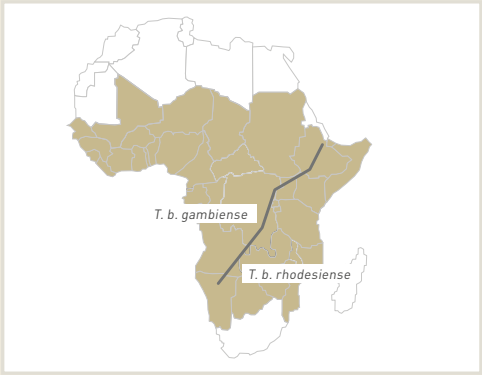
HUMAN AFRICAN TRYPANOSOMIASIS

Sleeping Sickness

- Caused by two subspecies of *Trypanosoma brucei* (*T. b.*) gambiense (g-HAT; 98% of reported sleeping sickness cases) and *T. b. rhodesiense* (r-HAT)
- Transmitted by the tsetse fly
- Occurs in two stages:
  - the early stage (stage 1) with non-specific symptoms, often un- or misdiagnosed
  - the late stage (stage 2) where the parasite crosses the blood-brain barrier, causing serious neurological disorders including sleep cycle disruptions, neurological manifestations, and progressive mental deterioration
- Without effective treatment, the disease usually leads to death
- The WHO Roadmap objective: to eliminate HAT as a public health problem by 2020

13
million people estimated to live in areas at moderate to very high risk

65
million people at risk



T. b. gambiense is endemic in

24
countries of West and Central Africa

2,733 new cases reported (2015)

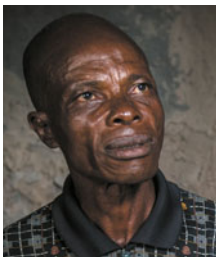
T. b. rhodesiense is endemic in

13
countries of Eastern and Southern Africa

71 new cases reported (2015)

The combination therapy Nifurtimox-Eflornithine (NECT), developed in 2009 (see p. 8), replaced the toxic treatments for HAT. NECT is now used to treat 100% of stage 2 HAT identified patients infected with *T.b. gambiense*, and has contributed to the fall in the case load. But treatment remains cumbersome, difficult to ship, store, and administer; patients must be hospitalized and undergo a complex and painful lumbar puncture to first determine the stage of the disease.

New oral treatments in combination with rapid diagnostic tests would shift the treatment paradigm, and are needed to reach the final mile of WHO's elimination target[1] and ensure its sustainability, particularly as HAT has a history of resurging in epidemics.



"I began to feel tired and weak. I was cold all the time even when it was hot. My bones ached terribly. I could sleep during the day but not at night. I didn't know what was wrong until I was diagnosed with sleeping sickness."

Jean de Dieu Liyande Walo
52, a survivor of sleeping sickness, a cassava and rice farmer, and a part-time preacher.
Yalikombo, a village located on the Congo river, DRC

DND*i* aims to deliver:

- **A safe, effective, and orally administered drug** to replace current first-line HAT treatments, and to improve and simplify current case management
- **The ideal goal is to develop two drugs** that are effective against both stage 1 and 2 HAT and both subspecies of the parasite

If successful, this would represent a fundamental shift in disease management, as it would remove the need both for a risky and painful lumbar puncture test to confirm the disease stage, and for hospitalization, as treatment would no longer rely on administering a drug intravenously.

(1) Less than one case per 10,000 inhabitants in at least 90% of endemic foci is expected.

RESEARCH

SCYX-1330682 and SCYX-1608210 oxaboroles

OBJECTIVE: Maintain back-up oxaboroles which could replace the drug candidate SCYX-7158 in case it does not succeed in development.

Background: These two back-up candidates from the oxaborole class have demonstrated cure for stage 2 of the disease in the mouse model. Given the current success of other projects for HAT, further development was put on hold in 2013, and will only recommence should problems be encountered with SCYX-7158 in clinical development.

TRANSLATION

SCYX-7158 oxaborole[1]

OBJECTIVE: Develop and register SCYX-7158 as a new, single dose, oral treatment for the treatment of stage 2 HAT caused by *T. b. gambiense* (g-HAT), ideally also for stage 1.

Background: SCYX-7158 was selected as a pre-clinical candidate for g-HAT in late 2009. This resulted from DND*i*'s own lead optimization project starting with an initial hit identified in the Anacor chemical library. In 2012, it became DND*i*'s first new chemical entity resulting from its own lead optimization programme to enter clinical development. SCYX-7158 is expected to be administered directly at home.

Phase I trials were completed in 2015, and allowed the therapeutic dose to be determined at 960mg administered orally in a single dose of three tablets.

11 patients recruited at 7 sites

2016 A pivotal Phase II/III study started in seven clinical sites – Katanda, Isangi, Dipumba, Ngandajika, Masi Manimba, Kwamouth, and Bolobo – in the Democratic Republic of the Congo (DRC). Eleven patients (out of a target 350) had been recruited by the end of 2016.

The submission of a regulatory dossier to the European Medicines Agency under Article 58 is planned for 2021.

(1) As of 2017, SCYX-7158 oxaborole will be named 'acoziborole'.

DEVELOPMENT

Fexinidazole

OBJECTIVE: Develop and register fexinidazole as a new oral drug for the treatment of stage 2 HAT caused by *T. b. gambiense*, ideally also for stage 1 HAT and for children between 6 and 14 years old.

Background: Fexinidazole, the result of successful compound-mining efforts pursued by DND*i* in 2005, entered clinical development in September 2009 and is being co-developed with Sanofi. The 10-days oral-only treatment could be administered at the primary healthcare level, ideally allowing patients to take the medicine at home.

In 2015, DND*i* and the National HAT Control Programme (PNLTHA) of the DRC completed the recruitment of 394 adult patients with stage 2 HAT at nine clinical sites in the DRC and one (supported by MSF) in the Central African Republic, for a pivotal Phase II/III study.

755 patients recruited at 10 sites

2016 Two complementary cohorts to the Phase II/III study were completed in 2016, one including 230 adult patients with stage 1 and early stage 2 of the disease, and another including 125 children between six and 14 years, both in DRC sites. Follow up of patients will be completed in 2017.

A Phase IIIb study aimed at getting more information about special population groups not included in previous fexinidazole trials (pregnant or lactating women, and patients with poor nutritional status or with chronic diseases) started in 2016. Patients will be treated either in hospital, or at home, thereby also providing preliminary information about the treatment compliance and final effectiveness in ambulatory patients. Three sites were initiated (Bandudu, Mushie, and Bagata) and six patients (out of a target of 174) had been recruited by the end of 2016.

The results of the Phase II/III study support the submission of a regulatory dossier to the European Medicines Agency under Article 58, planned for late 2017 for the treatment of g-HAT with fexinidazole. It aims to facilitate faster WHO prequalification of the medicine as well as regulatory approvals and implementation in endemic countries. A risk management plan to further monitor safety and efficacy in the field is under preparation in collaboration with Sanofi and WHO.

In addition, the protocol for a study to be undertaken in r-HAT patients is being finalized, sites in Uganda and Malawi have been identified.

The challenge of conducting clinical studies in remote areas

Masi-Manimba hospital in the province of Bandundu, DRC, one of the sites where DND*i* clinical trials for sleeping sickness take place

As fexinidazole enters the final stages of its clinical development, the fact it may become both DND*i*'s first new chemical entity and a new oral treatment that could radically transform sleeping sickness patient management, means there may be much to celebrate. Even more so when one considers how much of a daunting challenge running clinical trials in the remoter areas of a country like the Democratic Republic of the Congo (DRC) can be.

Because sleeping sickness occurs in very remote areas of the country, there are two major operational challenges that need to be overcome.

The first major challenge is infrastructure. Ensuring local physical capacities, including in-patient wards and onsite labs, are up to the task of conducting Good Clinical Practice (GCP) compliant clinical research and can deliver quality results is imperative. In the DRC, nine referral treatment units were renovated for the fexinidazole trials. Buildings were refurbished, with solar energy equipment and generators installed to ensure the regular supply of electricity needed to operate lab equipment and computers, and even to maintain the cold chain to store reagents. Emergency medical equipment such as defibrillators and technical equipment such as the Piccolo analyser, a fully automated system for blood testing, were brought in. Internet access was installed to enable transmission of electronic case report forms, particularly necessary for the monitoring of safety parameters.

Overcoming the lack of trained staff is the second big hurdle. Through the HAT Platform (a regional disease-specific clinical research network supported by DND*i*) trainings were provided in diagnostic techniques and treatment procedures, pharmacovigilance, GCP guidelines, in the performing and interpreting of electrocardiogram results, and even medical waste management.

Ensuring real-life field conditions are included in any trial set up is critical to its success. The joint experience of DND*i*, Médecins Sans Frontières, and the national sleeping sickness control programme in the DRC - notably thanks to the committed mobile teams - shows it is possible to build an environment conducive to running high quality clinical trials. In overcoming these challenges, our hope is that this effort serves not only to build and sustain the capacity to conduct a high standard of clinical research in endemic countries and particularly remote areas, but also to bring lasting benefits to researchers, staff and hospitals, as well as to health systems more broadly, and thus ultimately to local communities and patients ■

Dr Crispin Lumbala
Director, National Control Programme for Sleeping Sickness, DRC

"I have been involved in DND*i*'s clinical trials on NECT and fexinidazole. To ensure that they were Good Clinical Practice compliant, we needed to strengthen capacities in terms of infrastructure and expertise. These improvements will be useful to the Congolese research community and should last for future studies. More importantly, this will benefit our patients and will help us on our way to eliminate sleeping sickness as public health problem."