SCYX-6759, an Orally Bioavailable Oxaborole 6-carboxamide, Achieves Therapeutically Relevant Exposure in Brain and CSF Leading to 100% Cures in a Mouse Model of CNS-stage Human African Trypanosomiasis

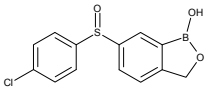
Stephen Wring, Bakela Nare, Cyrus Bacchi, Beth Beaudet, Tana Bowling, Daitao Chen, Robert Don, Yvonne Freund, Eric Gaukel, Kurt Jarnagin, Matthew Jenks, Luke Mercer, Andy Noe, Matthew Orr, Robin Parham, Jacob Plattner, Cindy Rewerts, Jessica Sligar, Nigel Yarlett, and Robert Jacobs.

steve.wring@scynexis.com

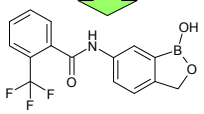
Scynexis Inc., Research Triangle Park, Durham, NC27709

DNDi Drugs for Neglected Diseases initiative | PACE UNIVERSITY | ANACOR PHARMACEUTICALS | SCYNEXIS

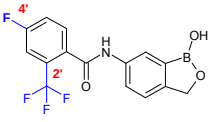
Oxaborole Lead Optimization Path for HAT



AN2920



AN3520



SCYX-6759

- AN2920
  - Discovered by Anacor, and recognized as lead optimization candidate for HAT treatment by DNDi
- Lead Optimization
  - Enhance PK
  - Improve CNS disposition
- Oxaborole-6-carboxamides
  - SCYX-6759
  - Potent *in vitro* activity against *T.b.b., T.b.g. and T.b.r*
  - Excellent *in vitro* ADMET profile
    - Metabolically stable (liver S9 half-life >350mins)
    - Permeable in MDCK-MDR1 transport assay (~350nm/s)
    - Non P-gp substrate (AQ <0.1)
    - Modest protein binding (fu ~2%)
    - Non-genotoxic in AMES
  - Enhanced PK and brain disposition in animals

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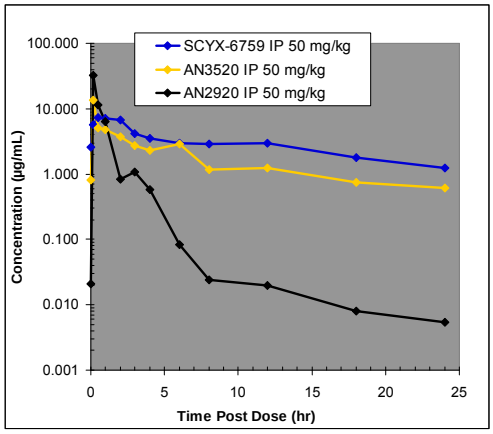
SCYX-6759 Improves Plasma Exposure Following IP Administration to Mice

- SCY-6759 improves exposure (AUC).
- Longer apparent elimination half-life after IV dose



	AN3520	SCYX-6759
Route	**IV**	**IV**
Dose (mg/kg	2	2*
$AUC_{0\text{-}inf}$ (µg.hr/mL)	18.1	33.4
CL	0.111	0.059
Half-life (hr)	2.9	11.4
Vdss (L/kg)	0.474	0.972

** Normalized from 3.3mg/kg dose to 2mg/kg*

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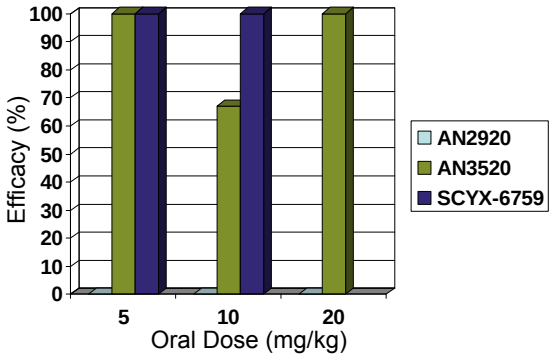
Efficacy: Stage 1 Murine HAT Model

- SCYX-6759 100% effective after 4 days of b.i.d. oral treatment in murine stage 1 model



	Dose (mg/kg)	Route	Cured/Total
AN2920	5	PO	0/3
	10	PO	0/3
	20	PO	0/3
	20	IP	3/3
AN3520	5	PO	3/3
	10	PO	2/3
	20	PO	3/3
SCYX-6759	5	PO	3/3
	10	PO	3/3

Infection with 250,000 T. b. brucei EATRO 110 parasites progressed 24h before treatment

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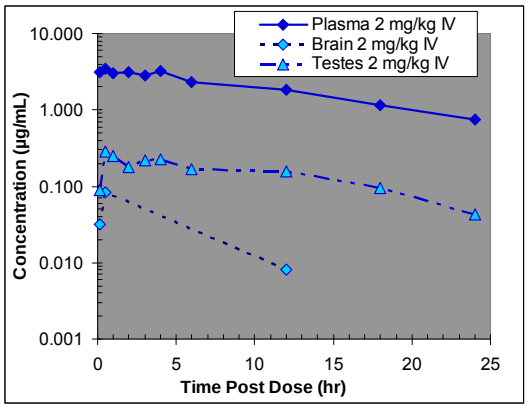
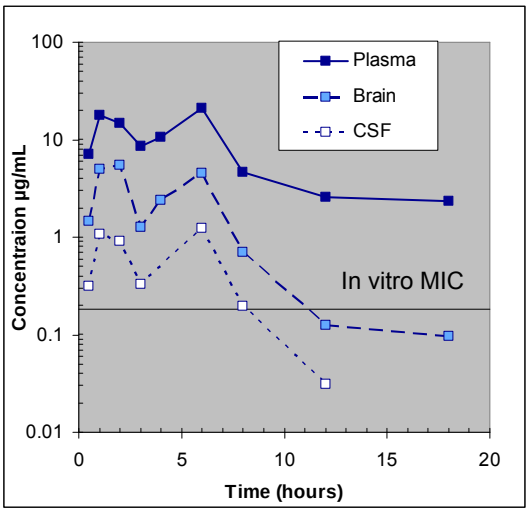
SCYX-6759 Distribution in Sanctuary Tissues



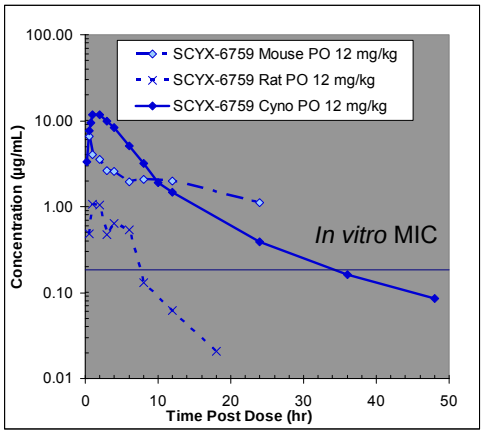
- SCYX-6759 crosses the blood-brain, and blood-testicular barriers in mice.

SCYX-6759: Disposition in Rat Plasma and CNS Compartments



- Therapeutic levels sustained in CNS for 10 hr after a single 50 mg/kg oral dose.
- Likely requires 50 mg/kg bid for CNS efficacy

Exposure Improved in Primates



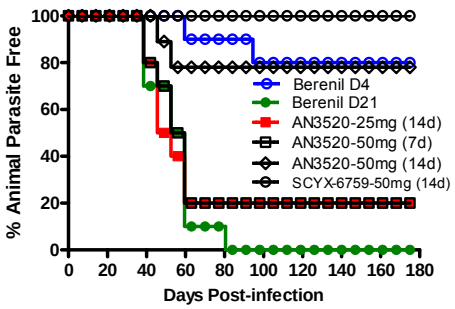
- Consistent with QD oral drug for Stage 1 HAT in mice and non-human primates.

Primate PK parameters

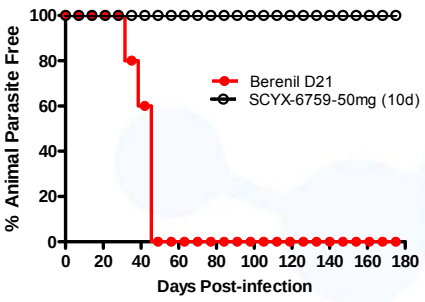
Dose	12 mg/kg
Route	Oral
$AUC_{0\text{-}inf}$	86 µg*hr/mL
Bioavailability	83%
Half-life	9 hr

Efficacy: Murine Stage 2 HAT Model

- SCYX-6759 Achieves 100% Cure following 14 days of oral 50 mg/kg bid (Q12hr) dosing.



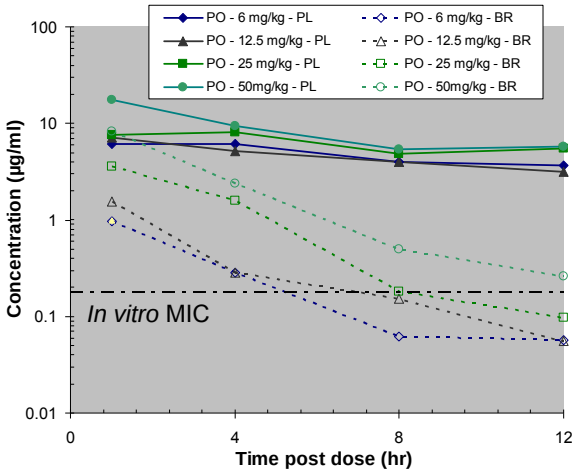
T.b. brucei: TREU-667



T.b. brucei: GVR-35

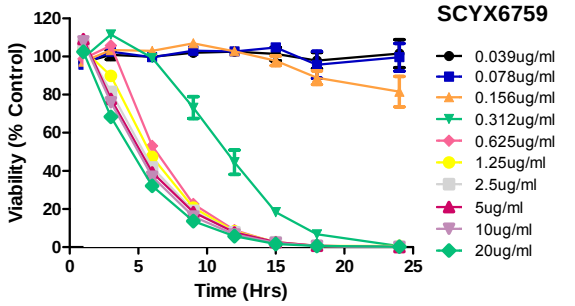
T.b. brucei: GVR-35 data were kindly provided by Dr Reto Brun, STI.

Understanding the PK-PD Relationship for SCYX-6759 in HAT



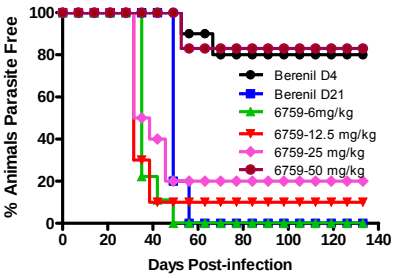
- After 7 days of Q12hr oral treatment 50mg/kg maintains exposure above MIC in brain.
- 50mg/kg b.i.d is the likely CNS efficacious dose.

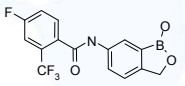
Impact of Concentration on *In Vitro* Time Kill



- >MIC exposure is required to kill within 24hr
- Maximum effect observed at 3 fold MIC.
- 50mg/kg oral b.i.d. in mice may not deliver maximal effect.

Dose Response in Murine Model of CNS HAT (Day 147 Update)





SCYX-6759

b.i.d. (Q12hr) PO

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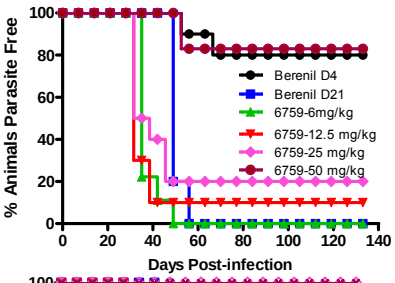
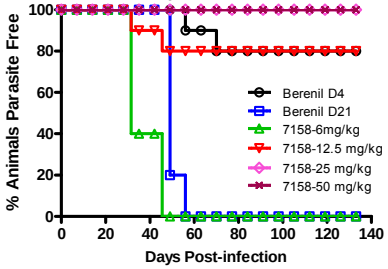
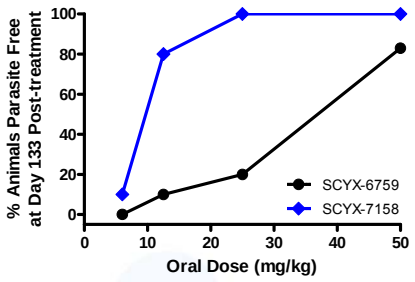
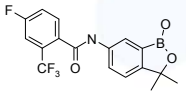
Dose Response in Murine Model of CNS HAT (Day 147 Update)

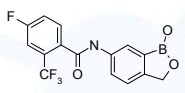








SCYX-7158



SCYX-6759

q.d. PO

b.i.d. (Q12hr) PO

Poster #829: Jacobs, B. *et al*
Session C, Exhibit Hall A, Noon- 1.30pm

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Conclusions

- SCYX-6759:
  - Discovered by a collaboration of DNDi, Anacor, PACE University and Scynexis.
  - A new class of anti-trypanosomal drug.
  - Achieved 100% efficacy in a murine stage 2 HAT model.
  - Readily crosses the blood-brain and blood-testicular barriers.
  - Efficacy can be predicted from brain exposure.
  - Led to SCYX-7158 - a pre-clinical candidate for HAT.

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Acknowledgments

- Multi-center collaboration:
  - DND*i*
  - Scynexis Inc.
  - Anacor Pharmaceuticals Inc.
  - Pace University - Haskins lab.
  - Swiss Tropical Institute
    - Dr Reto Brun
- For funding and leadership

DNDi
Drugs for Neglected Diseases *initiative*

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