NEW TREATMENTS FOR SLEEPING SICKNESS

SCYX-7158 (AN5568)
NECT: The Urgent solution

- Previous treatment for 2nd stage HAT
  - Too toxic. Melarsoprol, 5% mortality
  - Cumbersome. Eflornithine 56 IV infusions 14 days

- NECT, since September 2009
  - By adding oral Nifurtimox 3 times per day,
  - Eflornithine infusion reduced to 7 days, 14 infusions

- Still heavy logistics and high cost
  - Kits: 4 treatments, weight 38 kg and costs €1152

- Adverse events
  - 93% of patients, average of 4 per patient

- Not yet fulfilling TPP

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To deliver two new treatments for HAT by 2018

- Fexinidazole: Registration for treatment of stage 2 and stage 1 HAT by end 2016
- SCYX-7158: Registration for stage 2 and stage 1 HAT by 2018

Characteristics of such a treatment: (TPP)

- Short-course oral treatment of no more than 10 days
- Could be used to manage stage 1 and 2 of the disease
- Safe enough to be used after a very simple RD test at a local level
- Offering the possibility of horizontal program for the management of the disease
- Much simpler and much cheaper than existing therapies: less than 50US$ per patient versus 440 US$ for the stage 2 of the disease
Fexinidazole

- **Discovery**: 1970 HOE 239, discontinued 1980
- Resuscitated in 2003

- **5-nitro-imidazole family**

- **Characteristics**
  - MOL.Wt FEXI = 279 g/mol
  - MOL.Wt M1 = 295 g/mol
  - MOL.Wt M2 = 311 g/mol
  - pKa-value = very weak base
  - logD<sub>7.4</sub> = 2.8

- **Metabolism**

  ![Chemical Structures]

  Fexinidazole → CYP → Fexinidazole sulfoxide (M1) → Fexinidazole sulfone (M2)

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Time to Kill Assays
Fexinidazole and Metabolites

Activity is concentration-dependent till MIC
But time-dependent for parasite cidal effect

Fexinidazole (IC₉₀ = 5.00 µg/ml)

Fexinidazole-Sulfoxide (IC₉₀ = 4.74 µg/ml)

Fexinidazole sulfone (IC₉₀ = 2.20 µg/ml)
Key preclinical data

- The most active metabolite is M2: Fexinidazole sulfone
- IC\(_{90}\) of M2 is 2.200 ng/mL T1/2 > 24H
- No drug interaction expected as several CYP P450 involved

- ADME  Rat brain concentration:

<table>
<thead>
<tr>
<th>Met ID</th>
<th>Collection time</th>
<th>8 h</th>
<th>24 h</th>
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<tbody>
<tr>
<td>fexinidazole</td>
<td>3.3 %</td>
<td>nd</td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>36.1 %</td>
<td>12.3 %</td>
<td></td>
</tr>
<tr>
<td>M2</td>
<td>56.1 **%</td>
<td>76.2 %</td>
<td></td>
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</tbody>
</table>

No genotoxicity, no phototoxicity
NOAEL = 200 mg/kg  Safety margin= 800mg/kg
Efficacy concentration in mice : 8-10 µg/mL of M2

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118 /154 subjects have been exposed to Fexinidazole

- **Tolerability study**
  - **Part 1**: Single ascending dose study 100mg – 3600mg
  - **Part 2**: Cross-over bioequivalence and food effect study (high fat rich meal / placebo)
    - 1200mg single dose
  - **Part 3**: Multiple ascending dose study for 14 days 3 cohorts of 8 subjects
    - Three cohorts of 8 subjects (6 active, 2 placebo) 1200mg, 2400mg & 3600mg

- **Field food interaction study (3way cross-over study ,12 subjects)**
  - Plumpy nuts, rice and beans / placebo 1200mg single dose

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Phase I studies (2)

- **POP PK analysis to evaluated the best therapeutic dose**
  - Multiple scenarios were explored
  - 1 dose/day for 10 days with food
    - loading dose for 4 days of 1800mg /day
    - + treatment dose for 6 days of 1200mg /day

- **Multiple dose in fed condition with the therapeutic dose**
  - Randomized, double-blind versus placebo
  - Two cohorts of 18 subjects (12 active, 6 placebo/cohort)
    - loading dose of 1800mg for 4 days + 1200mg for 4 days
    - loading dose of 2400mg for 4 days + 1200mg for 4 days

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PK Results

- Absolute Bioavailability ≈ 41% in mice; 30% in rats
  - Fexinidazole: median Tmx: 3-4 H; mean T1/2: 9-15H
  - M1 sulphoxide: median Tmx: 2-5 H; mean T1/2: 18-20H
  - M2 sulphone: median Tmx: 18-24 H; mean T1/2: 18-25H
- Exposure increased linearly, but not proportional to dose administered
- No saturation of the metabolism
- Steady state in fasted conditions: D4 for fexi and M1, D9 for M2
- Food effect: 2-3 fold increase in plasma concentration / fasting
- High plasma free fraction of the metabolites M1: 59% and M2: 43%

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M2 fed: Mean Plasma levels

- **high fat breakfast:**
  - AUC FEXI  $\times$ 5
  - AUC M2  $\times$ 4

- **rice & beans or Plumpy nuts:**
  - AUC FEXI and M2 $\times$ 2.5-3

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PK results: 1800/1200mg

M2 plasma levels
- reached earlier
- maintained for 3 to 4 days above 10 mg/L.
- In more than 80% of the subjects

IC$_{90}$ 2200ng/ml
Fexinidazole phase II/III
Schedule of visits phase II/III study

D-15
To
D-3

D-1
To
D+1

D1
To
D10

D13
To
D18

hospitalisation

M3

M6

M12

M18

M24

Diagnosis, malaria and helminths screening & tt

Randomisation

Study Treatment

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Strategic Development Plan for HAT disease

- **FEXI ADULTS**
  - Pivotal study versus NECT
  - Extension adults patients HAT stage 1&2

- **FEXI CHILDREN**
  - 121 children > 5 years old

- ART 58 regulatory process
- 195 pts success rate 12M
- early submission
- early approval
- Full submission
- Final Approval

- FU 12/2 M
- 18 M FU

- Rhodesiense study

- IMPLEMENTATION STUDY
SCYX-7158 (AN5568)

In collaboration with:
Anacor Pharmaceuticals, Inc.
Pace University
SCYNEXIS, Inc.
SCYX- 7158 (AN5568)  
First DNDi Preclinical Candidate for HAT From Lead Optimization Program\(^1,2\)

- Initial screening hit identified at UCSF Sandler Center (J. McKerrow)

- Initial “lead” identified from further screening and early SAR development at SCYNEXIS

- Optimized lead which was progressed to pre-clinical and clinical evaluation\(^3\)

- Phase 1 clinical trials started in 2012

\(^1\)Jacobs, RT, et al., Future Med Chem 2011, 3, 1259  
\(^2\)Nare, B, et al., Antimicrobial Agents Chemotherapy 2010, 54, 4379  

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SCYX-7158 PROPERTIES¹

- Mol. Wt. = 367.11 g/mol
- Pka = 9.61
- logD = 3.51
- MDCK-MDR1 $P_{\text{app}}(A-B) > 350$ nm/s
- Vd > 0.6 L/Kg = distribution into the whole body water
- Half-life of around 16 days single dose administration ²
- Oxidative deboronation to SCYX 3109 is primary metabolism³

¹SCYX-7158 Investigational Medicinal Product Dossier, DNDi, 2012.
²Study report PH11015/DNDIOXA001, PhinC/DNDi, April 2014.
Observed individual $AUC_{72-96}$ superimposed with estimated GM (and 90% CI)$^1$

\[ \text{Study report PH11015/DNDiOXA001, PhinC/DNDi, April 2014.} \]
Probability of reaching $\text{AUC}_{72-96}$ of 290000 ng*h/mL in plasma (corresponding to 5800 ng*h/mL in CSF) according to dose.
Conclusions

- Two new oral compounds to treat sleeping sickness
  - Fexinidazole once a day for 10 days
  - SCYX- 7158 (AN5568): Potential for single oral dose

- Both active against *T. brucei gambiense and rhodesiense*

- Along with a simplified field adapted diagnostic test

- On the way to changing the paradigm of treatments for sleeping sickness

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Publications

- **Fexinidazole**

- **SCYX-7158 (AN5568)**
THANK YOU