Leveraging an Oxaborole in Clinical Trials for HAT to Develop Novel Compounds to Treat Animal African Trypanosomosis (AAT).

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ISCTRC, Khartoum, Sudan

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Anacor is active in 12 Neglected Disease Research Programs and has a long history with PDPs and the BMGF.

**Parasitic Diseases**

- African Sleeping Sickness
- Visceral Leishmaniasis
- Chagas disease
- Malaria – Lead Series
- Malaria (New Scaffolds)
- Onchocerciasis (Macrofilaricide)
- Onchocerciasis (Anti-Wolbachia)
- Cutaneous Leishmaniasis

- SCYX7158 / AN5568

**Bacterial Diseases**

- Tuberculosis (TB) - LeuRS
- Tuberculosis (TB)-non-LeuRS
SCYX7158 is Currently in Phase 1 and has the Potential to Be a Major Advancement as a Treatment for HAT

- Efficacy in Stage 1 & 2 HAT
  - Cures blood and CNS stage disease (mouse model)

- Safety
  - Good therapeutic index predicted based on preclinical safety studies

- Easy of use
  - Oral dosing, once daily
  - <5 days of treatment

- Cost
  - <$5 per treatment

Phase I data demonstrates probable single oral dose cure profile in humans. Brain concentration expected to be >5X MIC at single dose of 160 mg/kg in humans – sufficient to cure
### Highlights of GALVmed TPP for Therapeutic AAT Drug

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Minimum Required</th>
<th>Ideal</th>
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<tbody>
<tr>
<td><strong>Target Species</strong></td>
<td>Cattle (includes animals producing milk for human consumption)</td>
<td>Cattle, sheep, goat &amp; other ruminants, camels, horses, donkeys, pigs.</td>
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<tr>
<td><strong>Active ingredient</strong></td>
<td>Novel agent. Side-resistance to existing veterinary products acceptable if overcome by greater intrinsic potency or speed of action.</td>
<td>Novel agent with new mechanism of action. No cross- or side-resistance to existing product actives.</td>
</tr>
<tr>
<td><strong>Indication for use</strong></td>
<td>Treatment of <em>T. congolense</em> and <em>T. vivax</em> infections, including strains resistant to existing trypanocides.</td>
<td>Treatment of <em>T. congolense</em>, <em>T. vivax</em> and <em>T. evansi</em> infections, including strains resistant to existing trypanocides.</td>
</tr>
<tr>
<td><strong>Route of administration</strong></td>
<td>Injectable (preferably i.m. or s.c.) or Pour-on or Oral.</td>
<td>Injectable (i.m. and s.c.) plus oral option for sheep.</td>
</tr>
<tr>
<td><strong>Regimen</strong></td>
<td>Two administrations (provided the interval between the two administrations is short (≤1 day).</td>
<td>Single administration</td>
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<tr>
<td><strong>Formulation</strong></td>
<td>Injectable: Pre-formulated solution or suspension. If injectable not possible then consider either pre-formulated pour-on or oral (solid bolus or liquid).</td>
<td>Injectable: Pre-formulated solution. Oral: Solid bolus or suspension/solution drench.</td>
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<tr>
<td><strong>Withdrawal period</strong></td>
<td>Milk &lt;7 days. Meat &lt;28 days.</td>
<td>Milk zero. Meat &lt;14 days.</td>
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<td><strong>Price to User</strong></td>
<td>Higher prices than US$2/dose (300kg animal) are a major challenge unless justified by value-added properties and include syringes, etc.</td>
<td>&lt;US$2/dose (300 kg animal)</td>
</tr>
<tr>
<td><strong>Special requirements for animals</strong></td>
<td>None stated.</td>
<td>Compatible for concomitant use with common treatments e.g. ectoparasiticides, antimicrobials, anthelmintics &amp; vaccines.</td>
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</table>
AN7973 Derived from HAT Program Showed Single Dose Cure of *T. congolense* Infection

*AN7973*

T. *congolense* \(IC_{50} = 0.057 \mu M\)

T. *brucei* \(IC_{50} = 0.09 \mu M\)

T. *vivax* \(IC_{50} = 0.312 \mu M\)

Symptoms in cattle: wasting disease (rapid weight loss), massive immune stimulation, anemia

Screening to Discover AN7973

1. Started with the 20 most potent compounds against in *T. brucei in vivo*
2. *In vitro* screening against *T. congolense*
3. *In vivo* testing in mouse model against *T. congolense* (*T.c.*)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose (mg/kg)</th>
<th>Cured/Infected</th>
<th>Survival Days</th>
<th>Survival %</th>
</tr>
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<tbody>
<tr>
<td>Control</td>
<td>--</td>
<td>0/5</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>AN7973</td>
<td>4 x 10</td>
<td>5/5</td>
<td>60</td>
<td>100</td>
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<tr>
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<td>5/5</td>
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<tr>
<td>AN7973</td>
<td>1 x 10</td>
<td>5/5</td>
<td>60</td>
<td>100</td>
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AN7973 Showed 100% Cure of *T.c.* in Goats & Cattle 100 Days after Single 10 mg/kg Dose

**Goats:**
- Goats infected with STIB736/IL1180 strain of *T.congolense* and treated with IM 1x10 or 2x10 mg/kg AN7973
- 100% survival 100 days post-infection, both treatments

**Cattle:**
- Four calves infected with a diminazene- and isometamidium-resistant strain of *T. congolense* (Cameroon isolate KONT2/133**)
- Treatment initiated at high parasitemia, with >25% decrease in PCV and elevated temperature.
- Single IM dose of 10 mg/kg or 2 x 5 mg/kg (24h apart)
- 100% survival and parasite-free at Day 100 post-treatment, both treatments
- Saline-treated calves (n=6) failed rescue therapy with standard dose of diminazene aceturate at 3.5 mg/kg & also with the rescue dose of 7 mg/kg

No concerns for AN7973 in Safety Pharmacology / Gentox Studies

- Deductive Estimation of Risk from Existing Knowledge (DEREK) – no structural concerns for genotoxicity
- Ames - negative
- *In vitro* Micronucleus - negative
- Receptor/Enzyme Panel (109 enzymes) at 10μM - negative
  - No inhibition of hERG activity (<21% inhibition)
  - No CYP450 inhibition at 10μM:
    - CYP450 1A2 = 1%
    - CYP450 2C19 = 27%
    - CYP450 2D6 = 0%
    - CYP450 3A4 = 1%
- 7-day repeat-dose rat toxicity study: NOAEL ≥80 mg/kg (PO dosing)
- Target animal safety in cattle: Treated with 3 cycles of 3 x 10 mg/kg AN7973 (treatments separated by 2 weeks). No clinically significant signs, no evidence of relevant clinic-pathological changes and no evidence of macroscopic or microscopic tissue or organ damage (mild inflammatory lesions at injection sites)
Liver Microsome Stability
- Stable in murine and bovine LM (± NADPH) for 2 h
  - 93-100% recovery with NADPH, 100% without

Plasma stability
- Stable in uninfected murine and bovine plasma at 37°C >2h
  - 92-96% recovery

Protein binding
- 99% to murine plasma, 96% to bovine

Primary Metabolite:
- Oxidative deboronated product (AN10531): < 1% parent
  - Not significantly metabolized by non-oxidative deboronation
AN7973 Shows Efficacy Against *T. vivax* but Not Sufficient for Single Dose Cure

- **Mouse**: AN7973 cured with 4 doses of 10 mg/kg, not one dose of 10 mg/kg, as seen with *T. congolense*
- **Goat**: AN7973 cured with 2 doses of 10 mg/kg
- **Cattle**: AN7973 cured 50% at 2 doses of 10 or 1 dose of 20 mg/kg
- AN7973 was tested against 2 field isolates of *T. vivax* in cattle – single dose efficacy at 10 mg/kg not observed
Conclusions

- AN7973 shows excellent efficacy against *T. congolense* with single dose cure – 100 days, including strains with multi-drug resistance against both standard of care drugs
- No safety pharmacology issues: hERG, receptor panel, Ames, micronucleus, repeat dose rat toxicity study
- Good target animal safety in cattle at 3x efficacious dose
- TPP requirement of efficacy against *T. congolense* and *T. vivax* strain precludes development of *T. congolense*-only drug
- Further efforts to develop higher potency and metabolically stable back-up oxaborole to AN7973 that can meet the single-dose cure in cattle infected with both *T. congolense* and *T. vivax* look promising
# Thanks to GALVmed Project Team

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