DND*i* Research & Development progress to tackle Sleeping Sickness

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15 September 2015

DND*i* Portfolio-Building Model:

Address Immediate Patient Needs & Deliver Innovative Medicines

- **New chemical entities (NCEs)**

Long-term projects

- **New formulations (fixed-dose combinations)**
- **New indications of existing drugs**

Medium-term projects

- **Completing registration dossier**
- **Geographical extension**

Short-term projects

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Sleeping Sickness: From Unacceptable to Better, Simple Treatment for Elimination

15 years ago:

Eflornithine

Melarsoprol

Since 2009:

NECT

2017 & Beyond

Oral treatment

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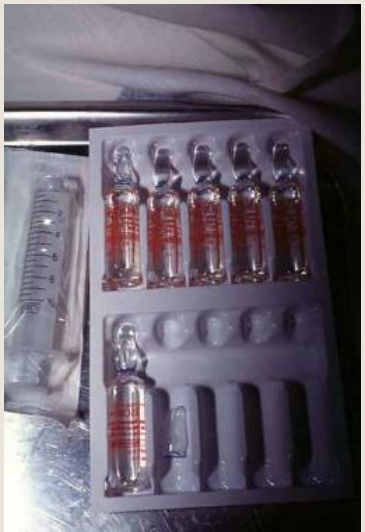
15 Years Ago: A Dire Situation

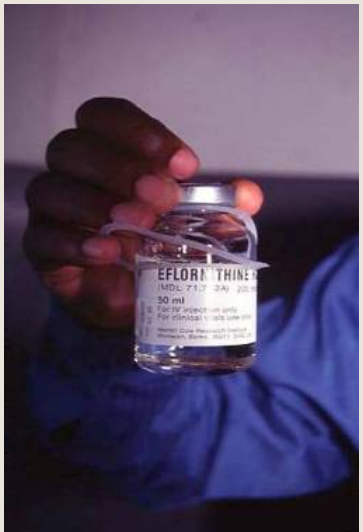
Melarsoprol

- Toxic (~5% mortality)
- Ineffective (resistance)
- Painful when delivered



Eflornithine

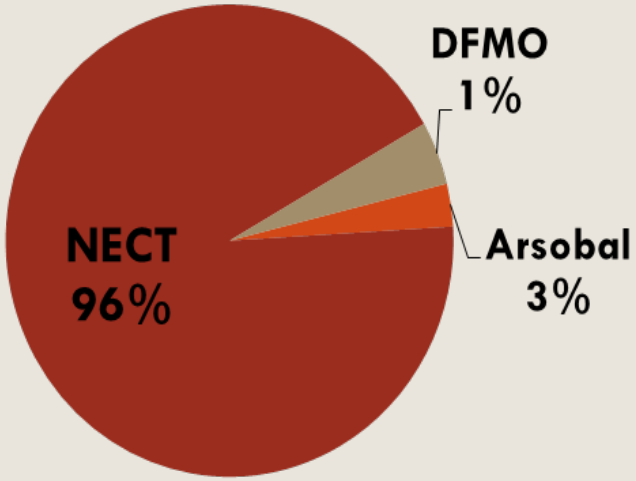
- Expensive
- Difficult to use
- Not registered in endemic regions



Since 2009, NECT: Improved Treatment But Still Not Ideal in Remote Areas

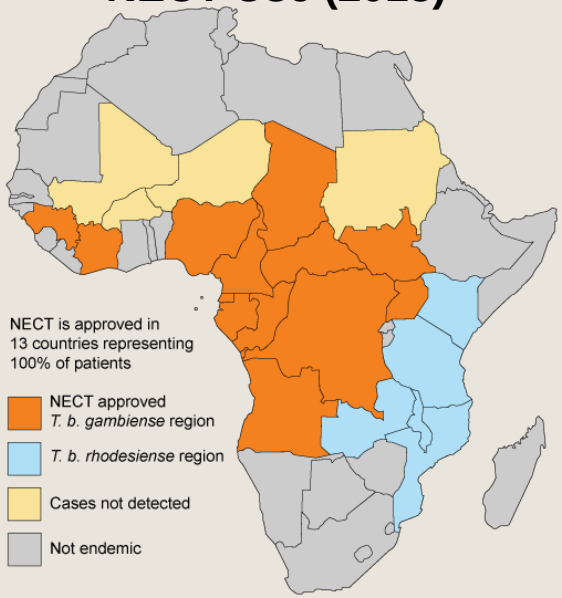
Nifurtimox-eflornithine combination therapy

- MSF & Epicentre initiated trial
- A simplified, safe & effective treatment for stage 2 HAT
- WHO Essential Medicines List (2009); Children (2013)
- Implemented in 13 countries, representing 100% of reported *T.b. gambiense* cases
- Drastic decrease in melarsoprol use



Treatments for stage 2 HAT in DRC (2012)

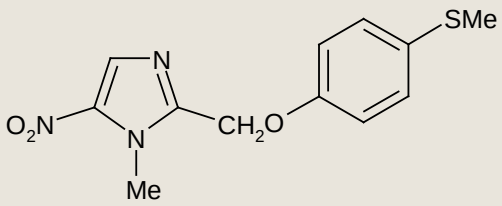
NECT Use (2013)



New Oral Treatment at Village Level

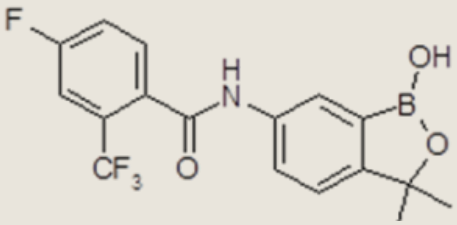
Fexinidazole

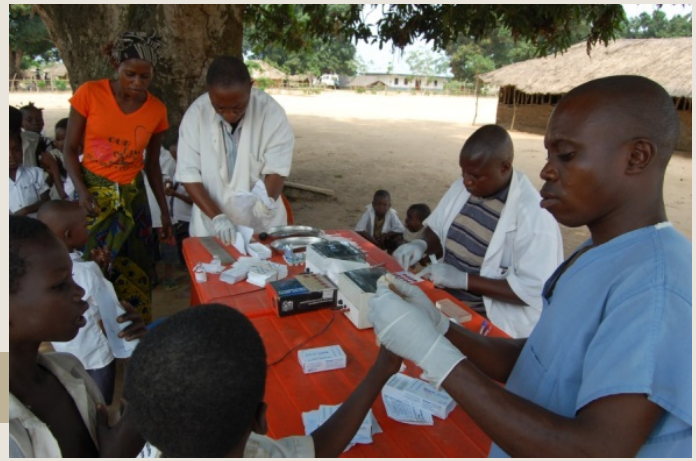
- A ‘rediscovered’ new chemical entity through compound mining
- Potential oral treatment 10 days one daily dose with food
- Phase II/III in DRC and CAR



Oxaborole SCYX-7158

- New chemical entity from the Lead Optimization programme
- Potential oral treatment with a single dose
- Entering Phase II/III in 2016





In partnership with Sanofi

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Fexinidazole: 3 clinical trials ongoing

FEX004: Pivotal phase II/III Stage 2 HAT in adults (n=390)
FEX005: Adult patients stage 1 and early stage 2 HAT (n=196)
FEX006: Children 6-14 years old, all stages (n=125)

Pivotal randomized control trial comparative with NECT. Blinded to sponsor.
PRIMARY END point at 18 months

CRITERIA OF SUCCESS

- ❑ CURE: Patient alive, no Tryps, < 20 WBC
- ❑ Probable CURE: if no LP but no signs and symptoms of HAT
- ❑ FAILURE: Other cases

Plugged in cohort open studies 005 and 006 endpoint at 12 months

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Fexinidazole: 2 new clinical trials in preparation

FEX007: Phase II Stage 2 r-HAT in adults (n=111)
FEX009: Cohort study all stages, all patients, field conditions

r-HAT 007: study shall be comparative with site matched historical cohort of melarsoprol treated patients.

Two sites identified: Lwala (Uganda); Rumphi (Malawi)
Primary end point survival at end of treatment (safety)
Secondary endpoint cure at 12 months

Implementation trial 009: To start in existing sites in DRC and to be extended afterwards to news sites in other countries (Guinea, Tchad)
Protocol in preparation

Both trials to start in 2016

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SCYX 7158: Phase 1 trial

- Randomized, double blind, placebo controlled
- Safety, tolerability, pharmacokinetics and pharmacodynamics
- Single oral ascending doses in healthy male volunteers from 20 to 1200 mg
- 3 years, 14 cohorts, 128 included (102 active)
- Few mild/moderate adverse events with similar percentage placebo & active
- Phase II/III to start in 2016

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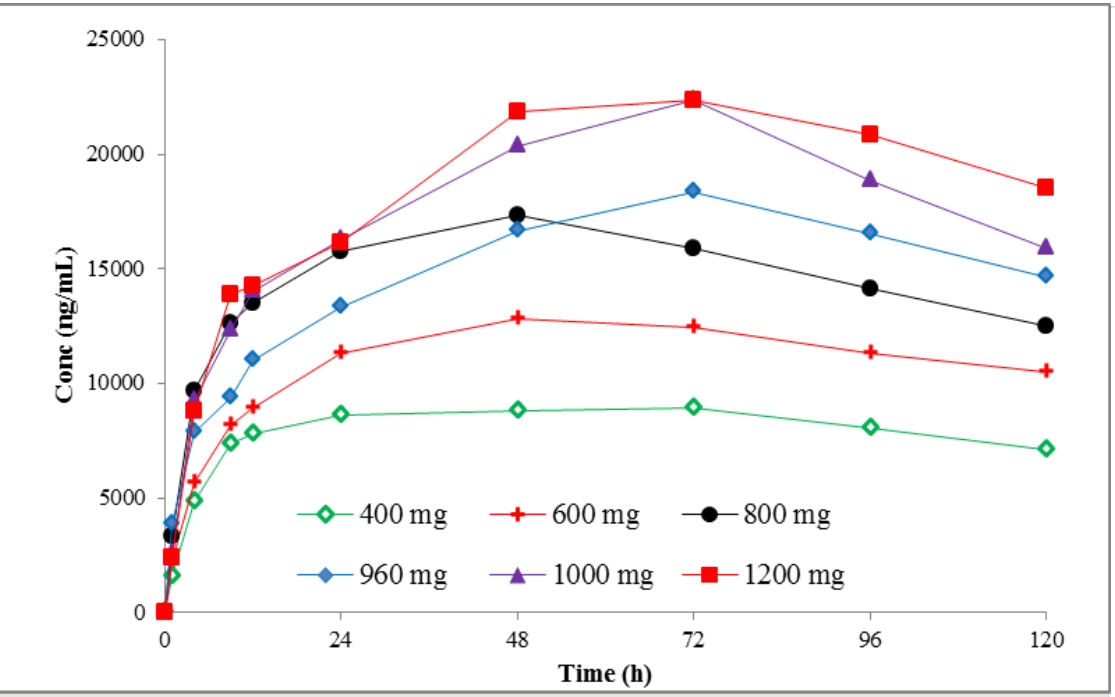
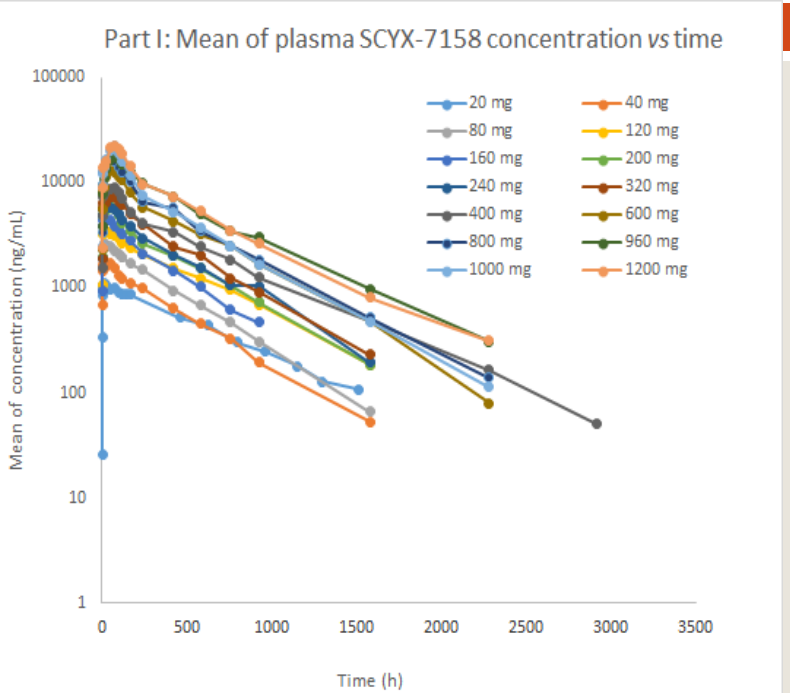
SCYX-7158 : Pharmacokinetic results

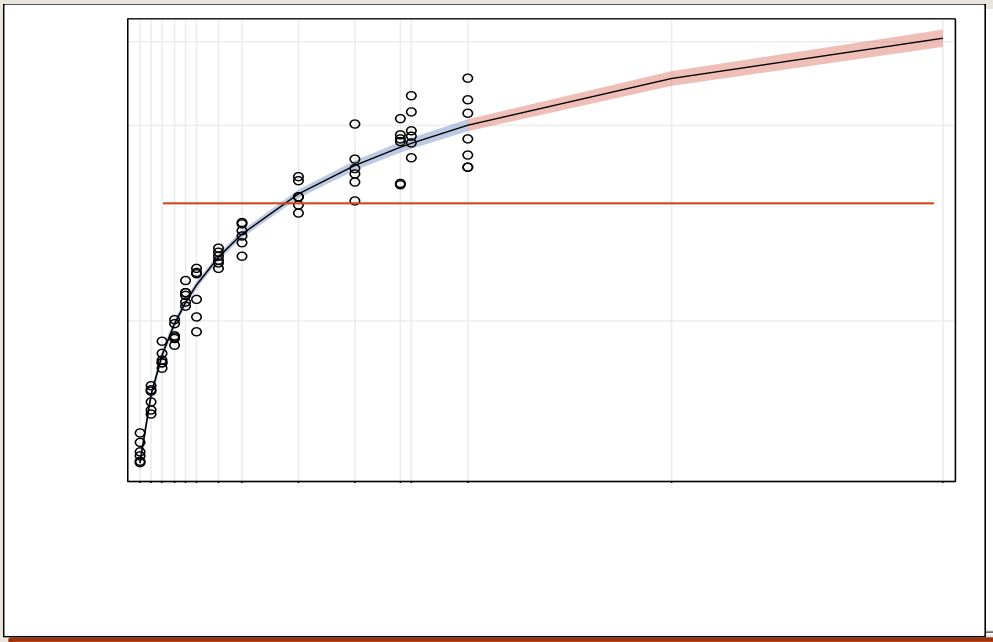




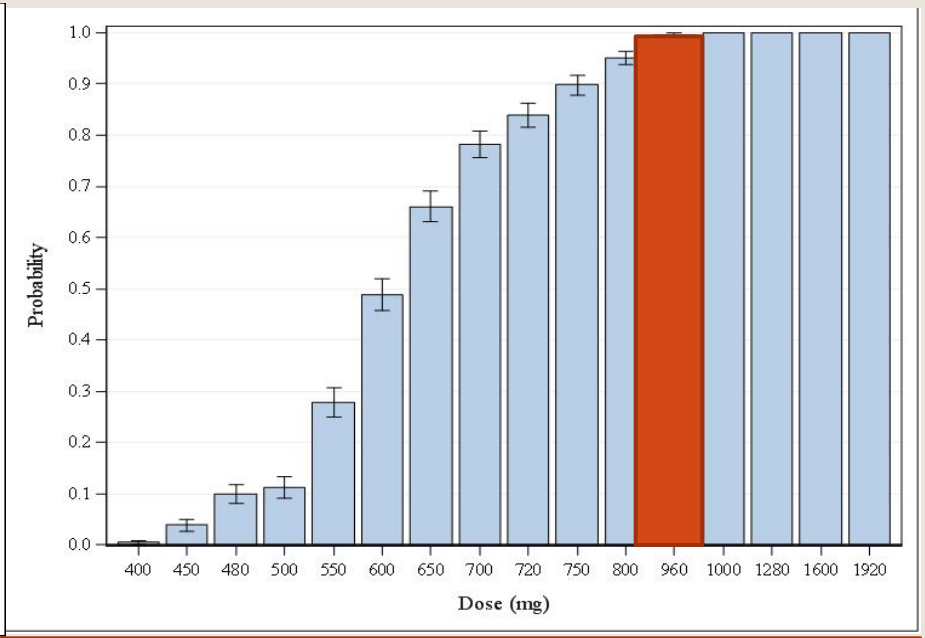
- T_{max} around 48h, stable for at least 4 days
- PK is linear but not dose proportional
- Slowly eliminated ($T_{1/2}$ of about 400h) ⟹ single dose
- Unbound fraction around 2.2%
- Ratio CSF/plasma ranged from 1.8% to 3.2% indicating brain penetration

SCYX-7158
Pharmacologically active exposure

Observed individual $AUC_{72\text{-}96}$ superimposed with estimated GM (and 90% CI)

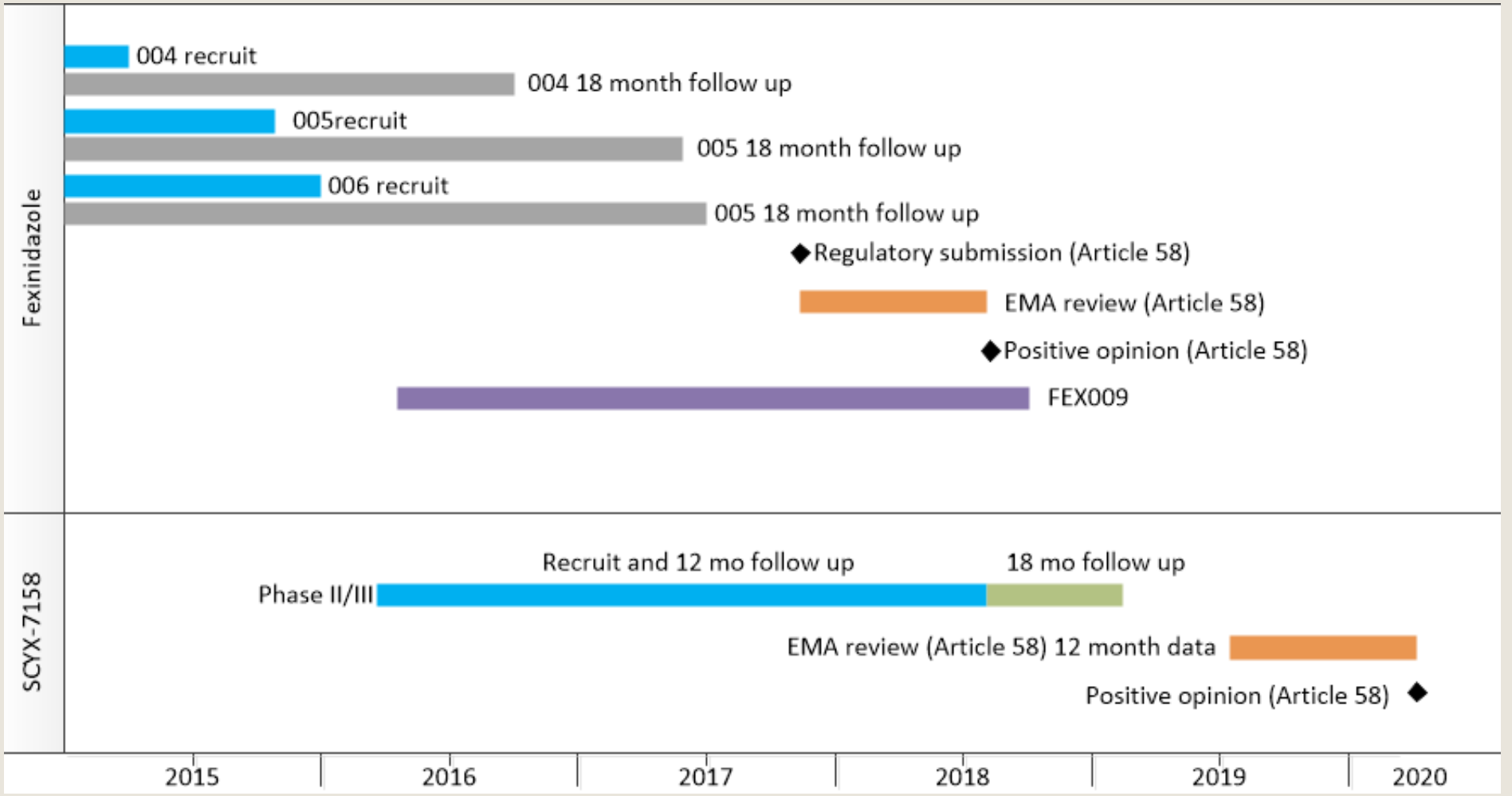


Probability of reaching the target exposure



TARGET = AUC $U_{0\text{-}24}$ of 5.8 µg.h/mL
960 mg single dose achieved an exposure of 1.5 times the target at AUC $_{72\text{-}96}$
To be tested in Phase II/III: 3 tablets of 320 mg given at once

HAT drugs development timeline



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