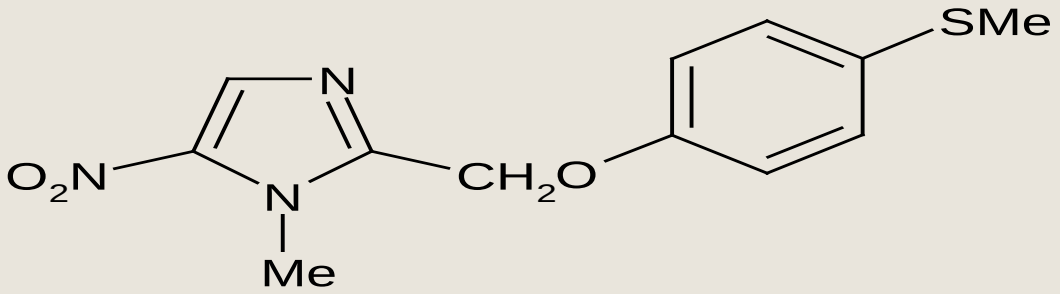
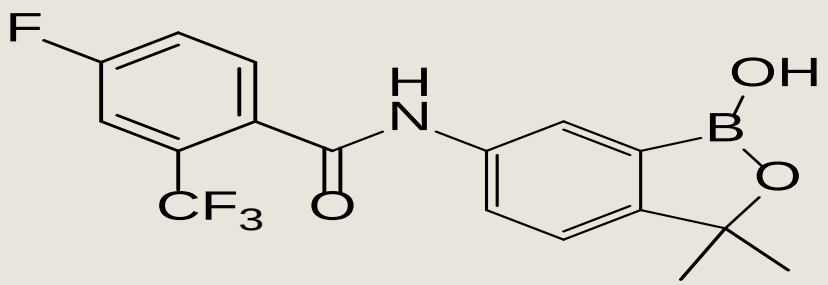




SCYX-7158 (AN5568)

NEW TREATMENTS FOR SLEEPING SICKNESS

DNDi
Drugs for Neglected Diseases *initiative*
Iniciativa "Medicamentos para Doenças Negligenciadas"

ASTMH NOV 2012

Antoine Tarral, MD, Head of HAT Clinical program

NECT: The Urgent solution

- Previous treatment for 2nd stage HAT
  - Too toxic. Melarsoprol, 5% mortality
  - Cumbersome. Eflornithine 56 IV infusions 14 days
- NECT, since September 2009
  - By adding oral Nifurtimox 3 times per day,
  - Eflornithine infusion reduced to 7 days, 14 infusions
- Still heavy logistics and high cost
  - Kits: 4 treatments, weight 38 kg and costs €1152
- Adverse events
  - 93% of patients, average of 4 per patient
- Not yet fulfilling TPP

DNDi HAT disease Strategy Objectives Update

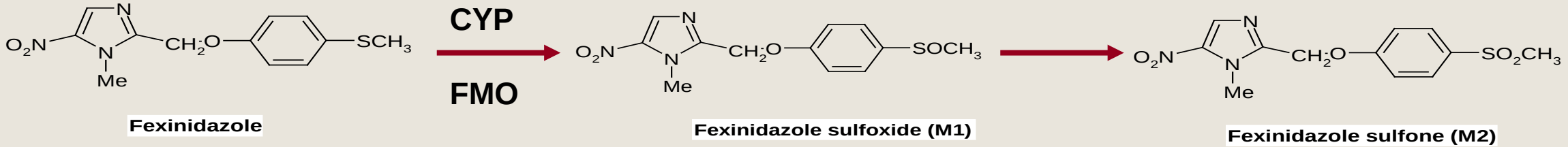
- To deliver two new treatments for HAT by 2018
  - Fexinidazole: Registration for treatment of stage 2 and stage 1 HAT by end 2016
  - SCYX-7158: Registration for stage 2 and stage 1 HAT by 2018
- Characteristics of such a treatment: (TPP)
  - Short-course oral treatment of no more than 10 days
  - Could be used to manage stage 1 and 2 of the disease
  - Safe enough to be used after a very simple RD test at a local level
  - Offering the possibility of horizontal program for the management of the disease
  - Much simpler and much cheaper than existing therapies: less than 50US$ per patient versus 440 US$ for the stage 2 of the disease

Fexinidazole

- Discovery : 1970 HOE 239, discontinued 1980

  Resuscitated in 2003

- 5-nitro-imidazole family
- Characteristics
  - MOL.Wt FEXI = 279 g/mol
  - MOL.Wt M1 = 295 g/mol
  - MOL.Wt M 2 = 311 g/mol
- pKa-value = very weak base
- $logD_{pH\ 7.4}$ = 2.8
- Metabolism



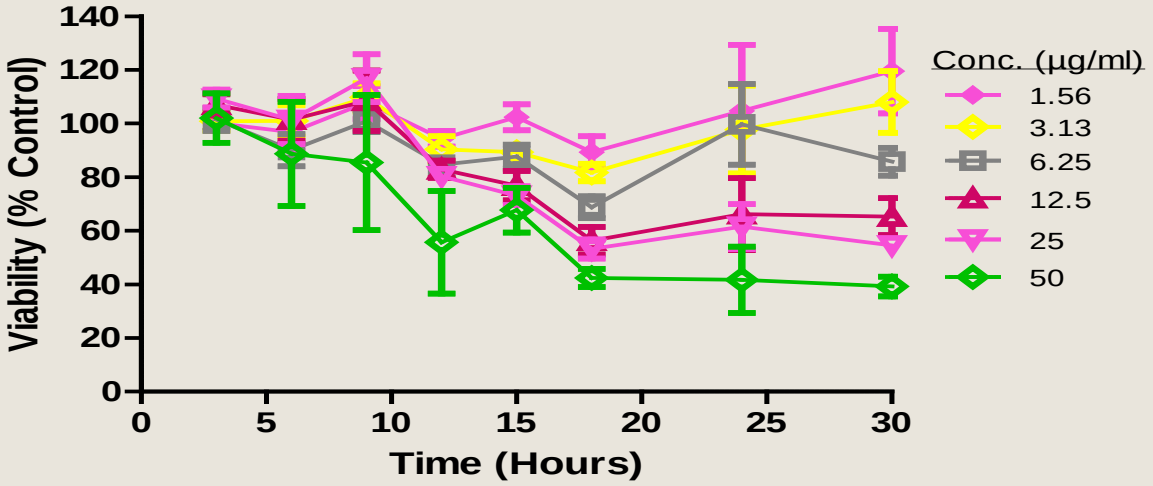
Fexinidazole — Fexinidazole sulfoxide (M1) — Fexinidazole sulfone (M2)

ASTMH NOV.2014

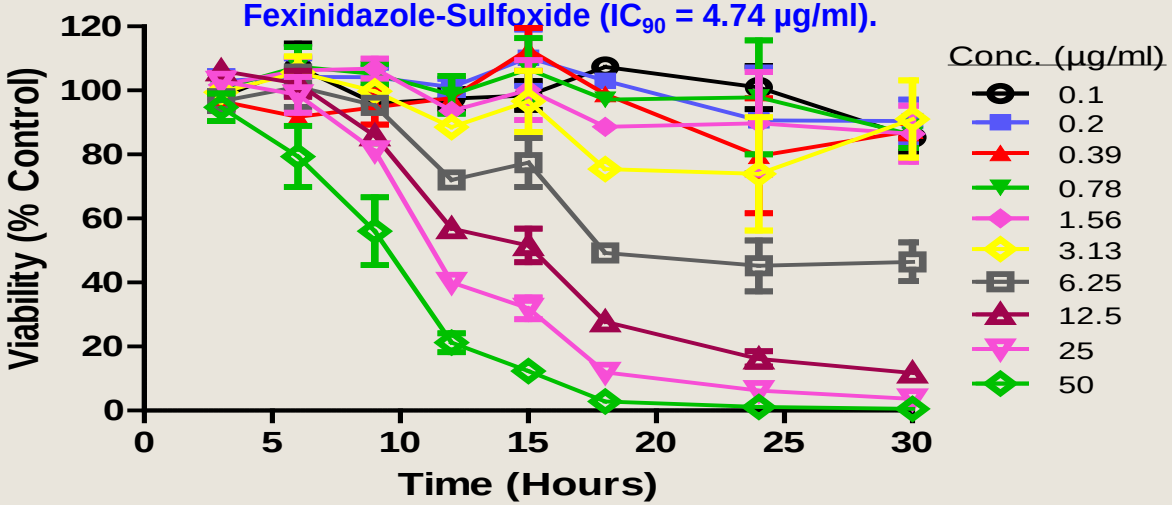
DNDi
Drugs for Neglected Diseases *initiative*
Iniciativa "Medicamentos para Doenças Negligenciadas"

Time to Kill Assays
Fexinidazole and Metabolites

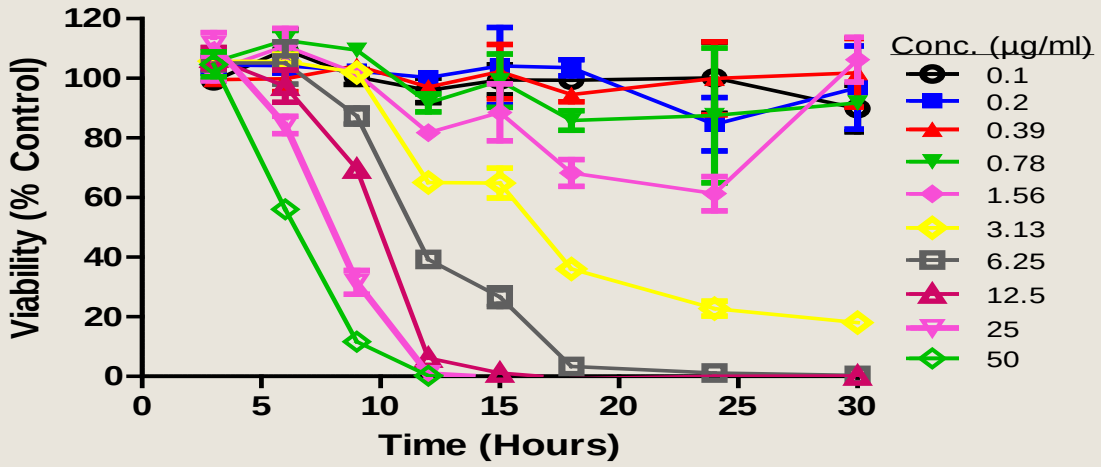
Fexinidazole (IC_{90} = 5.00 µg/ml)



Fexinidazole-Sulfoxide (IC_{90} = 4.74 µg/ml).



Fexinidazole sulfone (IC_{90} = 2.20 µg/ml)



Activity is concentration-dependent till MIC
But time-dependent for parasite cidal effet

DNDi
Drugs for Neglected Diseases *initiative*
Iniciativa "Medicamentos para Doenças Negligenciadas"

Key preclinical data

- The most active metabolite is M2: Fexinidazole sulfone
- IC_{90} of M2 is 2.200 ng/mL T1/2 > 24H
- No drug interaction expected as several CYP P450 involved

- ADME Rat brain concentration:

Met ID	Collection time	
	8 h	24 h
fexinidazole	3.3 %	nd
M1	36.1 %	12.3 %
M2	56.1¨%	76.2 %

No genotoxicity, no phototoxicity

NOAEL = 200 mg/kg Safety margin= 800mg/kg

Efficacy concentration in mice : 8-10 µg/mL of M2

Fexinidazole Clinical Studies

ASTMH NOV.2014

DNDi
Drugs for Neglected Diseases *initiative*
Iniciativa "Medicamentos para Doenças Negligenciadas"

Phase I studies (1)

118 /154 subjects have been exposed to Fexinidazole

- **Tolerability study**
  - *Part 1 :Single ascending dose study 100mg – 3600mg*
  - *Part 2 :Cross-over bioequivalence and food effect study (high fat rich meal / placebo)*
    - 1200mg single dose
  - *Part 3 (Multiple ascending dose study for 14 days 3 cohorts of 8 subjects*
    - Three cohorts of 8 subjects (6 active, 2 placebo) 1200mg, 2400mg & 3600mg
- **Field food interaction study (3way cross-over study ,12 subjects)**
  - Plumpy nuts, rice and beans / placebo 1200mg single dose

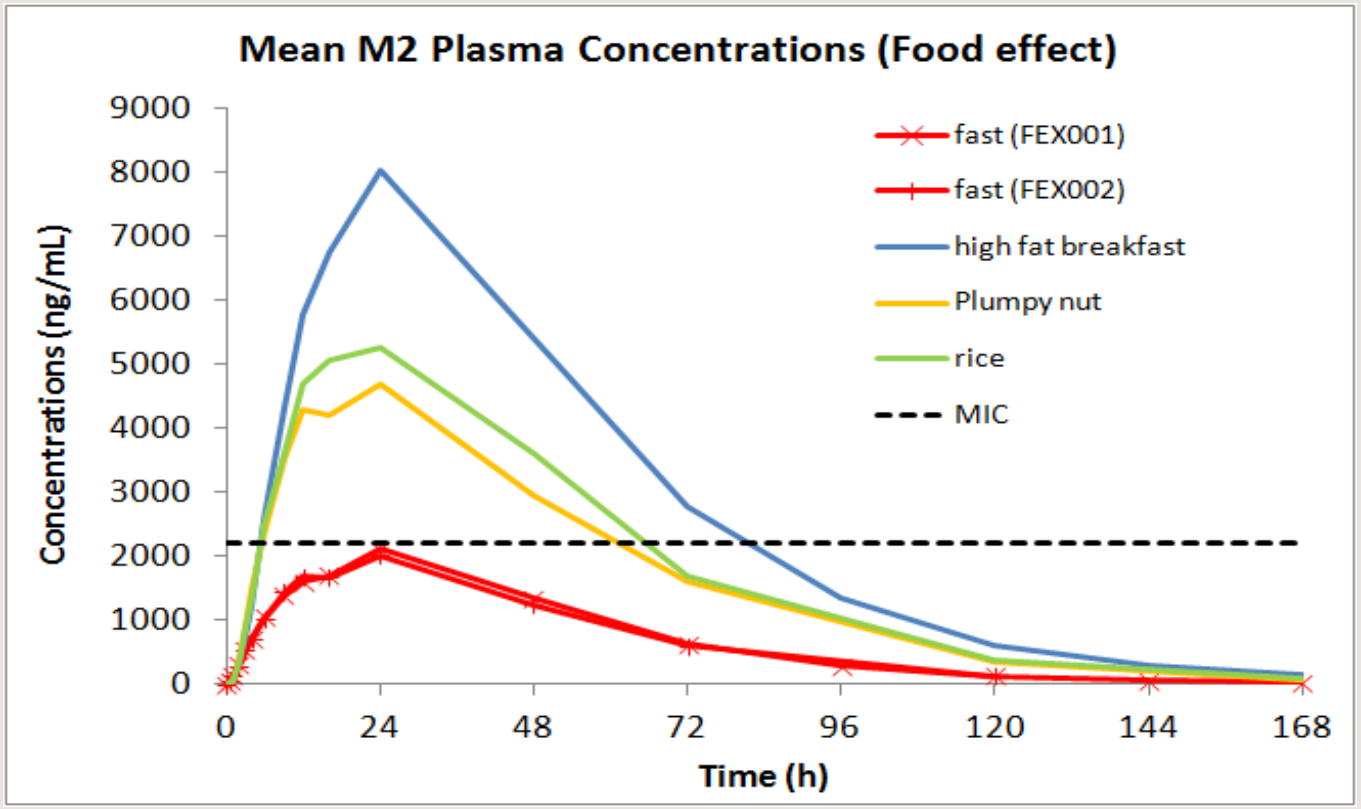
Phase I studies (2)

- **POP PK analysis to evaluated the best therapeutic dose**
  - Multiple scenarios were explored
  - 1 dose/day for 10 days with food
    - loading dose for 4 days of 1800mg /day
    - + treatment dose for 6 days of 1200mg /day
- **Multiple dose in fed condition with the therapeutic dose**
  - Randomized, double-blind versus placebo
  - Two cohorts of 18 subjects (12 active, 6 placebo/cohort)
    - loading dose of 1800mg for 4 days + 1200mg for 4 days
    - loading dose of 2400mg for 4 days + 1200mg for 4 days

PK Results

- Absolute Bioavailability ≈ 41% in mice; 30% in rats
  - Fexinidazole: median Tmx: 3-4 H; mean T1/2: 9-15H
  - M1 sulphoxide: median Tmx: 2-5 H; mean T1/2: 18-20H
  - M2 sulphone: median Tmx: 18-24 H; mean T1/2: 18-25H
- Exposure increased linearly, but not proportional to dose administered
- No saturation of the metabolism
- Steady state in fasted conditions: D4 for fexi and M1, D9 for M2
- Food effect: 2-3 fold increase in plasma concentration / fasting
- High plasma free fraction of the metabolites M1:59% and M2: 43%

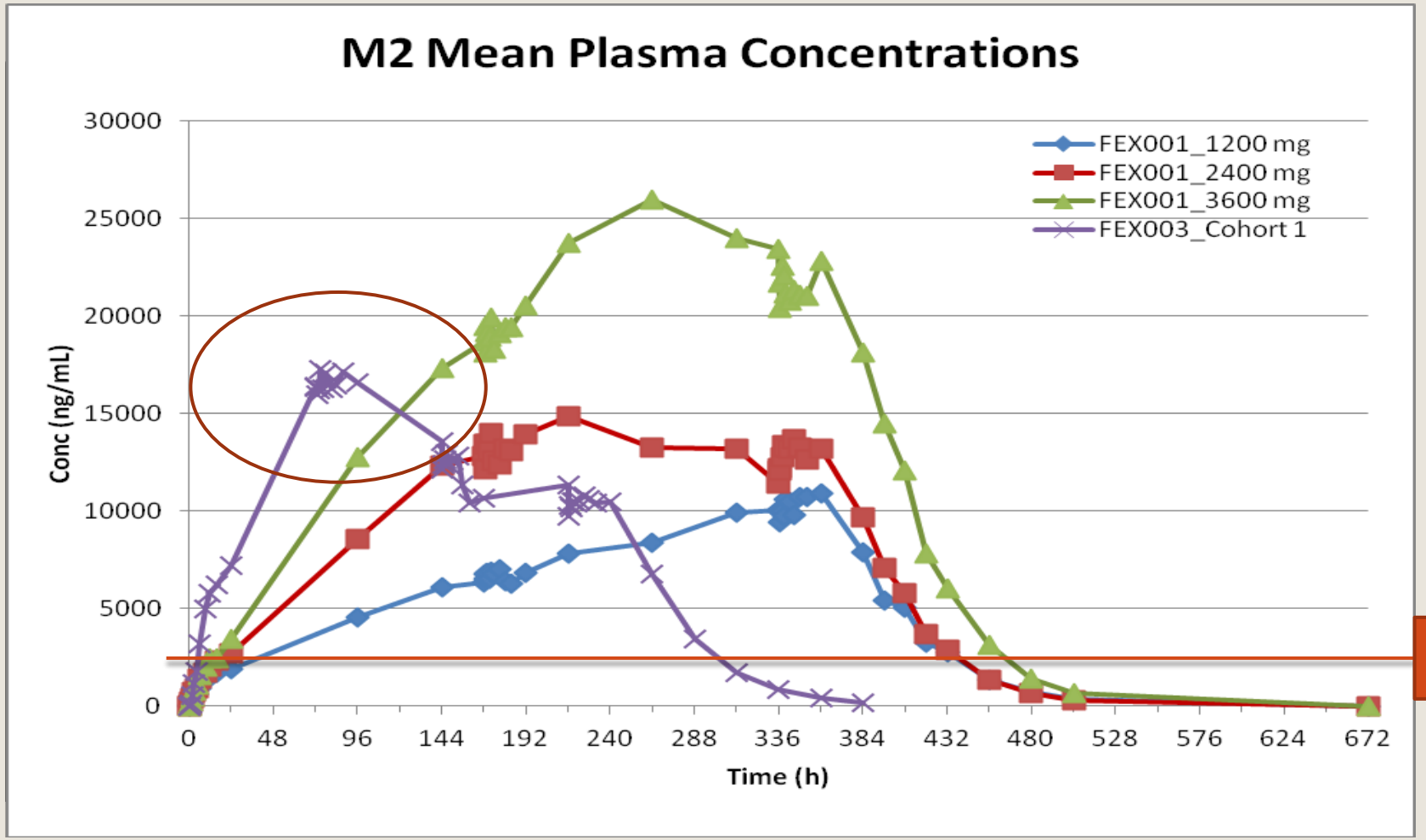
M2 fed : Mean Plasma levels



- ✓ high fat breakfast:
  - AUC FEXI x 5
  - AUC M2 x 4
- ✓ rice & beans or Plumpy nuts:
  - AUC FEXI and M2 x 2.5-3

DNDi
Drugs for Neglected Diseases *initiative*
Iniciativa "Medicamentos para Doenças Negligenciadas"

PK results : 1800/1200mg



M2 plasma levels

- reached earlier
- maintained for 3 to 4 days above 10 mg/L.
- In more than 80% of the subjects

IC_{90} 2200ng /ml

ASTMH NOV.2014

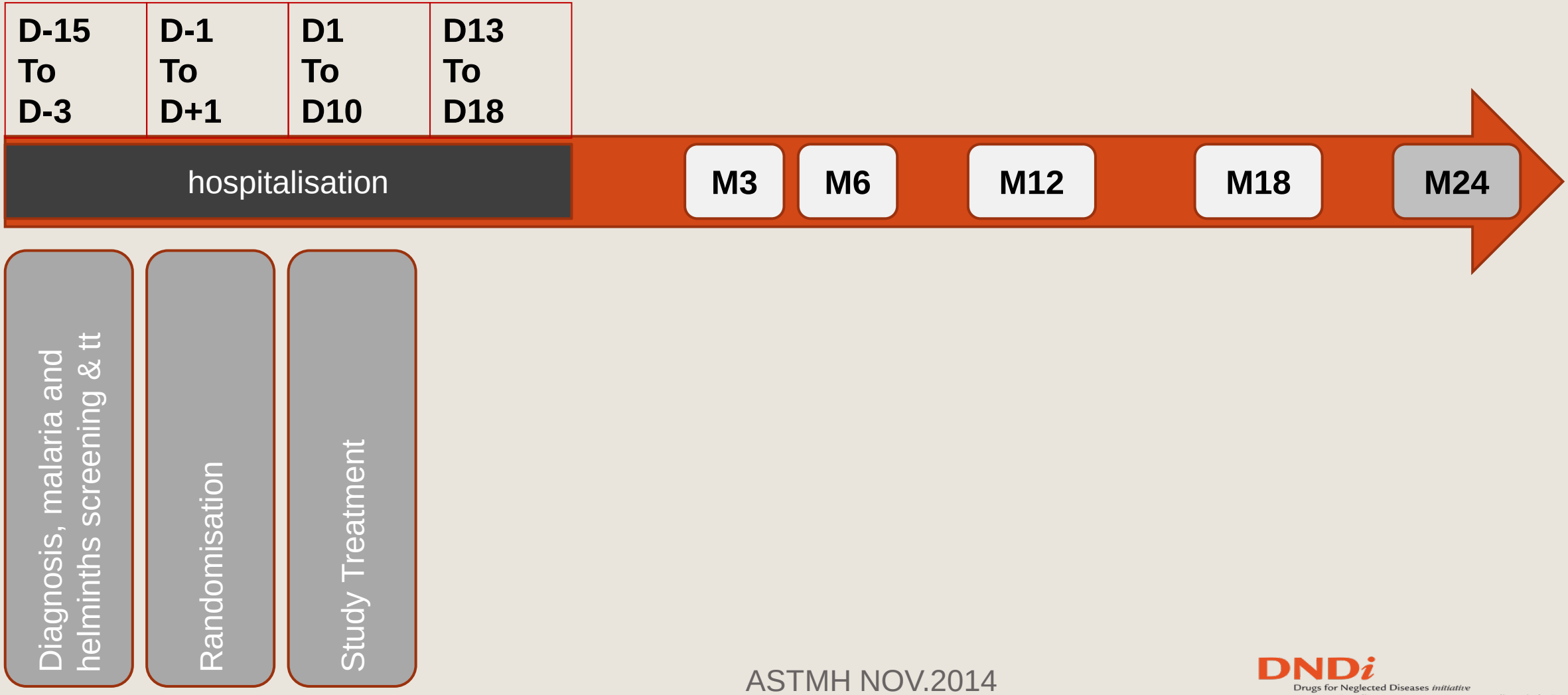
DNDi
Drugs for Neglected Diseases *initiative*
Iniciativa "Medicamentos para Doenças Negligenciadas"

Fexinidazole phase II/III

ASTMH NOV.2014

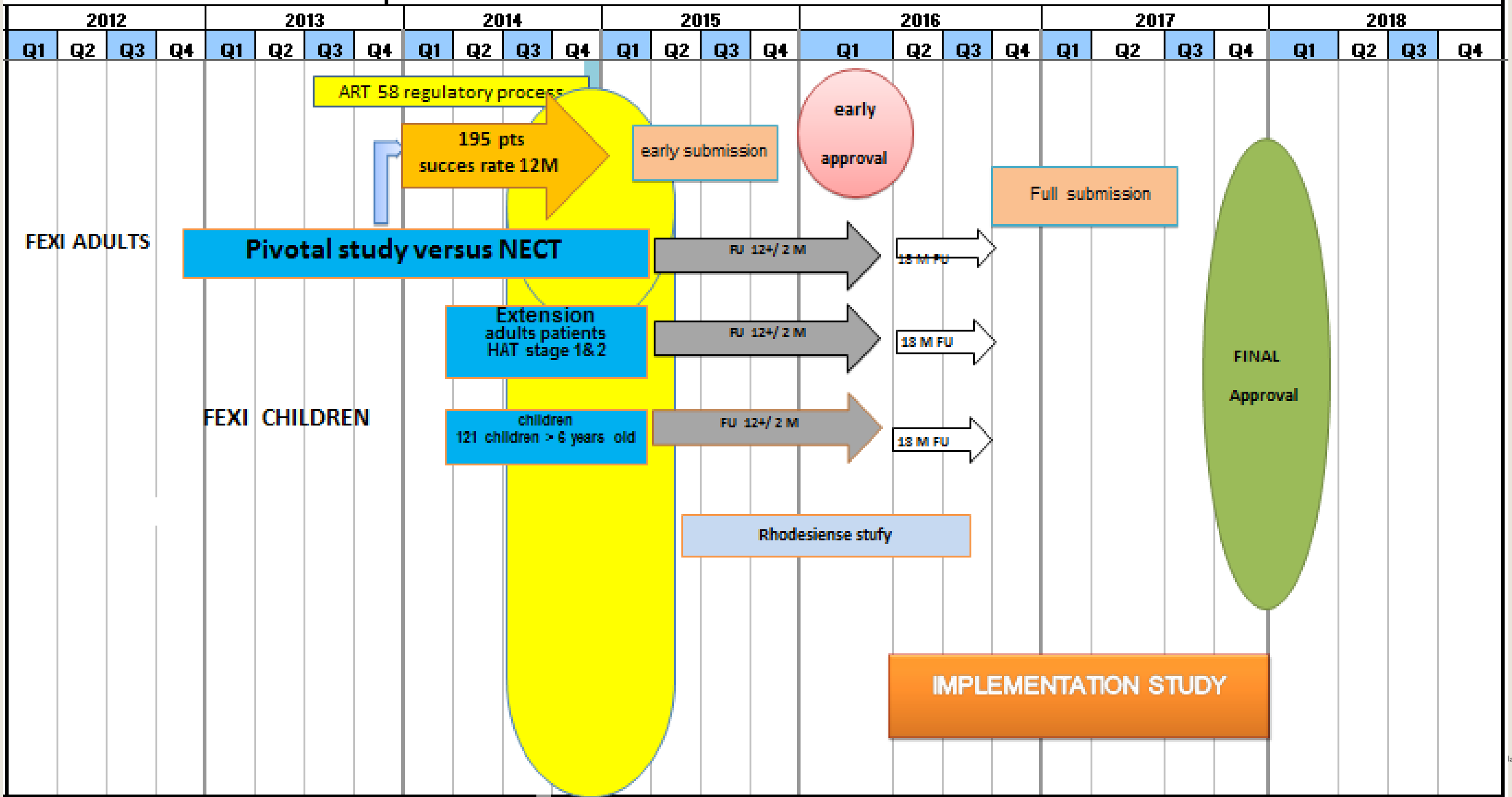
DNDi
Drugs for Neglected Diseases *initiative*
Iniciativa "Medicamentos para Doenças Negligenciadas"

Schedule of visits phase II/III study



DNDi
Drugs for Neglected Diseases *initiative*
Iniciativa "Medicamentos para Doenças Negligenciadas"

Strategic Development Plan for HAT disease



SCYX-7158 (AN5568)

In collaboration with:

Anacor Pharmaceuticals, Inc.

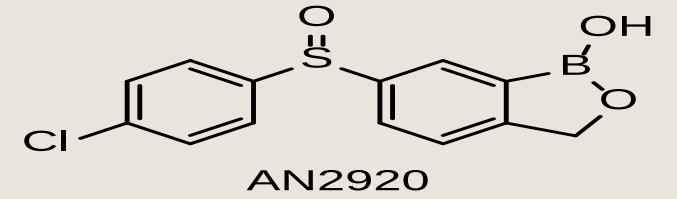
Pace University

SCYNEXIS, Inc.

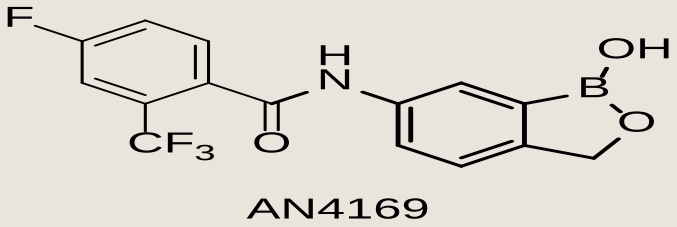
ASTMH NOV.2014

DNDi
Drugs for Neglected Diseases *initiative*
Iniciativa "Medicamentos para Doenças Negligenciadas"

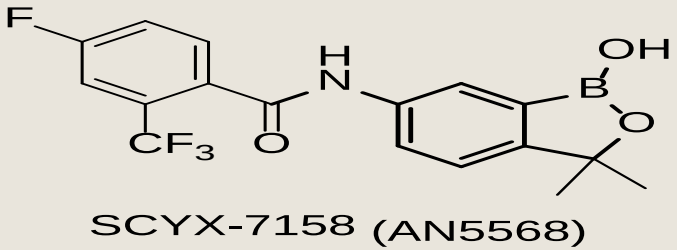
SCYX- 7158 (AN5568)
First DNDi Preclinical Candidate for HAT From Lead Optimization Program[1,2]



AN2920



AN4169



SCYX-7158 (AN5568)

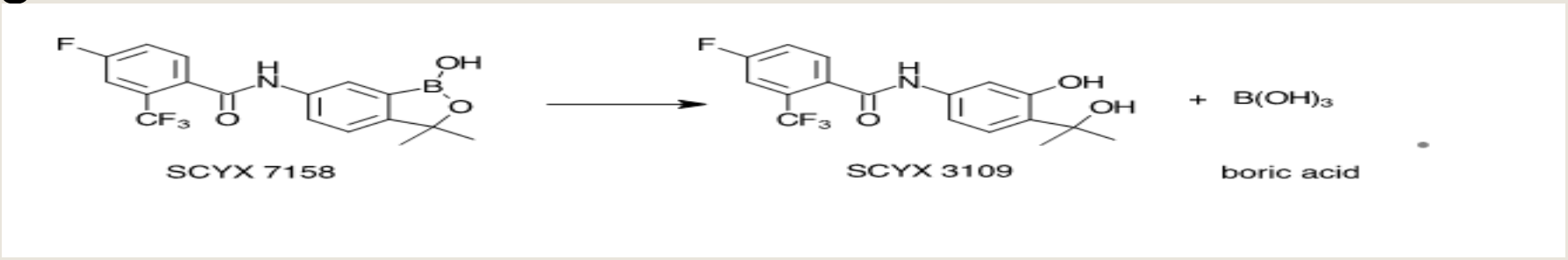
- Initial screening hit identified at UCSF Sandler Center (J. McKerrow)
- Initial "lead" identified from further screening and early SAR development at SCYNEXIS
- Optimized lead which was progressed to pre-clinical and clinical evaluation[3]
- Phase 1 clinical trials started in 2012

[1]Jacobs, RT, etal, Future Med Chem **2011**, 3, 1259
[2]Nare, B, etal, Antimicrobial Agents Chemotherapy **2010**, 54, 4379
[3]Jacobs, RT, etal, PLoS Negl Trop Dis **2011**, 5, e1151

DNDi
Drugs for Neglected Diseases *initiative*
Iniciativa "Medicamentos para Doenças Negligenciadas"

SCYX-7158 PROPERTIES[1]

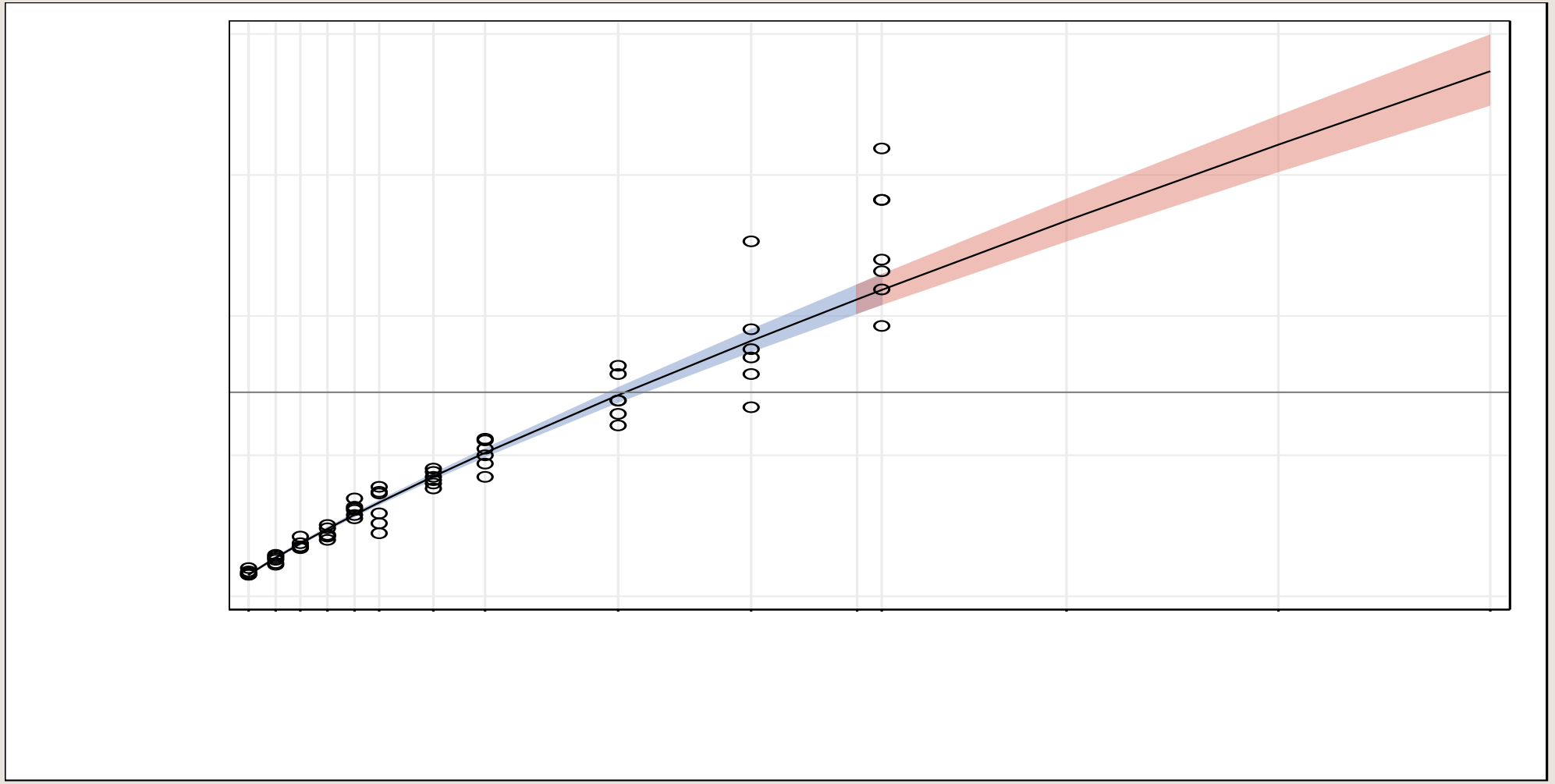
- Mol. Wt. = 367.11 g/mol
- Pka= 9.61
- logD=3.51
- MDCK-MDR1 P_{app}(A-B) > 350 nm/s
- Vd> 0.6 L/Kg = distribution into the whole body water
- Half-life of around 16 days **single dose administration** [2]
- Oxidative deboronation to SCYX 3109 is primary metabolism[3]



[1]SCYX-7158 Investigational Medicinal Product Dossier, DNDi, 2012.
[2] Study report PH11015/DNDiOXA001, PhinC/DNDi, April 2014.
[3] SCYX-7158 Investigator's Brochure, DNDi, 2012.

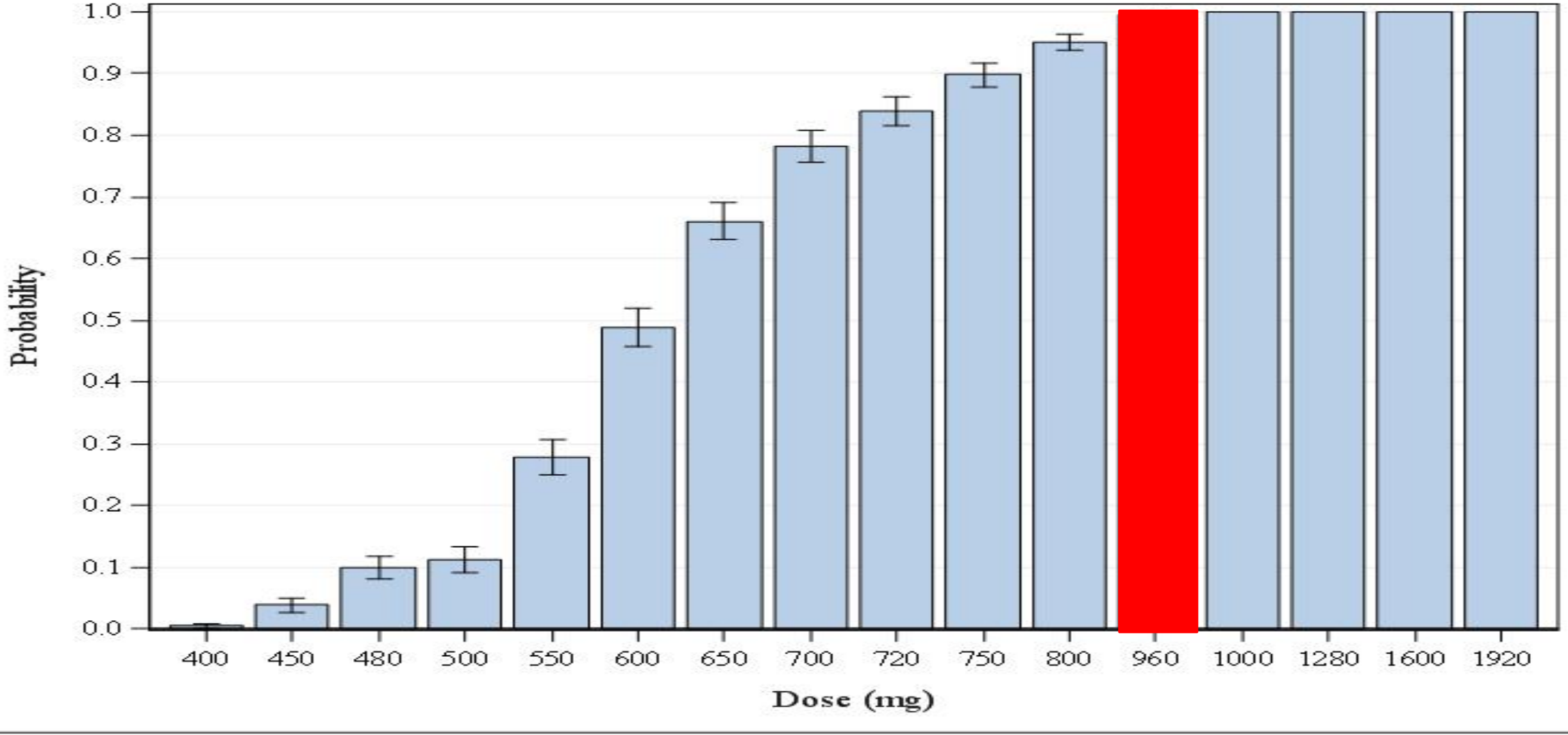
DNDi
Drugs for Neglected Diseases *initiative*
Iniciativa "Medicamentos para Doenças Negligenciadas"

Observed individual $AUC_{72\text{-}96}$ superimposed with estimated GM (and 90% CI)[1]



[1] Study report PH11015/DNDiOXA001, PhinC/DNDi, April 2014.

Probability of reaching $AUC_{72\text{-}96}$ of 290000 ng*h/mL in plasma (corresponding to 5800 ng*h/mL in CSF) according to dose



Conclusions

- Two new oral compounds to treat sleeping sickness
  - Fexinidazole once a day for 10 days
  - SCYX- 7158 (AN5568): Potential for single oral dose
- Both active against *T. brucei gambiense and rhodesiense*
- Along with a simplified field adapted diagnostic test
- On the way to changing the paradigm of treatments for sleeping sickness

Publications

Fexinidazole

- **Kaiser M &all** (2011). Anti-trypanosomal activity of Fexinidazole – A New Oral Nitroimidazole Drug Candidate for the Treatment of Sleeping Sickness. Antimicrobial Agents Chemotherapy. doi: 10.1128/AAC.00246-11.
- **Torreele E &all** (2010). Fexinidazole – A New Oral Nitroimidazole Drug Candidate Entering Clinical Development for the Treatment of Sleeping Sickness. PloS Negl Trop Dis 4:e923. doi:10.1371/journal.pntd.0000923
- **Tarral A & all** (2014) ; Determination of an optimal dosing regimen for fexinidazole, a novel oral drug for the treatment of human african trypanosimiasis:f irst in human studies clinicalapharmacokinetics 2014, 5,pp 565-580

SCYX-7158 (AN5568)

- **Jacobs RT & all(2010) B**enzoxaboroles: a new class of potential drugs for human african trypanosomiasis Future Med. Chem. 3(10) 1259-1278
- **Jacobs RT &all(2011)** SCYX- 7158, An orally active benzoxaborole for the treatment of stage 2 human African trypanosimiasis . PloS Negl Trop Dis 5(6), e1151.
- **Wring S & all (2013)** SCYX-7158 (AN5568) : CNS Exposure Predicted from First-in-Human Clinical Studies Indicates a Single Oral Dose Treatment is Possible for Sterile Cures of Stage 2 Human African Trypanosomiasis ASTMH 62nd Annual Meeting Washington D.C., 13-17th November 2013

THANK YOU

DNDi
Drugs for Neglected Diseases *initiative*
Iniciativa "Medicamentos para Doenças Negligenciadas"