Discovery, development and clinical trial of a single dose oral cure for sleeping sickness

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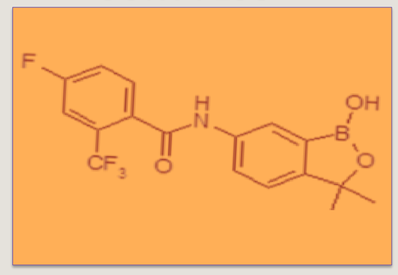
Introduction

Intensive active case finding over the last decade has decreased the number of cases of human African trypanosomiasis (HAT) significantly. Efforts are now concentrated on the WHO target for elimination of the disease by 2020. The current first-line treatment for second stage gambiense HAT, Nifurtimox-Eflornithine Combination Therapy, is a considerable improvement over previous treatments, but is limited by the need for staging of the disease and hospitalization during intravenous administration. SCYX-7158 is an oral treatment in clinical development by DND*i*; this single dose cure has potential for achieving sustained elimination since it is particularly adapted to endemic rural areas with weak health systems.

An oxaborole originally provided by Anacor Pharmaceuticals was found to be active against HAT parasites. Compound optimization over two years and examination of over 1,000 compounds produced SCYX-7158, the first new chemical entity to arise from DND*i*'s lead optimization programme, which was selected as a pre-clinical candidate for gambiense HAT (g-HAT) in late 2009.

SCYX-7158



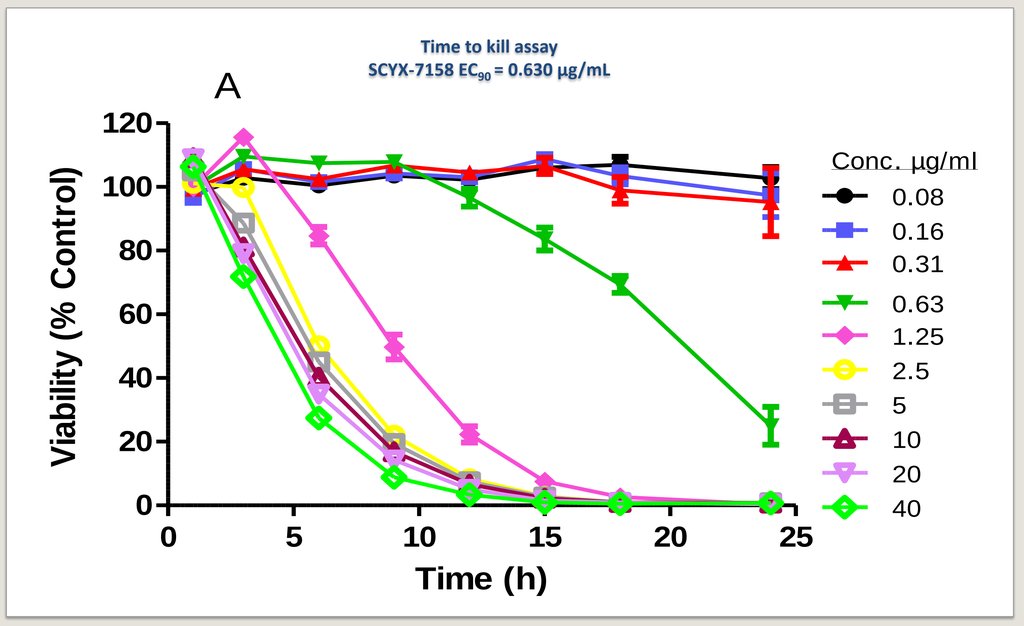
Pre-clinical development

studies provided evidence that SCYX-7158 was safe and efficacious to treat the second stage of the disease.

Pre-clinical/phase I profile of SCYX-7158

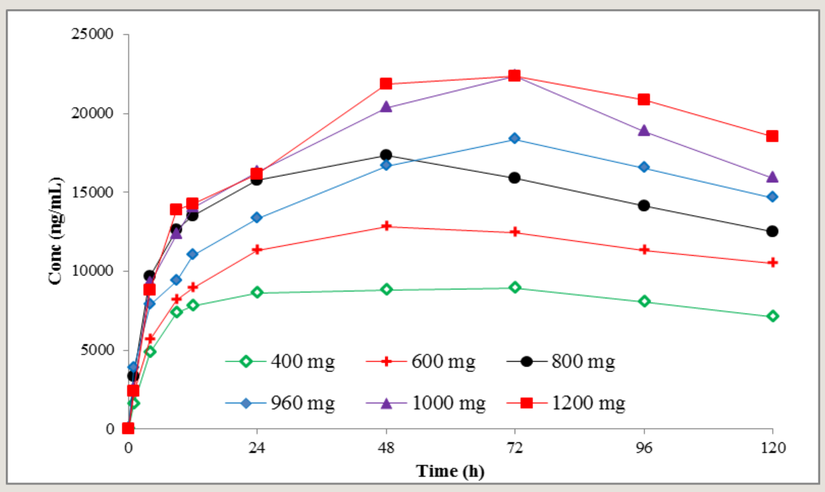
SCYX-7158 is a lipophilic drug with a high volume of distribution. It is highly protein bound in the blood and crosses the blood brain barrier. It is poorly metabolised with a half life of 16 days which allows it to be dosed in a single oral administration of 3 tablets of 320 mg in fasted conditions (total dose of 960 mg).

The target AUC $U_{0\text{-}24}$ is 5.8 µg.h/mL and the 960 mg single dose achieved an exposure of 1.5 times the target AUC $_{72\text{-}96}$

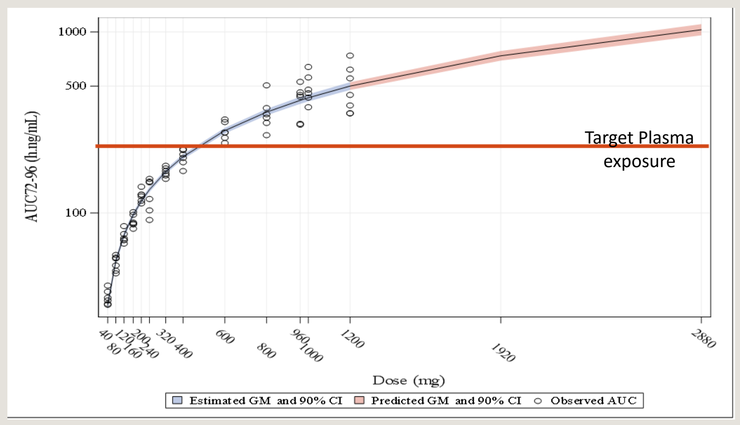


Phase 1

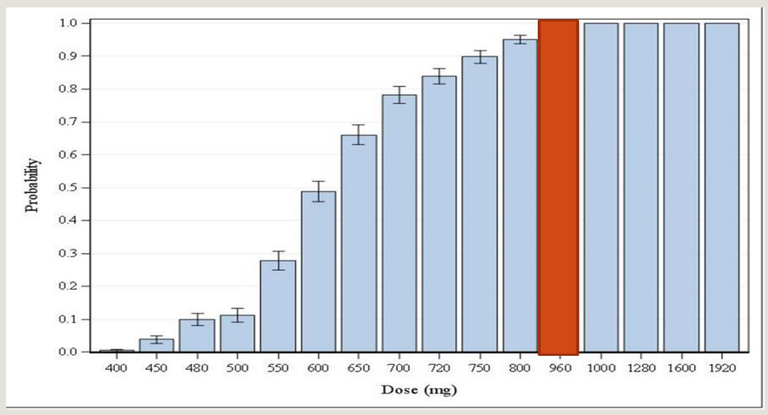
- 128 subjects were included in a Phase I single ascending dose safety and tolerability study in 2012.
- PK results from this first in man study showed that SCYX-7158 was quite rapidly absorbed and has long half-life ensuring an exposure over the IC90 for at least 69 days. This long half-life gives SCYX-7158 the potential to be a single-dose treatment.
- After clinical safety profiling, a therapeutic dose of 960mg was selected for a pivotal trial; this gives a 90% probability of reaching pharmacologically active free exposure in CSF.
- There were no dose related AEs in human volunteers.



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

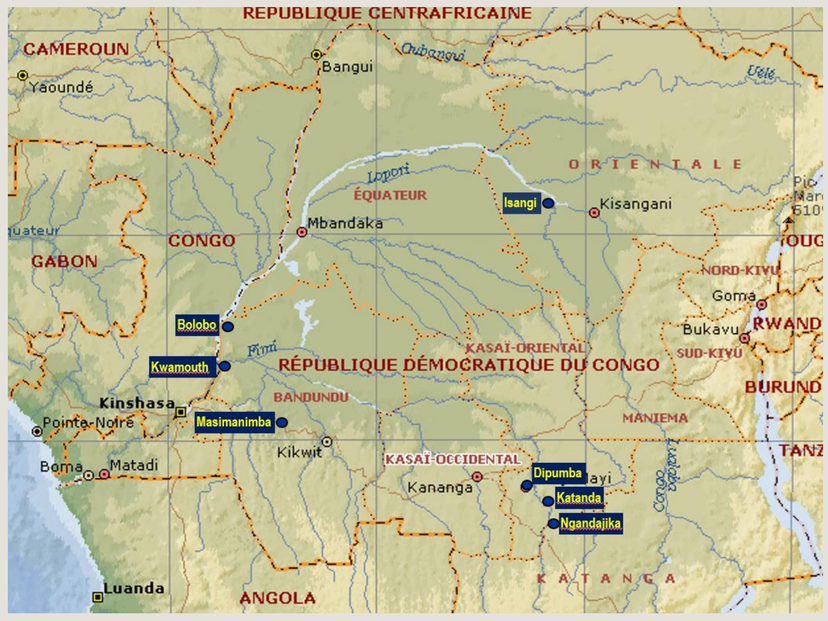


Probability of reaching the target exposure



Phase 2/3

- The single dose treatment is being tested in patients with stage 2 g-HAT in a Phase II/III trial. The first patient was enrolled in October 2016.
- The study use several sites in the Democratic Republic of the Congo that are already active, with addition of new sites selected from high-prevalence g-HAT areas. Patients will be followed up for 18 months after treatment to ensure long-lasting cure, with a preliminary evaluation of data performed after the first 12 months



Conclusion: SCYX-7158 – the tool for sustained elimination

The ambition for SCYX-7158 is for it to be:

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

DNDi Drugs for Neglected Diseases *initiative*

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