

NEWER, SIMPLER TREATMENTS FOR SLEEPING SICKNESS



An update on DNDi R&D
programmes

DNDi
Drugs for Neglected Diseases *initiative*



In its Roadmap on neglected tropical diseases published in 2012¹, the World Health Organization (WHO) targets the elimination of sleeping sickness (human African trypanosomiasis, or HAT) as a public health problem by 2020. While the caseload continues to fall, dropping to below 1,500 in 2017², innovative treatments to overcome the limitations of the current treatment options are needed to achieve, and importantly to sustain, this ambitious target.

HAT is a neglected tropical disease (NTD) affecting sub-Saharan African countries. Without prompt diagnosis and treatment, sleeping sickness is usually fatal, as the parasites invade the central nervous system causing neurological changes which include among other symptoms sleep disorder, sensory disturbances, psychiatric disorders, seizures, coma, and ultimately death. Sixty-five million people who live mainly in rural

Until 2009, treatments were very complex or highly toxic to the point they killed 5% of patients.

parts of East, West, and Central Africa are at risk of contracting sleeping sickness. At its creation in 2003, the non-profit research and development organization Drugs for Neglected Diseases *initiative* (DNDi) selected HAT as a priority for its R&D efforts in light of the acute need for newer, simpler, and safer treatments. At that time, treatments were highly complex or came with considerable side effects, to the point where up to 5% of patients receiving therapy died³.

¹ Accelerating work to overcome the global impact of neglected tropical diseases – A roadmap for implementation. WHO, 2012. http://unitingtocombatntds.org/wp-content/uploads/2017/11/who_ntd_roadmap.pdf

² http://www.who.int/neglected_diseases/news/criteria-eliminate-sleeping-sickness/en/

³ Treatment options for second-stage *gambiense* human African trypanosomiasis. Gilles Eperon, Manica Balasegaram, Julien Potet, Charles Mowbray, Olaf Valverde and François Chappuis. *Expert Rev Anti Infect Ther*. 2014 Nov 1; 12(11): 1407–1417. doi: 10.1586/14787210.2014.959496

To deliver rapid and tangible benefits for patients and health staff, DNDi first pursued a short-term strategy to demonstrate the safety and efficacy of combining existing drugs to treat HAT. The nifurtimox-eflornithine combination therapy (NECT) developed in 2009 was the first new treatment in 25 years against sleeping sickness.

However, despite the considerable improvements brought about by NECT, the challenge of making treatment accessible in very remote settings remained acute.

To change the course of the disease more radically and support sustainable global and national control or elimination

efforts, DNDi's long-term strategy thus focused on the development of entirely new and innovative oral treatments: fexinidazole, which was recommended by the European Medicines Agency as first all-oral treatment for HAT caused by *Trypanosoma brucei gambiense* in November 2018, and acoziborole.

“

I came to the hospital with my wife and I was diagnosed with sleeping sickness. My wife cried when she heard it. I'm the one who provides food for my nine children – being in the hospital means I can't provide for them.

Pablo Loela, 50 years old, a subsistence farmer, is receiving treatment for sleeping sickness at Masamuna hospital in Kwilu province in the Democratic Republic of Congo. Pablo started sleeping during the daytime and began getting splitting headaches, vertigo, and stomach pains, so he came to the hospital. Pablo had to stay 10 days at hospital to complete his treatment, 10 days away from his work to feed his family.

Sleeping sickness at the cusp of elimination

Sleeping sickness is caused by two subspecies of parasite, both transmitted by the tsetse fly:

Trypanosoma brucei gambiense (g-HAT), which accounts for 98% of reported sleeping sickness cases⁴, and *T. b. rhodesiense* (r-HAT). While humans are a reservoir for g-HAT, animals are a reservoir for r-HAT.

g-HAT is endemic in 24 countries of West and Central Africa; r-HAT in 13 countries of Eastern and Southern Africa. The majority of patients live in the Democratic Republic of Congo, where 78% of g-HAT cases were reported in 2017⁵, followed

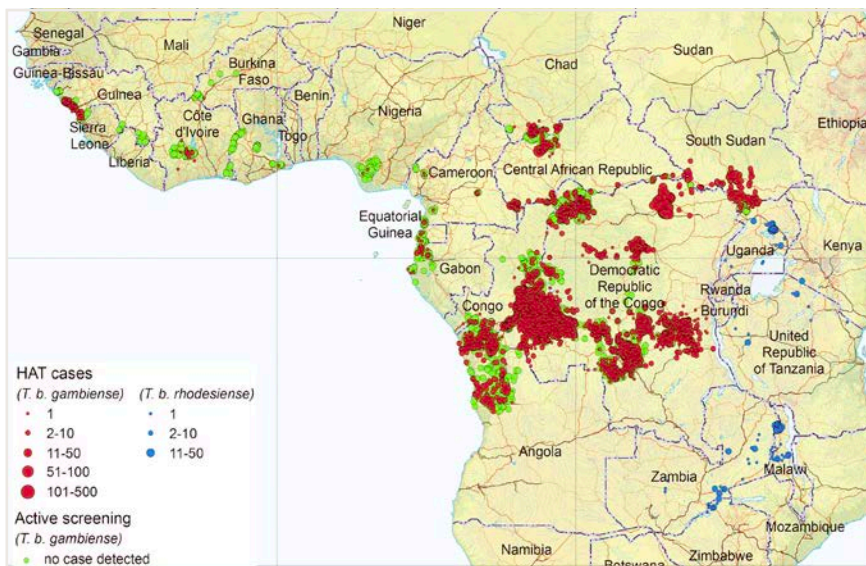
by the Central African Republic, Guinea, and Chad.

The disease occurs in two stages. The early, haemo-lymphatic stage (or stage 1) has symptoms such as fever or chills that make it hard to distinguish from malaria or other diseases, and as a result is often missed or misdiagnosed. In the later meningo-encephalitic stage (stage 2), the parasite crosses the blood-brain barrier and causes serious neurological disorders including sleep cycle disruptions, neurological manifestations, and progressive mental deterioration.



78%
of g-HAT cases reported
in the DRC in 2017.

**Sleeping sickness
is usually fatal
if left untreated.**



The distribution of human African trypanosomiasis (2012 – 2016)⁶

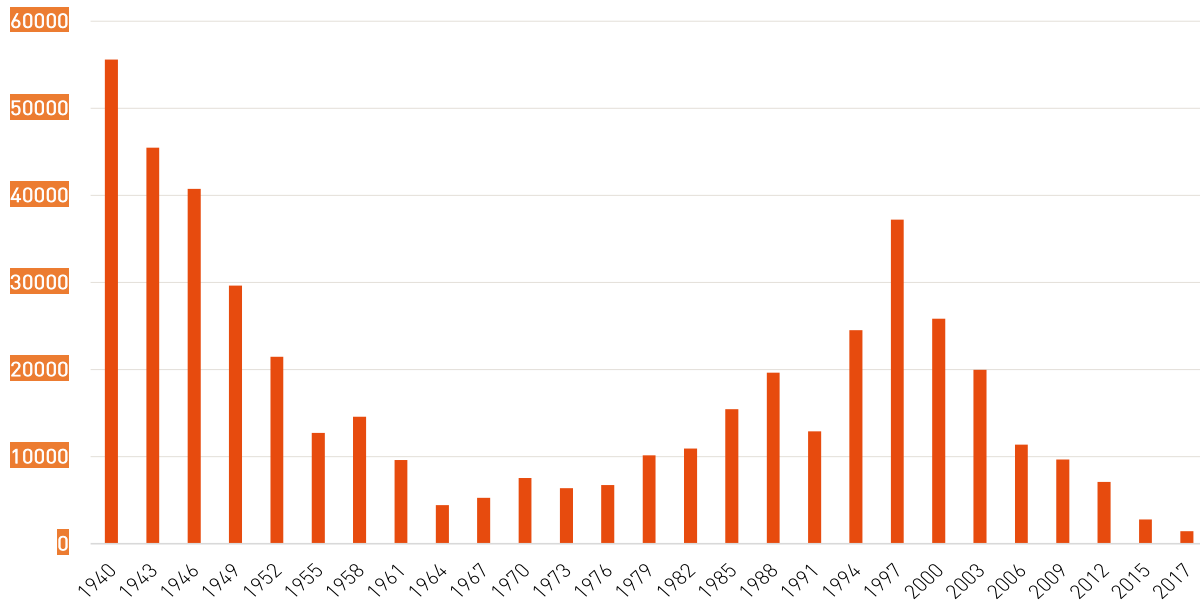
g-HAT is endemic in 24 countries of West and Central Africa; r-HAT in 13 countries of Eastern and Southern Africa.

⁴ WHO Factsheet on human African trypanosomiasis, February 2018. [http://www.who.int/news-room/fact-sheets/detail/trypanosomiasis-human-african-\(sleeping-sickness\)](http://www.who.int/news-room/fact-sheets/detail/trypanosomiasis-human-african-(sleeping-sickness)).

⁵ WHO Global Health Observatory data repository. 2017. <http://apps.who.int/gho/data/node.main.A1636?lang=en>

⁶ Franco JR, Cecchi G, Priotto G, Paone M, Diarra A, *et al.* [2018] Monitoring the elimination of human African trypanosomiasis: Update to 2016. *PLOS Neglected Tropical Diseases* 12(12): e0006890. <https://doi.org/10.1371/journal.pntd.0006890>

THE HISTORY OF SLEEPING SICKNESS



Colonial era: In the 1890s, 500'000 people in what is then the Belgian Congo and more than 200'000 in British-controlled Uganda die from sleeping sickness. In the 1920s, mobile teams are established and follow the "Jamot Method" of systematic active case detection and treatment, with the ultimate objective the elimination of the parasite from the human reservoir.

1960s: This approach succeeds in reducing the number of cases to below 5'000 per year. This decrease in prevalence, along with severely constrained resources following the independence of most endemic countries, means activities including vector control and mobile teams are drastically reduced, causing generalised resurgence of the disease.

1990s: The withdrawal of external aid leads to a collapse of the mobile team system, with conflict and instability fueling

further resurgence of sleeping sickness. A new epidemic occurs with a spike of 35'000 reported cases a year, including some villages reporting case levels as high as 50% of the entire population.

The history of sleeping sickness is one marked by the appearance of deadly epidemics interspersed by decades where the disease seems largely under control.

2000s: The World Health Organization (WHO) signs donation agreements with pharmaceutical companies such as Aventis (later Sanofi) and Bayer to access

treatments and control the disease. Donors, in particular Belgium, renew their support. In 2009, a new combination therapy known as NECT, developed by DNDi and partners, is introduced, replacing an arsenic-based highly toxic treatment that killed one in every 20 patients. The number of reported cases drops below 10'000 for the first time in decades.

2010s: In 2012, WHO launches its Roadmap, a comprehensive plan of control, elimination and eradication targets for 17 NTDs - including sleeping sickness - to be reached by 2020. Leaders from global health and development organizations and the pharmaceutical industry pledge in the London Declaration to work to reach WHO's 2020 elimination goals for 10 NTDs. In 2017, the total number of HAT reported cases was below 1'500, continuing the decreasing trend observed during the recent years after the introduction of NECT.

Bringing simple, safe, and effective treatments closer to a patient's home

DNDi's longer-term R&D strategy remains to identify and develop two entirely new oral drugs that are effective against both stages of the disease, both parasite subspecies, and can be used at home.

Before 2009, the best treatment for sleeping sickness, eflornithine, was extremely complex to distribute and administer in regions affected by the disease.

All-too-often, doctors would have no choice but to use melarsoprol, a highly toxic, arsenic-based drug. Treatments improved radically in 2009, when Epicentre/Médecins Sans Frontières (MSF)/DNDi clinical trials demonstrated the safety and efficacy of a safer and shorter nifurtimox and eflornithine combination therapy (NECT).

DNDi's longer-term R&D strategy remains to identify and develop two entirely new oral drugs that are effective against both stages of the disease, both parasite subspecies, and can be used at home. Today, with fexinidazole and acoziborole, that ambitious objective is almost within reach.



Photo: Neil Brandvold - DNDi

Before 2009: toxic or complex treatments

Melarsoprol - So painful that it was dubbed “fire in the veins”, this arsenic derivative killed 1 in 20 patients.

Eflornithine - So difficult to transport, distribute and administer, as it required 14 days of hospitalization and 56 intravenous infusions.

The first treatment revolution: NECT (2009)

NECT - Now used to treat 100% of all stage-2 patients with g-HAT in all endemic countries. Shorter and safer for patients and for health staff.

But treatment remains cumbersome, difficult to ship, store and administer; patients must still be hospitalized to receive the intravenous infusions, as well as undergo a lumbar puncture first to determine the stage of the disease. The need to bring a simple, safe, and effective treatment as close as possible to the patient's home remains.



Photo: Xavier Vahed - DNDi

Game-changing: Simpler, safe, and effective oral therapies that work for both disease stages will bring treatment closer to a patient's home.

FEXINIDAZOLE- THE FIRST ALL-ORAL CURE | The result of DNDi's compound mining activities, fexinidazole will consist of one daily dose of pills for ten days, and will be the same for both stages of the disease.

ACOZIBOROLE – ONE DOSE FOR A CURE? | Acoziborole is the first DNDi new chemical entity resulting from its own lead optimization programme to enter clinical development. Thanks to an unusually long half-life when tested in healthy volunteers, acoziborole could be administered as a single dose. If proved safe and effective, acoziborole will become a key tool to sustain the elimination after 2020.

Fexinidazole: The first all-oral treatment for sleeping sickness

Fexinidazole is the first new chemical entity to have been developed by DNDi, which has steered its progression through all stages of the drug development pipeline from lab to patient. The 'fexi' story is one which illustrates the benefits of DNDi's alternative R&D approach that puts patient needs at the centre and harnesses the capacities of actors from all sectors, including pharmaceutical companies, medical humanitarian organizations, Ministries of Health of endemic countries, and the World Health Organization.

2005

DNDi begins 'compound mining' to profile activity against the sleeping sickness parasite in more than 700 different potential compounds from 15 different sources in academia and industry, in collaboration with the Swiss Tropical and Public Health Institute (Swiss TPH). These efforts lead to the identification of fexinidazole, on which Hoechst (now Sanofi) had initiated pre-clinical development in the 1970s, but which had not entered clinical studies.

2009

DNDi and Sanofi team up on development and manufacturing. A collaboration agreement for the development, manufacturing, and distribution of fexinidazole gives DNDi the responsibility for pre-clinical, clinical, and pharmaceutical development, while Sanofi handles industrial development, registration, production, and distribution of the drug.

2011

DNDi and Sanofi request joint scientific advice from the US Food and Drug Administration and the European Medicines Agency, with WHO support, on the clinical development plan for fexinidazole. This leads to the development of a protocol for a single pivotal Phase II/III study to prove the safety and efficacy of fexinidazole, with NECT as the active comparator.

2007

Pre-clinical studies begin. Sanofi provides initial samples, data, and advice based on the previous Hoechst development programme. DNDi performs extensive regulatory toxicology studies, including safety pharmacology and animal studies, showing fexinidazole has a good safety profile.

2010

Phase I studies begin. DNDi carries out clinical trials assessing the safety and pharmacokinetics of fexinidazole in human volunteers given in single and multiple doses.

2018

The European Medicines Agency recommends fexinidazole as the first all-oral treatment that has been shown to be efficacious for both stages of HAT caused by *T.b. gambiense*. Fexinidazole could eliminate the need for systematic hospitalization and lead to potential reduction in number of lumbar punctures.



2012

Phase II/III pivotal clinical study in stage 2 g-HAT begins in the Democratic Republic of Congo (DRC) and Central African Republic (CAR), with the DRC national control programme (PNLTHA) playing a key role in study implementation. 394 patients were recruited at ten clinical sites in the DRC and CAR, with Médecins Sans Frontières supporting the management of two trial sites in hard-to-reach locations.

2016

A Phase IIIb study on special population groups excluded from previous studies is initiated, including pregnant or lactating women, and patients with poor nutritional status or with chronic diseases. Patients are treated either in hospital, or at home, thereby providing also preliminary information about treatment compliance and final effectiveness in ambulatory patients.

2014

Complementary cohorts are added to the study.

Two additional cohorts, one in 230 adult patients with stage 1 and early stage 2 of the disease, and another in 125 children between six and 14 years of age, are initiated, in eight of the DRC sites.

2017

Results confirm that fexinidazole is safe and effective, and presents significant advantages over NECT as it is all-oral and treats both stages of the disease. A dossier is submitted to the European Medicines Agency under Article 58 for the treatment of g-HAT, for both stages of the disease.

Overview of DNDi clinical trials on fexinidazole



> 2 million people screened for sleeping sickness

Over five years, across 10 sites in Democratic Republic of Congo (DRC) and the Central African Republic (CAR), 749 patients were included in three clinical trials to determine the safety and efficacy of fexinidazole. More than two million people were screened for sleeping sickness as a part of the trial. The DRC national sleeping sickness control programme (PNLTHA) was the principal investigator and various partners of the HAT platform collaborated.



749 patients included in 3 studies

The results, published in *The Lancet* in October 2017⁷, show that fexinidazole is safe and effective.

Prior to conducting the trial, an acceptable inferiority margin of fexinidazole versus NECT was set at 13%, following a survey with practitioners, based on the significant advantage of having a treatment that is oral, and that could remove both the need for a lumbar puncture to determine the stage of the disease, and the systematic hospitalization of patients.

FEX004 [2012-2016] 394 patients	To assess the efficacy and safety of fexinidazole in stage 2 g-HAT adults compared with NECT	Study confirms the efficacy of fexinidazole in stage 2 g-HAT patients with a success rate at 18 months post-treatment of 91.2% for fexinidazole, versus 97.6% for NECT within the margin of acceptable difference of -13%.
FEX005 [2014-2017] 230 patients	To assess the efficacy and safety of fexinidazole in stage 1 g-HAT and early stage 2 g-HAT adults compared with historical data on NECT	Studies confirm the efficacy of fexinidazole in stage 1 and early-stage 2 g-HAT patients with a success rate of 98.7% and in children with a success rate of 97.6% [95% CI [93.1% - 99.5%] at 12 months post-treatment.
FEX006 [2014-2017] 125 patients	To assess the efficacy and safety of fexinidazole in children compared with historical data on NECT	

Another study (FEX 009) which started in 2016 is currently on going to generate information on special population groups (including pregnant or lactating women, and patients with poor nutritional status or with

chronic diseases) not included in previous fexinidazole trials. Patients will be treated either in hospital, or at home depending on their clinical status, thereby providing preliminary information about the treatment

compliance and final effectiveness in ambulatory patients. 104 patients (out of 174) have been recruited so far (November 2018) in 9 clinical sites in Democratic Republic of Congo and Guinea.

⁷ Oral fexinidazole for late-stage African *Trypanosoma brucei gambiense* trypanosomiasis: A pivotal multicentre, randomized, non-inferiority trial. Kande Betu Ku Mesu V, Mutombo Kalonji W, Bardonneau C, Valverde Mordt O, Blesson S, Simon F, Delhomme S, Bernhard S, Kuziena W, Fina Lubaki JP, Lumeya Vuvu S, Nganzobo Ngima P, Mahenzi Mbembo H, Ilunga M, Kasongo Bonama A, Amici Heradi J, Lumaliza Solomo JL, Mandula G, Kaninda Badibabi L, Regongbenga Dama F, Kavunga Lukula P, Ngolo Tete D, Lumbala C, Scherrer B, Strub-Wourgaft N, Tarral A. *The Lancet* 2017, doi: 10.1016/S0140-6736(17)32758-7. <https://www.thelancet.com/action/showPdf?pii=S0140-6736%2817%2932758-7>

A REGULATORY STRATEGY DESIGNED TO FACILITATE ACCESS

The next steps will include working with WHO and HAT Platform member countries to expand access programmes.

Following these results, Sanofi, DNDi's industrial partner on fexinidazole, submitted in December 2017 a dossier for review by the European Medicines Agency (EMA).

The EMA reviewed fexinidazole under a special procedure called "Article 58", which allows the EMA to give a scientific opinion, in co-operation with World Health Organization (WHO), for the

evaluation of medicinal products that are intended exclusively for markets outside of the European Union.

Fexinidazole was previously granted accelerated assessment by the EMA, with a view to ensuring patient access to fexinidazole in HAT-endemic countries. Portugal was selected as rapporteur, UK, the Netherlands as the co-rapporteur,

and Uganda and Democratic Republic of Congo as observer countries for the submission and review of the dossier.

In November 2018, the EMA recommended fexinidazole as the first all-oral treatment for HAT caused by *T. b. gambiense*, paving the way for registration of fexinidazole in endemic countries and its distribution by WHO.

10 CLINICAL TRIAL SITES FOR THE FEXINIDAZOLE STUDIES (FEX004, FEX005, FEX006)



More than 200 people in the Democratic Republic of the Congo and Central African Republic have been actively engaged in DNDi's five-year clinical development effort for fexinidazole.

This unprecedented effort generated data enabling Sanofi to submit a regulatory dossier to the European Medicines Agency.

All data were collected and managed by Congolese, notably the Congolese National Sleeping Sickness Control Programme, working closely with the national and provincial health system.

Conducting clinical trials in remote and unstable areas



Photo: Neil Brandvold - DNDi

The journey to the sleeping sickness trial site in Isangi from the DNDi office in Kinshasa begins in the domestic airport of DRC's capital city and ends more than a day later halfway across the country in a barge crossing the Congo river. In between: hours spent navigating potholed dirt roads, collapsed bridges, checkpoints, and multiple river crossings. Once at Isangi, canoes must be used to reach many of the patients as there are no roads.

Yet for DNDi's clinical team in DRC, Isangi is one of the easier-to-reach sites. The DRC and the Central African Republic (CAR) both pose daunting challenges that must be overcome to develop better treatments for patients suffering from sleeping sickness.

The DRC and the Central African Republic (CAR) both pose daunting challenges that must be overcome to develop better treatments for patients suffering from sleeping sickness.

Political instability is a major challenge. Armed conflict in CAR forced DNDi to stop recruitment of patients in 2013. "Despite this constraint, we managed to follow-up more than half of the patients who had been treated," says Dr Francis Regongbenga, Principal Investigator for CAR at the Batangafo site.

A second important challenge is infrastructure. It is imperative that wards, labs, and other facilities conduct clinical research that is up to par with "Good Clinical Practice" (GCP).

Clinical trial sites were brought up to these standards – not a small task considering their remote location. Nine referral treatment units were renovated and refurbished, with solar energy equipment and generators installed. Equipment was brought in: new microscopes equipped with cameras and Piccolo analyser – a fully automated system for blood testing and defibrillators. Internet access was installed to enable transmission of case report forms, particularly necessary for the monitoring of safety parameters.

“With the fexinidazole clinical trial, everything changed. Not only does our hospital no longer look like a farm, but the community benefits from a modern facility and our work is easier,” says Watson Tawaba, nurse at the Bagata site in DRC.

Overcoming the lack of trained staff is another hurdle. Through the HAT Platform – a clinical research network to strengthen capacities in endemic regions set up with the support of DNDi in 2005 – trainings were provided in diagnostic and treatment procedures, pharmacovigilance, GCP guidelines, and even medical waste management.

The joint experience of DNDi and the national sleeping sickness programme in the DRC shows it is possible to build an environment conducive to running quality clinical trials. These efforts build and sustain the capacity to conduct a high standard of clinical research in endemic countries, but they also bring lasting benefits to researchers, staff and hospitals, as well as to health systems more broadly, and thus ultimately to local communities and patients.



Photo: Neil Brandvold - DNDi

Looking to the future: Acoziborole, a single-dose oral treatment to achieve sustained elimination of sleeping sickness

DNDi's investment into sleeping sickness R&D does not end with fexinidazole.

An oxaborole originally owned by Anacor Pharmaceuticals (later acquired by Pfizer) was found to be active against HAT parasites at the University of California San Francisco, and further investigated by a consortium consisting of DNDi, Anacor, SCYNEXIS, Pace University, and Swiss TPH.

Compound optimization involving the examination of over 1,000 compounds produced acoziborole, which was selected as a promising pre-clinical candidate for *T.b. gambiense* sleeping sickness in late 2009.

In pre-clinical studies, acoziborole was shown to be safe and efficacious in treating a brain form of the disease in animals, when administered orally in a single dose.

Acoziborole was found to have an unusually long half-life when tested in healthy volunteers. In March 2012, acoziborole became DNDi's first new chemical entity resulting from its own lead optimization programme to enter clinical development.

Phase I trials on this new chemical entity were completed in 2015, and allowed the therapeutic dose to be determined, administered as a single dose of three tablets. A pivotal Phase II/III trial started in

the last quarter of 2016. Eleven clinical sites in Democratic Republic of Congo and Guinea have so far (November 2018) recruited 136 late-stage 2 patients and 34 early-stage patients.

The submission of a regulatory dossier to the European Medicines Agency under Article 58 is planned for 2021, for the treatment of *T.b. gambiense* HAT (both stages) with acoziborole. Combined with a rapid diagnostic test, acoziborole promises to be a game-changer offering a "foci-based" treatment approach for remote areas, conflict zones and sentinel sites where re-emergence of sporadic cases occur after wider use of fexinidazole.

Acoziborole, if proved safe and effective, will thus be a key tool to achieve a sustained elimination of the disease.

In pre-clinical studies, acoziborole was shown to be safe and efficacious in treating a brain form of the disease in animals, when administered orally in a single dose.



Photo: Sébastien Bolesch



Photo: Xaxier Vahed- DNDi

“
NECT was the first revolution in the treatment of sleeping sickness. Fexinidazole could be the next. I am full of hope for patients and the national programmes.

Dr Wilfried Mutombo, DNDi Project Coordinator for HAT

DNDi Partners: Accelera, Italy; Advinus Therapeutics Ltd, India; Aesica, UK; Amatsi Aquitaine (formerly Bertin Pharma), France; Aptuit, Italy; Avista Pharma (formerly SCYNEXIS), USA; Biotrial, France; Cardiabase, France; CBCO, DR Congo; Centipharm, France; Creapharm, France; Drugabilis, France; Eurofins-Optimed, France; HAT Platform; Institut de Recherche pour le Développement, France; Institut National de Recherche Biomédicale, DR Congo; Institute of Tropical Medicine Antwerp, Belgium; Laboratory of Microbiology, Parasitology, and Hygiene, University of Antwerp, Belgium; Luxembourg Institute of Health, Luxembourg; Médecins Sans Frontières; National Control Programmes of the Democratic Republic of Congo, the Central African Republic, and of Guinea; Pace University, USA; Patheon, UK; Pfizer Inc., USA; Pfizer Inc. (formerly Anacor Pharmaceuticals Inc.), USA; PhinC, France; RCTs, France; Sanofi, France; SGS, Belgium; SGS, France; Swiss Tropical and Public Health Institute, Switzerland; Theradis Pharma, France; WHO-NTD (Neglected Tropical Diseases department).



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A not-for-profit research and development organization, DNDi works to deliver new treatments for neglected diseases, notably leishmaniasis, human African trypanosomiasis, Chagas disease, specific filarial infections, and mycetoma, and for neglected patients, particularly those living with paediatric HIV and hepatitis C.

Since its inception in 2003, DNDi has delivered eight treatments: two fixed-dose antimalarials (ASAQ and ASMQ), nifurtimox-eflornithine combination therapy (NECT) for late-stage sleeping sickness, sodium stibogluconate and paromomycin (SSG&PM) combination therapy for visceral leishmaniasis in Africa, a set of combination therapies for visceral leishmaniasis in Asia, paediatric dosage forms of benznidazole for Chagas disease, a 'super-booster' therapy for children co-infected with HIV and TB, and the first all-oral drug for sleeping sickness (fexinidazole).

For sleeping sickness, DNDi aims to develop two drugs that are safe, effective against both stages of the disease and both subspecies of the parasite, and orally administered, in order to replace current first-line treatment and to simplify case management. The ultimate goal is to achieve and sustain the elimination of the disease as a public health problem by 2020 as targeted by WHO.

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