

**PROTOCOL SUMMARY**

<b>Title:</b> Pharmacokinetic, efficacy, safety, and tolerability study of a single dose of acoziborole under fasting conditions in paediatric patients from 1 to 14 years of age and with human African trypanosomiasis due to <i>T.b. gambiense</i> : a multicentre, open-label study
<b>Short title:</b> OXA005
<b>Protocol number:</b> DNDi-OXA-05-HAT
<b>Phase:</b> II/III
<b>Indication:</b> Human African trypanosomiasis (HAT) due to <i>Trypanosoma brucei gambiense</i> (g-HAT)
<p><b>Background Information and Study Rationale:</b></p> <p>Human African trypanosomiasis (HAT), or sleeping sickness, is a life-threatening disease transmitted by tsetse flies and caused by a single-celled extracellular parasite that lives free in the bloodstream and other body fluids, including lymph and cerebrospinal fluid (CSF). There are many species of African trypanosomes; however, only two subspecies of the <i>Trypanosoma brucei</i> (<i>T.b.</i>) species are causative of HAT. <i>T.b. gambiense</i> is endemic in West and Central Africa and causes over 98% of current cases. It progresses at a more indolent pace than that of <i>T.b. rhodesiense</i>.</p> <p>Approximately 5 million people live in areas, mainly in rural parts of 24 disease endemic countries in West and Central Africa, where HAT due to <i>T.b. gambiense</i> (g-HAT) is still considered a public health problem; whereas, 51 million people are estimated to be at risk of infection on the African continent. With 864 cases of g-HAT reported in 2019, the global goal of sustainable disease elimination by 2030, including the interruption of the transmission of g-HAT, is foreseeable. Consistently falling numbers of cases are thanks to efforts from national control programmes, supported by the World Health Organization (WHO), non-governmental organisations, bilateral cooperation, the private sector (including pharmaceutical companies), and philanthropic organisations.</p> <p>As the numbers of reported cases diminish, resources for surveillance and specialised screening will also taper. This decrease, coupled with the loss of diagnostic skills and disease management expertise, will lead to a weak and less specialised HAT technical environment. The history of g-HAT has shown that outbreaks or re-emergence of the disease have already happened under different circumstances when surveillance was relaxed, e.g. South Sudan and the Democratic Republic of the Congo (DRC) or simply because the populations at risk live in areas of political instability, limiting access to specialised care. Even with a steady decrease of reported incidence, no model can currently predict that HAT could not re-emerge.</p> <p>Although g-HAT is predominantly a disease of adults, children are also affected at diverse rates depending on the geographical and behavioural characteristics in the different areas of disease transmission. Globally, the WHO Expert Committee on control and surveillance report states: "rates in children are usually less than half of those in adults, reflecting less exposure to flies during daily activities". In data from the Médecins Sans Frontières Database on HAT control projects, out of 684 second stage HAT patients included, 17.5% were children under the age of 15 hence efforts are needed to develop a paediatric formulation from a new generation of oral HAT treatments. The majority of signs and symptoms associated with HAT occur at similar frequencies in paediatric patients with first and second stage disease compared with adults, including sleep disturbances. The presence of trypanosomes in cervical lymph nodes is less frequent in preschool children than in older children and adults. More infants are seen at the second stage, most likely due to delayed diagnosis and the immaturity of the blood-brain barrier. In some studies, fever, hepatomegaly, splenomegaly</p>

and facial oedema were observed more frequently in children aged 2 to 15 years than in adults.

As per the WHO 2019 interim guidelines for the treatment of HAT, the choice treatment is determined by a two-step assessment. The first step is the clinical assessment and the second step is the CSF examination (lumbar puncture), which is required only for patients with clinical symptoms and signs suggestive of the severe meningo-encephalitic stage.

For children <6 years old and <20 kg body weight who are second stage g-HAT, a 7-day, twice a day intravenous course of NECT or eflornithine is the sole treatment option. Treatment in first stage g-Hat involves intramuscular injections of pentamidine for 7 days. Both treatments require pre-treatment lumbar puncture and hospitalisation with a specialised health care environment that is not always possible in remote rural African areas where g-HAT is prevalent.

The aim of the current study is to validate the weight-based exposure based on the population pharmacokinetic (pop-PK) modelling, efficacy, and safety of acoziborole in first and second stage g-HAT paediatric patients from 1 to 14 years of age enabling a paradigm shift in the management of paediatric g-HAT patients reducing the subsequent burden on families (i.e. mothers and the entire family will spend less time providing care). Furthermore, if the clinical status permits, administering a single-dose oral drug at the point of diagnosis will avoid the need for costly hospitalisation in specialised health centres, lumbar puncture and parenteral treatments. Compliance and adherence of children to treatment will be more straightforward and will shorten the delay between diagnosis and effective treatment, which will contribute to stopping disease progression and the avoidance of neurological sequelae in this population.

Achieving the challenging objective of g-HAT elimination by 2030 requires a safe, effective, and easy-to-use tool that enables treatment at the point-of-diagnosis for all individuals, including children. As a single administration oral drug, acoziborole would facilitate treatment access for children.

### **Study Objectives**

#### Primary objective

- To validate weight-based exposure based on pop-PK modelling

#### Secondary objectives

- To assess the efficacy of acoziborole
- To estimate the time course of the efficacy response
- To assess the safety profile of acoziborole
- To assess the potential relationship between concentration of acoziborole and corrected QT interval (QTc)
- To assess the palatability and acceptability of the paediatric formulation in paediatric patients

### **Study Endpoints**

#### Primary endpoint

- Primary PK parameters in blood:
  - Maximum concentration ( $C_{max}$ )
  - Area under the curve from time 0 to 96 hours ( $AUC_{0-96h}$ )
- Secondary PK parameters in blood:
  - Time to maximum concentration ( $T_{max}$ )
  - Area under the curve from time 0 to infinity ( $AUC_{0-\infty}$ )
  - Clearance, volume of distribution (Vd) and half-life ( $t_{1/2}$ )
- Acoziborole concentration in CSF (on Day 11)

### Secondary endpoints

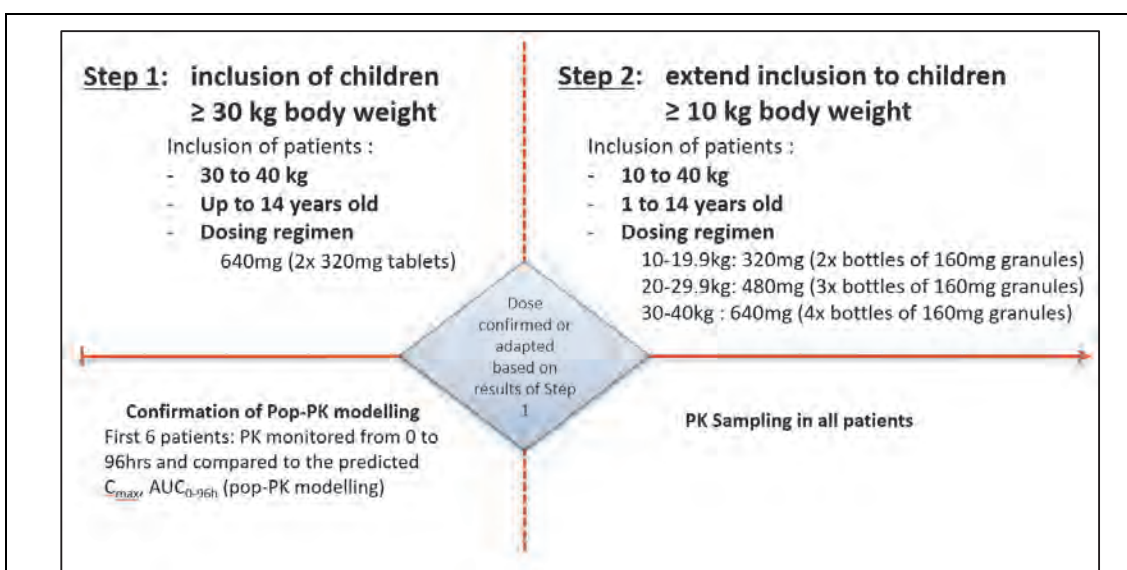
- **Efficacy:** the secondary efficacy endpoints are the outcome (success or failure) according to the algorithm, observed at the last visit, 12 months after the end of treatment. This will involve estimating the treatment efficacy at 6 and 12 months post-treatment, based on:
  - The criteria for success (according to the algorithm) specific to each visit
  - Cumulative risk of proven failure over time (Kaplan-Meyer estimate)
- **Safety**
  - Occurrence of any treatment-emergent adverse events (TEAEs) (any grade) during the observation period (3 months)
  - Occurrence of any TEAEs (grade  $\geq 3$  or severe) and relatedness to medication during the observation period (3 months)
  - Occurrence of any serious adverse events (SAEs) during the study up to the 12-month follow-up visit
- **Electrocardiogram (ECG) Endpoints**
  - Categories of QTc and changes in digital ECG recording with centralised re-reading. The timepoints for ECG recording will match the PK sampling timepoints for PK/PD (pharmacodynamic) analysis.
- **Palatability/Acceptability**
  - Scores of the 5-point hedonic scale (questionnaire about palatability to be completed by the patient and questionnaire about acceptability to be completed by caregiver)

### **Study Design**

This is an open-label, non-randomised, single arm, multicentre, phase II/III study, to be conducted in DRC and Guinea, to determine weight-based exposure based on pop-PK modelling, efficacy, safety, and tolerability of acoziborole in the treatment of first or second stage g-HAT in paediatric patients from 1 to 14 years of age.

The enrolment of patients will be done in two steps:

- Initially, recruitment will be limited to paediatric patients weighing 30 to 40 kg who will receive the 320 mg tablet formulation. Blood samples from a cohort of the first six patients of this weight range will be analysed for up to 96 hours following IP administration. The observed PK data will be compared to the predicted data.
  - If  $>80\%$  of the observed  $C_{max}$  and  $AUC_{0-96h}$  values fall inside the 5th to 95th percentile band of the simulated concentrations and the pattern of median concentrations (simulated and observed) over time is consistent, the study will continue with the planned dose regimen.
  - If  $\geq 20\%$  of the observed  $C_{max}$  and  $AUC_{0-96h}$  results fall outside the 5th to 95th percentile band of simulated concentrations and the pattern of median concentrations over time does not fit the values predicted by the model, the pop-PK model will be refined using the first six patients'  $C_{max}$  and  $AUC_{0-96h}$  values as covariates and the total dose (mg/kg) will be reassessed.
- Once the PK data from the first six patients have been analysed and the dosing regimen confirmed or adapted, inclusion will resume and be extended to allow enrolment of paediatric patients weighing  $>10$  kg with the granule formulation (including for paediatric patients weighing 30 to 40 kg).



$AUC_{0-96h}$  = area under the curve from time 0 to 96 hours;  $C_{max}$  = maximum concentration; PK = pharmacokinetics; pop-PK = population pharmacokinetics.

### Inclusion criteria

- Signed informed consent from one parent or from the legal representative
- Assent from the paediatric patient (for paediatric patients >6 years of age) to participate in the study, collected in the presence of an impartial witness
- Between 1 and 14 years of age and between 10 and  $\leq 40$  kg (as per the requirements of step 1 and step 2)
- Male or female
- Evidence of trypanosomes in any body fluid (blood or lymph or CSF)
- Having a permanent address and able to comply with the schedule of follow-up visits
- Agreement to not take part in any other clinical trials during the participation in this study
- For pubescent girls of childbearing potential must agree to have protected sexual relations to avoid becoming pregnant from enrolment up to 3 months after dosing (contraceptive protection will be advised and offered at no cost)

### Exclusion criteria

- Previous treatment for g-HAT
- Refusal to participate in the study, expressed by the paediatric patient and/or parent or legal representative
- Complicated severe acute malnutrition as defined by weight for height (-3 standard deviations [SDs] Z score)
- Unable to take medication by the oral route
- Clinically significant medical condition (other than HAT) that could, in the opinion of the Investigator, jeopardise the patient's safety or interfere with participation in the study
- Any condition (excluding HAT-specific symptoms) that affects the patient's and/or parent's ability to communicate with the Investigator as required to complete the study
- Prior enrolment in the study or prior intake of acoziborole
- Foreseeable difficulty complying with follow-up, including family of migrant workers, refugee status, itinerant trader, etc.
- Clinically significant laboratory test abnormality, with:
  - Alanine aminotransferase and/or aspartate aminotransferase more than twice the upper limit of normal (ULN)
  - Total bilirubin more than 1.5 x ULN
  - Severe leukopenia at  $<2000/mm^3$

- Potassium <3.5 mmol/L
- Any other clinically significant laboratory test abnormality
- Pregnancy confirmed by a positive urine pregnancy test (during the screening period and/or within 24 hours prior to the start of treatment) for pubescent girls of childbearing potential
- Not tested for malaria and/or not having received appropriate treatment for malaria
- Not having received appropriate treatment for soil-transmitted helminthiasis

### Study Duration

The duration of the enrolment period is estimated to be approximately 18 months.

Each patient's participation in the study will last approximately 12 months and will include:

- Pre-treatment period (screening and baseline assessments, and treatment of concurrent diseases) up to 15 days
- A treatment period of 1 day
- An observation period in hospital for a total of 15 days, including the treatment day (Day 1)
- An outpatient follow-up period of 12 months with visits at 3, 6 and 12 months

The total duration of the study is estimated to be approximately 30 months.

### Study treatment

The study treatment is acoziborole and two different formulations will be used during the study depending on the body weight and on the step of the study:

- Tablets of 320 mg dose for paediatric patients weighing 30 to 40 kg in step 1. It is the same formulation as the one used in the pivotal study DNDi-OXA-02-HAT in adults and adolescents.
- Granules in bottle for paediatric patients weighing 10 to 40 kg in step 2. This is an adapted paediatric formulation of acoziborole. Granules will be packed in bottles of 160 mg dose. These granules are the intermediate product of the 320 mg tablet prior to blending with 1% lubricant (magnesium stearate) and compression.

The IPs will be provided by DNDi, Chemin Camille-Vidart 15, 1202 Geneva, Switzerland.

Acoziborole will be administered to patients by the oral route in the fasting state as a single dose.

Patients will receive either the tablet formulation or the adapted paediatric formulation as a single dose according to the body weight (following predicted dose regimen based on the pop-PK modelling) and the step of the study:

Body weight	Step 1	Step 2
10 to 19.9 kg	Not Applicable	320 mg (2 bottles of 160 mg granules)
20 to 29.9 kg	Not Applicable	480 mg (3 bottles of 160 mg granules)
30 to 40 kg	640 mg (2 tablets of 320 mg)	640 mg (4 bottles of 160 mg granules)

After step one is completed, the dose regimen may be adapted.

### Statistics

#### Sample size

The sample size mirrors the epidemiological context of a decline in the number of g-HAT cases due to the elimination efforts put in place by the WHO and partners. The PNLTHA in DRC and Guinea reported in 2019, in areas where clinical sites will be based, 50 patients were detected in the age range of 0 to 15 years old. The number of patients per age group is not critical for the pop-PK model since the model can adapt the results to the population. A proposed sample size of 35 patients reflects operational feasibility and should provide sufficient model-informed safety and efficacy under the epidemiological elimination context

of g-HAT.

Since this is not a controlled study with an active comparator, the efficacy in this paediatric study will be descriptive. A sample size of 35 patients is targeted to obtain limits of the 95% confidence interval (CI) of rates as "reasonable" as possible. With 35 patients, if no patients have the attribute of interest such as failure of treatment, the exact limits of the 95% CI would be 0% to 10%. If one patient has the attribute of interest (one failure) the 95% CI would be 0.072% to 14.92% and in the case of two failures, the 95% CI would be 0.069% to 19.16%. The upper limit would be close to 20% for two observed cases, 15% for one case and 10% for no cases observed. The expected success rate in efficacy should be approximately 95% (as large as NECT in second stage and better than pentamidine in first stage). In this case, the chance of observing no failures is 16.6%,  $\leq$ one failure is 47.2%, and  $\leq$ two failures is 74.6%. Consequently, even if a power of 80% is not reached, the chance of observing a success rate  $>94\%$  (i.e.  $\leq$ two failures out of 35 patients) is not negligible, if the expectation is correct (which is pending results of the ongoing pivotal study in adults). With regards to the safety analysis, a sample size of 35 patients gives a 95% chance of observing an event with an occurrence probability of at least 0.082. The chance of observing uncommon events ( $<1\%$ ) is 16.6%. In conclusion, a sample size of 35 patients will ascertain whether the order of magnitude of the success rate is similar to that observed in adult patients and whether common adverse events (AEs) are similar to that of observed in the adult population.

#### Pharmacokinetic analysis

The first validation of the weight-based exposure model will be done using data from the first six paediatric patients. The bioavailability (concentration) obtained for each paediatric patient will be compared to the initial model predicted. This will allow assessment of whether exposure is acceptable and, if required, to adjust the exposure for subsequent patients by changing the weight band for a given exposure. If the concentration is, on average, too small or too large, the weight band will be adapted.

The complete data collected from the included patients at the end of study will be included in the model, to complete the validation of the predicted model.

A final validation of the pop-PK model of acoziborole will use the pooled data from adults and adolescents with g-HAT included in the DNDi-OXA-02-HAT pivotal Phase II/III study and paediatric patients from this current study. All observed data will be used to confirm or adjust (if needed) the prediction of the efficacy and dose for each formulation and bodyweight, to estimate pop-PK parameters in paediatric patients, and to determine the related variability. The observed mean concentration and its 95% CI will be calculated to assess the compatibility, on average, of observed data with predicted data.

Acoziborole PK parameters will be calculated using a noncompartmental analysis method to derive the following parameters:  $C_{max}$ ,  $T_{max}$ ,  $AUC_{0-96h}$ , and  $AUC_{0-\infty}$ .

#### Efficacy analysis

Efficacy will be assessed according to the algorithm for treatment outcomes at 6 and 12 months post-treatment.

The efficacy analysis will estimate the success rate at 12 months of follow-up. The 95% Jeffreys CI of the estimate will be provided. The success rate at 12 months in adults will be used as a yardstick.

Changes in the rate of success outcomes over time will be studied descriptively.

Time to proven relapse will be analysed in each cohort using the Kaplan-Meier approach 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.