HAT DNDi program progress and evolution in the path to elimination

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HAT Platform, Kampala
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DNDi’s Mission

• To develop new drugs or new formulations of existing drugs for **people suffering from neglected diseases**.

• To develop drugs for the **most neglected diseases** (such as sleeping sickness, leishmaniasis, and Chagas disease), while considering engagement in **R&D projects for other neglected patients** (e.g. malaria, paediatric HIV, filarial infections).

• To **strengthen capacities in a sustainable manner**, including through know-how and technology transfers in the field of drug R&D for neglected diseases.

• To adopt a **dynamic portfolio approach**
Responding to the needs of patients suffering from neglected diseases

DNDi’s PRIORITY: Neglected Patients

- Hepatitis C
- Sleeping sickness
- Mycetoma
- Malaria
- Chagas disease
- Paediatric HIV
- Leishmaniasis
- Filarial diseases

+ incubation with WHO of:

...from bench to bedside
Sleeping Sickness

Search for a simplified and improved treatment
Two new treatments in development to achieve and sustained elimination

15 years ago
Melarsoprol: Toxic, resistant
Eflornithine: Unavailable

Since 2009
NECT Improved therapy

2018
Fexinidazole Oral treatment (10 days)

Future objective
Acoziborole Single-dose, oral treatment
A better, simpler treatment for sleeping sickness

Nifurtimox-eflornithine combination therapy

**Objective:** Develop and implement a safe, effective, and adapted treatment for stage 2 *gambiense*

- **2003:** single study by MSF and Epicentre in Congo
- **2004:** additional sites in DRC by DNDi in collaboration with Epicentre, MSF, STI (now Swiss TPH), and DRC National Control Programme (PNLTHA)
- **2008:** multi-centre clinical study comparing efficacy and safety in 287 patients finds NECT as well-tolerated as eflornithine monotherapy
- **2009:** NECT included in WHO Essential Medicines List
- **2010-2012:** Implementation study including adults, pregnant and breastfeeding women, and children
- **Ongoing:** DNDi continues to support access to NECT in endemic countries
**Fexinidazole**

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

**PARTNERS:** BaseCon; Bertin Pharma; Venn Life Sciences (previously Cardinal Systems); Cardiabase; Médecins Sans Frontières, and other HAT Platform members; Phinc Development; National Control Programmes of the Democratic Republic of Congo and the Central African Republic; RCTs; Sanofi; Swiss Tropical and Public Health Institute (Swiss TPH); SGS; Theradis Pharma

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2007: Selection of fexinidazole as pre-clinical candidate for HAT

2008: Pre-clinical development completed. Prototype tablets available

2009: Phase I starts in France

2010: Phase I completed

2012: Phase II/III starts in DRC and CAR. Sanofi industrial partner. Comparing fexinidazole vs NECT in patients with stage 2

2015: Phase II/III completed. Inclusion of 394 patients. 2 additional studies for stage 1 and early stage 2 (230 p.) and children (125 p.) patients also completed recruitment.

2016: follow-up for the 3 studies + start of an implementation study in outpatients

2017: **Phase II/III results:** 91.2% efficacy + submission to EMA in December 2017

2019: EDCTP funded Trial for *Tb rhodesiense* to start
Promising Oral-only Single Dose Treatment for Sleeping Sickness to Enter Phase II/III Clinical Study

**ACOZIBOROLE**

**Objective:** Develop and register acoziborole as a new drug for the treatment of stage 2 *T. b. gambiense*, ideally also for stage 1.

**PARTNERS:** Anacor Pharmaceuticals; Advinus Therapeutics; SCYNEXIS; Swiss Tropical and Public Health Institute; Institute of Tropical Medicine – Antwerp; Institut de Recherche pour le Développement; Institut National de Recherche Biomédicale

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- Identified as hits against *T. b. brucei* at Sandler Center, University of California San Francisco
- Innovative partnership with 2 biotechs (Anacor, Scynexis) and 1 university (Pace) in the US
- End 2009: First NCE resulting from DNDi lead optimization programme
- 2011: Pre-clinical development
- 2012: Phase I study in France
- June 2016: Start of Phase II/III clinical study in DRC in adults with stage 2 HAT
- May 2017: inclusion of adults with stage 1 HAT
- Jan 2019: Inclusions to be completed
The challenge of conducting Phase II/III trial

• Site selection oriented by epidemiology

• Infrastructure
  • Patient wards, Laboratory, Pharmacy, Invest. office
  • Telecommunication, electricity, cold chain
  • Water, sanitation and waste disposal

• Staff training
  • GCP, Clinical, Nursing, Lab procedures, electronic data transfert

• Equipment
  • Microscopy with camera (video),
  • HAT diagnosis, Biochemistry, haematology, digitalised ECG recording, PK/PD sample collection
DNDi HAT Clinical trial sites
The challenge of recruitment: support to case detection in 2017-18

• Active case detection
  • Support 10 NSSCP Mobile teams
    • 1,000,000 examined persons
    • 110 detected HAT cases

• Passive case detection
  • 10 hospitals (study sites)
  • Since 2018 additional centers at the peripheral level:
    • 9 able to do serological + parasitological testing
    • 22 only serological testing + trypanolysis sampling to send to INRB
    • Reactive screening of those serologically identified previously
    • Additional PNLTHA active case detection with ITM collaboration
FEX009 STUDY UPDATE

Recruitment status as of 31-August

<table>
<thead>
<tr>
<th>Screened Patients</th>
<th>Screen Failures</th>
<th>In screening</th>
<th>Included</th>
<th>D11</th>
<th>M3</th>
<th>M6</th>
<th>M12</th>
<th>M18</th>
<th>Withdrawals, LFU, death</th>
</tr>
</thead>
<tbody>
<tr>
<td>106</td>
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<td>3</td>
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</tbody>
</table>

Patient disposition:
- 67 in- / 24 out-patients
- 61 stage 2 and 30 stage 1
**OXA 002 recruitment update**

- Recruitment by August 31, 2018

<table>
<thead>
<tr>
<th>Screened patients</th>
<th>Screen Failures</th>
<th>On Screening</th>
<th>Stage 2 patients &gt; 20 Cells in CSF</th>
<th>M3 FU</th>
<th>M6 FU</th>
<th>M12 FU</th>
<th>M18 FU</th>
</tr>
</thead>
<tbody>
<tr>
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<td>124</td>
<td>123</td>
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<td>58</td>
<td>23</td>
</tr>
</tbody>
</table>

![Graph of OXA002 recruitment](image-url)

- New forecast (until Dec 18)
- Late Stage 2 (stage 2 AND GB>20/μL)
- Stage 2 (stage 2 AND GB>20/μL)/Early/Intermediate Stages
- Recruitment trend

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*DNDi*

*Drug for Neglected Disease Initiative*
Conclusion: Sustained disease elimination requires new tools

- A **paradigm shift** in diagnosis and treatment is needed:
  - Treatment effective for stage 1 and 2 and for *T.b. gambiense* and *rhodesiense* => could avoid the need for staging lumbar puncture
  - Oral simplified treatment
  - Patients screened and diagnosed close to their village

- Efforts in **control and surveillance** (mobile teams, passive case-detection centres, sentinel surveillance sites) need to be sustained to avoid re-emergence of the disease.
Partners on sleeping sickness R&D

**CLINICAL PARTNERS: REGIONAL PLATFORM FOR CLINICAL RESEARCH**

- National sleeping sickness control programmes, research institutions and national laboratories of public health of the most affected endemic countries:
  - Swiss Tropical and Public Health Institute (Swiss TPH), Switzerland; Institute of Tropical Medicine-Antwerp, Belgium; Institut National de Recherche Biomédicale (INRB), DRC; University of Makerere, Uganda; Kenya Agricultural Research Institute – Trypanosomiasis Research Centre (KARI-TRC), Kenya; Tropical Medicine Research Institute (TMRI), Sudan; Institut Pasteur Bangui, University of Juba, South Sudan; CAR; Médecins Sans Frontières (MSF); Foundation for Innovative New Diagnostics (FIND), Switzerland; Eastern Africa Network for Trypanosomosis (EANETT); Centre interdisciplinaire de Bioéthique pour l’Afrique Francophone (CIBAF); The National Sleeping Sickness Control Programme of Guinea; INZI Project of the University of Edinburgh. WHO Department of Neglected Tropical Diseases, as observer.

**INDUSTRIAL PARTNERS**

- Bayer
- Sanofi
- SCYNEXIS
- Avista Pharma
- Anacor Pharmaceuticals
- Adivus

**DONORS**

- Norad
- giz
- Ministry of Foreign Affairs of the Netherlands
- Bill & Melinda Gates Foundation
- Swiss Agency for Development and Cooperation (SDC)
- AECID

**NGOs**

- World Health Organization
- The University of Edinburgh
- Makerere University

**UNIVERSITIES**

- LMMP
  University of Antwerp
- University of Juba

**RESEARCH INSTITUTES**

- Swiss TPH
  Institut National de Recherche Biomédicale (INRB), DRC
- INZI Project of the University of Edinburgh
Thank you
Merci

DNDi
Drugs for Neglected Diseases initiative