FEXINIDAZOLE FOR HAT
Fexinidazole for HAT

- Preclinical results
- Multiple ascending dose in fasted conditions
- Food interaction
- Therapeutic dose regimen assessment
Fexinidazole preclinical results
Fexinidazole

- **Discovery**: 1970, HOE 239, discontinued 1980
- **Chemical Name**: 1H-imidazole, 1-methyl-2-[[4-methylthio) phenoxy] methyl] 5-nitro-imidazole
- **Metabolism**

  ![Chemical Structures]

  - PM FEXI = 279 g/mol
  - PM M1 = 295 g/mol
  - PM M2 = 311 g/mol
  - pKa-value = very weak base
  - $\log D_{pH \ 7.4} = 2.8$
In vitro activity of fexinidazole

<table>
<thead>
<tr>
<th>Compound Tested</th>
<th><em>T. b. rhodesiense</em> (IC$_{50}$ µg/ml)</th>
<th><strong>T. b. brucei</strong> (IC$_{50}$ µg/ml)</th>
<th><strong>T. b. brucei</strong> (IC$_{90}$ µg/ml)</th>
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<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>
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<tr>
<td>Fexinidazole sulfoxide</td>
<td>0.487</td>
<td>1.96</td>
<td>4.74</td>
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<tr>
<td>Fexinidazole sulfone</td>
<td>0.354</td>
<td>0.89</td>
<td>2.20</td>
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</table>

*Data from STI
**Data from SCYNEXIS

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Time to Kill Assays - Fexinidazole and Metabolites

Fexinidazole (IC$_{90}$ = 5.00 µg/ml)

Fexinidazole-Sulfoxide (IC$_{90}$ = 4.74 µg/ml)

Fexinidazole sulfone (IC$_{90}$ = 2.20 µg/ml)

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Mice PK profile (at the efficacious dose of 200 mg/kg)

- Concentration of Fexi-sulfone is above IC_{90} for 22 hrs
The most active metabolite is M2: Fexinidazole sulfone

No drug interaction expected as several CYP P450 involved

IC$_{90}$ of M2 is 2.200 ng/mL

Killing curve test:

- Time dependent: 24h if concentration $\geq$ 3X MIC
- Killing rate (irreversibility) 12h if concentration $\geq$ 3X MIC
Key preclinical Data (2)

- Chronic Infection  Mice model for HAT
  - Dose  200mg/kg for 5 days  7/8 mice cured
  - plasma concentration ~8-10,000 ng/mL (mice data)

- No toxicological target organ
  - NOAEL = 200 mg/kg
  - ADME  Rat brain concentration:

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

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Phase I studies

118 /154 subjects have been exposed to Fexinidazole

- **Tolerability study**
  - **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 interaction study (3way cross-over study ,12 subjects)**

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

- **POP PK analysis**
Mean (+SD) plasma concentration of fexinidazole, (M1) (M2) vs. time profiles - 3600 mg fexinidazole
PK Results SAD

- **Bioavailability**
  - Fexinidazole: median Tmx:3 – 4 H; mean T1/2: 9-15H
  - M1: median Tmx: 2-5 H; mean T1/2: 18-20H
  - M2: 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: D4 for fexi and M1, D9 for M2
Multiple ascending dose fasting

- Randomized, double-blind, placebo-controlled design
- Cohorts of 8 subjects (6 A, 2 P) sub-Saharan origin
- Oral fasting tablets of 600g - once daily for 14 days
- Ascending dose levels: 1200mg; 2400mg; 3600mg.
Multiple ascending dose fasting

- Subjects hospitalized from D-2 through D16
- Ambulatory visit D17- D21 morning (EOS)
- Standard safety lab, ECGs, AEs, PK
- 24h ECG holter
- Validation DBS method for PK
Fexinidazole was administered once daily for 14 days.
Frequency of ALT/AST increases/FEX001

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<th>cohort 1</th>
<th>cohort 2</th>
<th>cohort 3</th>
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<tr>
<td>nb volunteers</td>
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</tr>
<tr>
<td>≤1N</td>
<td>4</td>
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<tr>
<td>1N&lt;x≤2N</td>
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<tr>
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<td>1</td>
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</tr>
<tr>
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<td>30N&lt;x≤40N</td>
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<td><strong>ASAT</strong></td>
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<td>≤1N</td>
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<td>7</td>
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<td>1N&lt;x≤2N</td>
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<td>30N&lt;x≤40N</td>
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Food interaction studies

- 2 studies: open, 3 way cross-over design
  - 1200mg (2X600mg tablets) single dose
- 1st study: high fat rich breakfast
  - relative bioavailability Cmax and AUC₀⁻ᵗ:
    - 4 fold increase of absorption of fexinidazole
    - M1 & M2 increased proportionally
  - intra-individual variability
    - Cmax and AUC₀⁻ᵗ markedly reduced (10 – 15%)
Food interaction studies

- 2nd study: Plumpy Nuts®(Fed1), rice and beans(Fed2)
  - 3 way cross-over: fasted / fed 1/ fed2
  - Determination of free fraction
- Relative bioavailability Cmax and AUC₀₋ₜ:
  - 2.5 – 3 fold increase in of absorption of fexinidazole
  - M1 & M2 increased proportionally
- Intra-individual variability
  - Cmax and AUC₀₋ₜ markedly reduced (10 – 15%)
- Free fraction
  - Fexi:3%, M1:59%, M2: 43%
M2 fed: Mean Plasma levels
Key Pharmacokinetic Data

- Human Clinical Pharmacology data

- Long Lag time to reach steady state of M2 in fasting dosing
- Food effect: 2-3 X increase in plasma concentration / fasting
- M2 $T_{1/2} \geq 24h$
- Free fraction of M1= 59%  M2= 43%: prediction of high body diffusion
- Best Treatment duration should be less than 14 days
Rationale for population PK simulation

Targets:

- Simulate M2 plasma levels after multiple dosing over 10 days under fed conditions
- M2 concentrations 2-3 times > the IC\textsubscript{90} (2200ng/mL)
- M2 plasma levels around 10,000 ng/mL for at least 72H (mice data)
- M2 plasma level should be reached within 2-3 days
- M2 C\textsuperscript{max} plasma levels ≤ 20,000-25,000 ng/mL
Population PK model used for the simulations of several dosing regimens in patients

Population PK scenarii tested

Tested 5 Scenarii

- 1200 mg once daily for 10 days with food
- 1800 mg once daily for 10 days with food
- 2400 mg once daily for 10 days with food
- 1800 mg for 4 days followed by 1200 mg for 6 days once daily with food
- 2400 mg for 4 days followed by 1200 mg for 6 days once daily with food
POP PK: Median of M2 simulation predose concentrations as function of dosing
Population PK probability calculations

% of subjects with M2 simulated predose concentrations >10 mg/L

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Based on the results, the 2 mixed dosing regimens were selected to be tested in healthy volunteers in ascending order:

- 1800 mg 4d, followed by 1200 mg 6d
- 2400 mg 4d, followed by 1200 mg 6d
MAD in fed condition design
selection of therapeutic dose

- Design: 10 Days MD, Randomized, Double-blind, Placebo controlled

- N= 18 subjects/ cohort (12 A + 6 Pl )
  - 1800 mg loading dose from D1 – D4 + 1200 mg D5 –D10,
  - 2400 mg loading dose from D1 – D4 + 1200 mg D5 –D10,

- Evaluations
  - PK + Holter ECG at baseline D4; D7; D10
  - PK at D1; D4; D7; D10 + through levels D2, D5, D8, D9, D11 - D18
  - Safety LFT : D4; D7; D10 + follow up for 7 days
MAD in fed condition

Results

Overall results

- **1800mg D1-D4 + 1200mg D6 - D10 completed**
  - Detection of a safety group effect in 1st sub-cohort of 9 subjects
  - All subject were replace
  - dosed in sub-groups of 3  no drop out
  - Total subjects  N= 24  (n= 18 active + 6 placebo)
  - No biological safety concern
  - Majors Aes: Headache nausea vomiting at loading dose

- **2400mg D1-D4 + 1200mg D6 - D10**
  - 2 sub-groups of 3 subjects dosed
  - 1 subjects withdrawn in each dose for anxiety and episode of panic attack
  - Dosing stopped for safety reason
pK result

Geometric means of Cmax at D1, D4, D7, D10

Plasma drug concentrations (Geometric Mean of Cmax in µg/mL)

- Fexinidazole
- Fexinidazole sulfoxide (M1)
- Fexinidazole sulfone (M2)

Predicted CNS IC₉₀ range of M2 required

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M2 Mean Plasma levels 1800/1200 mg
PK results: 1800/1200mg

Active metabolite M2 plasma concentration was reached rapidly and maintained for 3 to 4 days in all cases and more than 80% of the subjects had pre-dose plasma levels above 10 mg/L.

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Fexinidazole Safety results
### Safety Biology / FEXI003

#### Parameter

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (N=8)</th>
<th>Dose 1 (N=18)</th>
<th>Dose 2 (N=4)</th>
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<tbody>
<tr>
<td></td>
<td>1N&lt;x≤2N n</td>
<td>2N&lt;x≤3N n</td>
<td>&gt;3xN n</td>
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<tr>
<td>ALAT</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ASAT</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
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<td>0</td>
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<tr>
<td>Gamma-GT</td>
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<td>0</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>0</td>
<td>6</td>
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<tr>
<td>Creatinine</td>
<td>0</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

**Total bilirubin:** abnormalities were present at screening and don’t increased under treatment

**Liver function test:** No abnormal values in liver function test

**Plasma creatinine:** variation related to class abnormalities.

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Adverse events / FEXI003

Number of subjects with AEs per dose group

- **ABDOMINAL PAIN**
- **DIARRHOEA**
- **GOR**
- **NAUSEA**
- **VOMITING**
- **ASTHENIA**
- **CHEST PAIN**
- **FATIGUE**
- **NASOPHARYNGITIS**
- **DIZZINESS**
- **HEADACHE**
- **ANXIETY**
- **INSOMNIA**
- **PANIC ATTACK**
- **SLEEP DISORDER**
- **HYPERHIDROSIS**
- **HOT FLUSH**

- Dose 1 (N=18)
- Dose 2 (N=4)
- Placebo (N=8)

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Conclusion

- Fexinidazole and its metabolites are active against *T. brucei gambiense and rhodesiense*

- The most active metabolite is M2: Fexinidazole sulfone

- No drug interaction expected as several CYP P450 involved

- Fexinidazole should be taken in fed conditions at once a day dosing

- The best regimen is 1800mg for 4 days followed by 1200mg for 6 days
THANK YOU