



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

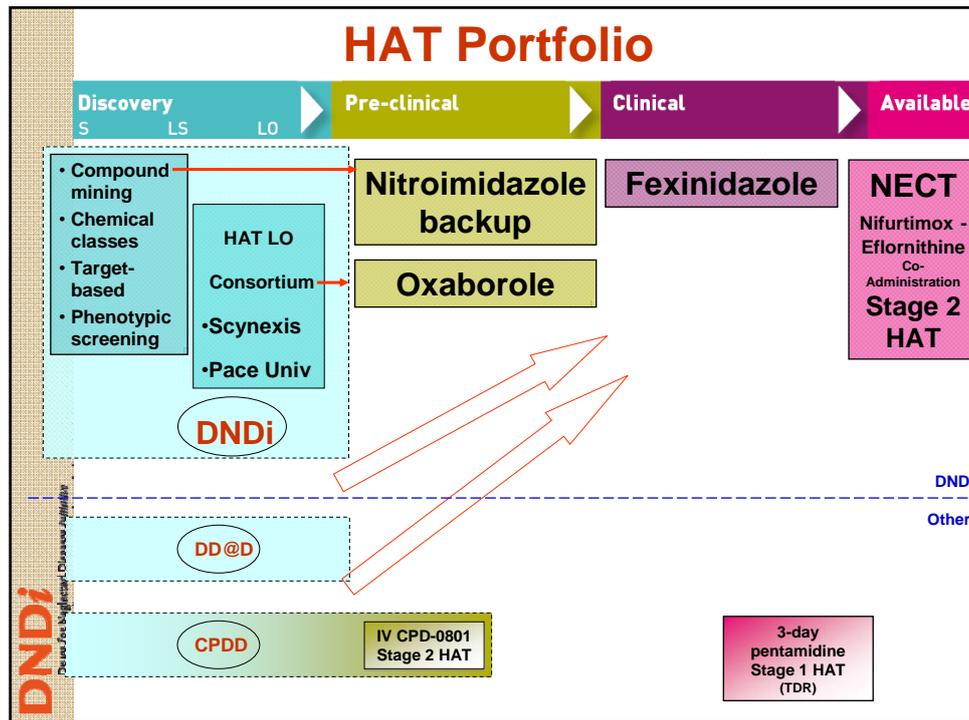
ISCTRC Meeting,
September 22, 2009, Kampala

Olaf Valverde
Project Manager

DNDi
Drugs for Neglected Diseases *initiative*

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 $\geq 95\%$ 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 \gg iv
 - Preferably once a day treatment
- **Affordable**
- Stability in tropical climate (min. 2 year)



DNDi's HAT Strategy

Discovery (S, LS, LO) → **Pre-clinical** → **Clinical** → **Available**

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)

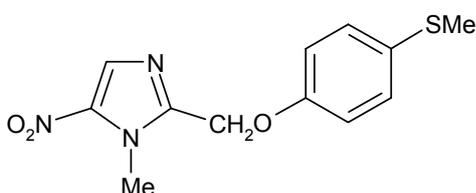
Key partners include:

- Swiss Tropical Institute, SGS Accelera, Aptuit, Axyntis, Covance, Drugabilis, LPU,
- Agreement signed with **sanofi-aventis** for joint development

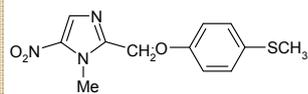


Fexinidazole

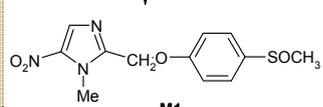
- 5-nitroimidazole
- in preclinical development by Hoechst in 80s as broad-spectrum anti-protozoal but not progressed



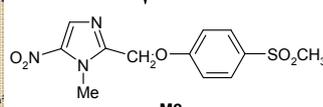
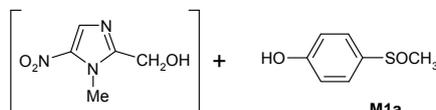
Fexinidazole metabolism



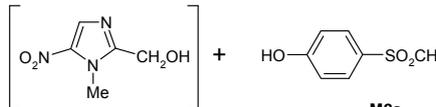
Fexinidazole

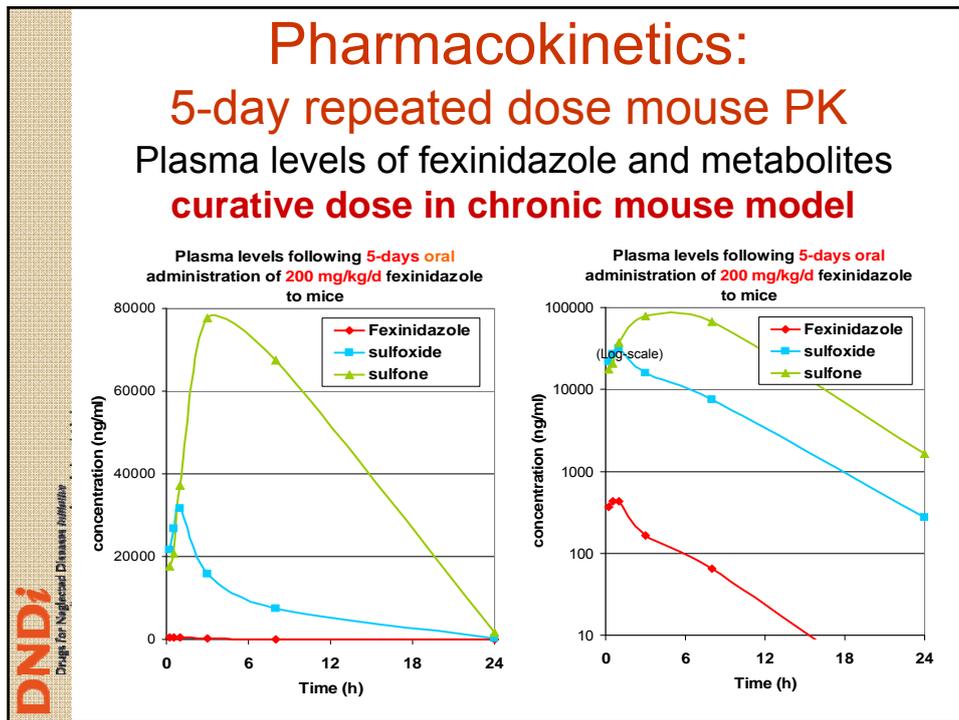


M1
Fexinidazole sulfoxide



M2
Fexinidazole sulfone





Pharmacology

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

compound	#days x daily dose	route	cured/infected	Avg* survival time (days)
Diminazene diaceturate	1 x 40	ip	0/5	69.4
melarsoprol	5x 10	ip	2/8	>122
fexinidazole	5x 50	po	0/8	63.8
fexinidazole	5x 100	po	2/8	>107
fexinidazole	5x 200	po	7/8	>169
nifurtimox	5x 50	po	0/8	50.4
nifurtimox	5x 100	po	0/8	47.9
nifurtimox	5x 200	po	0/8	79.1

* 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)



HAT Platform



Progress made and
Challenges ahead in Clinical
Research and **Development**
of New Treatments
for Human African Trypanosomiasis

WHO and DNDi Symposium
ISCTRC Meeting, Kampala, Uganda
Tuesday, September 22, 2009
6 pm - 7:20 pm, in Victori Ballroom



Asanti Sana!
Obrigado!

Merci!
Thank you!



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