P-1.158

SCYX-7158: HARD TIMES FOR *TRYPANOSOMA Brucei* PARASITES

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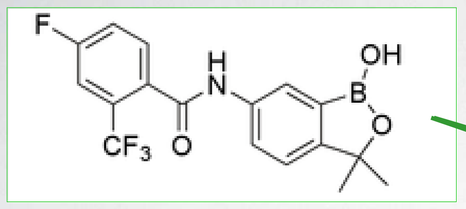
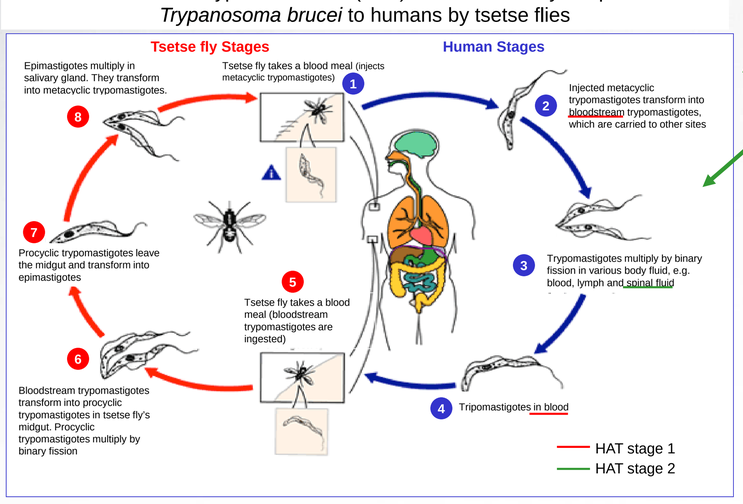
SCYX-7158: A BORON-BASED SMALL MOLECULE



Active against HAT stages 1 and 2

Human African Trypanosomiasis (HAT) is transmitted by the parasite *Trypanosoma brucei* to humans by tsetse flies



Available Pre-clinical Data

Available pre-clinical data on SCYX-7158 were published in *PLoS NTDs* in June 2011 [*Jacobs RT. et al. (2011) SCYX-7158, an orally-active benzoxaborole for the treatment of stage 2 human african trypanosomiasis. PLoS Negl Trop Dis 5: e1151]*

ACTIVITY

- Potent trypanocidal effect *in vitro.*
- Attractive *in vitro* physicochemical and ADME properties consistent with the compound being orally available, metabolically stable and CNS permeable.
- Significant activity in murine models of HAT (acute and chronic), following oral administration as low as 12.5 mg/kg.
- High bioavailability across species; *in vivo* pharmacokinetic profile confirmed that it crosses the blood-brain barrier to achieve therapeutically-relevant concentrations in the brain and cerebrospinal fluid.

SAFETY

- Not Genotoxic (Ames, micronucleus)
- Safe in the hERG evaluation (IC_{50}> 100 μM)
- In the rat the only remarkable toxic effect was reduced food consumption up to anorexia and consequent loss of weight and dehydration (limiting factor) mainly in females.

  - MTD single dose: 200 mg/kg
  - MTD 7-day: 50 mg/kg/day
  - NOAEL 28-day: 15 mg/kg/day

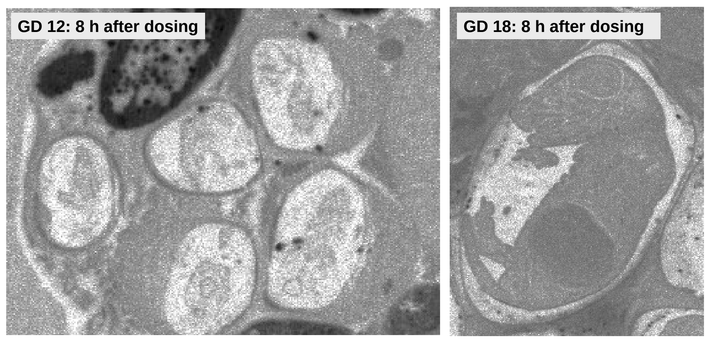
ACTUAL STUDY OUTCOMES

New perspectives arise for an effective and safe cure **for the whole population** with no restrictions during pregnancy, lactation and infancy.

REPRODUCTIVE TOXICITY STUDIES IN Crl:CD(SD)Br RATS

STUDY 1: Placental Transfer

- Single oral administration of [^{14}C]-SCYX-7158 at the dose of 10 mg/kg to pregnant rats on Gestation Days (GD) 12 or 18 (organogenetic stage or fetal stage, respectively)
- Animals sacrificed 1, 4, 8, 24 and 48 hours post-dose
- Radioactivity distribution evaluated by Quantitative Whole Body Autoradioluminography (QWBA)



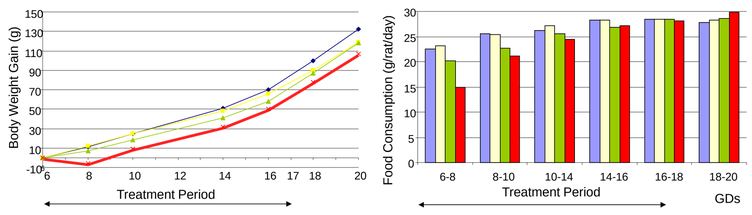
Representative autoradiograms showing enlargement of uterus (GD12) / fetus (GD18). Darker areas indicate a higher relative concentration of radiolabeled material.

☑ Radiolabeled drug related material crossed the placenta and distributed within the embryo/fetus during the periods of organogenesis and post-organogenesis.

STUDY 2: Embryofetal Developmental Toxicity

- Treatment Period: Gestation Day 6 to 17
- Oral Doses: 0, 5, 15 and 25 mg/kg/day

Maternal outcomes:



Vehicle 5 mg/kg/day 15 mg/kg/day 25 mg/kg/day

Fetal outcomes:

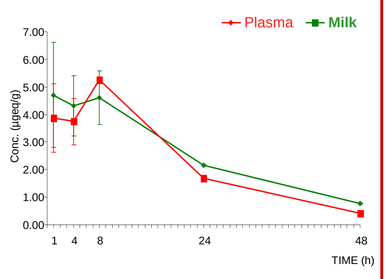
Test Item	Vehicle	SCYX-7158		
Daily Dose (mg/kg)	0	5	15	25
Live fetuses	14.6	12.3	13.7	13.8
Mean fetal weight	3.80	3.73	3.63	3.30
Mean placental weight	0.574	0.610	0.616	0.537
Fetuses examined (litters)	307(21)	307(21)	287(21)	276(20)
Fetuses with malformations (litters)	1(1)	0(0)	0(0)	1(1)

☑ The dose of 15 mg/kg/day was considered the NOAEL both for the mothers and the developing embryos.

STUDY 3: Milk Excretion

- Single oral administration of [^{14}C]-SCYX-7158 at the dose of 10 mg/kg to pregnant rats on Lactation Day (LD) 5±1
- Milk and Plasma collected at 1, 4, 8, 24 and 48 hours post-dose
- Radioactivity levels determined by Liquid Scintillation Counting (LSC)

Parameter (Unit)	Plasma	Milk
C_{max} (μgeq/g)	4.71	5.25
t_{max} (h)	1	8
t_{last} (h)	48	48
$AUC_{0-t(last)}$ (μgeq ·h/g)	122.88	111.85
$t_{½,z}$ (h)	15.55	10.94
$AUC_{0-\infty}$ (μgeq ·h/g)	140.15	118.32



☑ The pharmacokinetic parameters (systemic exposure and half-life) of total radioactivity were similar in plasma and milk.

STUDY 5: Combined Fertility Study

- Treatment Period:
  - Males: 4 weeks before mating and during mating period
  - Females: 2 weeks before mating, during mating and up to Gestation Day 7
- Oral Doses: 0, 5, 15 and 25 mg/kg/day

General toxicity outcomes at 25 mg/kg/day:
- Males: food consumption slightly reduced; body weight gain slight reduced.
- Females: food consumption moderately to markedly reduced; body weight loss from Day 1 to Day 8 of treatment, followed by a tendency to recover, albeit not complete.

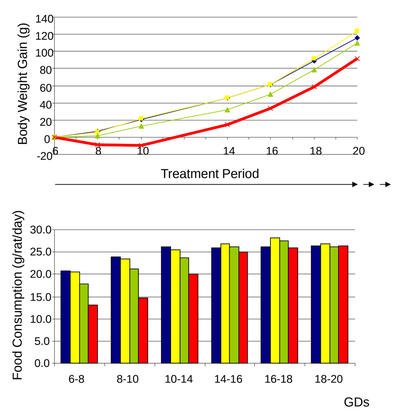
Fertility outcomes at 25 mg/kg/day:
- No adverse effects on mating behavior, gonadal function and reproductive capacity for both sexes

☑ The dose of 15 mg/kg/day was considered the NOAEL for adult animals of both sexes.
The dose of 25 mg/kg/day was the NOEL for fertility and reproductive performance in both sexes.

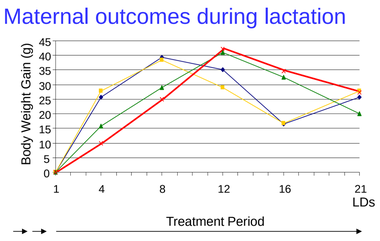
STUDY 4: Pre- and Postnatal Developmental Toxicity

- Treatment: F_0 Generation from Gestation Day 6 to Lactation Day 21 (F_1 generation untreated, but pups exposed to SCYX-7158 via maternal milk)
- Oral Doses: 0, 5, 15 and 25 mg/kg/day

Maternal outcomes during gestation



Maternal outcomes during lactation

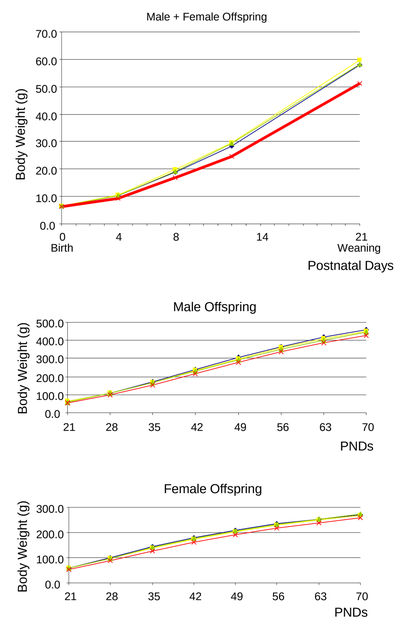


Vehicle 5 mg/kg/day 15 mg/kg/day 25 mg/kg/day

Test Item	Vehicle	SCYX-7158		
Daily Dose (mg/kg)	0	5	15	25
F_0 Females during labour				
No. Pregnant	18	23	21	18
With Live Pups at Birth	18	23	21	18
Mean Duration of Gestation (days)	21.9	22.2	22.2	22.3
F_1 Litters (Pre-weaning)				
Mean No. Pups/Litter at Birth	13.3	13.7	13.6	13.4
Mean No. Pups/Litter at PND4 before culling	13.3	13.5	13.5	12.9
Mean No. Pups/Litter at PND4 after culling	7.7	8.0	8.0	8.0
Mean No. Pups/Litter at PND21	7.7	7.9	8.0	7.9
Pup Body Weight at birth (g) (M+F)	6.54	6.63	6.57	6.26
Pup Clinical Signs	-	-	-	-
Pre-weaning Physical Development	-	-	-	-
Pre-weaning Functional Development	-	-	-	-
Pup Necropsy Observations	-	-	-	-
F_1 Generation (Post-weaning)				
No. Evaluated Post-weaning/Sex	20	23	21	20
Mean Age of Preputial Separation (days)	42.0	42.4	42.8	43.1
Mean Age of Vaginal Patency (days)	31.1	30.8	31.0	30.5
Psychomotor Activity	-	-	-	-
Learning and Memory	-	-	-	-
Reproductive Performance	-	-	-	-
Clinical Signs	-	-	-	-
Necropsy Observations	-	-	-	-

PND=Postnatal Day; - = No adverse effects

F_1 Generation: Growth development from birth to adulthood



Vehicle 5 mg/kg/day 15 mg/kg/day 25 mg/kg/day

☑ The dose of 15 mg/kg/day was considered the NOAEL for the mother and the NOEL for F_1 generation.

Overview of Toxicokinetic Data

Comparative SCYX-7158 exposure in non pregnant, pregnant and lactating rats orally treated with 15 mg/kg and in healthy human volunteers at a single dose of 600 mg

Parameter	Non pregnant female rats	Pregnant rats (Study 2)	Lactating rats (Study 4)	Suckling Pups (Study 4)			Healthy human volunteers
	Day 1 of treatment						
C_{max} (ng/mL)	12586	13400	Na (see Study 2)	Na			12800
AUC (ng.h/mL)	230859	259000	Na	Na			174568
	Repeated doses (number of treatments)						
	Day 28 (28 days)	GD17 (12 days)	LD21 (37-39 days)	PND4	PND10	PND21	Na
C_{max} (ng/mL)	25690	19900	11300	7480	6930	2650	Na
AUC (ng.h/mL)	588196	378000	507000	Na	Na	Na	Na

☑ SCYX-7158 in plasma: exposure (C_{max} and AUC) generally increased in direct proportion with the dose. A prolonged half-life was detected.

☑ Oxidative metabolite SCYX-3109 in plasma: approximately 1% of SCYX-7158.

☑ Boric acid in plasma (not measured but estimated as it is generated on an equimolar basis to SCYX-3109): In the pre- and post-natal study, rats administered with an oral dose of 15 mg/kg/day showed on LD21 a C_{max} for SCYX-3109 of 0.131 μg/mL. In this case, boric acid (borate) would be no greater than 0.02 μg/mL, well below the concentration of 1.27 μg/g reported as a NOAEL in rats.

- *Murray FJ (1998) A comparative review of the pharmacokinetics of boric acid in rodents and humans. Biol Trace Elem Res 66: 331–341.*
- *Price CJ, Strong PL, Murray FJ, Goldberg MM (1997) Blood boron concentrations in pregnant rats fed boric acid throughout gestation. Reprod Toxicol 11: 833–842.*

CONCLUSIONS

NOAEL for adult animals before/during mating and for dams during pregnancy and lactation was set at 15 mg/kg/day which gave a C_{max} of 11300 ng/mL and an AUC of 507000 ng.h/mL on Lactation Day 21.

SCYX-7158 passed the placenta, reached embryo/fetus during all stages of its development and it was secreted in the maternal milk.
Despite this, at 15 mg/kg/day embryofetal development *in utero,* duration of gestation, physiology of parturition, pup survival were unaffected by treatment. Pup development during lactation and post-weaning development and behavior up to adulthood and including the reproductive performance of the F_1 generation were also unaffected.

These data corroborate the **good safety profile of SCYX-7158** already demonstrated in non-pregnant animals. They indicate that SCYX-7158 could be an **effective treatment, safe for the whole population,** including men and women of childbearing age, pregnant and lactating women and infants.

SCYX-7158: Reproductive Toxicity Studies

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DNDi Drugs for Neglected Diseases *initiative*

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