	• CSF WBC > 20/µL and significant increase from a clinical standpoint in relation to prior value(s) • Neurological signs or symptoms leading to use of rescue treatment	• Evidence of trypanosomes in any body fluid
18 months	*18 months* *± 4 weeks*	• Patient alive with no evidence of trypanosomes in any body fluid and CSF WBC ≤ 20/µL • Patient with no signs of HAT and who refuses to undergo lumbar puncture and who, in the opinion of the Investigator does not require rescue treatment or an additional follow-up visit	• Any reason prompting the Investigator to request an additional follow-up visit	• CSF WBC > 20/µL • Neurological signs or symptoms leading to use of rescue treatment	• Evidence of trypanosomes in any body fluid

Any discrepancy between the clinical features and laboratory findings may also be an uncertain outcome, or any situation that leads the Investigator or the study team to consider that an additional follow-up visit is required to decide whether or not to provide rescue treatment.

6. Schedule of Study Procedures and Assessments

6.1. Timing of Assessments

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 (see Table 2 – Theoretical Schedule of Visits and Acceptable Leeway). The timing of follow-up visits is calculated from D1.

Table 2 - Theoretical Schedule of Visits and Acceptable Leeway

Theoretical schedule of visits	Ideal timing of visits	Acceptable leeway*
End-of-hospitalisation (EoH) visit	Between D13 and D18 after D1	D18 at the latest
3 months	3 months ± 1 week after D1	2-4 months after D1
6 months	6 months ± 2 weeks after D1	5-9 months after D1
12 months	12 months ± 4 weeks after D1	10-16 months after D1
18 months	18 months ± 4 weeks after D1	17-21 months after D1

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

Any additional unscheduled visits that may take place must be recorded in the CRF.

In addition to this study, patients will be invited to participate in a prospective study, DiTECT-HAT-WP4, the aim of which is to assess tests to predict the efficacy of treatment of HAT. If the patient declines the invitation to participate in the DiTECT-HAT-WP4 study, this will have no effect on his/her participation in the study on acoziborole or on the care s/he receives. For patients who accept the invitation to participate in the DiTECT-HAT-WP4 study, and only for these patients, additional blood (+ 2.5 mL) and CSF (+ 2.5 mL) samples will be collected at the same time as samples are collected in the present study, i.e. at

baseline, on D11 and at the follow-up visits at 6 months, 12 months and 18 months, to avoid subjecting the patient to additional invasive procedures.

See also Table 6 - Schedule of Procedures (Appendix 4 p89).

6.2. Pre-screening, Screening and Baseline Assessment

6.2.1. Diagnosis of HAT

- In the context of active screening, the mobiliser of the mobile team will inform the communities in the villages of the HAT screening activities, as is usually the case (see Section 14.1 Information of the Communities; p66). Specific information concerning the study will be provided to the community, i.e. a brief description of the aim of the study, explanation of the process for collecting informed consent, duration and importance of follow-up.
- In the context of passive screening, specific information concerning the study will be provided by static healthcare structures located near the investigational centre in order to refer patients to the investigational centre.
- Diagnosis of HAT and staging of the disease will be performed at the investigational centre. (see Section 4.1. Enrolment and Inclusion Procedures; p32).

6.2.2. Pre-screening and Screening

The following procedures will be carried out to confirm the diagnosis of HAT, to collect historical safety data and to check the inclusion and exclusion criteria.

- Collection of informed consent / assent prior to administering any additional medication or to performing any non-routine assessment;
- Review of inclusion and exclusion criteria;
- Collection of blood and/or lymph samples for testing for parasites (see Sections 4.1 and 4.2 Enrolment and Inclusion Procedures; p32);
- Collection of CSF sample for disease staging. Confirmation of the laboratory and parasitological diagnosis by a second technician at the investigational centre and, if necessary, by the local supervisor must be obtained in accordance with the operating method described in the Laboratory Manual. If possible, images of cell counts and/or videos (approximately 5 seconds) showing the presence of parasites will be used for the traceability of the microscopy diagnosis;
- Collection of full medical history, with special attention to HAT, in particular severity and time since the start of symptoms;
- Collection of demographic and geographical data;

- Karnofsky performance status;
- Height, weight and BMI;
- Vital signs: body temperature, blood pressure, heart rate, respiratory rate and general status;
- Diagnosis of malaria using RDT and/or thick blood smear;
- Treatment of helminthiasis and, if necessary, malaria;
- Laboratory safety assessments – samples will be collected in the morning from patients in the fasting state:
  - Haemoglobin;
  - Haematology: WBC, platelet count;
  - Biochemistry: albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), chloride, creatinine, glucose, potassium, sodium, calcium, total bilirubin, bicarbonates and total protein;
- Urine pregnancy test for women of child-bearing potential;
- Collection of concomitant medication and adverse events.

6.2.3. Baseline Assessment

The baseline assessment will be performed between Day -4 and Day -1 to assess the patient's baseline status just prior to administration of the IP. The patient's eligibility to participate in the study will also be reconfirmed. The following procedures will be performed:

- Review of informed consent/assent;
- Review of Karnofsky performance status;
- Review of inclusion/exclusion criteria;
- Height, weight and BMI;
- Vital signs: body temperature, blood pressure, heart rate, respiratory rate and general status;
- Physical and neurological examinations; questionnaire on symptoms;
- Collection of concomitant medication and adverse events;
- Urine pregnancy test for women of child-bearing potential;
- Thyroid function test: TSH, free T3, free T4;
- Laboratory safety assessments, if the following tests were performed before D-4 during the Pre-screening / Screening period or if the tests found abnormalities requiring repeat tests – sampling will be performed in the morning on patients in the fasting state:

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

If the assessments were performed within 4 days prior to administration of the IP, those findings will be considered as baseline values and recorded in the CRF.

6.3. Assessments during Hospitalisation: D1 to D15

The following procedures will be performed every day throughout the hospitalisation period:

- Collection of concomitant medication;
- Collection of adverse events.

6.3.1. Laboratory Tests

Blood haematology and biochemistry assessments will be repeated on D5 and D11. Blood samples will be analysed in the laboratory in each centre using standard equipment specifically provided for the study by the Sponsor. The samples will be collected in the morning from patients in the fasting state.

The samples for the thyroid function tests will be collected on D11 and will be analysed centrally at the [redacted].

The urine pregnancy test will be repeated on D11.

During hospitalisation, additional safety assessments, such as haematology, biochemistry or urinalysis may be performed at the Investigator's discretion in order to monitor abnormal parameters.

The volume and number of samples required for each patient are presented in Appendix 3 – Laboratory Tests (p84).

6.3.2. Digital ECG

Two ECG tracings will be recorded in duplicate prior to administration of acoziborole on D1. Triplicate ECG will be recorded after administration of acoziborole to assess QT interval, in accordance with the schedule of recordings in Table 3. The tracings will be recorded after a 20-minute rest interval and before collection of the blood samples for the PK analyses.

Table 3 - Schedule of ECG Recordings

Ideal timing of ECG recordings (after 20-minute rest interval and before PK sampling)	Acceptable leeway
D1: before intake of IP	1 hour -1 hour 30
D1: 4 hours after intake of IP	± 1 hour
D1: 9 hours after intake of IP	± 1 hour
D2: 24 hours after intake of IP	± 1 hour
D3: 48 hours after intake of IP	± 1 hour
D4: 72 hours after intake of IP	± 1 hour
D5: 96 hours after intake of IP	± 1 hour
D11: 240 hours after intake of IP	± 1 hour

6.3.3. Pharmacokinetic Analyses

PK analyses will be performed regularly on samples collected from the first 20 patients in order to obtain information on exposure to acoziborole in the blood. Depending on the results, it may be decided not to perform PK analyses on the subsequent patients.

The procedure for sampling and the assay method will be described in the corresponding laboratory manual.

- Whole blood, approximately 300 µL per sample, will be collected and deposited on filter paper using the dry blood spot (DBS) technique in accordance with the following schedule of sample collection:

Table 4 - Schedule of PK Sample Collection

Ideal timing of PK sample collection	Acceptable leeway
D1: before intake of IP	
D1: 4 hours after intake of IP	± 1 hour
D1: 9 hours after intake of IP	± 1 hour
D2: 24 hours after intake of IP	± 1 hour
D3: 48 hours after intake of IP	± 1 hour
D4: 72 hours after intake of IP	± 1 hour
D5: 96 hours after intake of IP	± 1 hour
D11: 240 hours after intake of IP	± 1 hour

- The timepoints for sampling were chosen in order to best predict the concentrations of acoziborole during the absorption and elimination phases.

Lumbar puncture will be performed on Day 11, 240 hours after the intake of acoziborole, and the CSF sample will be used for initial assessment of the treatment effect, based on WBC and screening for trypanosomes, as well as for assays of acoziborole. The samples will be destroyed at the latest once the final

study report has been validated and signed. The destruction procedure will be recorded in a certificate of destruction.

The blood and CSF samples collected on filter paper will be stored at room temperature (see Laboratory Manual).

6.3.4. Assessments on Day 1 - Treatment Day

The following procedures will be performed on Day 1 (see also Table 6 - Schedule of Procedures; p89).

- Collection of concomitant medication;
- Collection of adverse events;
- Two duplicate ECGs and blood sampling for PK analyses prior to administration of acoziborole (cf. Table 3 and Table 4);
- Triplicate ECG and blood sampling for PK analyses after administration of acoziborole (cf. Table 3 and Table 4).

6.3.5. Assessments at the Visit on Day 5

The following procedures will be performed at the visit on Day 5.

- Height, weight and BMI;
- Vital signs: body temperature, blood pressure, heart rate, respiratory rate and general status;
- Physical and neurological examinations;
- Collection of concomitant medication and adverse events;
- Laboratory safety assessments (see Appendix 3 – Laboratory Tests; p84) – samples will be collected in the morning from patients in the fasting state:
  - Haemoglobin
  - Haematology: WBC, platelet count;
  - Biochemistry: albumin, ALP, ALT, AST, BUN, chloride, creatinine, glucose, potassium, sodium, calcium, total bilirubin, bicarbonates and total protein;
- Blood sampling for PK analyses;
- Triplicate digital ECG (CarTouch®) to assess QT interval.

6.3.6. Assessments at the Visit on Day 11

The following procedures will be performed at the visit on Day 11.

- Height, weight and BMI;
- Vital signs: body temperature, blood pressure, heart rate, respiratory rate and general status;

- Physical and neurological examinations;
- Urine pregnancy test for women of child-bearing potential;
- Sampling for testing for trypanosomes in the blood (Woo test/CTC, mAECT, mAECT-BC) and lymph (test on fresh lymph node aspirate, if swollen lymph nodes present, with microscopy examination);
- CSF sampling for WBC and testing for trypanosomes;
- Laboratory safety assessments (see Appendix 3 – Laboratory Tests; p84) – samples will be collected in the morning from patients in the fasting state:
  - Haemoglobin;
  - Haematology: WBC, platelet count;
  - Biochemistry: albumin, ALP, ALT, AST, BUN, chloride, creatinine, glucose, potassium, sodium, calcium, total bilirubin, bicarbonates and total protein;
- Blood sampling for PK analyses;
- CSF sampling for PK analyses (if possible on CSF sample collected to test for trypanosomes);
- Thyroid function test: TSH, free T3, free T4;
- Triplicate digital ECG (CarTouch®) to assess QT interval;
- Collection of concomitant medication and adverse events.

6.3.7. Assessments on Day 15 - End-of-Hospitalisation Visit

The following procedures will be performed at the visit on Day 15:

- Height, weight and BMI;
- Vital signs: body temperature, blood pressure, heart rate, respiratory rate and general status;
- Physical and neurological examinations;
- Collection of concomitant medication and adverse events.

6.4. Assessments at Out-patient Follow-up Visits

6.4.1. At the 3-month Follow-up Visit

The following procedures will be performed at the 3-month visit:

- Karnofsky performance status;
- Height, weight and BMI;
- Vital signs: body temperature, blood pressure, heart rate, respiratory rate and general status;
- Physical and neurological examinations;

- Collection of concomitant medication and adverse events;
- Laboratory safety assessments (see Appendix 3 – Laboratory Tests; p84) – samples will be collected in the morning from patients in the fasting state:
  - Haemoglobin
  - Haematology: WBC, platelet count
  - Biochemistry: albumin, ALP, ALT, AST, BUN, chloride, creatinine, glucose, potassium, sodium, calcium, total bilirubin, bicarbonates and total protein;
- Thyroid function test: TSH, free T3, free T4;
- Urine pregnancy test for women of child-bearing potential;
- Blood sampling for PK analyses.

6.4.2. At the 6-month Follow-up Visit

The following procedures will be performed at the 6-month visit:

- Karnofsky performance status;
- Height, weight and BMI;
- Vital signs: body temperature, blood pressure, heart rate, respiratory rate and general status;
- Sampling for testing for trypanosomes in the blood (Woo test/CTC, mAECT, mAECT-BC) and lymph (test on fresh lymph node aspirate, if swollen lymph nodes present, with microscopy examination);
- CSF sampling for WBC and testing for trypanosomes;
- Physical and neurological examinations;
- Collection of concomitant medication and adverse events;
- Laboratory safety assessments (see Appendix 3 – Laboratory Tests; p84) – samples will be collected in the morning from patients in the fasting state:
  - Haemoglobin
  - Haematology: WBC, platelet count
  - Biochemistry: albumin, ALP, ALT, AST, BUN, chloride, creatinine, glucose, potassium, sodium, calcium, total bilirubin, bicarbonates and total protein;
- Thyroid function test: TSH, free T3, free T4;
- Urine pregnancy test for women of child-bearing potential;
- Blood sampling for PK analyses.

6.4.3. At the 12-month and 18-month Follow-up Visits

The following procedures will be performed at the 12-month and 18-month visits:

- Karnofsky performance status;
- Height, weight and BMI;
- Vital signs: body temperature, blood pressure, heart rate, respiratory rate and general status;
- Sampling for testing for trypanosomes in the blood (Woo test/CTC, mAECT, mAECT-BC) and lymph (test on fresh lymph node aspirate, if swollen lymph nodes present, with microscopy examination);
- CSF sampling for WBC and testing for trypanosomes;
- Physical and neurological examinations;
- Collection of serious adverse events;
- Laboratory safety assessments (see Appendix 3 – Laboratory Tests; p84) – samples will be collected in the morning from patients in the fasting state:
  - Haemoglobin
  - Haematology: WBC, platelet count
  - Biochemistry: albumin, ALP, ALT, AST, BUN, chloride, creatinine, glucose, potassium, sodium, calcium, total bilirubin, bicarbonates and total protein;
- Thyroid function test: TSH, free T3, free T4.

6.4.4. At Unscheduled Visits

If a relapse of HAT is suspected on the basis of physical examination findings or CSF WBC at any visit, the patient must attend a return visit within 1 to 3 months, at the discretion of the Investigator.

The patient must also return to the investigational centre if s/he does not feel well, even if there is no apparent relationship with treatment or HAT.

The following assessments will be performed:

- Karnofsky performance status;
- Height, weight and BMI;
- Vital signs: body temperature, blood pressure, heart rate, respiratory rate and general status;
- Physical and neurological examinations (including signs and symptoms of HAT since the previous visit);
- Investigation of any concomitant condition that may have led to the visit;
- Testing for *T.b. gambiense* in blood and lymph, if indicated;
- CSF sampling, only if symptoms suggesting relapse are present;
- Laboratory safety assessments at the discretion of the Investigator (see Appendix 3 – Laboratory Tests; p84) – if possible, samples will be collected in the morning from patients in the fasting state:

- Haemoglobin
- Haematology: WBC, platelet count
- Biochemistry: albumin, ALP, ALT, AST, BUN, chloride, creatinine, glucose, potassium, sodium, calcium, total bilirubin, bicarbonates and total protein;

- Thyroid function test, if indicated: TSH, free T3, free T4;
- Additional safety assessments, e.g. ECG or urine analysis, may be performed at the discretion of the Investigator;
- Urine pregnancy test for women of child-bearing potential, at the discretion of the Investigator;
- Collection of concomitant medication and adverse events.

6.5. Safety Assessment, Definitions and Reporting of Adverse Events

6.5.1. Definition of Adverse Event

In accordance with current regulations (7), an AE is defined as any untoward medical occurrence in a patient or clinical trial subject and which does not necessarily have a causal relationship with the trial or the IP.

An AE can therefore be any unfavourable and unintended sign (including a clinically significant abnormal ECG or laboratory test finding with accompanying clinical signs or symptoms, or aggravation of any pre-existing condition), symptom or disease temporally associated with the use of the IP, whether or not it is considered to be related to the IP.

Any abnormality on a laboratory test, i.e. haematology or biochemistry, that is assessed as “clinically significant” must be reported as an AE if it appears or worsens after administration of the IP and if it is above CTCAE grade 1, unless it is associated with a previously reported clinical event.

Laboratory abnormalities assessed as “clinically significant” must be reported as an AE if they correspond to any of the following situations:

- The abnormality suggests a disease and/or organ toxicity ***and*** the abnormality was not present at the baseline assessment or is considered to have worsened since the baseline assessment;
- The abnormality is considered to be an SAE (see Section 6.5.2 Definition of Serious Adverse Event; p49);
- The abnormality leads to discontinuation of the IP;
- The abnormality requires a medical procedure or treatment.

When a laboratory abnormality is reported, whenever possible, a clinical diagnosis should be reported rather than simply an abnormal value, e.g. “anaemia” instead of “reduced red blood cell count”.

The Investigator or appropriate personnel at the investigational centre must examine any patient who experiences an AE as soon as possible. The Investigator will take whatever medical measures are necessary to ensure the patient's safety and well-being. The patient will remain under observation up to the final day of the hospitalisation period (Day 15), or longer if medically indicated in the opinion of the Investigator. All AEs observed or reported after administration of the IP must be followed until they resolve or until the Investigator considers them to be "chronic" or "stable", or until the end of the patient's participation in the study, i.e. until the End-of-Study page in the CRF for the patient has been completed.

All AEs must be recorded in the appropriate section of the CRF using concise medical terminology and avoiding vague, ambiguous or colloquial language. SAEs must be reported to the study monitor by telephone, short message service (SMS) or e-mail (see Section 6.5.5 Requirements for AE Reporting; p50).

6.5.2. Definition of Serious Adverse Event

An SAE is any event that:

- results in death;
- is life-threatening;
- requires hospitalisation or prolongation of existing hospitalisation:
  - i.e. the AE requires admission for at least 24 hours or prolongs hospitalisation beyond the expected length of stay. Hospital admissions for surgery planned before study entry, for social reasons, for any elective surgery (e.g. plastic surgery) or for normal disease management (including treatment adjustment) will not to be considered as SAEs;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- is an important medical event in which the patient is not at risk of death or which does not directly result in death or hospitalisation, but which may jeopardise patient safety or may require an intervention to prevent one of the above-mentioned outcomes;
- In this study, ALT or AST above 3 ULN accompanied by total bilirubin above 2 ULN will be considered as an SAE;
- Any suspected transmission of an infectious agent via a medicinal product will also be considered as an SAE.

Any other event defined as serious in this protocol or by the Regulatory Authorities in the countries where the study is being conducted will also be considered as an SAE.

For the purposes of this study, hospitalisation for uncomplicated delivery will not be considered as an SAE.

Use of the Glasgow coma scale (Appendix 5 - Glasgow Coma Scale

The scale was developed at the Institute of Neurological Sciences in Glasgow, Scotland in the early 1970s to assess the extent of a coma following a head injury and to monitor the course of the coma. It is now widely recognised by the international community.

The patient's level of consciousness is assessed based on three criteria: eye opening (E score), motor response (M score) and verbal response (V score).

Eye Response (E)	**Motor Response (M)**	**Verbal Response (V)**
Opens eyes spontaneously: 4	Obeys verbal commands: 6	Orientated and clear: 4
Opens eyes in response to speech: 3	Localises painful stimuli: 5	Confused: 3
Opens eyes in response to painful stimuli: 2	Withdraws from painful stimuli: 4	Inappropriate: 3
No response: 1	Abnormal flexion to painful stimuli: 3	Incomprehensible: 2
	Extension to painful stimuli: 2	No response: 1
	No response: 1	

The Glasgow score is obtained by adding the three scores.

By definition:
- if the **Glasgow score is > 12**, the patient is considered to have **mild head injury**;
- if the score is **between 9 and 12 inclusive**, the patient is considered to have **moderate head injury**;

- if the **Glasgow score is ≤ 8**, the patient is considered to have **severe head injury**.) is recommended in patients with coma.

6.5.3. Collection of Information on AEs

The Investigator must collect all AEs s/he observes directly, as well as all AEs spontaneously reported by the patient, using concise medical terminology. In addition, during the hospitalisation period (Day 1 to Day 15) and at subsequent follow-up visits, a physical examination will be performed to detect any potential AEs.

6.5.4. AE Collection Period

The periods for the collection of AEs that occur in the context of the study are defined as follows:

- For **any AE** that is not considered to be an SAE: from the time of

administration of the IP on Day 1 until the 6-month follow-up visit;

- For **any SAE**: from the time of enrolment of the patient in the study (after signature of informed consent form) and **until the end of follow-up** (18 months). SAEs will be followed and analysed up to 18 months.

AEs considered to be possibly related to study participation that occur during the screening period, i.e. after signature of the informed consent form and before administration of the IP, will also be collected by the medical personnel and recorded in the CRF.

6.5.5. Requirements for AE Reporting

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

All SAEs must be reported immediately, and no later than 24 hours after the Investigator becomes aware of the SAE, to the clinical study monitor, first by telephone and/or SMS, then by e-mail using the SAE reporting form. This report should include a description of the event, onset date and type, duration, severity, relationship to IP (assessed with the assistance of the Coordinating Investigator, as needed), measures taken and outcome, as well as any other relevant clinical or laboratory data. Any additional information, including responses to data queries concerning SAEs, must be sent on an SAE follow-up form as it becomes available. Follow-up reports should be submitted as soon as possible, and, if possible, within 5 working days after the new information becomes available. A close-out follow-up report must be sent after the final assessment of the case, specifying the outcome of the SAE as “recovery”, “recovery with sequelae”, “death” etc.

SAEs must be reported using the AE reporting form in the CRF and the SAE reporting form. It should be noted that the SAE reporting form is not the same as the form in the AE section of the CRF. The two forms must be completed in a consistent manner, using the same medical terminology.

All AEs must be recorded in the CRF.

For the purposes of this study, the Coordinating Investigator will be responsible for reporting serious unexpected adverse events to the ethics committees in the countries where the study is being conducted and to the other appropriate governing bodies. DNDi will be responsible for reporting serious unexpected adverse events to the Regulatory Authorities in accordance with current regulations.

6.5.6. Grading of AE Severity

The severity of the AE will be graded according to NCI CTCAE, version 4.03 (16). If the AE is not described in the CTCAE, version 4.03, the Investigator will use the terms “mild”, “moderate” or “severe” to describe the maximum severity, as defined below:

Mild	The patient is aware of the event or symptom, which is easily tolerated; the event does not lead to any reduction in the patient’s usual activities (easily tolerated).
Moderate	The patient feels discomfort such that it reduces or interferes with the patient’s usual activities.
Severe	Significant functional impairment: the patient is unable to carry out usual activities and/or the event is life threatening.

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

It is important to distinguish between the severity and the seriousness of an AE: a severe AE is not necessarily a serious AE, since the criteria for seriousness (see Section 6.5.2 Definition of Serious Adverse Event; p49) are different from the criteria for severity.

6.5.7. Assessment of AE Causality

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

The causal relationship between the IP and the AE is assessed by the Investigator after a detailed analysis of the event in terms of the biological plausibility, taking into account possible unrelated causes, pre-existing medical conditions, concomitant medication, the temporal relationship between intake of the IP and onset or worsening of the AE, and the known patterns of response to acoziborole in general.

The two types of causal relationships are defined as follows:

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

6.5.8. Exposure *in utero*

At least five pregnancy tests are planned during the study: at the screening visit, at the baseline assessment (between Day -4 and Day -1), on Day 11 and at the

out-patient follow-up visits up to 6 months. Among women of child-bearing potential, only those who have a negative result on the pregnancy test at the baseline assessment will be eligible to participate in the study.

Pregnancy is not considered to be an AE.

The Investigator must report any pregnancy using the appropriate pregnancy reporting form (see Investigator Manual). The pregnancy must be reported whether or not an AE occurred. If known, the due date should be specified.

The Investigator must monitor the patient until the full term of the pregnancy or preterm in the event of a miscarriage. The Investigator must provide information on the outcome of the pregnancy using the pregnancy follow-up reporting form.

A physician, preferably a paediatrician, should examine the newborn at birth and submit a report using a Newborn Follow-up form. The Investigator will offer the parents follow-up on infants exposed to the IP *in utero* until they reach 24 months of age. As far as possible, stillborn infants should be examined by a physician to ascertain the cause of death.

Any SAE that occurs in a pregnant patient (exposed to the IP or who is found to be pregnant any time up to the 6-month visit) and that concerns the pregnancy or the foetus, will be reported using the SAE reporting form in the same manner as any other SAE. Any non-serious AE concerning a pregnant patient will be collected using the AE form in the CRF.

6.5.9. Follow-up on AEs

All AEs and SAEs must be followed until they resolve completely or until the Investigator considers them to be “chronic” or “stable”, or until the end of the patient’s participation in the study, i.e. until the End-of-Study page in the CRF for the patient has been completed.

In addition, all SAEs that the Investigator considers as having a reasonable causal relationship with the IP must be followed even after the end of the patient’s participation in the study. These events must be followed until they resolve completely or until the Investigator considers them to be “chronic” or “stable”. The outcome of the events must be recorded in the CRF up to the end of the patient’s participation in the study and, in addition, for SAEs, using the SAE reporting form.

7. Study Duration

The duration of the enrolment period is estimated to be approximately 28 months.

Each patient’s participation in the study will last approximately 18 months and will include:

- pre-treatment period (pre-screening and screening, treatment of concurrent diseases) up to 15 days;
- a treatment period of 1 day;

- an observation period in hospital of a total of 15 days, including the treatment day (Day 1);
- an out-patient follow-up period of 18 months with visits at 3, 6, 12 and 18 months.

The total duration of the study is estimated to be 46 months.

8. Withdrawal Criteria

8.1. Patient Withdrawal from the Study and Replacement of Patients

A patient may be withdrawn from the study in the following cases:

- withdrawal of consent by the patient or his/her legal representative;
- study termination by the Sponsor.

If the patient withdraws his/her consent, no further study assessments will be performed and no further data will be collected, with the exception of safety data and data on the patient's clinical status, which must be collected whenever possible.

If a patient decides to withdraw from the study, the reason must be recorded in the CRF. If a patient is withdrawn from the study due to an AE, all necessary measures must be taken to clearly document the outcome of the AE.

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

Patients withdrawn from the study will not be replaced.

If a patient is lost to follow-up for reasons related to armed conflict or natural disaster, after several unsuccessful attempts have been made to contact him/her, and if no data are available after the treatment period, the patient will be removed from the primary analysis and another patient will be added in order to maintain the planned sample size, provided that the enrolment period is still on-going.

8.2. Patients Lost to Follow-up

In order to ensure adequate follow-up on patients, a schedule of patient follow-up will be made available to the Investigator. If a patient does not attend a protocol-planned visit, all possible measures must be taken to contact him/her. In all cases, the Investigator must take all possible measures to document the course of the patient's condition.

9. Data Analysis and Statistical Methods

An initial draft of the Statistical Analysis Plan (SAP) will be prepared and approved prior to database lock. It will provide a more detailed description of the statistical methods. The SAP will be reviewed and, if necessary, amended prior

to final database lock. The different approved versions will be dated and numbered.

9.1. Sample Size Determination

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%) for an 89% success rate. 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 of the order of 17%.

9.2. Definition of Study Populations included in the Analyses

Populations Used in the Analyses

The population of late-stage patients will be separated from the population of early- and intermediate-stage patients.

The primary analysis will be performed on late-stage patients in the modified intention-to-treat (mITT) population and who received at least one tablet of acoziborole. Patients lost to follow-up who fled the region due to armed conflict or natural disaster will not be included in the mITT population and will be replaced by other patients.

The analysis of the primary endpoint for early- and intermediate-stage patients, which is considered to be a secondary analysis, will also be performed on the mITT population.

The sensitivity analyses will also be performed by cohort, separating late-stage patients from early- and intermediate-stage patients (see Table 5 - Populations Used in the Analyses).

Table 5 - Populations Used in the Analyses

Type	Aim	Definition
Primary: modified intent-to-treat (mITT) patients	Primary analysis	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 post-treatment data are available. These patients will be included in the population as failures for an "all-patient" sensitivity analysis.
All patients	Safety analyses and sensitivity analyses on efficacy	All patients who received at least one tablet of acoziborole. There will be no exceptions to this rule.
Secondary: evaluable patients	Sensitivity analyses on efficacy	Patients in the mITT population for whom at least one lumbar puncture is available (at 6, 12 or 18 months), and excluding patients who died for reasons clearly unrelated to efficacy or safety, or who fled the region due to armed conflict or natural disaster.
Secondary: per-protocol patients	Sensitivity analyses on efficacy	Patients in the mITT population with no major protocol violations. Major violations will be described by patient, and exclusion will be decided during the data review.

9.3. Patient Disposition

At the end of the study, patient disposition will be presented using the following categories:

- Number of patients included, by cohort;
- Number of patients included by cohort who received at least one tablet of acoziborole;
- Number of patients included by cohort and who received at least one tablet of acoziborole, except those who died for reasons clearly unrelated to the IP (evaluable patients);
- Number of patients included by cohort who had no major protocol violations (*per-protocol* patients);
- Number of patients by cohort who received at least one tablet of acoziborole and who attended the end-of-hospitalisation visit. The same count for patients who attended the 6-month visit, the 12-month visit, the 18-month visit and beyond the window of the 18-month visit;
- Number of patients by cohort who received at least one tablet of acoziborole and who underwent lumbar puncture at the end-of-hospitalisation visit, at the 3-month visit, the 6-month visit, the 12-month visit, the 18-month visit and beyond the window of the 18-month visit;
- Number of patients by cohort who received at least one tablet of acoziborole and who withdrew from the study prematurely, listed by reason for withdrawal;

- Number of patients by cohort who received at least one tablet of acoziborole and who had at least one minor protocol violation;
- Number of patients by cohort who received at least one tablet of acoziborole and who had at least one major protocol violation.

9.4. Demographic and Baseline Data

Summary descriptive statistics (N, mean, standard deviation, median, minimum, maximum) or frequencies and percentages will be presented for the following baseline characteristics for each of the study cohorts:

- Demographic data
- Medical history
- Physical examination
- Vital signs
- Urine pregnancy test (for women of child-bearing potential)
- Laboratory assessments
- Karnofsky performance status
- Neurological examination
- Concomitant medication

A summary table of baseline characteristics of patients in each study involving NECT will be provided.

9.5. Treatment Compliance

Administration of acoziborole will be recorded in the CRF.

9.6. Efficacy Analyses

9.6.1. Primary Efficacy Analysis

Primary Efficacy Analysis: Success Rate at 18 Months in Late-stage Patients

The primary analysis is based on the mITT set and will consist in an estimate of the success rate at 18 months of follow-up.

The 95% Jeffreys confidence interval of the estimate will be provided. The Jeffreys confidence interval has a coverage probability that does not exceed 95% to any large extent and is equal tailed, i.e. the probability 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.

Analysis of Surrogate Primary Endpoint for Late-stage Patients

Amendment 2 dated 07/01/2020 deletes this analysis, as the data set required for early submission at 12 months is not available in its entirety.

Success Rate for the Yardstick

The current standard of care for late-stage 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. (18) involving 143 patients exposed to NECT; the WHO-TDR study (13) involving 55 patients exposed to NECT; and the DNDiHATFEX004 study involving approximately 130 patients exposed to NECT. Data from the NECT-Field 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 months (20). All of the results will be represented together in graphic format using a Forest plot.

The method described in Section 2.2.1 Primary Endpoint - Efficacy concerning analysis of the primary endpoint will not be used directly on the historical data as no raw data are available. However, all deaths, regardless of the cause, will be considered as failures. For estimates in the literature, the classification method described in the publications will be applied to the data on acoziborole to ensure that successes are the same in nature. Differences in the definitions will be explicitly identified. In all cases, the mITT set of patients will be used. In all cases, the Jeffreys confidence interval will be used.

9.6.2. Futility Analyses

An independent DSMB (see Section 10 Data and Safety Monitoring Board; p61) will be appointed, among other things, to supervise and review the futility and PK analyses, as well as the safety data. The DSMB will make recommendations on study continuation based on all available information.

The first futility analysis will be performed once the first 20 late-stage patients reach the 3-month visit. If the failure rate at Day 11 is significantly higher than the failure rate for melarsoprol, (19) 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), then the DSMB should recommend stopping the study, unless the rate can be explained by exceptional circumstances.

The second futility analysis will be performed once 70 late-stage 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).

The last futility analysis will be performed once 70 late-stage 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. $\geq$ 22 out of 70 patients (p = 0.016, one-sided), the DSMB should recommend stopping the study.

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 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 with the historical data, taking into account the obvious advantage of having a single oral dose for patients living in remote areas.

9.6.3. Secondary Analyses

Efficacy Analysis at 12 Months in Late-stage Patients

The estimated success rate at 12 months in late-stage patients is a secondary analysis. The 95% Jeffreys confidence interval for the estimated rate will be provided.

Efficacy Analysis in Early- and Intermediate-stage Patients

The efficacy analysis for early- and intermediate-stage patients is a secondary analysis, similar to the primary analysis for late-stage patients, and concerns the success rate at 12 months and at 18 months in early- and intermediate-stage patients. The 95% Jeffreys confidence interval for the estimated rates will be provided.

Other Secondary Analyses

- The correlation between acoziborole concentrations in the blood and CSF and the success rate in late-stage patients will be determined using logistic regression with success or failure as the response (dependent variable) and two covariables (explanatory variables): blood and CSF concentrations.
- The correlation between acoziborole concentrations in the blood and CSF and the occurrence of AEs in late-stage patients will be determined using logistic regression with the occurrence of AEs during hospitalisation as the response (dependent variable) and two covariables (explanatory variables): blood and CSF concentrations.
- Changes in the rate of favourable outcomes over time for late-stage patients on the one hand, and for early- and intermediate-stage patients on the other hand, will be studied using the mixed model for repeated measures (Glimmix).
- Time to proven relapse will be analysed in each cohort using the Kaplan-Meier approach in order to estimate, at each follow-up visit, the cumulative rate of proven failures. Patients lost to follow-up will be censored at the last available visit, unless the outcome at that visit was failure.

9.7. Safety Analyses

All patients who received at least one tablet of acoziborole will be included in the safety analyses.

The percentage of patients who experienced an SAE will be described by system-organ class using MedDRA terms and/or according to NCI CTCAE, version 4.03 (16).

The percentage of patients who experienced at least one AE will be described. 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. In addition, each SAE will be described in a narrative presenting all aspects of the medical event and the causality assessment.

The incidence of AEs and of SAEs and their respective 95% confidence intervals will be presented by category and by frequency. In other cases, only descriptive statistics will be presented.

Laboratory safety parameters, i.e. haematology and biochemistry, will also be described individually, indicating the percentages of patients, the size of the increase in relation to the ULN and to baseline values, as well as changes in blood levels over time. Shift tables will be provided. A listing of patients with increases in laboratory parameters will be provided.

Abnormalities on ECG tracings will be described for each timepoint.

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

The primary endpoint is the outcome at 18 months. If outcome assessed at the final visit is missing, the **primary imputation method** will consist in imputing a probable success (considered as a success) to patients who attended the 18-month visit, but who refused the lumbar puncture planned at the visit, who showed no signs or symptoms of HAT at 18 months, who did not subsequently report any symptoms of relapse and for whom the outcome was considered as favourable at the last available assessment (17). If these criteria are not fulfilled, the patients will be considered as treatment failures. The outcome for patients who did not attend the 18-month visit or later will also be considered as a failure, except for patients who fled the region due to armed conflict or natural disaster.

Because the historical data may not allow for other imputation methods to be applied, only the primary imputation method will be used. The method will be described in detail in the SAP. Sensitivity analyses will be performed to assess the impact of missing data on acoziborole. The method will be described in detail in the SAP.

9.9. Handling of Centres

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

9.10. Analyses of Other Endpoints

Pharmacokinetic Analyses

- Concentrations of acoziborole in whole blood and CSF, and PK parameters derived from a population PK model.
- All PK samples will be analysed centrally. A population PK model will be developed using Nonmem software.
- The model will be used to estimate the population PK parameters. All of the analyses and the statistical methods, including the conventions relating to data handling, will be described in detail in a separate SAP, which will be finalised prior to database lock.
- The correlations between the concentrations in the blood and in the CSF will be described based on the samples collected at the end-of-treatment visit. The correlations between, on the one hand, the blood and CSF concentrations and, on the other hand, the success rate and rate of AEs will be described.

Based on analysis of the PK data from the study, it will be possible to confirm the data from the Phase-I study on a larger sample size, to analyse individual intolerance or treatment failures and to predict the dose for a future study on HAT in children.

10. Data and Safety Monitoring Board

A DSMB, composed of at least 3 members independent of the Investigators and the Sponsor, will be set up prior to the start of the study. The DSMB will monitor the study in order to minimise any risk of harm to the patients included in the study. At each of its meetings, the DSMB will examine safety data 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.

11. Quality Assurance and Quality Control Procedures

11.1. Investigator Site File

The Investigator must maintain appropriate accurate records to ensure that all aspects of study conduct are fully documented, and that study data can be verified at the end of the study. These documents include the Investigator Site File, the patients' clinical source documents, screening/enrolment logs and other study-specific forms.

The Investigator Site File must contain the protocol and protocol amendments, Independent Ethics Committee (IEC) and regulatory approval with all correspondence, a copy of the patient information and informed consent form, the Investigator Brochure, drug accountability records and curriculum vitae for study personnel, as well as authorisation forms and any other relevant documents or correspondence.

11.2. Case Report Forms

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

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

data and, for verbatims, single entry with review by another data entry operator) in the database. The CRF will be signed by the Investigator at each visit.

11.3. Source Documents

The data in the CRF must be verified by direct inspection of the source documents. The source documents are the patients' medical files, the physicians' and nursing staff's notes, appointment books, originals of laboratory test results, ECG tracings, reports on specific assessments, signed informed consent forms, recorded images of microscopic examinations, data clarification forms and patient screening/enrolment logs.

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

The Investigator must keep the source documents up to date, i.e. reports on laboratory tests and consultations, records of medical history and physical examination reports, so that they can be examined and/or audited by designated personnel and/or by the Regulatory Authorities, as required.

11.4. Retention of Documents

The Investigator must retain all essential documents for at least 2 years after approval of the last marketing authorisation is obtained, and until there are no on-going or planned applications for marketing authorisation, or until at least 25 years after the end of the study. However, study documents may need to be retained for a longer period of time if required by local regulations in effect or by agreement with DND*i*. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained. After that date, the documents may be destroyed with prior permission from DND*i*, subject to local regulations.

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

11.5. Monitoring

Clinical monitors will perform regular monitoring visits, in accordance with the monitoring plan, during which they will verify source data, informed consent forms, medical records, laboratory test results, imaging reports if present, CRFs, drug dispensing logs and protocol violations. The monitors will be given access to the corresponding source documents for each patient on condition that patient confidentiality is maintained in accordance with local regulations. Monitoring will be more intensive for the first patients included in the study.

Monitoring visits at the investigational sites will be performed periodically by *DNDi* representatives or designated clinical monitors to ensure compliance with Good Clinical Practice and all aspects of the protocol. Source documents will be

reviewed for verification of consistency with the data in the CRFs (and any additional data provided on Data Clarification Forms concerning SAEs). The clinical monitor will be responsible for inspecting the CRFs at regular intervals. The Investigator will ensure that DND*i* designated representatives have direct access to source documents. It is important that the Investigators and the personnel concerned are available during monitoring visits. The Investigator agrees to cooperate with the clinical monitor to ensure that any problems detected during monitoring visits are resolved.

The monitoring visits provide DND*i* with the opportunity to assess progress of the study, to verify the accuracy and completeness of the CRFs and to resolve any inconsistencies in the study records, as well as to ensure compliance with all protocol requirements, applicable regulations and Investigator obligations.

Four types of visits are planned: a centre evaluation visit in centres where the Sponsor has no prior experience, an initiation visit, monitoring visits and a close-out visit.

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

11.6. Audits and Inspections

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

The purpose of the audits and/or inspections is to verify protocol adherence and to ensure that the study is being conducted in accordance with Good Clinical Practice. It is important that the Investigators and the personnel concerned are available for any audits or inspections.

11.7. Data Management

A CRF must be completed for each patient who gives informed consent to participate in the study. A paper CRF will be used in the study. The study data will be stored in a computer database that ensures confidentiality of the data, in accordance with national legislation on data protection.

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

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

11.8. Confidentiality of Information, Study Documents and Patients' Files

The Investigator must ensure that the anonymity of patients is maintained and that their identity is protected from unauthorised third parties. Patients must not be identified by their names in the CRF or on any other documents or imaging submitted to the Sponsor. Only the patient number should appear. The Investigator must keep a patient enrolment log containing the number, name and address of patients. The Investigator must ensure the confidentiality of all documents submitted to the Sponsor's authorised representatives, including the signed informed consent form.

The findings of any assessments, including laboratory tests, will remain strictly confidential to the patient him/herself. This includes patients under legal age and vulnerable patients. Particular attention will be paid to the confidentiality of the results of pregnancy tests and tests related to concomitant diseases.

12. Protocol Amendments

The Investigators will ensure that the study is conducted in strict compliance with the protocol, and that all data are collected and recorded in the CRF.

All protocol modifications must be documented in writing. A protocol amendment can be initiated by the Sponsor, by the DSMB or by any Investigator. The Investigator will provide the reasons for the proposed amendment in writing and will discuss it with the Sponsor and the Principal Investigator.

Any protocol amendment must be approved and signed by the Sponsor and the Principal Investigator, and must be submitted to the appropriate IEC for information and approval in accordance with local requirements, and to regulatory agencies, if required. A favourable opinion must be received from the IEC, and the regulatory authorities, if applicable, before any changes can be implemented, with the exception of changes required to avert an immediate danger for study participants, or when the change involves only logistical or administrative aspects of the study, e.g. changes in telephone numbers.

13. Early Termination of the Study

Both the Sponsor and the Principal Investigator will have the right to terminate the study early, i.e. at any time prior to inclusion of the planned number of patients, however they may exercise this right only for valid scientific or administrative reasons. If necessary, after consultation, the two parties will define the procedures for terminating the study. The Sponsor and the Principal Investigator will ensure that early termination of the study takes place in such a way as to protect the patients' interests.

Reasons for which the Sponsor may terminate the study include, but are not limited to:

- Insufficient enrolment rate;
- Protocol violations;
- Inaccurate or incomplete data;
- Dangerous or unethical practices;
- Recommendation from the DSMB or IEC.

Reasons for which the Investigator may terminate the study include, but are not limited to:

- Insufficient time or resources to conduct the study;
- Lack of eligible patients.

If the study is terminated early by the Sponsor or the Investigator, the latter must:

- Complete all CRFs to the fullest extent possible;
- Return all study-related articles and equipment to the Sponsor who provided them;
- Answer all queries from the Sponsor, or delegated representatives, related to data on patients enrolled by the centre prior to study termination;
- Ensure that patients enrolled in the study who have not yet attended any follow-up visits receive all necessary medical care;
- Provide the IEC, the regulatory authorities and, if appropriate, the Sponsor with a written explanation of the decision to terminate the study.

14. Ethical Considerations

The protocol for this study was prepared in accordance with the general ethical principles set out in the Declaration of Helsinki of the World Medical Association (see Appendix 1 – Declaration of Helsinki; p77) and ICH guidelines for Good Clinical Practice (ICH Harmonised Tripartite Guideline - Guideline For Good Clinical Practice E6(R1) - current Step 4 version, dated 10 June 1996). DNDi commits to respect all applicable laws for the protection of the rights and welfare of human subjects.

The study was submitted to the Ethics Committee for Health Research in Central Africa (CERSAC), an independent institution common to several central African countries including Cameroon, the Republic of the Congo, Gabon, Equatorial Guinea, the Central African Republic and Chad. It is based in Yaoundé, Cameroon, at the Organisation for Coordination in the Fight against Endemic Diseases in Central Africa.

The CERSAC is mandated to ensure that, prior to implementation and throughout their conduct, research projects involving human subjects comply with ethical principles. The projects involve research scientists, students and members of research organisations based in central African countries. A single, multinational

ethics committee provides adequate and appropriate ethical evaluation to ensure that clinical research conducted in the region reflects the values of African communities. [redacted].

The minutes of the meeting, as well as the responses from the Sponsor, are presented in appendix to the dossier for submission of the protocol to the various national ethics committees.

The protocol was submitted by the Principal Investigator for official approval from the Ethics Committee of the Ministry of Health of the DRC and in Guinea.

Specific approval must be obtained from each country before any study-specific procedures are performed on any patient in the countries concerned.

Any changes made to the protocol after it has been approved by the IEC must be submitted in writing to the IEC by the Principal Investigator in accordance with local procedures and regulatory requirements in effect (see Section 12 Protocol Amendments; p64).

The protocol must be submitted along with the appendices related to the information and safety of patients, including the Patient Information Sheet, the Informed Consent/Assent Form and the Investigator Brochure.

14.1. Information of Communities

14.1.1. In the Democratic Republic of the Congo

The study will be conducted in collaboration with the National Programme for the Control of Human African Trypanosomiasis (PNLTHA). The programme is responsible for all prevention and treatment activities regarding HAT within the country, and in particular for the supervision and coordination of the mobile teams in charge of HAT screening activities. PNLTHA is fully involved in the design and implementation of the study on acoziborole.

Information of the communities participating in the study will be provided at three different levels.

Firstly, the study will be presented to the public health representatives of the provinces concerned, i.e. the Provincial Medical Inspectors (*Médecins Inspecteurs Provinciaux*) and District Medical Officers (*Médecins Chefs de Zones*), as well as the District Administrators prior to any study-related activity in their respective geographic area of responsibility. Information on the study will be provided by the Provincial Coordinators of the PNLTHA (*Médecins Coordinateurs*), if possible in conjunction with a DNDi representative. The information will be based on the study protocol summary, the patient information sheet and consent form, and a summary of the Investigator Brochure.

Secondly, and before starting screening activities for the study in a given area or health zone, an adequate, HAT-experienced person with good knowledge of the area and local culture and good communication skills, i.e. either a member of a mobile team or a community mobiliser, will visit the local authorities, and tribal or village chiefs a few days before arrival of the mobile team, and inform them about the study on acoziborole and the related activities. In agreement with the local chiefs, an additional information session for the local population should be held, possibly during the usual community information session, which routinely takes place just before the start of screening activities by mobile teams. HAT is endemic in the regions where the study is to be conducted, and therefore, individuals already have a basic knowledge of the disease. In addition, most of the community mobilisers and many mobile team members have received specific training in community communication and HAT and will also receive additional study-specific training. Their experience and knowledge will therefore be highly useful in promoting a good understanding of the study.

The following information on the study will be disseminated at the community level:

- Routine procedures for detection and diagnosis of HAT;
- Primary objective of the study, i.e. to develop a safe oral drug to treat HAT that will be made available to the local population;
- Information on the new drug, the availability of a rescue treatment and on concomitant treatments as needed;
- Information on the duration of hospitalisation, number of follow-up visits up to 18 months as compared to routine treatment, importance of attending follow-up visits and possibility of visits by study staff at village level if the patient does not attend the follow-up visits at the centre;
- Information on provision of food to all HAT patients, regardless of whether they are included in the study;
- Information on organisation of transportation and/or reimbursement of transportation costs for patients included in the study;
- Importance of the freedom of each individual to accept or to refuse to take part in the study, after full explanation of the study. Availability of treatment in either case;
- Need for minors and patients with impaired cognitive capacities to come to the centre accompanied by a legal representative/guardian.

The third level of information concerns the individual consent of each patient (see Section 14.2. Informed Consent Process; p69).

At the end of the study, the community will receive information on the results using the same means of communication, i.e. community mobilisers.

14.1.2. In Guinea

The study will be conducted in collaboration with the National HAT Control Programme (PNLTHA) in Guinea. The programme brings together all of the activities for prevention and treatment of HAT in that country and, in particular, supervision and coordination of the teams in charge of all HAT screening activities, including survey activities. The PNLTHA is fully involved in planning and implementing the study in Guinea.

Information of the communities who will participate in the study will follow the procedures of the PNLTHA.

The following information on the study will be disseminated at various levels within the communities:

- Routine screening and diagnostic procedures for HAT;
- Primary objective of the study, i.e. to have an oral drug that is safe to use in the treatment of HAT and that will be made available to the local population;
- Information on the new treatment, on the rescue treatment and on concomitant treatments if necessary;
- Information on the duration of hospitalisation and the number of follow-up visits up to 18 months, as compared to the usual treatment, on the importance of attending follow-up visits and the possibility of visits in the village by the study personnel if the patient does not attend follow-up visits at the investigational centre;
- Information on the fact that food will be provided to all patients with HAT treated at the centre in Dubreka;
- Information on the organisation of travel and/or reimbursement of travel costs from their village to the investigational centre for patients included in the study and the person accompanying them;
- Information on the importance of free choice, expressed by each individual patient, to decide whether or not s/he wishes to participate in the study, after receiving full information on the study and on the possibility of receiving treatment in any case;
- Information on the need for patients under legal age or those with impaired cognitive faculties to come to the centre accompanied by a guardian/legal representative.

At the end of the study, the community will receive information on the results using the same means of communication, i.e. community mobilisers.

14.2. Informed Consent Process

14.2.1. General Process

The patient will not be included in the study until after s/he has given informed consent in writing. It is the responsibility of the Investigator to obtain, for each

individual who participates in the study, voluntary written informed consent after having provided adequate explanation of the aims, methods, anticipated benefits and potential risks of the study. This task can be performed by a designee, referred to as a “facilitator”, who may be a study nurse.

The written informed consent document will be translated into the local language or a language understood by the patients, and submitted to the IEC in each country for approval. The informed consent document will not be translated into the local language in Guinea because a version already exists in French, which is the official written language. The oral information provided to patients may however be delivered by the investigator in the local language.

A written information sheet, more extensive than the patient information, will be used as a tool for the facilitator to provide oral explanations. The facilitator will be chosen within the team for her/his good knowledge of the patients’ preferred local language, and for her/his skills in interacting with patients. More than one facilitator may be chosen in each centre to cover all local languages and dialects.

Visual aids, including photographs, drawings and samples, will also be made available to the facilitator, describing the activities performed during the study, e.g. lumbar puncture, finger pricks and ECG.

The patient will be invited to attend the information session alone or together with family or friends if s/he wishes. The session will be held in a separate room in order to ensure patient confidentiality, with only one facilitator present.

The patient will first be informed about the disease, i.e. HAT, with a clear description of the signs and symptoms.

The information provided during the session will address the following topics:

- Currently available treatments;
- Study objective and need for scientific evaluation of a new treatment;
- Information on the new drug from previous study (safety, PK/PD…);
- Number of patients to be enrolled and the duration of the study;
- Criteria to fulfil to be eligible for inclusion in the study;
- Patients’ commitments during the study, i.e. time, compliance with study-specific procedures and attendance at follow-up visits;
- Samples to be collected for laboratory tests and purpose of tests;
- Benefits and risks associated with study participation;
- Compensation for travel costs and provision of food during hospitalisation;
- Patients’ rights regarding withdrawal, rescue treatment, additional information, etc.

If the patient wishes, s/he will be given time to discuss the information received with members of his/her community or family before giving consent. Written consent will be given after the information session (or later) by signing the form, provided the facilitator is convinced that the patient has fully understood what was explained.

The informed consent form has been translated into the local/national languages/lingua franca spoken in the areas where the study is being conducted. If the patient does not speak the national/local language/lingua franca and if pre-specified and authorised staff with knowledge of the dialect/local language are present, an *ad hoc* oral translation may be acceptable. The oral translation will be supported by the use of the available visual aids. The document signed by the patient will be the form in the lingua franca of his/her country/region. The procedures for illiterate patients should apply. The oral translation should be documented on the signed consent form, i.e. the person who did the translation will indicate her/his name and the language/dialect used, and will sign the form.

14.2.2. Impartial Witness

The presence of an impartial witness is mandatory when illiterate patients are recruited and/or the legal representative is illiterate. Other situations may also require such a witness (see Section 14.2.3. Illiterate Patients; p71 and Section 14.2.4. Patients Unable to Give Consent; p71).

The witness should have no connection with the study team, and, whenever possible, should be chosen by the patient. The witness must be literate, i.e. able to read. If the patient does not know any appropriate witness, the team will propose someone from the hospital staff who is not working in the HAT clinical unit, or any literate person from the neighbourhood who is willing to act as a witness. The study team will take all necessary measures to prepare a list of possible witnesses before the start of the study and keep this list updated, in order to find a witness quickly, whenever necessary.

The witness will sign the consent form to attest to the completeness of the information given to the patient, and its compliance with the written information in the patient information sheet. The witness must be present throughout the entire information session.

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

14.2.3. Illiterate Patients

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

The facilitator will explain the information contained in the written document to the patient and ask whether s/he gives his/her consent to participate. The patient’s

consent will be documented with his/her fingerprint on the form, and the witness will sign the form.

14.2.4. Patients Unable to Give Consent

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

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

Consequently, for patients who present with symptoms of psychological or behavioural disturbances and/or with impaired mental status, such as memory or vigilance disorders, disorientation, etc., consent will be requested from an accompanying family member, acting as legal representative. It should be noted that patients with very advanced late-stage HAT will not be invited to participate in the study (see Section 4.3 Exclusion Criteria, item 3; p33).

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

In addition, the consent process should be conducted in the presence of an impartial witness who will attest that the patient's wishes and best interests have been respected.

As soon as the patient has recovered his/her capacity to decide, s/he will be asked to confirm his/her desire to participate in the study, usually during the hospitalisation period, attested by the signature of an additional consent form. If the patient decides not to continue to participate in the study, no additional data concerning him/her will be collected, however data collected up to that time may be used in the analyses.

14.2.5. Patients Under Legal Age

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

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

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

should replace the signature. If the legal representative is illiterate, an impartial witness must attend the assent process and the consent process for the legal representative (see Section 14.2.2. Impartial Witness; p70).

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

14.2.6. Changes in the Benefit-to-Risk Assessment during the Study

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

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

Experimental data suggest that acoziborole has significant potential for the treatment of *T.b.* gambiense infections. Phase-I studies in healthy volunteers who received acoziborole suggest that the benefit-to-risk ratio of the dose selected is acceptable.

No screened patients will be left without treatment. Patients not eligible for the study will be offered alternative treatment.

Sampling will be performed only for the purposes of safety assessments and PK analyses. The volume of blood collected will be reduced to a minimum.

The PK analyses will be performed on a sufficient number of patients using a DBS assay method involving 2 µL of venous blood, i.e. about 20 µL in total throughout the study (see Section 6.3.1 Laboratory Tests; p42).

CSF samples will be collected from a sufficient number of patients in order to assess exposure to acoziborole in the brain. The samples will be collected, whenever possible, using atraumatic needles and, if possible, using a local anaesthetic cream, i.e. Emla®, in order to reduce pain and limit the adverse effects related to sampling. This analysis will be performed on the sample used in the efficacy analyses, collected as per usual practice in the investigational centre. The PK analyses will require 40 µL of CSF.

The samples collected on filter paper will be sent out of the country where the study is being conducted for centralised assessment of exposure to acoziborole.

The samples will only be identified by the study number and the patient number. Thus, no information identifying the patient personally will leave the country.

In the DNDi-OXA-02-HAT study, none of the samples will be retained after the end of the study. All remaining biological material will be destroyed at the latest once the final study report has been validated and signed. The destruction procedure will be recorded in a certificate of destruction.

[redacted]

Images of cell counts and/or detection of trypanosomes will be recorded for quality control purposes only and sent to the Sponsor. The images will be identified only by the study number and the patient number. Thus, no information identifying the patient personally will be sent to the Sponsor.

14.4. Costs for Patients

Patients will be reimbursed for their travel costs to and from the investigational centre, but will not receive any payment for participation in the study. During the in-patient treatment phase, food will be provided to the patients free of charge. Food may or may not be prepared for the patients, depending on usual practice in each investigational centre. If not, the family will prepare it. Enough food will be provided to cover the needs of the relatives accompanying the patient during hospitalisation.

For follow-up visits, the patients' travel costs will be covered by the Sponsor, based on centre-specific procedures, e.g. payment of taxi, use of study-specific vehicle, transport by mobile teams, reimbursement at flat rate. Food will be provided for the patient during his/her stay in hospital. Missed days of work due to travel for follow-up visits may be compensated, depending on requirements from local IECs.

Any medication that is required during the study, i.e. at any time during the 18-month follow-up period, will be provided to the patient free of charge. The WHO List of Essential Medicines and the guides entitled "Clinical Guidelines" and "Essential Medicines" (2013 edition), published by Doctors Without Borders, will be used as reference guides for the treatment of all concomitant conditions. For any chronic condition, the study team will take all necessary measures to ensure that the patient is referred to the most appropriate healthcare facility in the region.

To ensure that participation in the study is voluntary, all patients diagnosed with HAT during the screening period at hospital/at the investigational centre will be treated at the hospital/investigational centre, in accordance with current guidelines for treating HAT, even if they are not included in the study, whether this is because they do not fulfil the inclusion criteria or because they do not wish to participate in the study. The patients may be hospitalised, if necessary, for treatment and will also receive food during this period.

15. Insurance and Liability

DND*i* will take out an insurance policy to cover any claims arising from the study, with the exception of claims that arise from malpractice and/or negligence, in which case the Investigator or the institution will be held liable. In addition, DND*i* will cover the costs of treating patients in the study in the event of study-related injuries, in accordance with applicable local regulatory requirements.

16. Reports and Publication

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

The results of the study may be published or presented at scientific meetings. If this is the case, the Investigator agrees to submit all manuscripts or abstracts to DND*i* prior to publication.

In accordance with standard editorial and ethical practices, the Sponsor will generally support publication of the results of multicentre studies only in their entirety and not as individual centre data. Any formal publication on the results of the study in which input from DND*i* personnel exceeded that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate DND*i* personnel. Authorship will be decided by mutual agreement.

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Appendices

Appendix 1 – Declaration of Helsinki

World Medical Association - Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964,
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington, DC, USA, October 2002
55th WMA General Assembly, Tokyo, Japan, October 2004
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

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

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient’s best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens And Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups And Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements And Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy And Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group.

In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use Of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

- Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

- Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention; and

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

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

Post-Trial Provisions

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

Research Registration And Publication And Dissemination Of Results

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

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

Unproven Interventions In Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be

made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Appendix 2 – Karnofsky Performance Scale

Karnofsky Performance Status Scale
Definitions of Rating Criteria (%)

The Karnofsky Performance Status Scale allows patients to be classified in terms of their functional impairment. This can be used to compare the efficacy of different treatments and to assess the prognosis in individual patients. The lower the score, the greater the disability.

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

Appendix 3 – Laboratory Tests

Laboratory Tests and Methods

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

Biochemical tests

14 parameters will be analysed:

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

Thyroid function tests: TSH, free T3 and free T4

Haematological tests

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

Urine pregnancy test

CSF analysis (see Investigator Manual)

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

Blood parasitology tests (see Investigator Manual)

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

Quantity of biological fluid required at each sampling timepoint

Pre-screening and Screening Visit

	Type of test	Specific test	Number of samples	Quantity per sample (approx.)	Total quantity
Blood	Parasitology	Woo/CTC	1	100 µL	≤ 400 µL
		Thin/thick blood smear	1	≤ 300 µL	
		mAECT (±BC)	1	5 mL	5 mL
	Haematology	Haemoglobin	1	20 µL	Between 170 µL (capillary blood[1)] and 9 mL (venous blood)
		WBC	1	20 µL	
		Platelet count	1	10 µL	
		Differential WBC	1	20 µL	
	Biochemistry	14 parameters	1	100 µL	
	Thyroid function test	TSH, free T3, freeT4	1	5 mL	
Lymph	Parasitology	If lymph nodes detectable			
CSF	Parasitology	Modified Single Centrifugation	1	4 mL	4 mL
Urine	Pregnancy		1	5 mL	5-10 mL

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

Hospitalisation (Baseline, D5 and D11)

	Type of test	Specific test	Number of samples	Quantity per sample (approx.)	Total quantity (3 visits)
Blood	Parasitology	Woo/CTC	1	100 µL	≤ 400 µL
		Thin/thick blood smear	1	≤ 300 µL	
		mAECT (±BC)	1	5 ml	5 mL
	Haematology	Haemoglobin	3	20 µL	Between 510 µL (capillary blood[1)] and 22 mL (venous blood)
		WBC	3	20 µL	
		Platelet count	3	10 µL	
		Differential WBC	3	20 µL	
	Biochemistry	14 parameters	3	100 µL	
	Thyroid function test	TSH, free T3, freeT4	2	5 mL	
CSF	Parasitology	Modified Single Centrifugation	1	4 mL	4 mL
Urine	Pregnancy		1	5 mL	5-10 mL

Follow-up visits (by visit)

	Type of test	Specific test	Number of samples	Quantity per sample (approx.)	Total volume per visit
Blood	Parasitology	Woo/CTC	1	100 µL	≤ 400 µL
		Thin/thick blood smear	1	≤ 300 µL	
		mAECT (±BC)	1	5 mL	5 mL
	Haematology (M3, M6, M12 and M18)	Haemoglobin	4	20 µL	Between 680 µL (sang capillary blood[1)] and 36 mL (venous blood)
		WBC	4	20 µL	
		Platelet count	4	10 µL	
		Differential WBC	4	20 µL	
	Biochemistry (M3, M6, M12 and M18)	14 parameters	4	100 µL	
	Thyroid function test (M3, M6, M12 and M18)	TSH, free T3, freeT4	4	5 mL	
Lymph	Parasitology	If lymph nodes detectable			
CSF	Parasitology	Modified Single Centrifugation	1	4 mL	4 mL
Urine*	Pregnancy		1	5 mL	5 mL

* Only at visits at 3 months and 6 months.

Quantity of biological fluids required for PK analyses

Entire study

	Type of test	Number of samples	Quantity per sample (approx.)	Total volume
Blood	PK	10	2 mL	20 mL
CSF	PK	1	Included in sample collected for detection of parasite (4x10µL)	

Appendix 4 - Schedule of Events

Table 6 - Schedule of Events

Protocol procedures and forms to be completed	**Pre-screening and screening**	**Baseline**	**Observation Period until End of Hospitalisation Visit (EOH)**															**Out-patient Follow-up Period**	
Timing →	D-15 to D-1	D-4 to D-1	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15 (EoH)	3, 6, 12 & 18 months	Unscheduled Visit[1]
Diagnosis, i.e. detection of parasite in blood and/or lymph	x												x					x (6, 12 & 18 months only)	x
Lumbar puncture (parasite and WBC in CSF)	x												x					x (6, 12 & 18 months only)	x
Informed consent	x	Check																	
Pre-treatment of helminthiasis (+ 3-day recovery period)	x																		
Rapid diagnostic test and/or thick blood smear for malaria	x																		
Pre-treatment of malaria as needed (+3-day recovery period)	x																		
Karnofsky index	x	Check																x	x
Urinary pregnancy test (only for women)	x	x											x					x (up to 6 months)	x
Inclusion/exclusion criteria	x	Check																	
Demographic data	x																		
Geographical data	x																		
Medical history, incl. symptoms, severity and time since start of disease	x																		
Weight, height and body-mass index	x	x					x						x				x	x	x
Vital signs[2]	x	x					x						x				x	x	x
Physical examination		x					x						x				x	x	x
Neurological examination		x					x						x				x	x	x
Haematology/biochemistry	x	x*					x						x					x	x
Thyroid function tests		x											x					x	x

Timing →	D-15 to D-1	D-4 to D-1	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15 (EoH)	3, 6, 12 and 18 months	Unscheduled visit[1]
ECG (2 duplicates)[3]			x																
ECG triplicate recording[4]			x	x	x	x	x						x						
Administration of SCYX-7158			x																
Collection of adverse events[5]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Collection of concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x (up to 6 months)	x
Blood sampling for pharmacokinetic analyses[6]			x	x	x	x	x						x					x (up to 6 months)	
CSF sampling for pharmacokinetic analyses[7]													x						

** If the tests were performed prior to D-4 in the Pre-screening/Screening Period or if the findings included abnormalities requiring repeat tests.*

[1] If relapse of the disease is suspected or if the patient does not feel well, s/he is to attend an unscheduled visit during which assessments, including additional safety assessments (at the Investigator's discretion) will be performed, as well as investigation of concomitant disease.

[2] Body temperature, blood pressure, heart rate, respiratory rate and general status.

[3] Prior to administration of SCYX-7158, D1H0: 2 x 2 ECG.

[4] D1H4, D1H9, D1H24 (D2), D1H48 (D3), D1H72 (D4), D1H96 (D5), D1H264 (D11).

[5] Adverse events will be collected up to the 6-month visit. Serious adverse events will be collected up to the 18-month visit.

[6] D1H0, D1H4; D1H9; D1H24 (D2); D1H48 (D3); D1H72 (D4); D1H96 (D5); D1H264 (D11); D90 (M3); D180 (M6).

[7] Pharmacokinetic analyses performed on CSF sample collected for detection of parasites.

Appendix 5 - Glasgow Coma Scale

The scale was developed at the Institute of Neurological Sciences in Glasgow, Scotland in the early 1970s to assess the extent of a coma following a head injury and to monitor the course of the coma. It is now widely recognised by the international community.

The patient's level of consciousness is assessed based on three criteria: eye opening (E score), motor response (M score) and verbal response (V score).

Eye Response (E)	**Motor Response (M)**	**Verbal Response (V)**
Opens eyes spontaneously: 4	Obeys verbal commands: 6	Orientated and clear: 4
Opens eyes in response to speech: 3	Localises painful stimuli: 5	Confused: 3
Opens eyes in response to painful stimuli: 2	Withdraws from painful stimuli: 4	Inappropriate: 3
No response: 1	Abnormal flexion to painful stimuli: 3	Incomprehensible: 2
	Extension to painful stimuli: 2	No response: 1
	No response: 1	

The Glasgow score is obtained by adding the three scores.

By definition:
- if the **Glasgow score is > 12**, the patient is considered to have **mild head injury**;
- if the score is **between 9 and 12 inclusive**, the patient is considered to have **moderate head injury**;
- if the **Glasgow score is ≤ 8**, the patient is considered to have **severe head injury**.