PK/PD modelling of eflornithine:
Assessment of an oral treatment for the fatal parasitic disease human African trypanosomiasis

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Early Career Investigator Webinars

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Outline

Introduction – Human African trypanosomiasis (HAT) and eflornithine

Enantiospecific antitrypanosomal *in vitro* activity of eflornithine

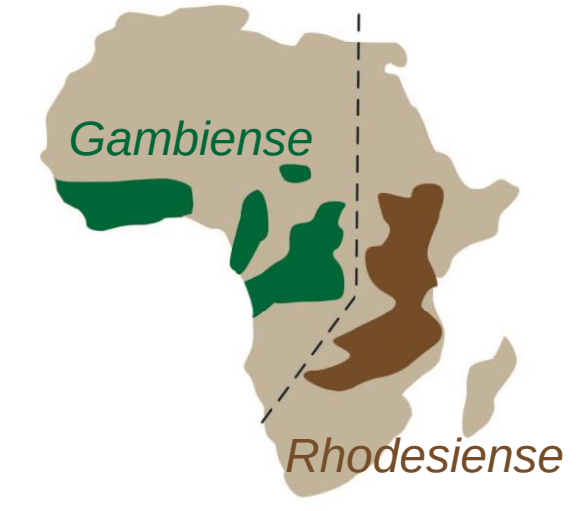
Population pharmacodynamic modeling of eflornithine-based treatments against late-stage g-HAT and efficacy predictions of L-eflornithine-based therapy

Enantiospecific *in vivo* pharmacokinetics after enantiopure and racemic dosing of eflornithine

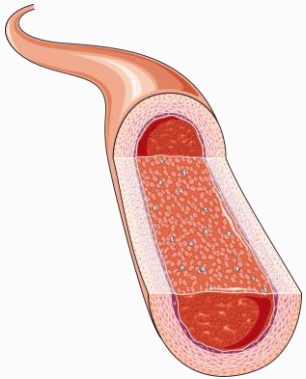
Pharmacokinetics of racemic eflornithine in human plasma and cerebrospinal fluid: Clinical perspectives for L-eflornithine against HAT

Introduction – Human African trypanosomiasis (HAT)

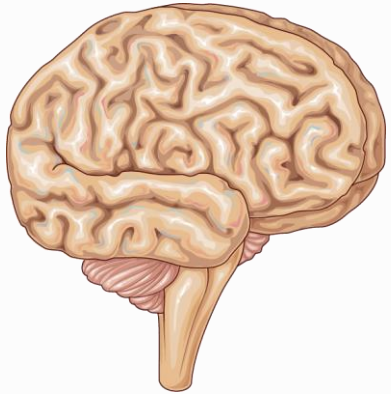
Two parasite strains



Early-stage HAT



Late-stage HAT

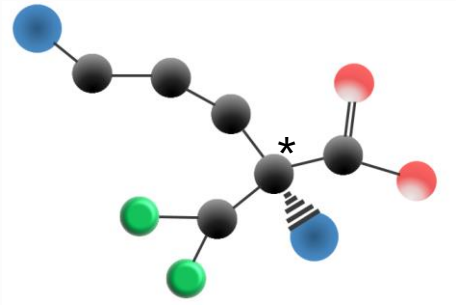


g-HAT treatments
Fexinidazole
Nifurtimox-eflornithine combination therapy (NECT)
Pentamidine
Eflornithine monotherapy
Melarsoprol

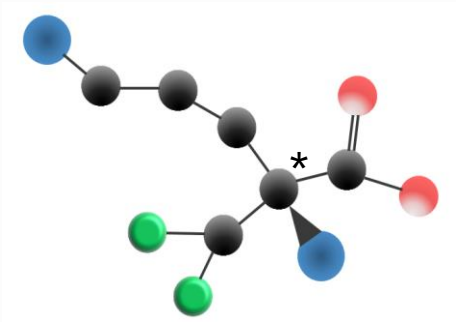
1: Kennedy P. (2008) Annals of Neurology. 64: 116 – 127

Introduction – Eflornithine

D-eflornithine



L-eflornithine



Nitrogen
Carbon
Oxygen
Fluorine

Are D-eflornithine and L-eflornithine different?

- Similar pharmacokinetics after intravenous dosing[2]

- Higher oral absorption of D-eflornithine compared to L-eflornithine when dosed as racemic mixture[2,3]

2: Johansson CC *et al*. J Pharmacokinet Pharmacodyn. 2013;40(1):117-28.
3: Jansson-Löfmark R *et al.* Antimicrob Agents Chemother. 2015;59(2):1299-307.

Enantiospecific antitrypanosomal *in vitro* activity of eflornithine

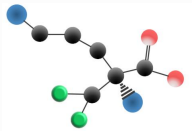
Methods – *AlamarBlue serial drug dilution assay*[4]

Trypansoma brucei gambiense

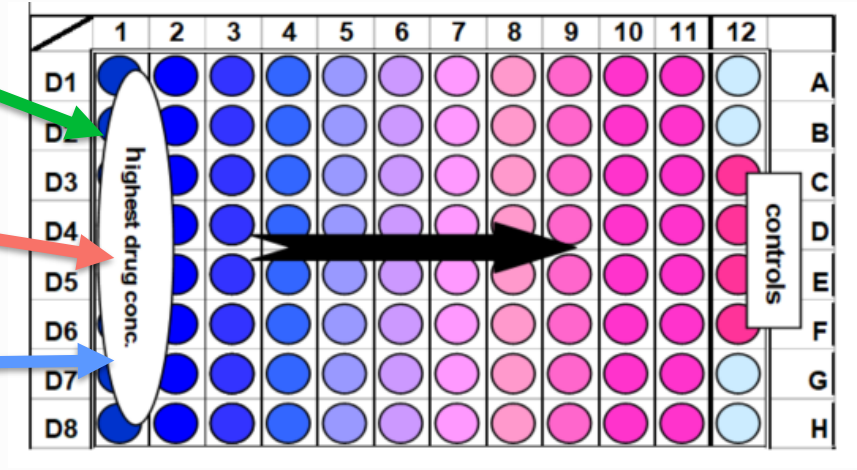
STIB930[5] K03048[6] 130R[7]

L-eflornithine

D-eflornithine



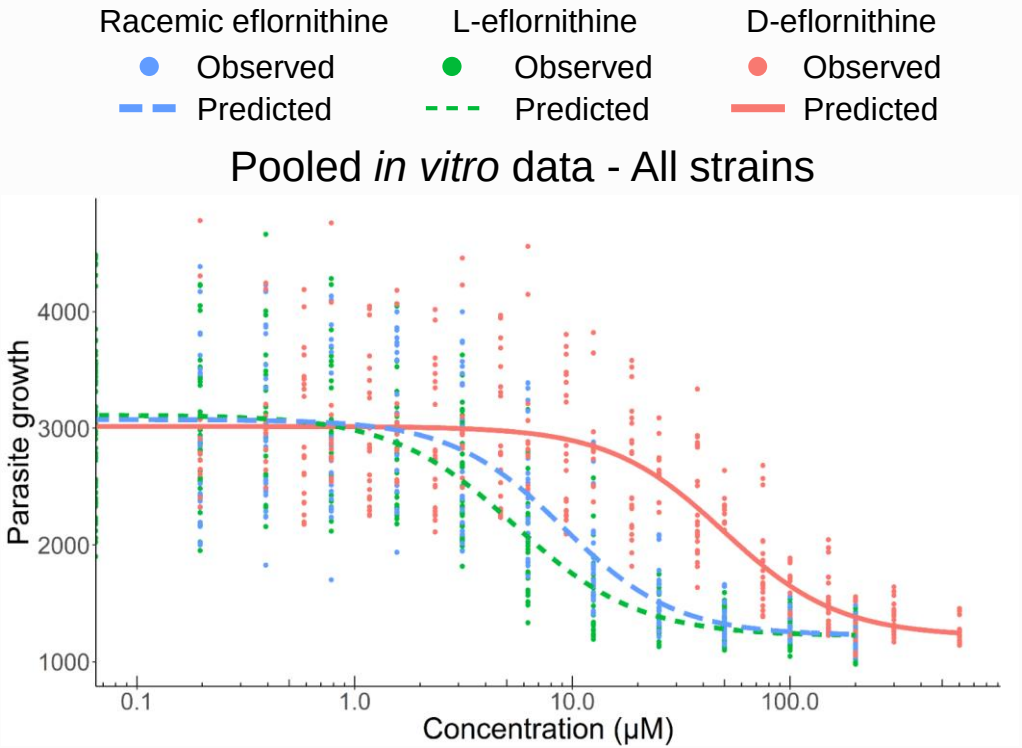
Racemic eflornithine



4: Raz B *et al.* Acta tropica. 1997;68(2):139-47.
5: Felgner P *et al.* Tropenmedizin und Parasitologie. 1981;32(3):134
6: Maina N *et al.* Acta tropica. 2007;104(2-3):84-90.
7: Pyana PP *et al.* PLoS Negl Trop Dis. 2011;5(4):e1025.

Published: Boberg *et al* (2021), PLoS Negl Trop Dis 15(7): e0009583

Results – *In vitro* parasite growth inhibition



$$\text{Inhibition} = I_0 - \frac{I_{max} \times \text{Concentration}^{\gamma}}{IC_{50}^{\gamma} + \text{Concentration}^{\gamma}}$$

Published: Boberg *et al* (2021), PLoS Negl Trop Dis 15(7): e0009583

Results – Overall *in vitro* parameter estimates by final model

Parameter	Drug	Estimate	95% CI
IC_{50} (µM)	Racemic eflornithine	9.1	8.1; 10
	L-eflornithine	5.5	4.5; 6.6
	D-eflornithine	50	42; 57
Gamma	Racemic eflornithine	1.7	1.5; 2.1
	L-eflornithine	1.6	1.3; 1.8
	D-eflornithine	1.7	1.3; 2.2
I_{max}	Racemic eflornithine	0.9	0.9; 1.0
	L-eflornithine	0.9	0.9; 1.0
	D-eflornithine	1.0	0.9; 1.0

95% CI – 95% confidence interval

Published: Boberg *et al* (2021), PLoS Negl Trop Dis 15(7): e0009583

Conclusions

1. L-eflornithine showed 9-fold higher *in vitro* potency than D-eflornithine against *Trypanosoma brucei gambiense*

2. This new knowledge could potentially be used to predict *in vivo* efficacious doses of L-eflornithine

PD modeling of eflornithine-based treatments

Methods – Clinical data on racemic eflornithine

- Data on late-stage g-HAT treatment outcome, i.e., treatment failure or cure, from three clinical studies with racemic eflornithine

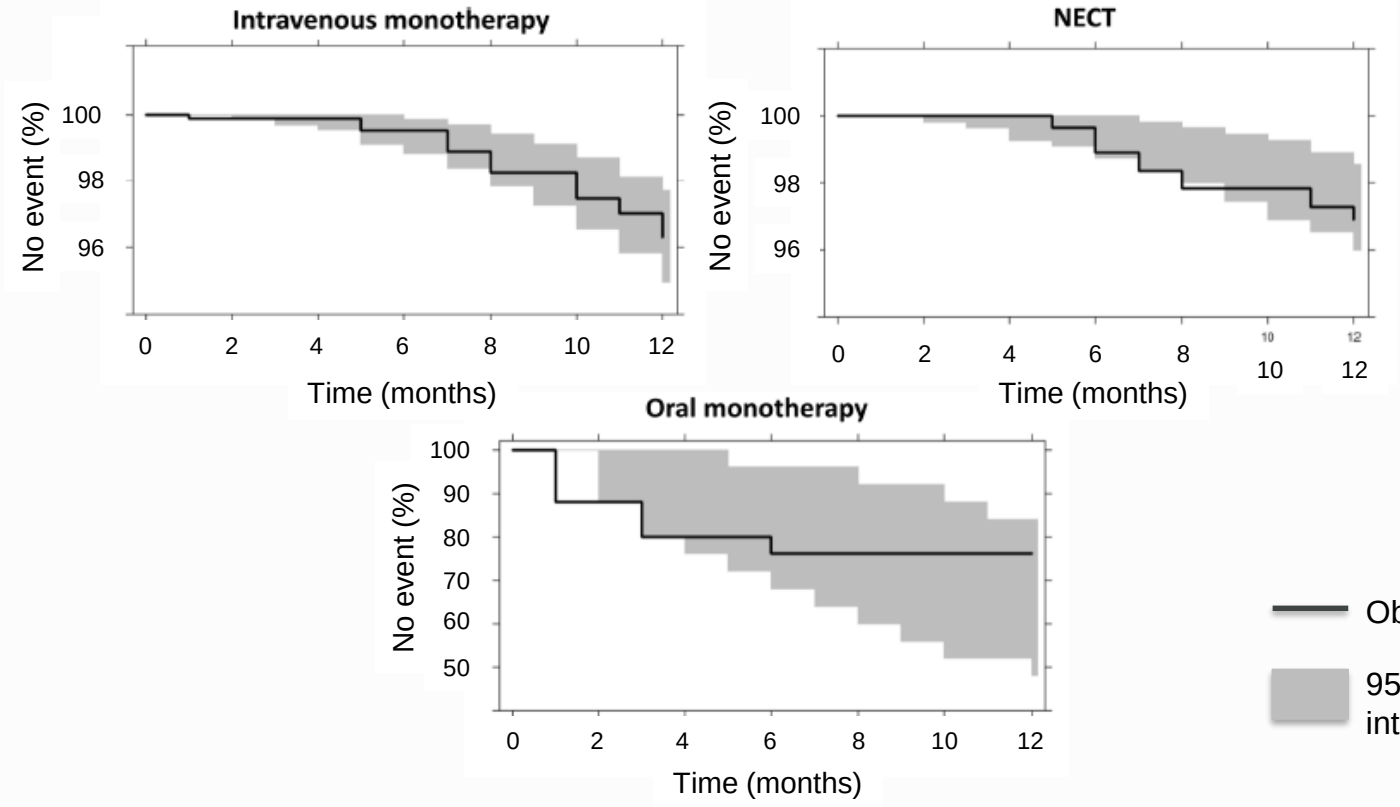
Study	1	2	3
Therapy	Intravenous eflornithine monotherapy[8]	Intravenous eflornithine + oral nifurtimox (NECT)[9]	Oral eflornithine monotherapy[10]

- Time-to-event pharmacodynamic modeling in NONMEM

8: Priotto G *et al.* BMJ. 2008;336(7646):705-8.
9: Franco JR *et al.* Res Rep Trop Med. 2012;3:93-101.
10: Na-Bangchang K *et al.* Eur J Clin Pharmacol. 2004;60(4):269-78.

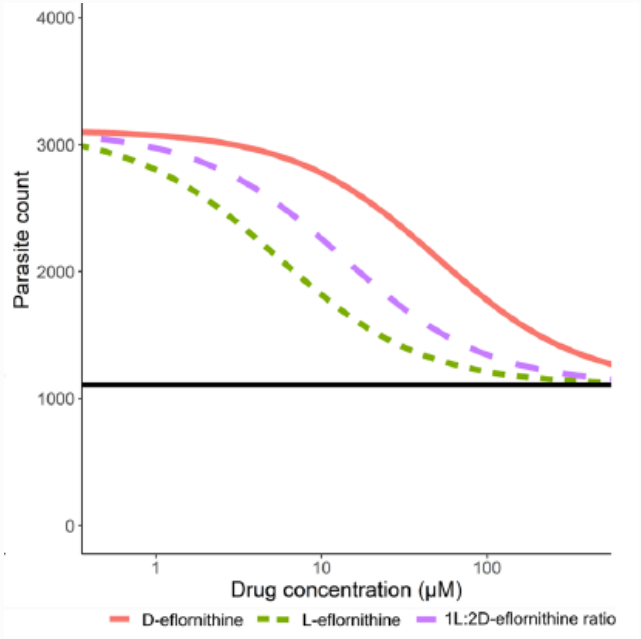
Published: Amilon *et al* (2022) Mar 25;24(3):48

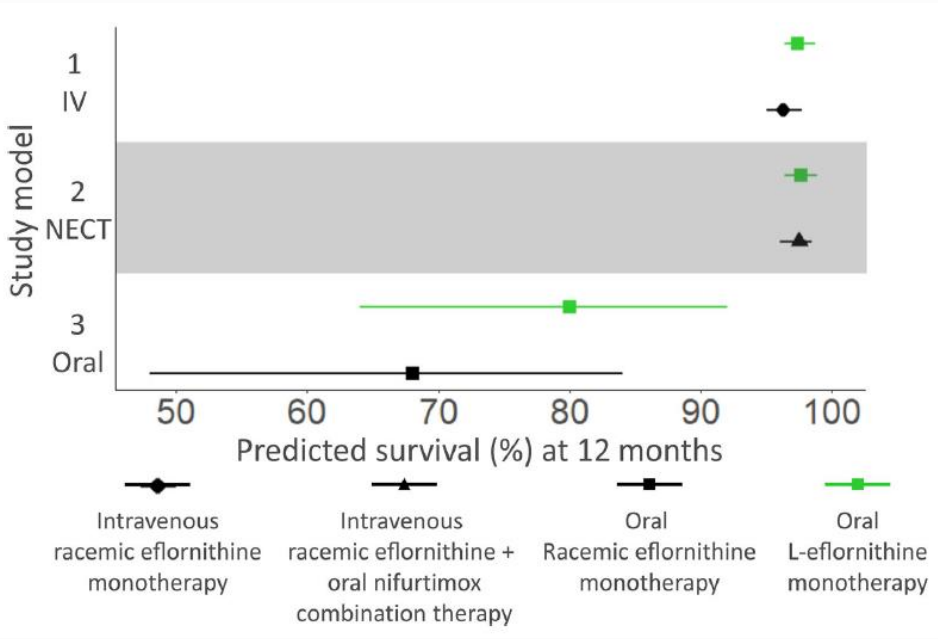
Results – Observed and predicted survival



Published: Amilon *et al* (2022) Mar 25;24(3):48

Results – Efficacy predictions for L-eflornithine





Published: Amilon *et al* (2022) Mar 25;24(3):48

Conclusions

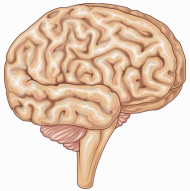
1. Oral L-eflornithine doses of 400 to 500 mg/kg/day were predicted to have a median survival of 80% against late-stage g-HAT

2. Oral L-eflornithine as monotherapy is unlikely to be efficacious at clinically relevant doses

3. Oral L-eflornithine could be combined with other g-HAT treatments

In vivo PK of eflornithine

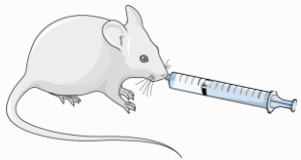
Methods – In vivo study design



L-eflornithine
394 µmol/kg (72 mg/kg)

Study arm 1

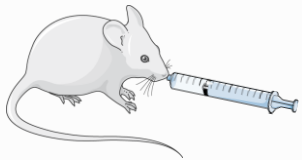
Study arm 2



Racemic eflornithine
634 µmol/kg (150 mg/kg)

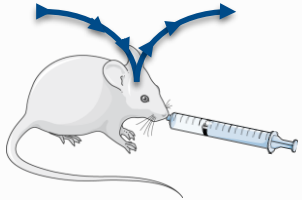
Study arm 3

Study arm 4



Racemic eflornithine
5071 µmol/kg (1200 mg/kg)

Study arm 5
Microdialysis

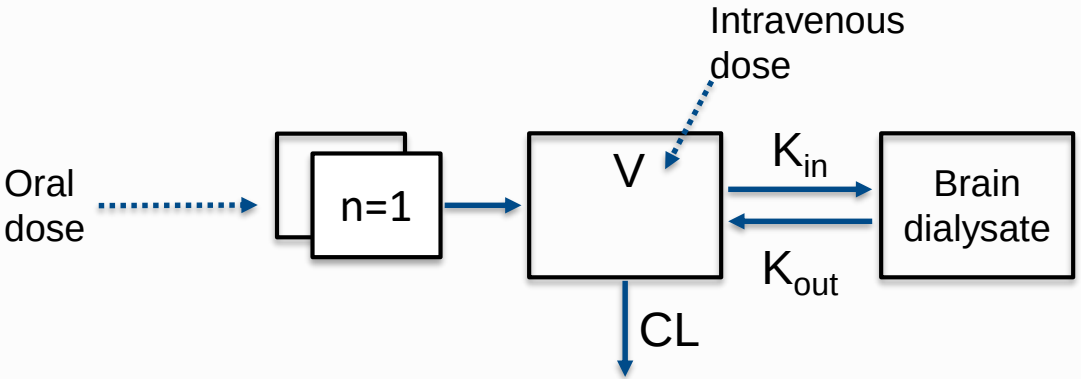


Unpublished manuscript

Methods – Data acquisition and analysis

- Bioanalysis was performed using a validated high performance liquid chromatography method[11]

- Nonlinear mixed effects modeling in Phoenix



11: Jansson-Löfmark R *et al*. Biomed Chromatogr. 2010;24(7):768-73.

Unpublished manuscript

Results – Pharmacokinetics of eflornithine

Pharmacokinetic parameter	L-eflornithine vs D-eflornithine	Enantiopure L-eflornithine vs L-eflornithine in racemate
Clearance		
Volume of distribution		
Absorption rate		
Bioavailability	**D > L = Enantioselective**	
Plasma-to-brain ratio		**Not tested**

Unpublished manuscript

Conclusions

1. Enantiopure L-eflornithine and L-eflornithine administered in racemate showed similar bioavailability and *in vivo* pharmacokinetics

2. No complex formation affected oral absorption of L-eflornithine

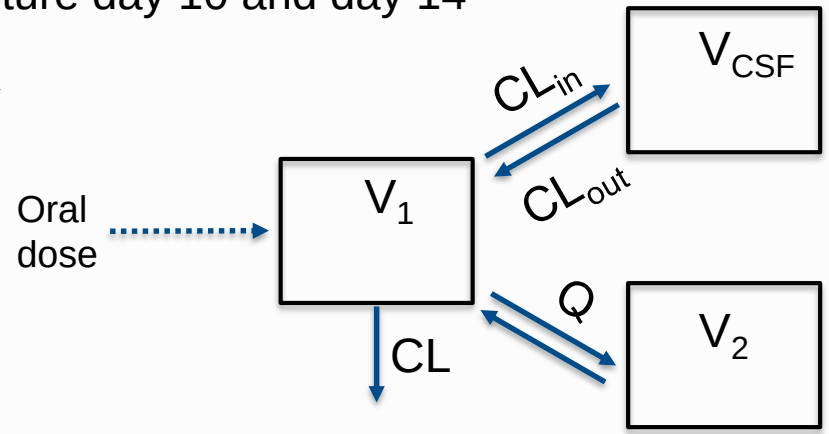
3. Non-enantioselective uptake of eflornithine to the third brain ventricle in the rat

4. Future possibilities to use the findings to predict clinical pharmacokinetics of L-eflornithine

Unpublished manuscript

Clinical PK of eflornithine – Methods

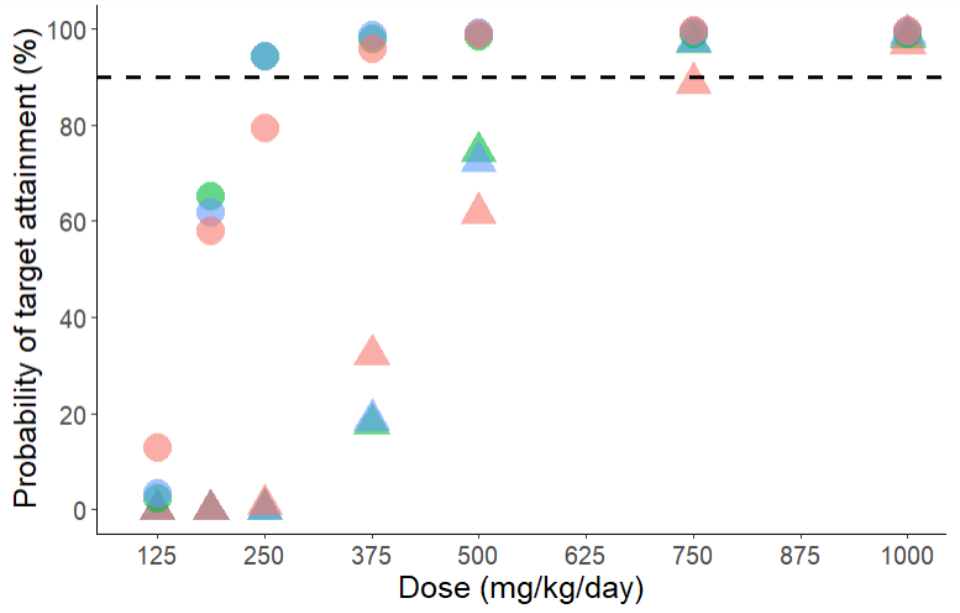
- Literature data on clinical pharmacokinetics after oral dosing of racemic eflornithine[3]
- Late-stage g-HAT patients (n = 25) dosed 400 mg/kg (n = 12) or 500 mg/kg (n = 13) per day for 14 days
- Cerebrospinal fluid sampling by lumbar puncture day 10 and day 14
- Nonlinear mixed effects modeling in Phoenix
- External validation data[12,13]



3: Jansson-Löfmark R *et al.* Antimicrob Agents Chemother. 2015;59(2):1299-307.
12: Haegele KD *et al.* Clin Pharmacol Ther. 1981;30(2):210-7.
13: Milord F *et al.* Trans R Soc Trop Med Hyg. 1993;87(4):473-7.

Unpublished manuscript

Results



L-eflornithine + nifurtimox (15 mg/kg/day)

L-eflornithine monotherapy

2 times daily	4 times daily	12 times daily

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Conclusions

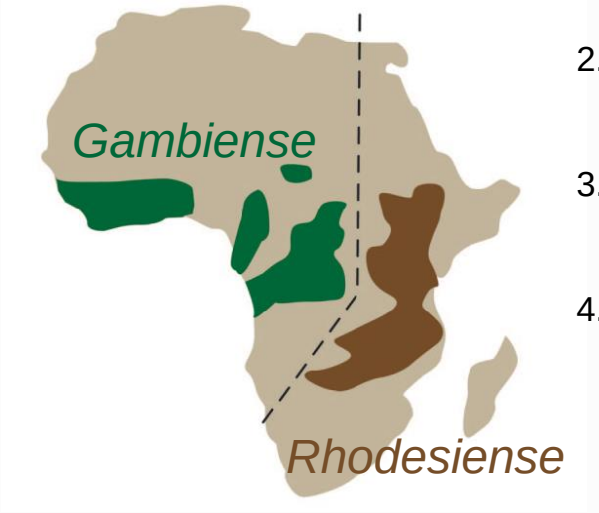
1. Clinical pharmacokinetics of L-eflornithine were adequately described by the final pharmacokinetic model

2. Non-enantioselective exposures of L- and D-eflornithine in cerebrospinal fluid in late-stage g-HAT patients after oral dosing of racemate

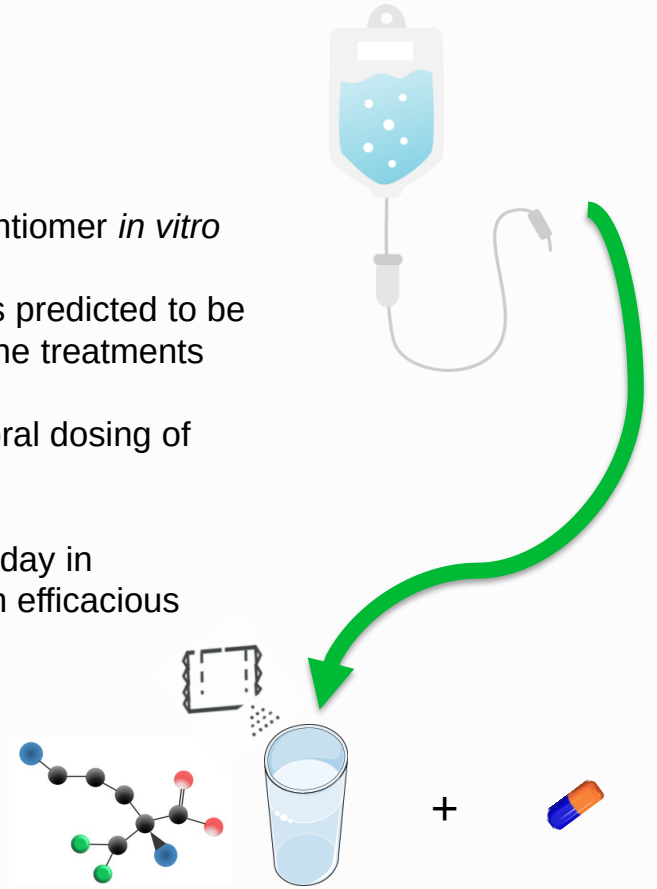
3. Based on the probability of target attainment analysis, L-eflornithine dosed 375 mg/kg/day in combination with nifurtimox could potentially be efficacious regimen

Unpublished manuscript

Conclusions



1. L-eflornithine was the more potent enantiomer *in vitro*
2. Oral L-eflornithine as monotherapy was predicted to be inferior to current intravenous eflornithine treatments
3. Similar *in vivo* pharmacokinetics after oral dosing of enantiopure L-eflornithine in the rat
4. Oral L-eflornithine dosed at 375 mg/kg/day in combination with nifurtimox could be an efficacious regimen against late-stage g-HAT



L-eflornithine-based treatment with nifurtimox

1: Kennedy P. (2008) Annals of Neurology. 64: 116 – 127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Thank you!