Clinical Development of New Treatments for Sleeping Sickness

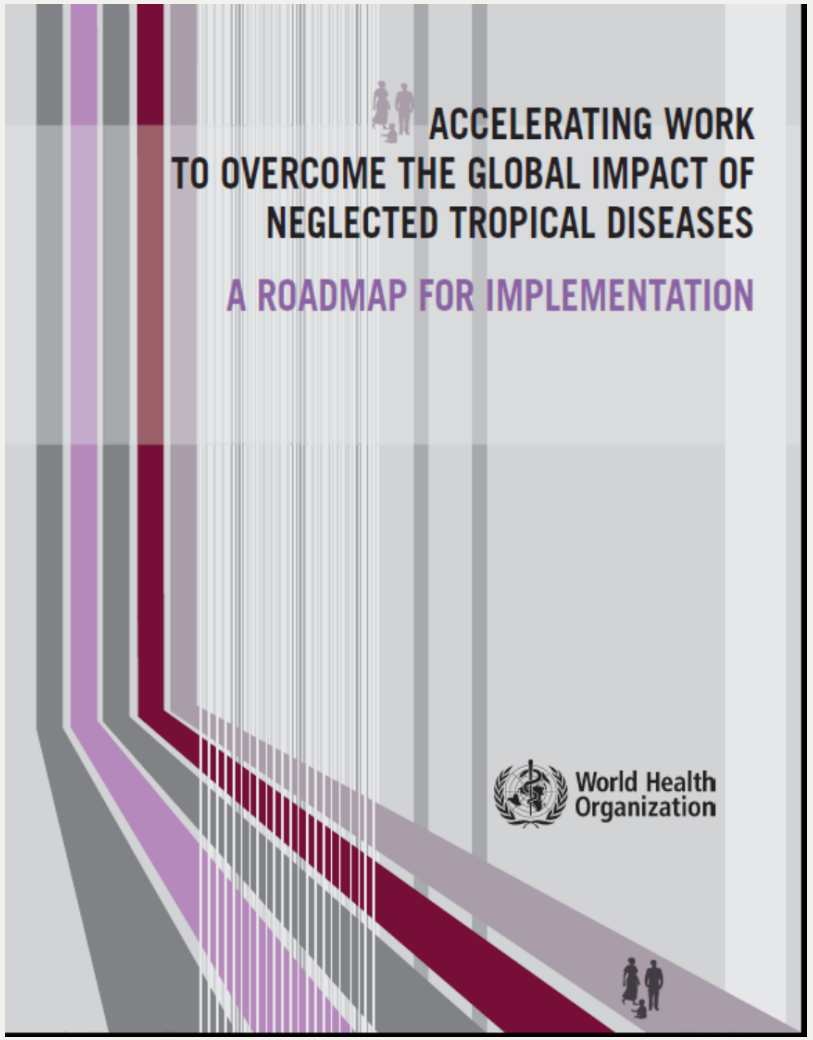
Antoine TARRAL

ASTMH Nov. 2016 , Atlanta

DNDi
Drugs for Neglected Diseases *initiative*

Supporting WHO HAT elimination goals

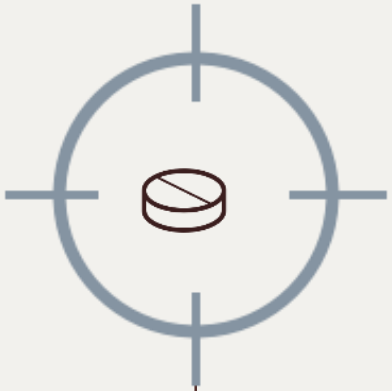
WHO set goals for Global Elimination of sleeping sickness by 2020, supported by London Declaration (2012)



DNDi contributes by:

- **Developing two new oral treatments for both stages of the disease**
- **Supporting mobile teams for the village screening**
- **Preforming capacity building**
- **strengthening clinical staff competencies**

Sleeping sickness: Two new treatments in development to support sustainable elimination



13 years ago

Melarsoprol:

Toxic, resistant

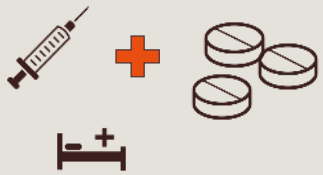
Eflornithine:

14 Days IV infusion

Since 2009

NECT= nifurtimox+ efflortinitne

Improved therapy



2018?

Fexinidazole

once daily Oral treatment for 10 days

2020?

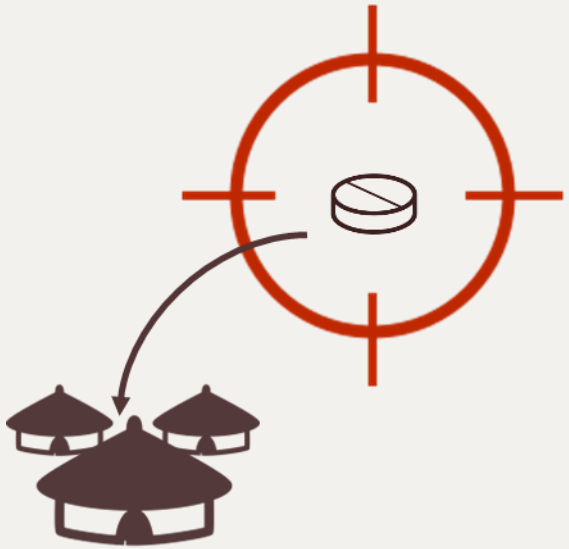
SCYX-7158

Single-dose, oral treatment

By 2018, DND*i* aims to deliver an oral, safe, effective treatment for both stage 1 and stage 2 g-HAT disease

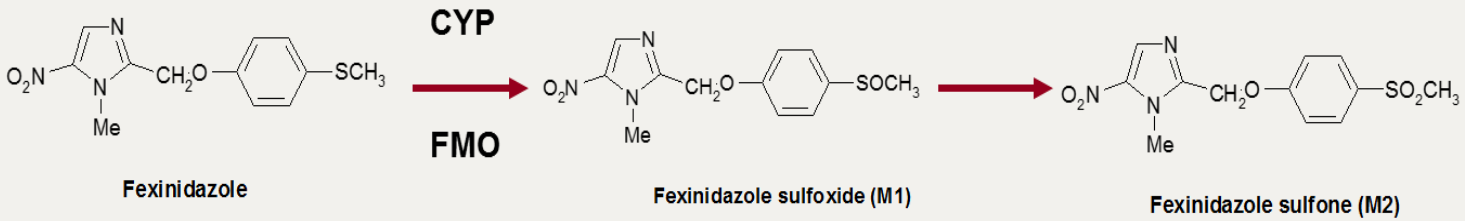
Target product profile (main points):

- Effective against stage 1 and 2
- Broad spectrum (*T.b. gambiense* and *T.b. rhodesiense*)
- Non inferior efficacy to NECT in *T.b gambiense*
- Safe in pregnancy and for lactating women
- Adult and paediatric formulations
- No need for monitoring of AEs
- 10 days p.o. once daily (equal to NECT)
- Stability in zone 4 for >3 years
- Cidal
- Affordable and <100€/ course

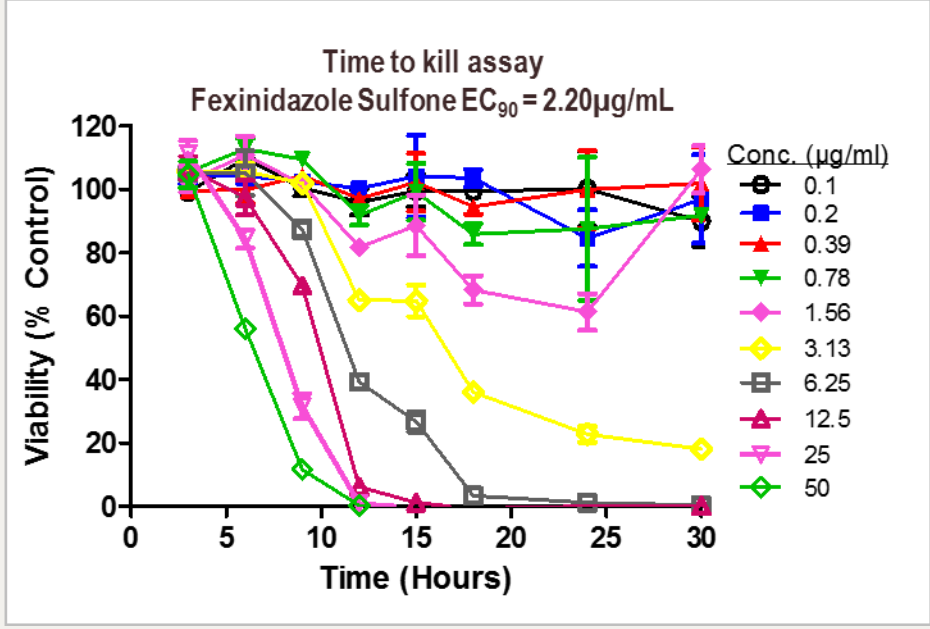


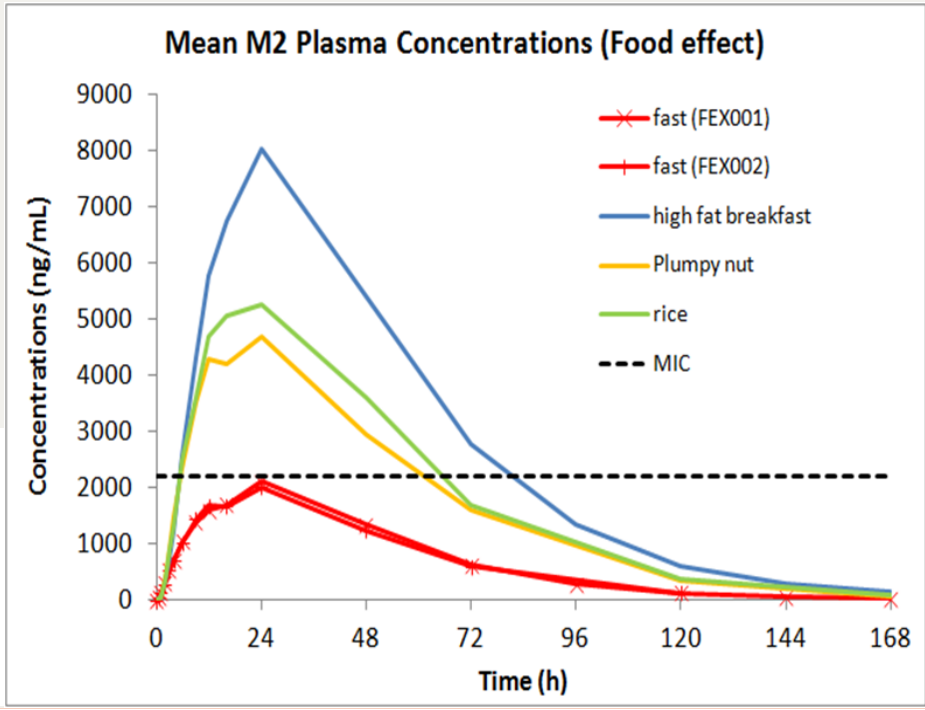
Fexinidazole

- A chemical entity ‘rediscovered’ through compound mining



- Once daily ORAL administration with food for 10 days
- 600 mg tablets
  - Loading dose on D1-D4, 3 tablets /day +
  - Maintenance dose on D5-D10, 2 tablets /day





PARTNERS: *BaseCon; Bertin Pharma; Venn Life Sciences; Cardiabase; MSF; Phinc Development; National Control Programs of the Democratic Republic of Congo and the Central African Republic; RCTs; Sanofi; Swiss Tropical and Public Health Institute; SGS; Theradis Pharma*

Fexinidazole - 4 clinical trials on going

Swiss TPH
Swiss Tropical and Public Health Institute
Schweizerisches Tropen- und Public Health-Institut
Institut Tropical et de Santé Publique Suisse

Associated Institute of the University of Basel

Example of the site laboratory renovation

FEX004: Single blind Pivotal phase II/III randomized versus NECT
NCT01685827 Stage 2 g-HAT in adult patients (n=390)
FPI Nov 2012
LPO Nov 2016 (18 months FU)

FEX005: Open, adult patients stage 1 and early stage 2 g-HAT (n=230)
NCT02169557 FPI June 2014
LPO Nov 2016 (12 months FU)

FEX006: Open, children 6-14 years old + > 20kg bodyweight
NCT02184689 Stage1 and Stage 2 g-HAT patients (n=125)
FPI June 2014
LPO Dec 2016 (12 months FU)

FEX009: Open, implementation study in-patients + out-patients cohort
(N=170) all stages g-HAT patients Adult + children
FPI started Nov 2016

DNDiFEX004 protocol V3.0,
Protocol DNDi/HAT FEX005 & 006 & DNDI-fEX-O9-HAT


RÉPUBLIQUE CENTRAFRICAINE
Batangafo
CAMEROUN
Bangui
Oubangui
Yaoundé
Dingila
Uélé
ORIENTALE
Lopori
ÉQUATEUR
Isangi
Kisangani
Mbandaka
CONGO
GABON
NORD-KIVU
Goma
Bolobo
Mushie
Bukavu
RWANDA
Fimi
KASAÏ-ORIENTAL
Bandundu
RÉPUBLIQUE DÉMOCRATIQUE DU CONGO
Kwamouth
SUD-KIVU
Bagata
BURUNDI
BANDUNDU
Kinshasa
Vanga
MANIEMA
Masimanimba
Kikwit
KASAÏ-OCCIDENTAL
Boma
Matadi
Dipumba
Mbuji-Mayi
Katanda
Ngandajika
Luanda
ANGOLA
KATANGA

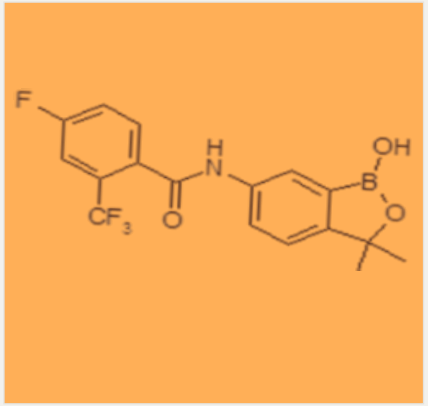
Oral Single Dose Treatment for Sleeping Sickness to Enter Phase II/III Clinical Study

Development

Pre-clinical | Phase1 | *Phase IIa/PoC*

SCYX-7158 (AN5568)

Objective: Develop and register SCYX-7158 as a new drug for the treatment of all stages of *T.b. gambiense*

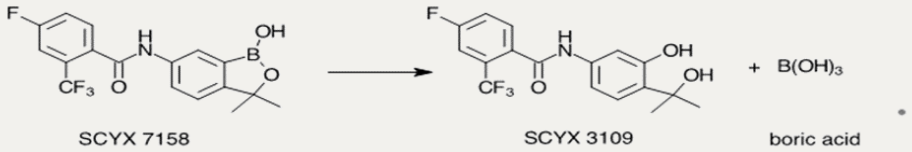


- Early oxaboroles identified as hits against *T.b. brucei* at Sandler Center, University of California San Francisco
- Two year lead optimisation programme led and managed by DNDi in an innovative partnership with 2 biotechs (Anacor, Scynexis) and 1 university (Pace) in the US
- 2011: Pre-clinical development
- 2012: Phase I study in France
- Nov -2016 Initiation pivotal study in stage 2 g-HAT adults patients

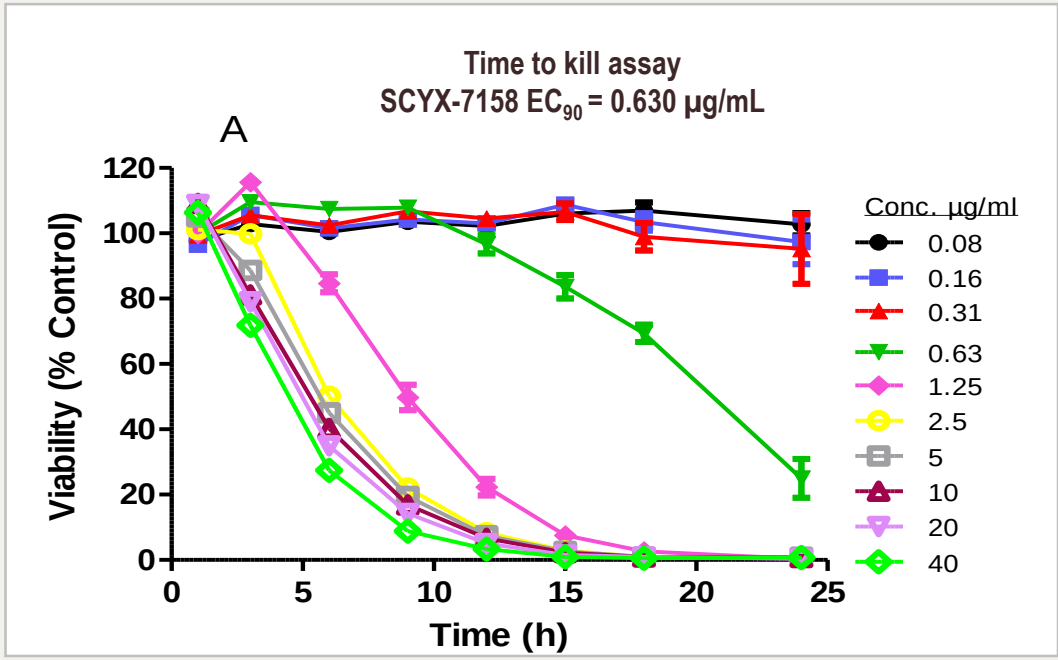
PARTNERS: *Anacor Pharmaceuticals; Advinus Therapeutics; SCYNEXIS; Swiss Tropical and Public Health Institute; Institute of Tropical Medicine – Antwerp; Institut de Recherche pour le Développement; Institut National de Recherche Biomédicale*

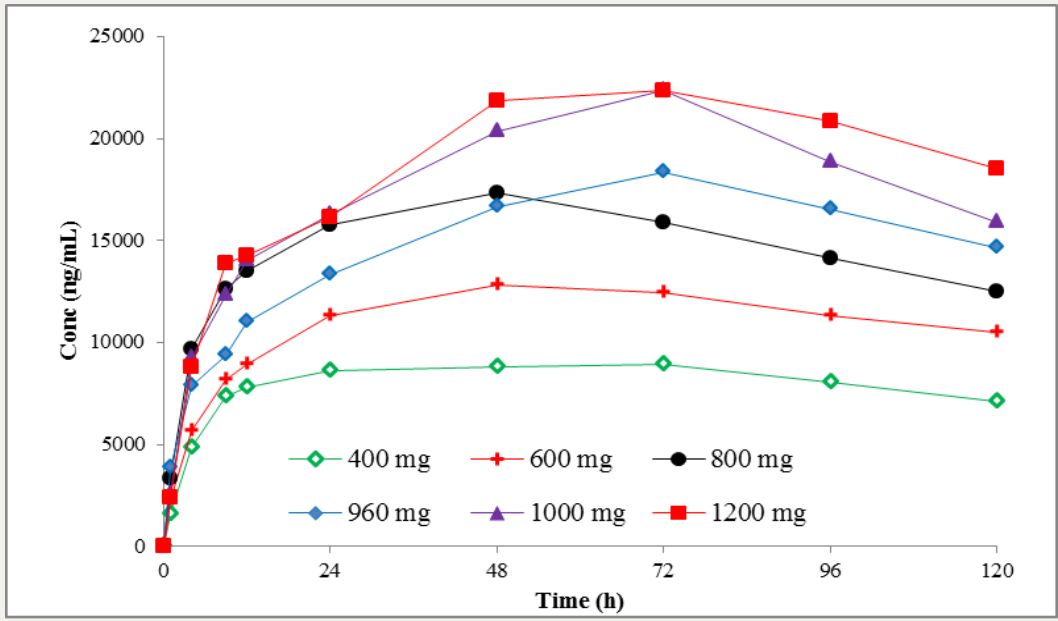
SCYX-7158 (AN5568)

- Lipophilic drug
- High volume of distribution
- High protein bound
- Cross the blood brain barrier
- Poorly metabolised



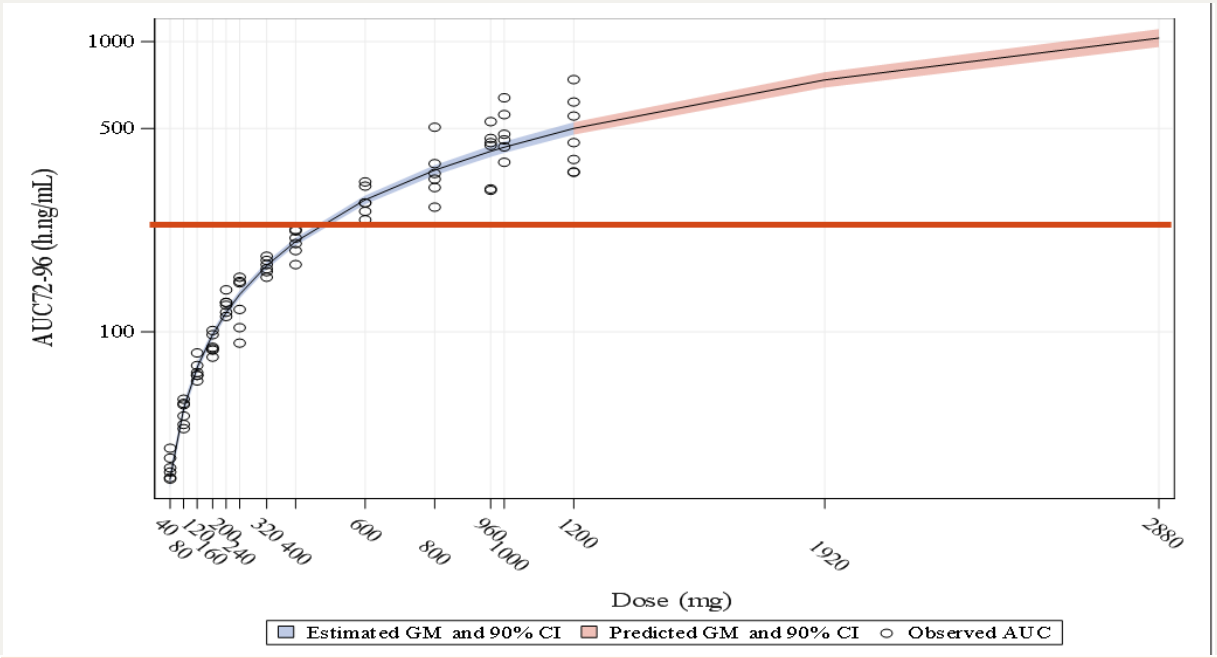
- half-life of 16 days
- Single oral administration of 3 tablets of 320 mg in fasted conditions (total dose 960mg)



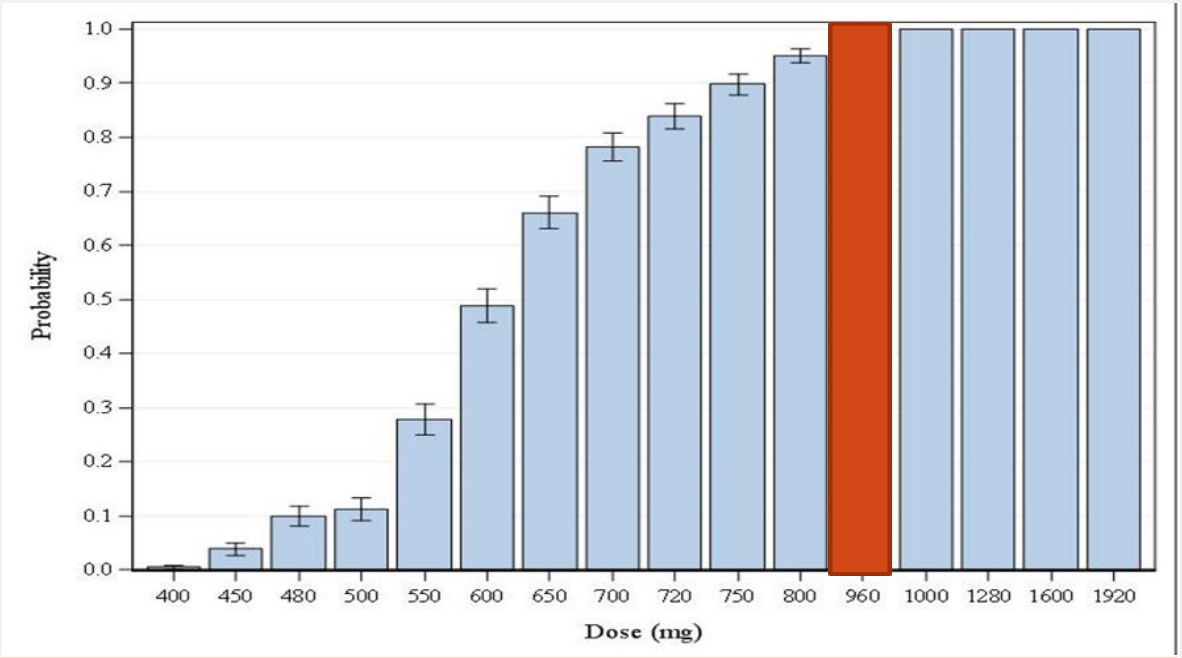


SCYX-7158 Pharmacologically active exposure

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



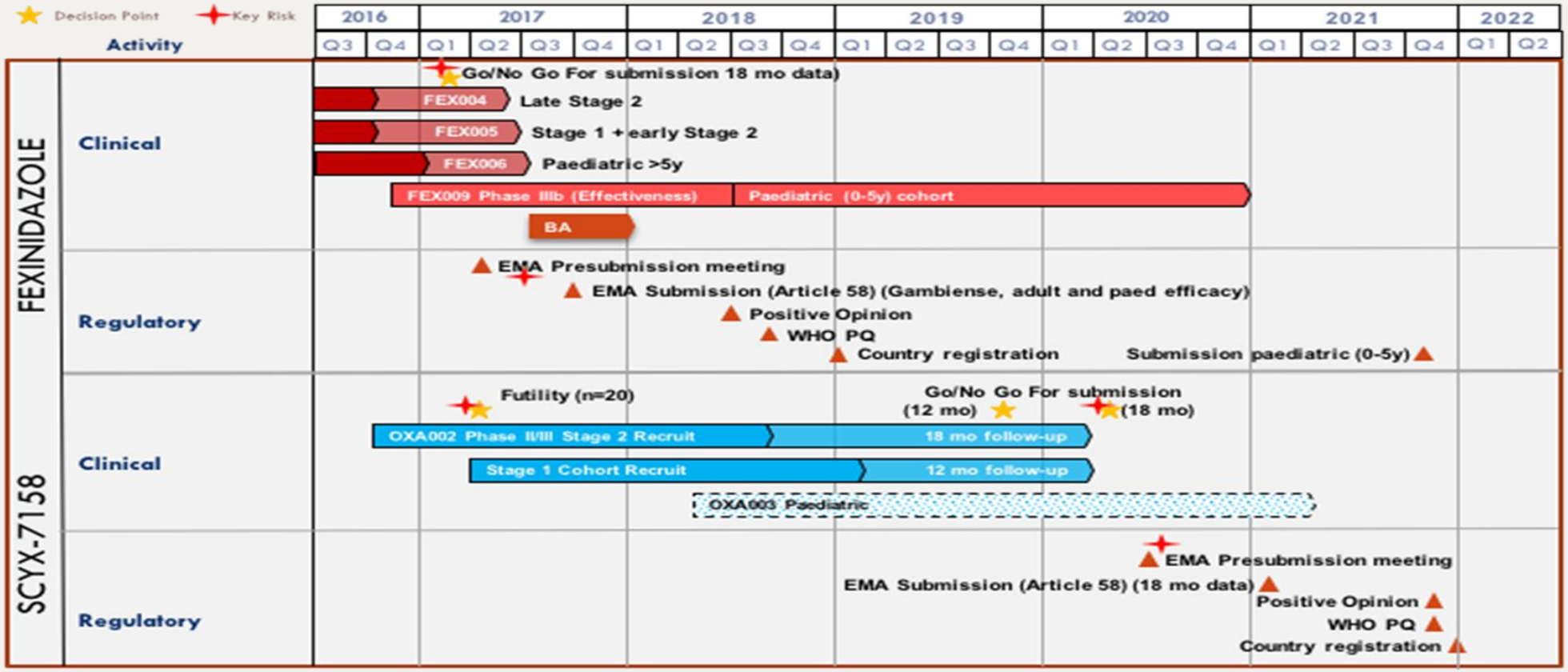
Probability of reaching the target exposure



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 $_{72\text{-}96}$

[1]S.Wring & all, Parasitology (2014), 141, 104-118
[2]Study report (final draft) PH11015/DNDiOXA001, PhinC/DNDi, August 2015.

High level planning



From toxic drugs and long hospital treatments towards a medicine for use at village level

Fexinidazole – a breakthrough stage-independent oral treatment

- Oral treatment for all stages, adults and children
- Once daily administration with food for 10 days
- Available progressively in existing HAT centres as 1st line treatment

SCYX-7158 – the tool for sustained elimination

- Oral treatment for all stages, adults and children
- Single dose treatment – no compliance issue
- Available as village-based treatment coupled with RDT
- Available in sentinel sites and unstable political regions

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