Fexinidazole a new oral treatment for sleeping sickness – update of development

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September 2011

DNDi
Drugs for Neglected Diseases initiative
Fexinidazole

- Discovery: 1970, HOE 239, discontinued 1980

- Chemical Name: 1H-imidazole, 1-methyl-2-[[4-methylthio) phenoxy] methyl] 5-nitro-imidazole

- PM = 279.31 g/mol

- Metabolism

![Fexinidazole Metabolism Diagram]

- Fexinidazole
- Fexinidazole sulfoxide (M1)
- Fexinidazole sulfone (M2)
**In vitro** activity of fexinidazole

<table>
<thead>
<tr>
<th>Compound Tested</th>
<th><em>T. b. rhodesiense</em> (IC\textsubscript{50})</th>
<th><strong>T. b. brucei</strong> (IC\textsubscript{50})</th>
<th><strong>T. b. brucei</strong> (MIC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fexinidazole (Batch 1)</td>
<td>1.265</td>
<td>2.86</td>
<td>5.00</td>
</tr>
<tr>
<td>Fexinidazole (Batch 2)</td>
<td>0.719</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Fexinidazole sulfoxide</td>
<td>0.487</td>
<td>1.96</td>
<td>4.74</td>
</tr>
<tr>
<td>Fexinidazole sulfone</td>
<td>0.354</td>
<td>0.89</td>
<td>2.20</td>
</tr>
</tbody>
</table>

*Data from STI

**Data from SCYNEXIS
Time Kill Assays - Fexinidazole and Metabolites

Fexinidazole (IC$_{50}$ = 2.86 µg/ml)

Fexinidazole-Sulfoxide (IC$_{50}$ = 1.96 µg/ml)

Fexinidazole sulfone (IC$_{50}$ = 0.89 µg/ml)

Wash-out IC$_{50}$ Values
General pharmacology

- **Standard genotoxicity battery**
  - Ames \(\text{Ames -ve}\)
  - In vivo micronucleus + test \(\text{negative}\)
  - In vitro chromosomal aberration \(\text{negative}\)

- **Enzymes, Radioligand Binding Assay**: \(0 < 10 \mu M\)

- **hERG**: partially + for M2

- **Telemetry in Dog**: negative
  - NOEL CV parameters and ECG intervals \(\geq 1000\) mg/kg

- **Irwin test in rat**: general behavior and body temperature
  - NOEL \(\geq 1000\) mg/kg.

- **Respiratory Parameters in rat**:
  - NOEL \(\geq 1000\) mg/kg.
General pharmacology(2)

- Good intestinal permeability (Caco-2)
  no limiting factor for absorption

- Good potential for BBB permeability (MDR1-MDCK)

- High plasma protein binding
  Fexinidazole 95% (human); 93% (mouse)

• **Metabolism**

\[
\text{Fexinidazole} \xrightarrow{\text{CYP}} \text{Fexinidazole sulfoxide (M1)} \xrightarrow{\text{FMO}} \text{Fexinidazole sulfone (M2)}
\]
Toxicology

NOAEL  Rat + Dog:  200 mg/kg/Day
with a MTD at 800 mg/kg/d based on general toxicity, not hepatic effect

Reprotox : NOAEL 200mg/kg/day
RAT :NOAEL for the pregnant mother = 200 mg/kg/day
• NOAEL for the FO= 200 mg/kg/day
• NOAEL for the F1= 200 mg/kg/day

Phototox:  Negative
Fexinidazole Clinical Studies
Phase I studies

- So far 96 subjects have been dosed

- **Part 1 (SAD) Study Design**
  - oral suspension escalation from 100 up to 3600 mg

- **Part 2 Cross-over bioequivalence and food effect Study**
  - 1200 mg single dose

- **Part 3 (MAD) Study Design**
  - Three cohorts of 8 subjects (6 active, 2 placebo)
  - Oral tablet (600 mg) once a day for 14 days 1200mg, 2400mg & 3600mg

- **Field food effect study ( cross-over study )**
  - Three cohorts of 12 subjects

- **Multiple dose in fed condition (on going)**
  - Randomized, double-blind versus placebo
  - Two cohorts of 18 subjects (12 active, 6 placebo)

- **Pop pk analysis**
PK Results

**Bioavailability**
- Fexi: rapidly absorbed: median Tmx: 3 – 4 H; mean T1/2: 9-15H
- M1: occurred rapid: median Tmx: 2-5 H; mean T1/2: 18-20H

**Exposure** increased linearly
**but not proportional** to dose administered

No saturation of the metabolism

**Steady state**: D4 for fexi and M1, D9 for M2

**Free fraction in human**: fexi 3 %  M1 and M2 > 40%
Safety results

SAD
- No serious nor severe Aes, no discontinuation
- No trends nor relevant changes vs baseline in VS, ECG, safety lab tests
- Few mild transient AES (headache)

MAD
- Some ΔQTcB increases in the 3600 mg - Holter results to com
- Headaches and Gastro intestinal disorders (mild or moderate) mostly transient – no pattern
- Liver enzymes increase
- 2 SAEs
## Frequency of ALT/AST increases

<table>
<thead>
<tr>
<th></th>
<th>cohort 1</th>
<th>cohort 2</th>
<th>cohort 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>dose</strong></td>
<td>1200 mg</td>
<td>2400 mg</td>
<td>3600 mg</td>
</tr>
<tr>
<td>nb volunteers</td>
<td>8</td>
<td>9*</td>
<td>8**</td>
</tr>
<tr>
<td>≤1N</td>
<td>3</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>1N&lt;x≤2N</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2N&lt;x≤3N</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>3N&lt;x≤30N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30N&lt;x≤40N</td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

**ASAT**

<table>
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<td>6</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>1N&lt;x≤2N</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2N&lt;x≤5N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5N&lt;x≤6N</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>6N&lt;x≤9N</td>
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</tr>
<tr>
<td>9N&lt;x≤10N</td>
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<td></td>
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<tr>
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<td>1</td>
</tr>
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</table>

*one subject dropped on D9 with follow up until D28

** one subject stopped on D6 with follow up until D28
## ECG QT/QTC Results

### Categorical analysis for triplicate holter QTc

<table>
<thead>
<tr>
<th>Changes in QTcF (ms)</th>
<th>Placebo (N=6)</th>
<th>1200 mg (N=6)</th>
<th>2400 mg (N=6)</th>
<th>3600 mg (N=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔQTc&gt;30 ms</td>
<td>0 (0.0)</td>
<td>2 (33.3)</td>
<td>2 (33.3)</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>ΔQTc&gt;60 ms</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>
PK Food effect

Food effect 1200mg (2X600mg) single dose

- relative bioavailability Cmax and AUC$_{0-t}$:
  - 4 fold increase in the extend of absorption of fexinidazole

- M1 & M2 increased proportionally

- intra-indvidual variability:
  - Cmax and AUC$_{0-t}$ markedly reduced (10 – 15%)
M2 Mean Plasma levels

![Graph showing M2 Mean Plasma levels with different conditions: Plumpy, RICE, fasted, High Fat, and MIC. Each condition is represented by a different line color. The x-axis represents time in hours (0, 0.5, 1, 2, 3, 4, 6, 9, 12, 16, 24, 48, 72, 120, 168), and the y-axis represents mean plasma levels. The graph shows peaks for each condition at different times.](image-url)
POP PK calculations

Dose regime 1 = 1800 mg (QD) for 4 days + 1200 mg (QD) for 6 days

Dose regime 2 = 2400 mg (QD) for 4 days + 1200 mg (QD) for 6 days

Dose regimen 1800 mg (D1-D4) + 1200 mg (D6-D10)

Dose regimen 2400 mg (D1-D4) + 1200 mg (D6-D10)
Fexinidazole
Next Steps
NEXT studies

- Validation of the highest safety and efficacy dose
- Phase II/III study 2012
- Study in stage 1 of HAT with the same dose
Vision for FEXINIDAZOLE

• Having oral efficacy and safety dose
• Available as once a day dosing
• Treatment for all stages of the disease
Thank you