SYNOPSIS

Recently acoziborole, a non-toxic single dose oral drug for *gambiense* human African trypanosomiasis (gHAT), has passed phase 3 evaluation in adult patients.[1] This drug is envisioned to be used to treat gHAT irrespective of disease stage, thus rendering the lumbar puncture for stage determination redundant. Having available a single dose oral treatment with limited risk of toxicity opens up new perspectives for eliminating the disease. Treating anyone testing positive to a serological screening test, without further need for on the spot parasitological confirmation and stage determination, will greatly simplify procedures in the field, avoid missing many cases, has the potential to increase uptake of screening and may thus even curb transmission of the causative parasite, which is assumed to have only a human reservoir.

Although this innovative option for gHAT control is now feasible, its true effectiveness and cost effectiveness for curtailing transmission remain to be determined. We hypothesize that by systematically screening the populations of all endemic villages and treating with acoziborole all serological suspects identified in a well-defined HAT focus, we will be able to arrive at a zero prevalence over a three-year period. Bearing in mind that acoziborole has not yet been registered and that 'screen & treat' has not yet been adopted as the new policy, we will for the duration of this study continue performing parasitological confirmation on the spot and treat anyone confirmed by parasitology with standard of care. Any serological suspect not confirmed by parasitology on the spot will be offered treatment with acoziborole (study Part B), conditional on a set of inclusion and exclusion criteria.

For this study we have selected an area in the north west of the Democratic Republic of the Congo (DRC), which according to the WHO definition is still at moderate to high-risk for gHAT, i.e. an estimated annual risk of infection of 1/10,000 or above. The area selected is surrounded by areas of low or negligible risk. Within the area there are 94 villages that would need to be screened according to the current strategy, 58 because they had incident cases in the last three years (2019-2021, list 1 of WHO) plus 36 that had no cases in the last three years but did have cases less than five years ago (2017-2018, list 2 of WHO). Three mobile teams are active in the area and will continue active case finding as foreseen. For the purpose of the study they will synchronize their activities in adjacent villages and will set up a joint site for parasitological confirmation in a nearby location that will move as the teams move.

Screening is based on the card agglutination test for trypanosomiasis (CATT), a highly specific serological test. Anyone testing positive will be taken to the confirmation site where a venous blood sample will be collected. This sample will be used for classical parasitological confirmation on the spot and as well for remote post hoc confirmation of infection by *T.b. gambiense* through immunological and molecular testing at a referral laboratory (INRB in Kinshasa). For the latter purpose a sampling kit has already been introduced by the national sleeping sickness control program (PNLTHA) as such remote diagnostic confirmation is already in place in passive case finding in three other provinces and used for quality assurance purposes for cases identified in active screening. Serologically suspect individuals who are parasitologically confirmed on the spot will be offered standard of care treatment by the PNLTHA, those testing negative to parasitological confirmation on the spot will be asked to participate in the study part B and to provide informed consent. In parallel to intake in active screening, the study will also

recruit among non-parasitologically confirmed gHAT suspects identified in passive screening, testing positive to a rapid serological screening test (RDT). This passive screening will take place in 30 facilities already involved in HAT screening and treatment. Whereas previously dried blood spots were forwarded to the referral laboratory, the same sampling kit described earlier will now be used. Thus at the referral laboratory both immunological tests and molecular tests can be performed.

Recruitment from active and passive screening activities will continue for three consecutive years. During the fourth and final year of the study, recruitment will stop but we will screen all villages that were originally endemic (list 1 and 2 of WHO) as well as a cluster random sample from villages in the study area that have not been screened (total 403 villages, estimated population 2-2.5 million). Similar as in the previous screening rounds, for all serological suspects we will draw a venous blood specimen to perform the parasitological confirmation on the spot (or lymph node sample if appropriate) and for remote testing. This will allow us to verify whether a zero prevalence has been achieved in the villages targeted for active screening as well as in the wider surroundings. The prevalence of gHAT after 3 years of the test and treat approach in this area in the northwest of DRC (including both the originally endemic and non-endemic villages) is the primary objective of the trial (Part A).The clinical study primary objective (study Part B) is to assess the safety profile of acoziborole in this population of gHAT serological suspects. To date results of treatment of confirmed cases of gHAT have shown a favorable risk: benefit profile. A phase II/III study on safety among gHAT seropositives subjects not parasitologically confirmed is currently ongoing (Sponsor DNDI DNDI-OXA-04-HAT, clinicaltrials.gov NCT05256017). In this study, 1200 seropositive individuals (900 receiving active treatment with acoziborole and 300 receiving a matched placebo) were included. However, before adopting a large-scale screen and treat approach, it is imperative that larger numbers are assessed in detail.

We will additionally evaluate the cost of a screen and treat approach, which will be of key importance for a decision to roll it out on a larger scale; and we will evaluate the specificity and positive predictive value of the screening tests used in the field and at reference laboratory level.

This protocol describes both the epidemiological study which aims at assessing whether over a three-year period a zero prevalence can be achieved when implementing a screen & treat approach with acoziborole, as well as a nested clinical study aimed at generating further evidence on safety of acoziborole in gHAT seropositives individuals. The overall coordinator will be ITM. ITM will be fully responsible for the epidemiological study (study Part A), including cost effectiveness and evaluation of diagnostic tests. DNDi will be the legal sponsor of the nested safety clinical study (study Part B) and will ensure compliance with regulatory requirements and good clinical practices (GCP) for this part of the study.