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

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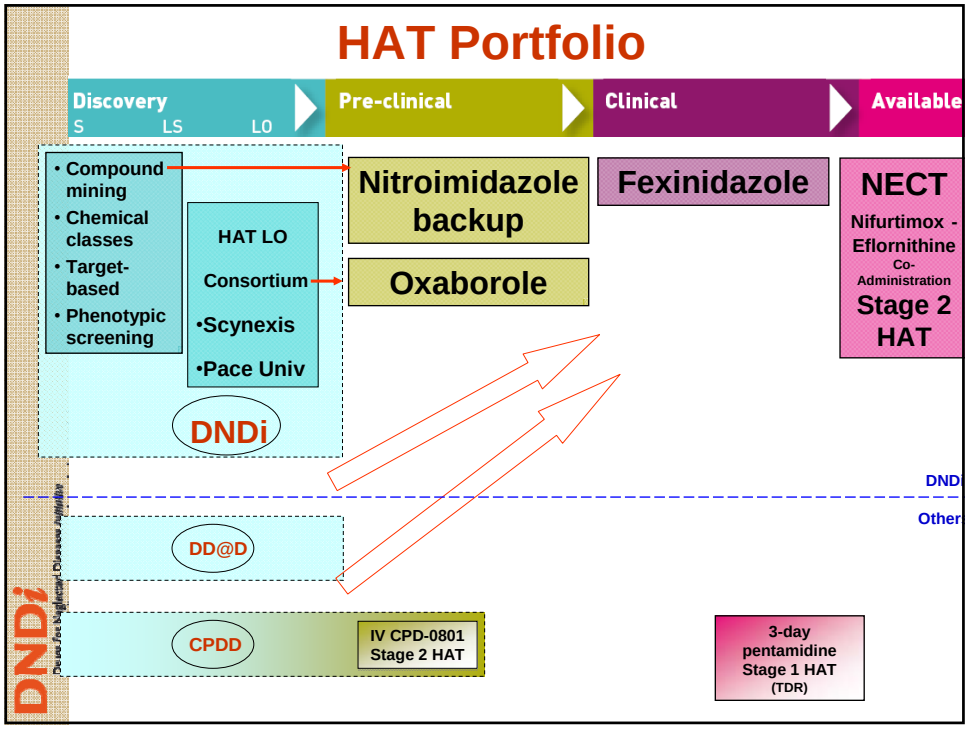
DNDi
Drugs for Neglected Diseases *initiative*

Target Product Profile for HAT

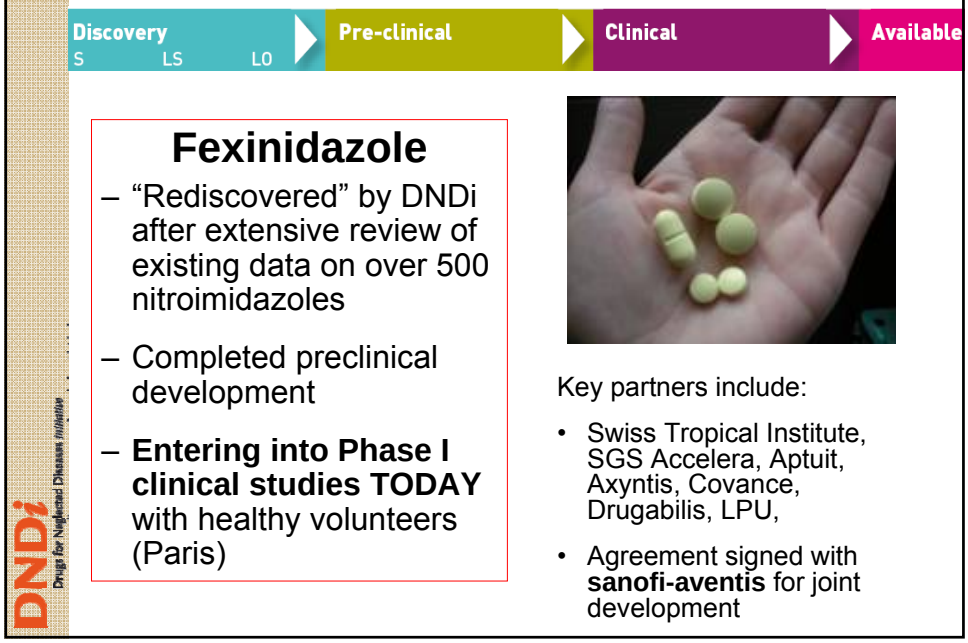
- A new treatment for **stage 2 HAT** in adults and children
  - Preferably useful for both stages 1 and 2
  - *T.b.gambiense* and *T.b.rhodesiense*
- Better **safety** profile than existing drugs
  - Ideally requiring little or no monitoring
- Equal or better **efficacy** profile than existing drugs
  - Ideally ≥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)

DNDi Drugs for Neglected Diseases initiative

HAT Portfolio

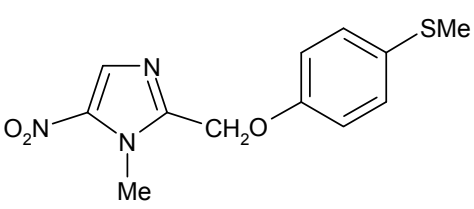


DNDi's HAT Strategy

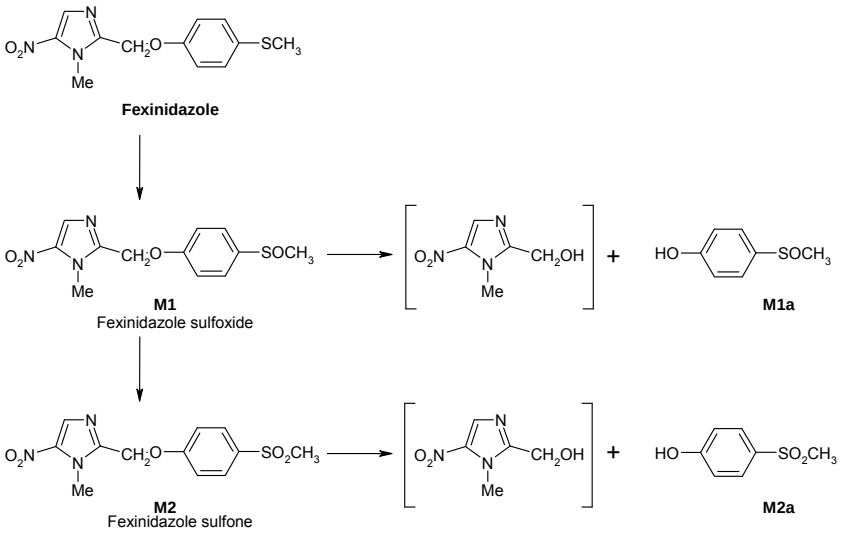


Fexinidazole

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



Fexinidazole metabolism

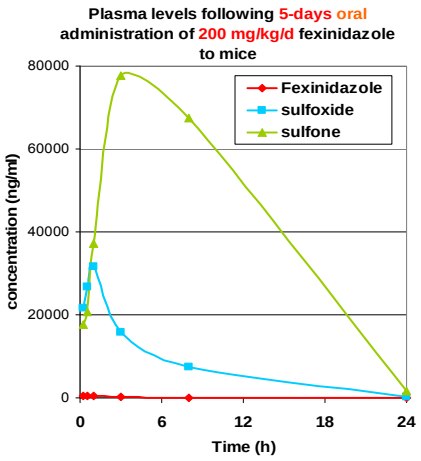


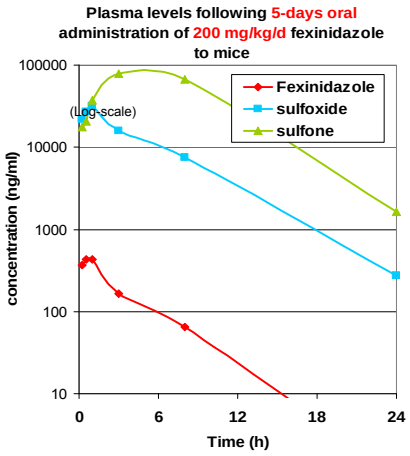
Pharmacokinetics:

5-day repeated dose mouse PK

Plasma levels of fexinidazole and metabolites

curative dose in chronic mouse model





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

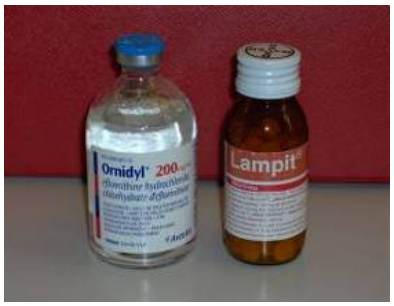
- Phase I (First in Human): safety, PK in healthy volunteers
- Phase IIa: Proof of concept of efficacy (and safety) in patients
- Phase IIb: dose finding / comparative efficacy (safety) on small patient number
- Phase III: confirmatory safety and efficacy

DNDi's HAT Strategy

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

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



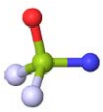
Key partners include:
- National HAT control programmes
- Epicentre
- MSF
- Swiss Tropical Institute
- WHO
- Drug donors: s-a, Bayer

HAT: DNDi Achievements

Success & progress at each stage

Discovery → Preclinical → Clinical → Available to patients

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

Asanti Sana! Merci! Obrigado! Thank you!