Clinical Development of New Treatments for Sleeping Sickness

Antoine TARRAL
ASTMH Nov. 2016, Atlanta
Supporting WHO HAT elimination goals

WHO set goals for Global Elimination of sleeping sickness by 2020, supported by London Declaration (2012)

DNDi contributes by:

- Developing two new oral treatments for both stages of the disease
- Supporting mobile teams for the village screening
- Preforming capacity building
- Strengthening clinical staff competencies
Sleeping sickness: Two new treatments in development to support sustainable elimination

13 years ago
Melarsoprol: Toxic, resistant
Eflornithine: 14 Days IV infusion

Since 2009
NECT= nifurtimox+ eflornithine
Improved therapy

2018?
Fexinidazole
once daily Oral treatment for 10 days

2020?
SCYX-7158
Single-dose, oral treatment
By 2018, DNDi aims to deliver an oral, safe, effective treatment for both stage 1 and stage 2 g-HAT disease

Target product profile (main points):

• Effective against stage 1 and 2
• Broad spectrum (\textit{T. b. gambiense} and \textit{T. b. rhodesiense})
• Non inferior efficacy to NECT in \textit{T. b. gambiense}
• Safe in pregnancy and for lactating women
• Adult and paediatric formulations
• No need for monitoring of AEs
• 10 days p.o. once daily (equal to NECT)
• Stability in zone 4 for >3 years
• Cidal
• Affordable and <100€/ course
Fexinidazole

- A chemical entity ‘rediscovered’ through compound mining
- Once daily ORAL administration with food for 10 days
- 600 mg tablets
  - Loading dose on D1-D4, 3 tablets /day +
  - Maintenance dose on D5-D10, 2 tablets /day

**PARTNERS:** BaseCon; Bertin Pharma; Venn Life Sciences; Cardiabase; MSF; Phinc Development; National Control Programs of the Democratic Republic of Congo and the Central African Republic; RCTs; Sanofi; Swiss Tropical and Public Health Institute; SGS; Theradis Pharma
### Fexinidazole - 4 clinical trials on going

<table>
<thead>
<tr>
<th>Trial Code</th>
<th>Description</th>
<th>Enrollment Details</th>
<th>Study Design</th>
<th>Registration ID</th>
<th>Start Date</th>
<th>End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEX004:</td>
<td>Single blind Pivotal phase II/III randomized versus NECT</td>
<td>Stage 2 g-HAT in adult patients (n=390)</td>
<td>FPI Nov 2012</td>
<td>LPO Nov 2016 (18 months FU)</td>
<td>NCT01685827</td>
<td></td>
</tr>
<tr>
<td>FEX005:</td>
<td>Open, adult patients stage 1 and early stage 2 g-HAT (n=230)</td>
<td></td>
<td>FPI June 2014</td>
<td>LPO Nov 2016 (12 months FU)</td>
<td>NCT02169557</td>
<td></td>
</tr>
<tr>
<td>FEX006:</td>
<td>Open, children 6-14 years old + &gt; 20kg bodyweight</td>
<td>Stage1 and Stage 2 g-HAT patients (n=125)</td>
<td>FPI June 2014</td>
<td>LPO Dec 2016 (12 months FU)</td>
<td>NCT02184689</td>
<td></td>
</tr>
<tr>
<td>FEX009:</td>
<td>Open, implementation study in-patients + out-patients cohort</td>
<td>all stages g-HAT patients Adult + children</td>
<td></td>
<td></td>
<td>(N=170)</td>
<td>FPI started Nov 2016</td>
</tr>
</tbody>
</table>

DNDiFEX004 protocol V3.0, Protocol DNDi/HAT FEX005 & 006 & DNDi-EX-09-HAT
Oral Single Dose Treatment for Sleeping Sickness to Enter Phase II/III Clinical Study

**Development**
- **Pre-clinical**
- **Phase 1**
- **Phase IIa/PoC**

**SCYX-7158 (AN5568)**

**Objective:** Develop and register SCYX-7158 as a new drug for the treatment of all stages of *T. b. gambiense*

- Early oxaboroles identified as hits against *T. b. brucei* at Sandler Center, University of California San Francisco
- Two year lead optimisation programme led and managed by DNDi in an innovative partnership with 2 biotechs (Anacor, Scynexis) and 1 university (Pace) in the US
- 2011: Pre-clinical development
- 2012: Phase I study in France
- Nov -2016 Initiation pivotal study in stage 2 g-HAT adults patients

**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
SCYX-7158 (AN5568)

- Lipophilic drug
- High volume of distribution
- High protein bound
- Cross the blood brain barrier
- Poorly metabolised

- half-life of 16 days
- Single oral administration of 3 tablets of 320 mg in fasted conditions (total dose 960mg)
SCYX-7158 Pharmacologically active exposure

Observed individual AUC\textsubscript{72-96} superimposed with estimated GM (and 90% CI)

Probability of reaching the target exposure

TARGET = AUC \textsubscript{0.24} of 5.8 \mu g.h/mL
960 mg single dose achieved an exposure of 1.5 times the target at AUC \textsubscript{72-96}

1. S. Wring & all, Parasitology (2014), 141, 104-118
2. Study report (final draft) PH11015/DNDi/001, PhinC/DNDi, August 2015.
High level planning
From toxic drugs and long hospital treatments towards a medicine for use at village level

Fexinidazole – a breakthrough stage-independent oral treatment
- Oral treatment for all stages, adults and children
- Once daily administration with food for 10 days
- Available progressively in existing HAT centres as 1st line treatment

SCYX-7158 – the tool for sustained elimination
- Oral treatment for all stages, adults and children
- Single dose treatment – no compliance issue
- Available as village-based treatment coupled with RDT
- Available in sentinel sites and unstable political regions
Thank you to our Donors and R&D Partners