Oxaboroles SCYX-7158
First DNDi Preclinical Candidate for HAT
From Lead Optimization Program

- Identified as hit against *T. brucei* at the Sandler Center of UCSF
- Innovative chemistry with potential activity for HAT, VL, and Chagas disease
- Hundreds of analogs were made and tested
- Top candidate, SCYX 7158, starting clinical phase 1 studies in Q12012

Key partners include:
- SCYNEXIS
- Pace University
- Anacor Pharmaceuticals

2-bromo phenylboronic acid
SCYX-7158 - General information

PM = 367.11 g/mol
pKa = 9.61
LogD \text{ ph7.4} = 3.51

Chemical name: (4-Fluoro-N-(1-hydroxy-3,3-dimethyl-1,3-dihydro-benzo[c] [1,2] oxaborol-6-yl)-2-trifluoromethyl benzamide)

OXABOROLE-6 BENZAMIDE
# SCYX-7158 - In Vitro efficacy

<table>
<thead>
<tr>
<th>T. brucei Strain Tested</th>
<th>SCYX-7158 IC50 (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T. b. brucei SBRI 427*</td>
<td>0.267</td>
</tr>
<tr>
<td>T. b. rhodesiense STIB 900</td>
<td>0.294</td>
</tr>
<tr>
<td>T. b. gambiense 40R</td>
<td>0.363</td>
</tr>
<tr>
<td>T. b. gambiense 108R</td>
<td>0.165</td>
</tr>
<tr>
<td>T. b. gambiense DAL 1402</td>
<td>0.065</td>
</tr>
<tr>
<td>T. b. gambiense ITMAP 141267</td>
<td>0.092</td>
</tr>
<tr>
<td>T. b. gambiense Drani</td>
<td>0.129</td>
</tr>
</tbody>
</table>
SCYX-7158 - Time to kill plots

A = Time to kill

- 24H continuous exposure to SCYX-7158

B = rate to kill

- 10-12h pulse exposure of SCYX-7158, medium was washed, survival were evaluated at 72 h after initiation of incubation
SCYX-7158 - In vivo Efficacy – Stage 2 HAT model in murine

% Animals Parasite Free

Days Post-infection

- Berenil D4
- Berenil D21
- 7158-6mg/kg
- 7158-12.5 mg/kg
- 7158-25 mg/kg
- 7158-50 mg/kg
SCYX-7158 - Safety pharmacology (1)

Safety Pharmacology (GLP)

- Standard genotoxicity battery
  - Ames
  - In vivo micronucleus test
  - In vitro chromosomal aberration
- hERG
- Telemetry (cardiovascular) Dog
- Respiratory in Rat
- Functional Observation Battery in Rat

Toxicokinetics
SCYX-7158 - Safety Pharmacology (1)

- Standard genotoxicity battery
  - Ames negative
  - In vivo micronucleus test negative
  - In vitro chromosomal aberration negative
- hERG (10, 30, 60, 100 μM)
  IC50 >100 μM
- Telemetry Dog (5, 15, 40 mg/kg) No observations
- Respiratory in Rat (15, 40, 80 mg/kg) No observations
- Functional Observation Battery in Rat
  - (15, 40, 80 mg/kg) No observations
**SCYX-7158 - DMPK**

- **Absorption**
  - **In vitro** MDR1-MDCK cells system
  - **In vivo**
    - Dog: ≈ 100% in dog
    - Monkey: ≈ 80%
    - Rat, Mouse: ≈ 50%

- **Bioavailability**
  - **Tmax**: 4.5-9.5 H in all species
  - Linearity dose proportional

- **Volume of distribution**: ≈ 0.6 – 0.7 l/kg in all species

- **T$_{1/2}$ elimination**: ≈ 25H

- **High protein binding**: ≈ 95% in all species

- High absorption potential
- High distribution in brain
- No significant efflux
SCYX-7158 pk profil data normalised

![Graph showing concentration over time for different treatments]
SCYX-7158 - Metabolism

CYP Induction

- Inducer of CYP 2B6 and 3A4
### Mass balance in rats

<table>
<thead>
<tr>
<th></th>
<th>Faeces</th>
<th>Urine</th>
<th>F + U</th>
<th>Total measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>66%</td>
<td>20%</td>
<td>86%</td>
<td>89%</td>
</tr>
<tr>
<td>Female</td>
<td>73%</td>
<td>14%</td>
<td>87%</td>
<td>90%</td>
</tr>
</tbody>
</table>

Excretion after 14 days

### Tissue distribution

- Well distributed in all tissues Brain Rat ≈ 44% Mouse ≈ 38%
- Highest levels in liver kidney and subcutaneous fat
- Lowest levels in eye and brain 1.5 -2 fold lower than blood
SCYX-7158 - Rat Toxicokinetics

Toxicokinetics

- 7 days TK in rat  50, 140, 400mg/kg
  - weight loss and loss of appetite
  - Histopathology: stress related changes
- 28 days TK in rat  5, 15, 40, 80 mg/kg
  - Loss of appetite and weight loss at 80 mg/kg
  - Main target organ RBC: ↓ RBC:9-11%, ↓Hb 9%, ↓Hct 8-10%,
    ↑ Reticulocyte: 75-80%
  - No signs of bleeding nor hemolysis but
    ↑ Extra medullar hematopoiesis
  - Histopath: no signs of bleeding no hemolysis,
  - clinical chemistry: No abnormal signs
- NOAEL = 15 mg/kg
SCYX-7158 - DOG Toxicokinetics

Toxicokinetics

- 7 days study TK in Dog 5, 20, 50 mg/kg
  - weight loss and loss of appetite
  - Histopathology: stress related changes
  - Reduced weight of thymus and spleen
- 28 days TK in dog 5, 15, 40 mg/kg
  - Loss of appetite and weight loss (emesis) at 40 mg/kg
  - Main target findings; decrease in food consumption
  - clinical chemistry: - 40 mg/kg/d Hb, Ht, decrease
    -15 and 5 mg/kg: only anecdotic, ancillary variations (Haemato and BC)

NOAEL =15 mg/kg
Mean Pharmacokinetic Parameters of SCYX-7158 after Oral Administration of SCYX-7158 in Animal Species.

<table>
<thead>
<tr>
<th></th>
<th>Dose (mg/kg)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (h)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (µg/mL)</th>
<th>AUC (µg/mL.h)</th>
<th>F* (%)</th>
<th>T&lt;sub&gt;1/2&lt;/sub&gt; (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>12.5</td>
<td>6</td>
<td>6.96</td>
<td>104</td>
<td>54.5</td>
<td>7.7</td>
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<tr>
<td></td>
<td>25</td>
<td>0.5</td>
<td>9.75</td>
<td>134</td>
<td>45.3</td>
<td>6.93</td>
</tr>
<tr>
<td></td>
<td>39.9</td>
<td>4.0</td>
<td>24.4</td>
<td>320</td>
<td>71.4</td>
<td>5.5</td>
</tr>
<tr>
<td>Rat</td>
<td>10</td>
<td>8.0</td>
<td>12.7</td>
<td>362</td>
<td>53.0</td>
<td>16.9</td>
</tr>
<tr>
<td>Dog</td>
<td>10</td>
<td>4.5</td>
<td>8.36</td>
<td>1032</td>
<td>100.0</td>
<td>37.65</td>
</tr>
<tr>
<td>Monkey**</td>
<td>10.4</td>
<td>9.5</td>
<td>11.5</td>
<td>477</td>
<td>88.8</td>
<td>20.3</td>
</tr>
</tbody>
</table>

*The ratio AUC<sub>po</sub>/AUC<sub>iv</sub> was used for bioavailability (%F) calculation. The i.v. dose was 2 mg/kg in the dog and the monkey

**Nasogastric administration
PK in INFECTED MICE

Exposure in Rats
25 mg/kg 100% cure dose in mouse model
SCYX-7158 - Conclusion

- **New family of drug**: OXABOROLE-6 BENZAMIDE

- Exhibit a high in vitro potency vs *t. brucei brucei*

- *physicochemical properties compatible with high brain penetration*

- *Active in acute and chronic HAT disease mouse model*

- *PK properties compatible with a once a day dosing*

- *NOAEL: 15mg/kg in rat and dog*
Thank you