

# Development of PK-PD Models To Predict The Therapeutic Dose And CNS Disposition of SCYX-7158 In The Treatment Of Stage 2 Human African Trypanosomiasis

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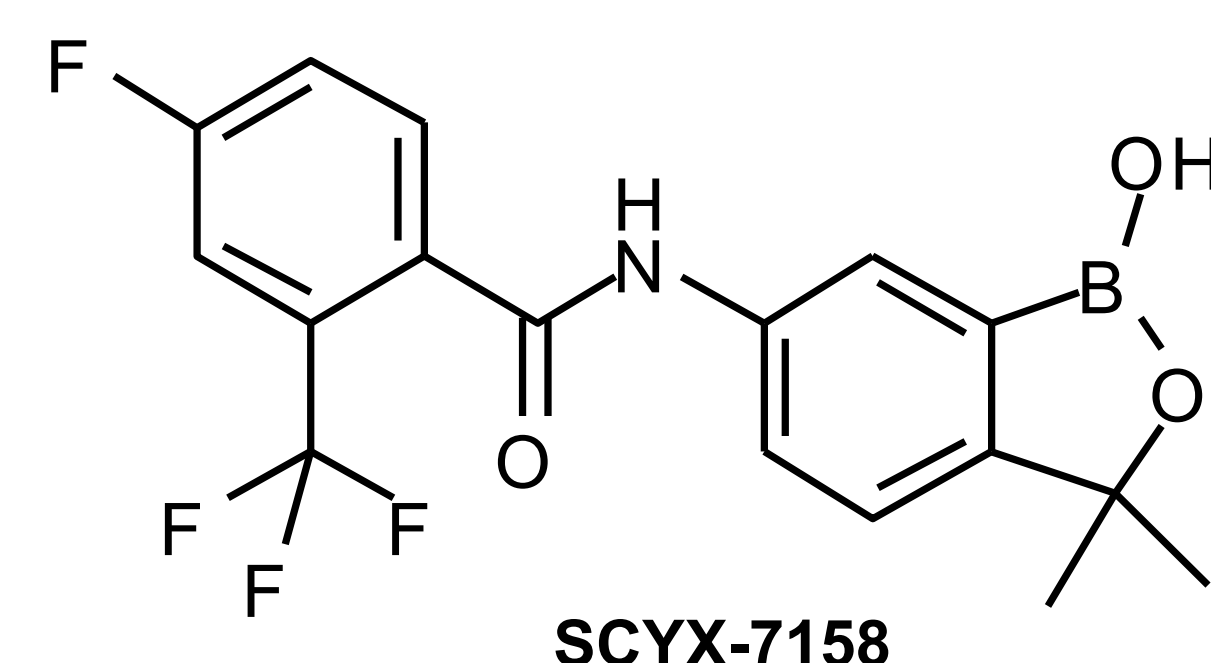
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## Abstract

SCYX-7158 is a potent trypanocidal oxaborole-6-carboxamide that DNDi is currently progressing through formal pre-clinical safety studies with the goal of becoming a first oral treatment for Stage 2 (neurological or CNS) Human African Trypanosomiasis (HAT).

SCYX-7158 is highly permeable in an *in vitro* MDCK-MDR1 model of the blood-brain barrier (Papp >400nm/s) and is not a substrate for the P-gp efflux transporter (absorption quotient <0.1), suggesting it should readily enter the CNS. It is stable *in vitro* when incubated with liver sub-cellular fractions (half-life >350 min) suggesting good pharmacokinetic properties.

SCYX-7158 achieves 100% cures in a murine Stage 2 model of HAT after 7 daily oral 25mg/kg doses. As expected from *in vitro* time-kill and reversibility studies efficacy *in vivo* correlated with SCYX-7158 concentration and exposure time in brain tissue.



This work presents 3 pivotal studies towards the development of a PK-PD model to predict the efficacious human equivalent dose (HED):

### 1) Predict exposure in brain tissue from plasma concentration data:

Goal: Prediction of brain exposure from plasma data is key to identifying the likely efficacious clinical dose in humans.

### 2) Correlate CNS exposure to therapeutic outcome:

Goal: Understanding the required concentration *versus* time profile of SCYX-7158 in brain tissue will help define clinical dosing interval and dose.

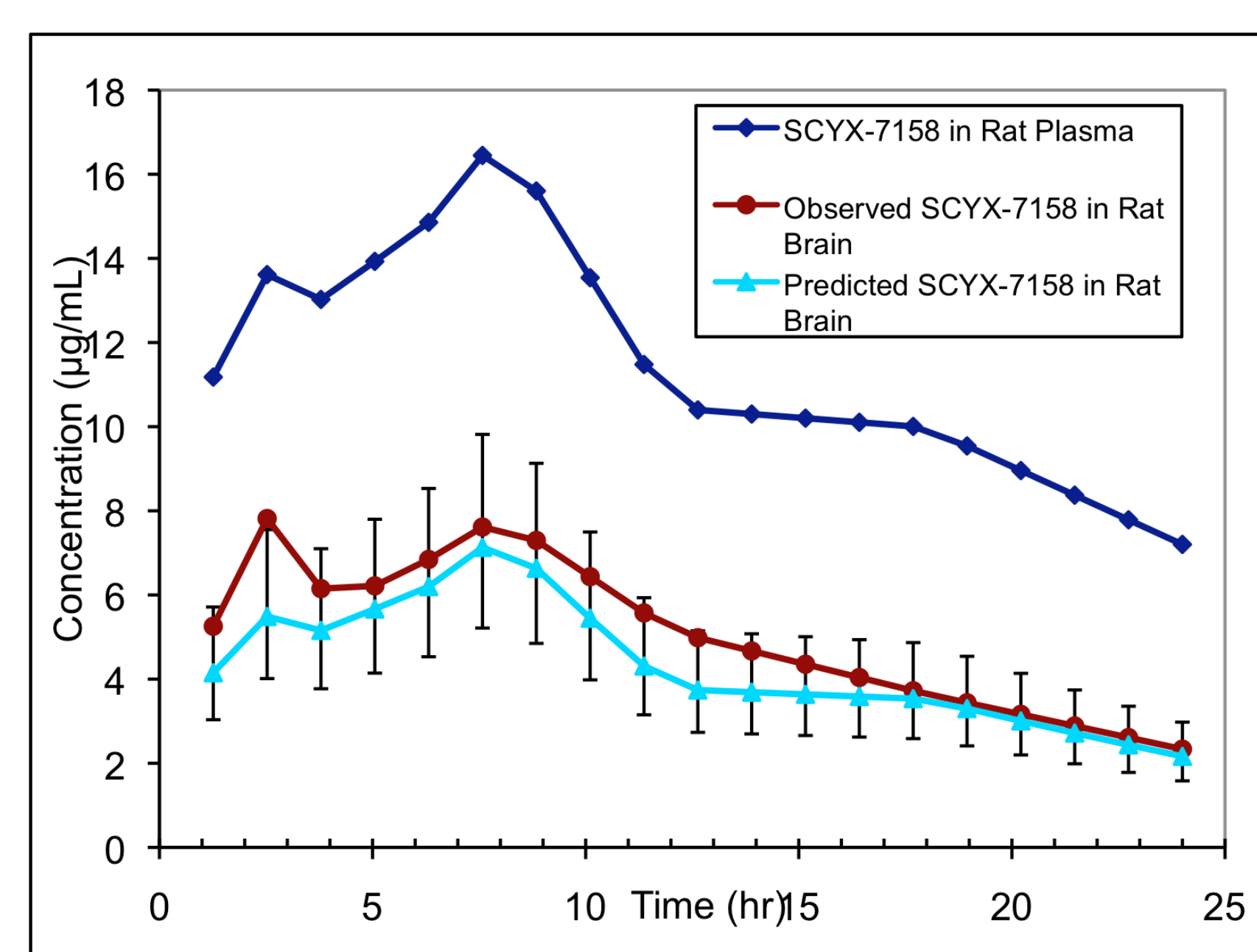
### 3) Develop allometric scaling parameters to predict the likely human equivalent dose (HED):

Goal: Leverage pre-clinical PK data in rodents and non-rodents to predict the likely clinical dose.

## Methods

*In vitro* DMPK and time-kill assays were performed as described previously [Nare, B. *et al* 2010]. Pharmacokinetics of SCYX-7158 were evaluated in infected or non-infected rodents following intravenous or oral administration of compounds. Pharmacokinetics and bioavailability of SCYX-7158 were also evaluated in non-infected beagle dogs and cynomolgus monkeys. All procedures were performed following IACUC review and in AAALAC approved facilities. In-life phases of rodent studies were performed at Vivisource (Waltham, MA); studies in non-naïve cynomolgus monkeys or beagle dogs were performed by SNBL USA (Everett, WA), or Sinclair Research Center (Columbia, MO), respectively [Jacobs, B. *et al*, 2010]. Bioanalysis of *in vitro* samples, plasma or brain tissue was performed by LC-MSMS using qualified methods [Tissue analysis: Gaukel, E. *et al* 2010].

## Prediction Of Brain Exposure From Plasma SCYX-7158 Levels



Error bars represent the lower (worse case) and upper (best case) limits of the predicted concentrations.

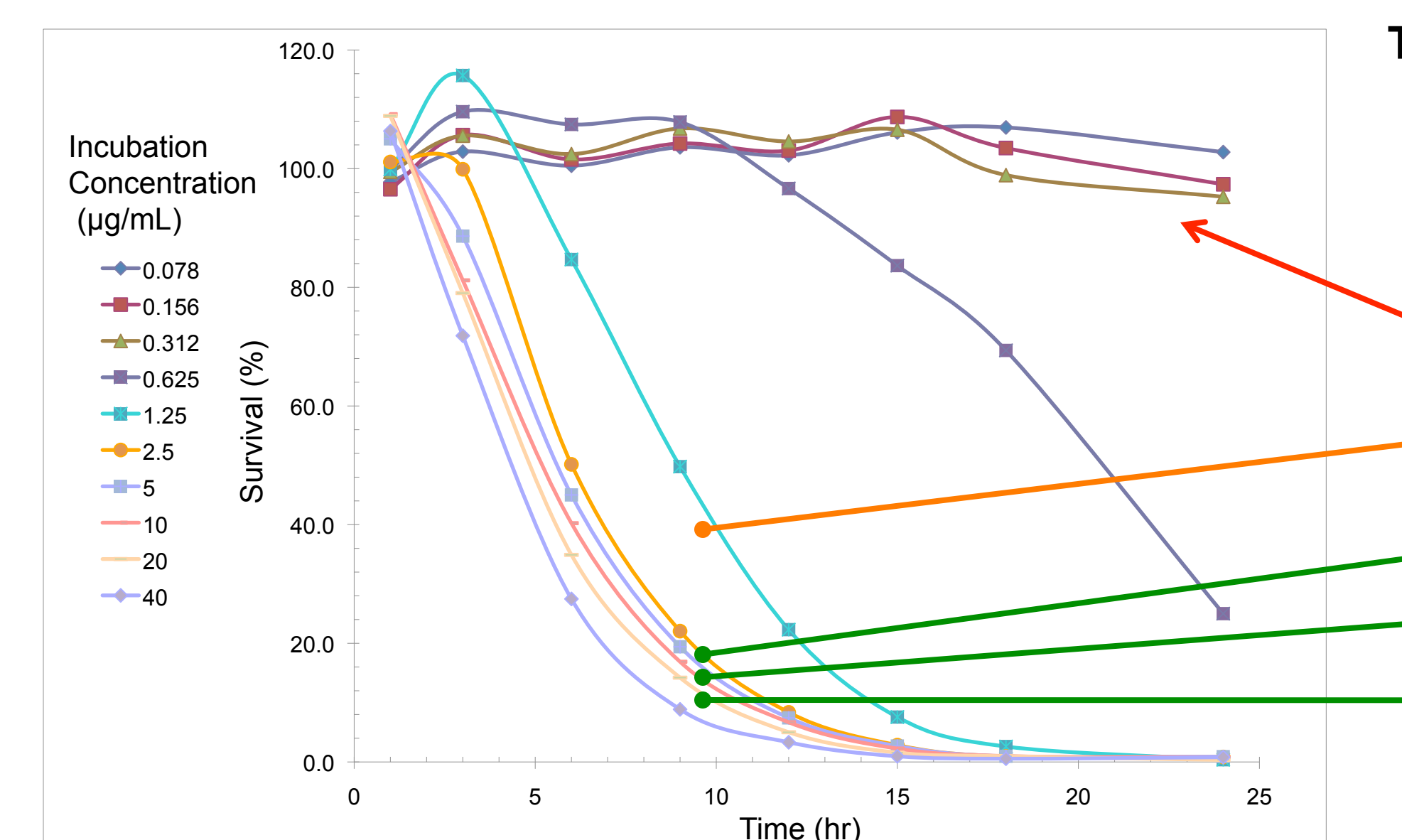
- Binding of SCYX-7158 to mouse and human plasma proteins was concentration dependent.
- The unbound fraction ( $f_u$ ) of SCYX-7158 in mouse plasma at the MIC (~0.6 µg/mL) was 0.3% rising to 3.2% at plasma concentrations equivalent to  $C_{max}$  at steady-state (~15 µg/mL, 25 mg/kg doses). At the highest concentration studied (50 µg/mL) the  $f_u$  was 4.6%.
- Binding to brain tissue appeared generally independent of concentration over the range 1-50 µg/mL (mean±SD  $f_u$ (brain) = 0.0775 ±0.0174).
- Observed plasma concentration data for SCYX-7158 in plasma collected during single dose PK studies in rats and cynomolgus monkeys (see adjacent column) were used to predict brain levels according to:

$$[\text{Predicted Brain SCYX-7158}] = [\text{Observed Plasma SCYX-7158}] \cdot f_u(\text{plasma}) / f_u(\text{brain})$$

Where:

$$f_u(\text{plasma}) = 0.0125 \ln[\text{observed plasma SCYX-7158}] - 0.0014$$

## Sustained $C_{AVESS} \geq 4$ fold MIC Achieves Complete Cures In Murine Stage 2 HAT Model



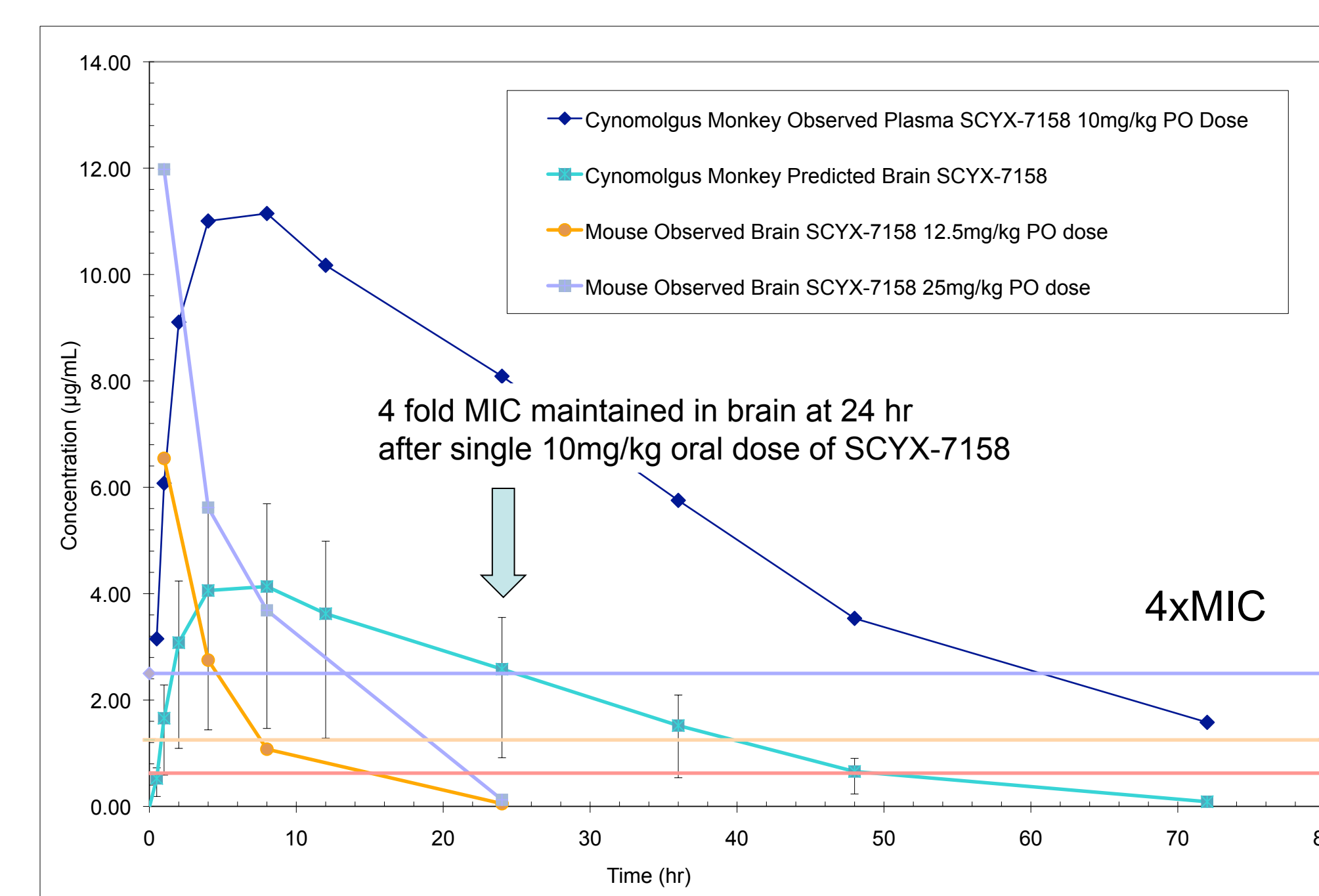
Time-Kill Curves and Murine Stage 2 HAT Efficacy Data

Dose (mg/kg)	Brain AUC <sub>0-24hr</sub> (µg.hr/mL)	Average Concentration at Steady-State (µg/mL)	Cure Rate
6	11.0	0.46	Zero
12.5	33.9	1.41	Partial (80%)
25	81.5	3.39	Complete (100%)
50	182.8	7.61	Complete (100%)
100	330.0	13.8	Complete (100%)

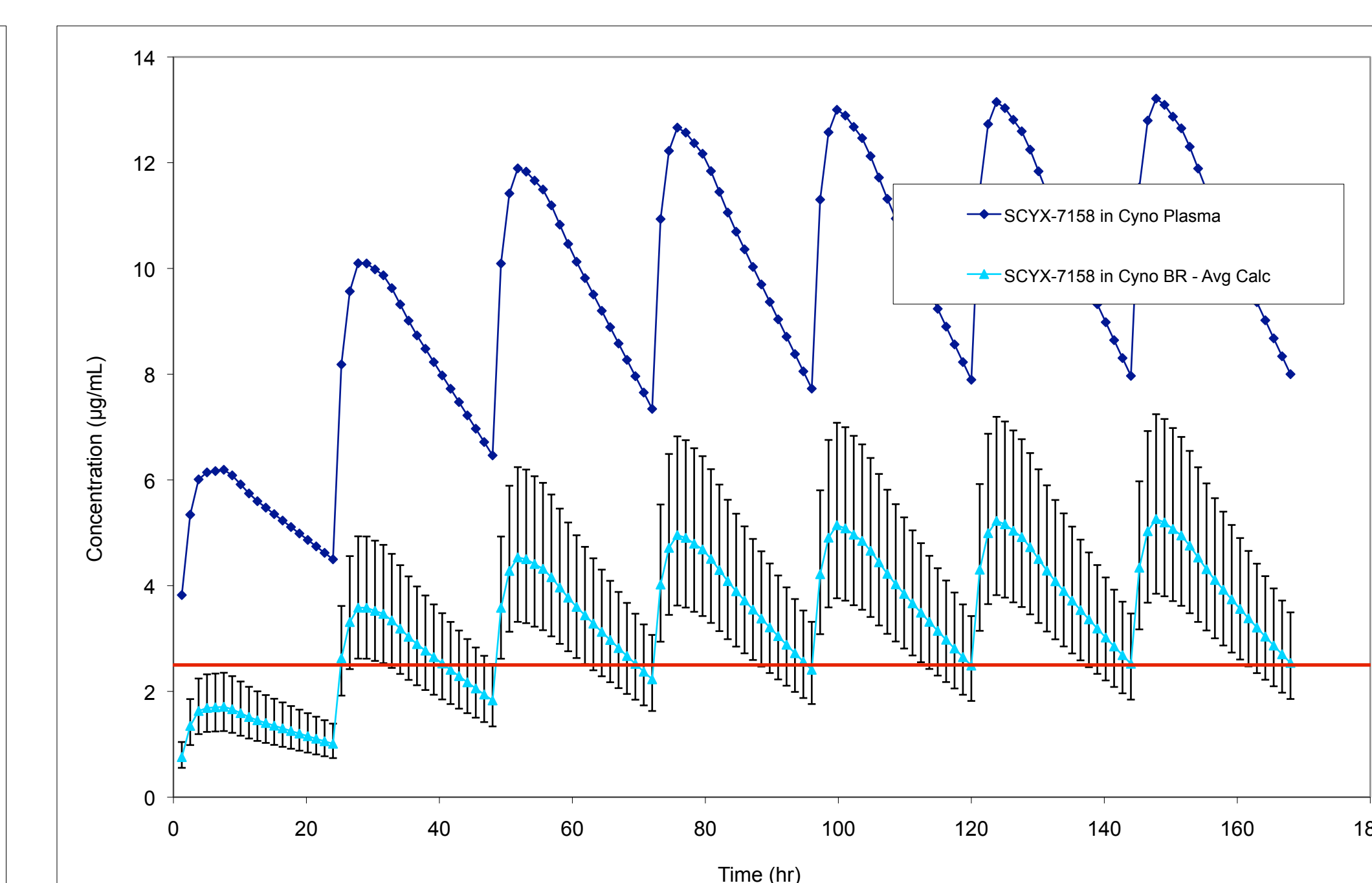
[Jacobs et al submitted 2010]

- In vitro* time-kill curves indicate that maximal trypanocidal activity is achieved at 4 times the *in vitro* MIC
- $C_{AVESS}$  appears predictive of complete cures. 25 mg/kg daily yields  $C_{AVESS}$  4 times the *in vitro* MIC and complete cures.
- Maintaining trough exposures ( $C_{min}$ ) above 4 times the *in vitro* MIC lowers risk of resistance.

## Prediction Of Steady-State Brain Exposure In Cynomolgus Monkeys



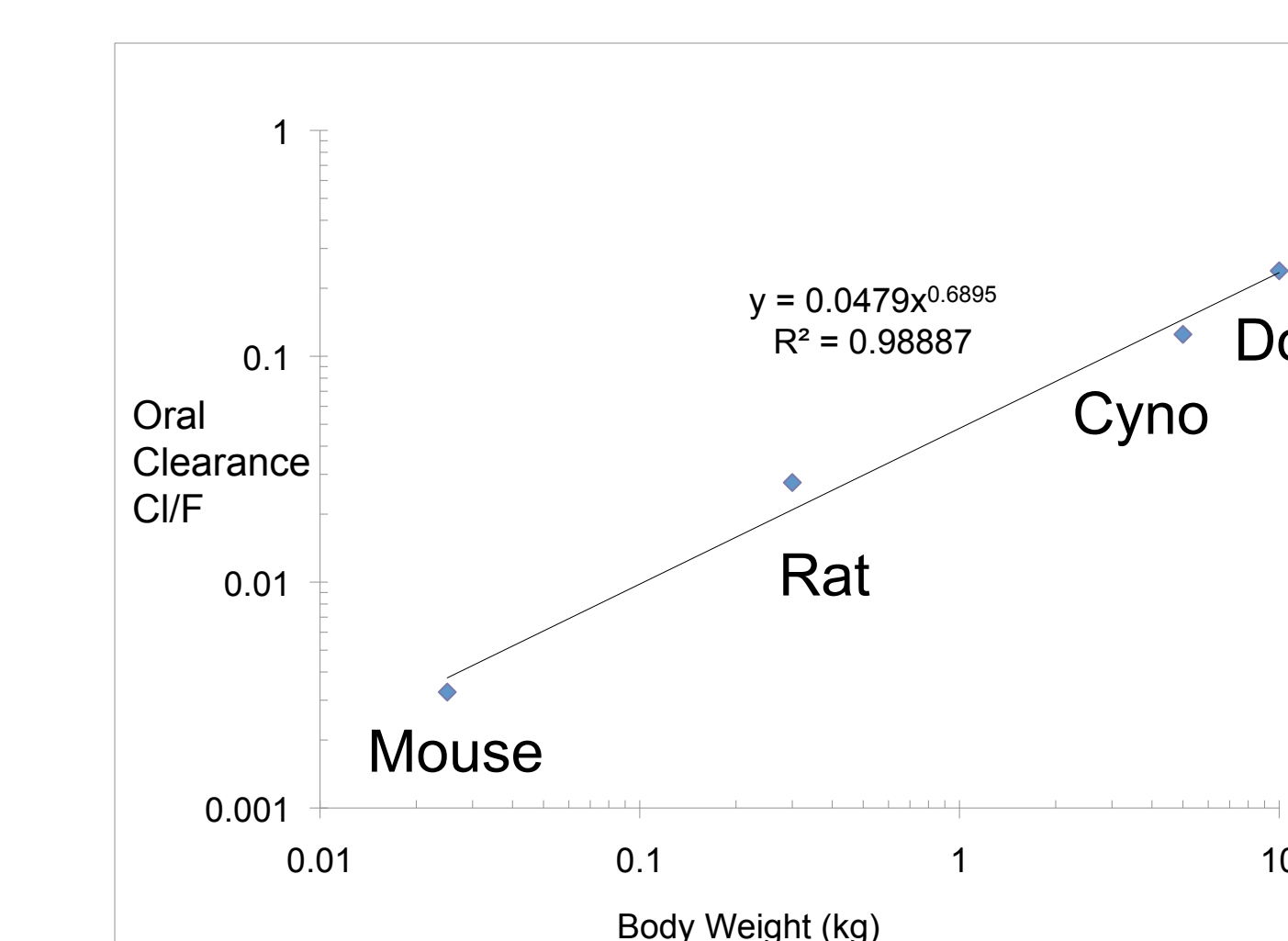
- 4 times the *in vitro* MIC (4xMIC) represents the efficacious 200 µg.hr/mL AUC<sub>0-24hr</sub>



Error bars represent the lower (worse case) and upper (best case) limits of the predicted concentrations.

- CNS exposure increases to achieve steady-state after 4<sup>th</sup> daily dose.
- A daily 5.77mg/kg oral dose at steady-state predicts achieving 4 times the *in vitro* MIC at 24 hr post dosing.

## Allometry: Prediction of Human Equivalent Dose (HED)



Species	Nominal BW (kg)	Measured Cl/F (L/kg/h)	t <sub>1/2</sub> (h)	Predicted Cl/F (L/kg/h)	Bias in Predicted Cl/F (%)	Dose (mg/kg)	Total dose (mg)	Predicted t <sub>1/2</sub> (hr)
Mouse	0.03	0.163	7.7	0.167	2.3%	33.4	0.8	8.4
Rat	0.30	0.092	15.5	0.073	-20.6%	14.6	4.4	13.2
Monkey	5.0	0.025	20.3	0.029	14.8%	5.7	28.7	21.9
dog	10.0	0.024		0.023	-4.6%	4.6	45.6	
Human	70.0			0.012		2.4	167.3	35.3

- Predicted HED is ~170mg daily based on an AUC<sub>0-24hr</sub> target of 200 µg.hr/mL
  - Based on single dose, modeling underway to predict steady-state dose)
- Actual HED will also depend on maintaining 4 times the *in vitro* MIC in brain.
- Calculations of the human profile are underway.

## Summary

- An integrated approach employing *in vitro* biological (potency) screening, medicinal chemistry, and DMPK has delivered an oral lead candidate with predictable efficacy for Human African Trypanosomiasis, a disease previously treated solely with parenteral medications.
- The developed CNS disposition model using *in vitro* brain and plasma binding data predicted brain exposure in rats and was applied to predict brain exposure in cynomolgus monkeys.
- Average concentration of SCYX-7158 in mouse brain tissue at steady-state when integrated with *in vitro* time-kill data correctly predicted efficacy in the murine stage 2 HAT model.
- Exposure scaled with body weight predicting a once daily HED of 170mg (based on AUC<sub>0-24hr</sub> target of 200 µg.hr/mL).

## References

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