Recent progress in discovering new drugs: fexinidazole and other candidates in the pipeline

ISCTRC Meeting,
September 22, 2009, Kampala

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Target Product Profile for HAT

- A new treatment for stage 2 HAT in adults and children
  - Preferably useful for both stages 1 and 2
  - *T.b.gambiense* and *T.b.rhodesiense*
- Better **safety** profile than existing drugs
  - Ideally requiring little or no monitoring
- Equal or better **efficacy** profile than existing drugs
  - Ideally ≥95% clinical efficacy at 18 months after treatment
- **Easy to use** treatment
  - Short course (ideally ≤7 days, up to 14 days is acceptable)
  - Preferably oral; if injectable: im >> iv
  - Preferably once a day treatment
- **Affordable**
- Stability in tropical climate (min. 2 year)
**Fexinidazole**

- "Rediscovered" by DNDi after extensive review of existing data on over 500 nitroimidazoles
- Completed preclinical development
- Entering into Phase I clinical studies TODAY with healthy volunteers (Paris)

Key partners include:
- Swiss Tropical Institute, SGS Accelera, Aptuit, Axyntis, Covance, Drugabilis, LPU,
- Agreement signed with sanofi-aventis for joint development
Fexinidazole

- 5-nitroimidazole
- in preclinical development by Hoechst in 80s as broad-spectrum anti-protozoal but not progressed

Fexinidazole metabolism

- M1: Fexinidazole sulfoxide
- M2: Fexinidazole sulfone
- M1a: [Formula]
- M2a: [Formula]
Pharmacokinetics:
5-day repeated dose mouse PK
Plasma levels of fexinidazole and metabolites
curative dose in chronic mouse model

Plasma levels following 5-days oral administration of 200 mg/kg/d fexinidazole to mice

Pharmacology
Comparison fexinidazole with other drugs in T. b. brucei GVR35 chronic model in mice.

<table>
<thead>
<tr>
<th>compound</th>
<th>#days x daily dose</th>
<th>route</th>
<th>cured/infected</th>
<th>Avg* survival time (days)</th>
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<tbody>
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<td>Diminazene diacetate</td>
<td>1 x 40 ip</td>
<td></td>
<td>0/5</td>
<td>69.4</td>
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<td>5x 10 ip</td>
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<td>2/8</td>
<td>&gt;122</td>
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<td>5x 50 po</td>
<td></td>
<td>0/8</td>
<td>63.8</td>
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</tbody>
</table>

* Avg calculated based on a survival of 180 days for the cured mice

Formulation of Fexinidazole and Nifurtimox: suspensions in Methocel 0.5%w/v with 5%v/v of Tween 80
Toxicology

• Fexinidazole and its metabolites are well tolerated after 4-wk repeated administration in rat and dog at doses up to 800 mg/kg/day
• NOAEL (No Observed Adverse Event Level) identified at 200 mg/kg/day in both species
• Fexinidazole and its metabolites do not cause any relevant effect in respiratory, CNS and CV Safety Pharmacology studies
• Although as common with many nitroimidazoles, fexinidazole is mutagenic in bacteria, it does not appear to be genotoxic to mammalian cells in vitro or in vivo.
• No major issues have been identified

Clinical development

• Phase I (First in Human): safety, PK in healthy volunteers
• Phase IIa: Proof of concept of efficacy (and safety) in patients
• Phase IIb: dose finding / comparative efficacy (safety) on small patient number
• Phase III: confirmatory safety and efficacy
DNDi’s HAT Strategy

**Nifurtimox-Eflornitine Combination Therapy (NECT)**
- Simplified treatment with less infusions, shorter course, safe & efficacious
- Added to WHO Essential Medicines List in May 2009
- NECT-FIELD study ongoing

Key partners include:
- National HAT control programmes
- Epicentre
- MSF
- Swiss Tropical Institute
- WHO
- Drug donors: s-a, Bayer

HAT: DNDi Achievements

Success & progress at each stage

**Lead Opt. Consortium (Scynexis/Pace) => Boron-based preclinical candidate (Anacor) OXABOROLES**

**FEXINIDAZOLE** (research partners: SGS and STI; dev. contract: sanofi-aventis)

**NECT (Epicentre/MSF, STI, WHO, Nat. Prog. DRC & Congo)**
Asanti Sana!    Merci!
Obrigado!    Thank you!