DNDi Research & Development progress to tackle Sleeping Sickness

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DNDi Portfolio-Building Model: Address Immediate Patient Needs & Deliver Innovative Medicines

- **Long-term projects**
  - New chemical entities (NCEs)
- **Medium-term projects**
  - New formulations (fixed-dose combinations)
  - New indications of existing drugs
- **Short-term projects**
  - Completing registration dossier
  - Geographical extension

**Portfolio-Building Model**

- **Discovery**
  - R
  - LS
  - LO
- **Pre-clinical**
- **Clinical**
- **Implementation**
Sleeping Sickness: From Unacceptable to Better, Simple Treatment for Elimination

15 years ago:
- Eflornithine
- Melarsoprol

Since 2009:
- NECT

2017 & Beyond:
- Oral treatment
15 Years Ago: A Dire Situation

<table>
<thead>
<tr>
<th>Melarsoprol</th>
<th>Eflornithine</th>
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<tbody>
<tr>
<td>Toxic (~5% mortality)</td>
<td>Expensive</td>
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<tr>
<td>Ineffective (resistance)</td>
<td>Difficult to use</td>
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<tr>
<td>Painful when delivered</td>
<td>Not registered in endemic regions</td>
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Since 2009, NECT: Improved Treatment
But Still Not Ideal in Remote Areas

Nifurtimox-eflornithine combination therapy
- MSF & Epicentre initiated trial
- A simplified, safe & effective treatment for stage 2 HAT
- WHO Essential Medicines List (2009); Children (2013)
- Implemented in 13 countries, representing 100% of reported T.b. gambiense cases
- Drastic decrease in melarsoprol use

Treatments for stage 2 HAT in DRC (2012)
New Oral Treatment at Village Level

- A ‘rediscovered’ new chemical entity through compound mining
- Potential oral treatment 10 days one daily dose with food
- Phase II/III in DRC and CAR

**Fexinidazole**

**Oxaborole SCYX-7158**

- New chemical entity from the Lead Optimization programme
- Potential oral treatment with a single dose
- Entering Phase II/III in 2016

In partnership with Sanofi
Fexinidazole: 3 clinical trials ongoing

<table>
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<tr>
<th>Study</th>
<th>Description</th>
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<tr>
<td>FEX004</td>
<td>Pivotal phase II/III Stage 2 HAT in adults (n=390)</td>
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<tr>
<td>FEX005</td>
<td>Adult patients stage 1 and early stage 2 HAT (n=196)</td>
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<tr>
<td>FEX006</td>
<td>Children 6-14 years old, all stages (n=125)</td>
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Pivotal randomized control trial comparative with NECT. Blinded to sponsor. PRIMARY END point at 18 months

CRITERIA OF SUCCESS
- CURE: Patient alive, no Tryps, < 20 WBC
- Probable CURE: if no LP but no signs and symptoms of HAT
- FAILURE: Other cases

Plugged in cohort open studies 005 and 006 endpoint at 12 months
Fexinidazole: 2 new clinical trials in preparation

FEX007: Phase II Stage 2 r-HAT in adults (n=111)
FEX009: Cohort study all stages, all patients, field conditions

r-HAT 007: study shall be comparative with site matched historical cohort of melarsoprol treated patients.

Two sites identified: Lwala (Uganda); Rumphi (Malawi)
Primary end point survival at end of treatment (safety)
Secondary endpoint cure at 12 months

Implementation trial 009: To start in existing sites in DRC and to be extended afterwards to new sites in other countries (Guinea, Tchad)
Protocol in preparation

Both trials to start in 2016
SCYX 7158: Phase 1 trial

- Randomized, double blind, placebo controlled
- Safety, tolerability, pharmacokinetics and pharmacodynamics
- Single oral ascending doses in healthy male volunteers from 20 to 1200 mg
- 3 years, 14 cohorts, 128 included (102 active)
- Few mild/moderate adverse events with similar percentage placebo & active
- Phase II/III to start in 2016
- $T_{\text{max}}$ around 48h, stable for at least 4 days
- PK is linear but not dose proportional
- Slowly eliminated ($T_{1/2}$ of about 400h) single dose
- Unbound fraction around 2.2%
- Ratio CSF/plasma ranged from 1.8% to 3.2% indicating brain penetration
SCYX-7158
Pharmacologically active exposure

TARGET = AUC of 5.8 µg.h/mL
960 mg single dose achieved an exposure of 1.5 times the target at AUC
To be tested in Phase II/III: 3 tablets of 320 mg given at once