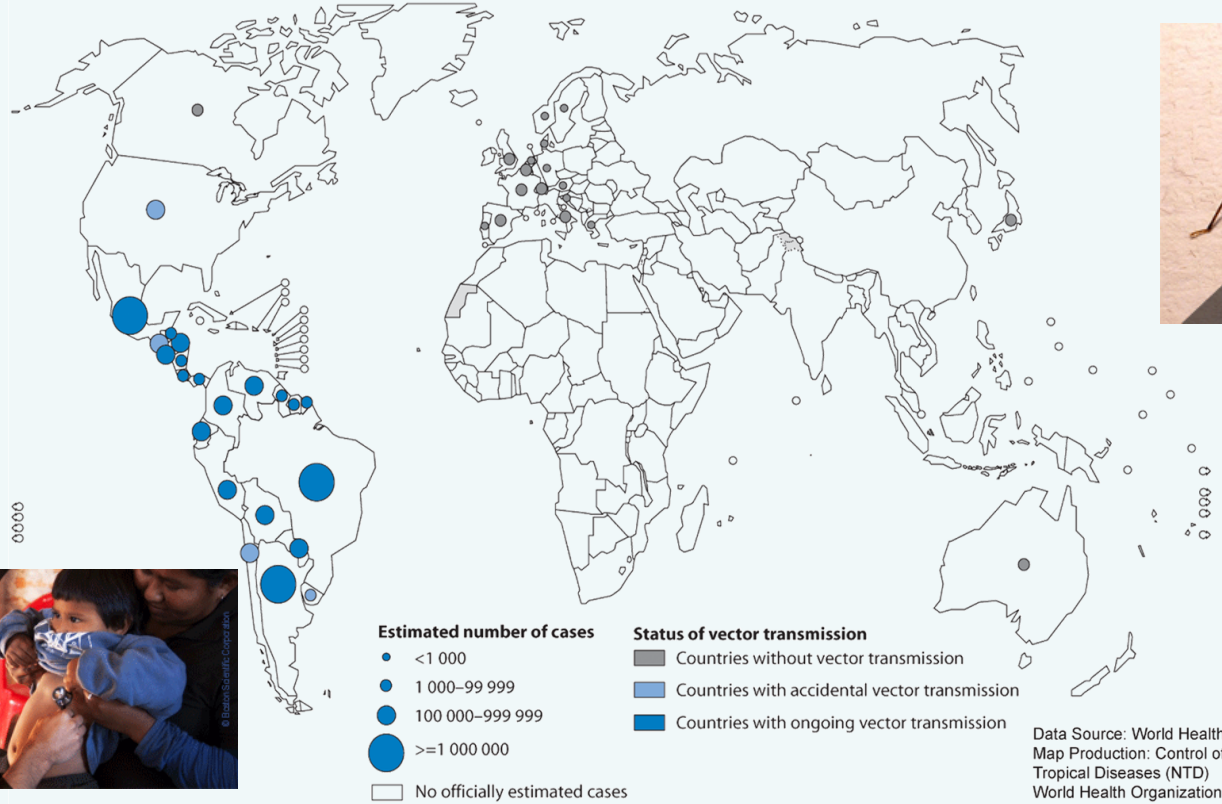
Model-based screening of compounds for the treatment of Chagas disease, a neglected tropical disease

S. D'Agate[1], I. Cotillo Torrejon[2], P. Healy[1], O. Della Pasqua[1,3]

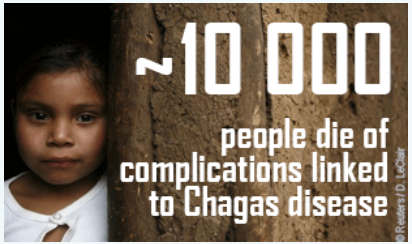
[1]Clinical Pharmacology & Therapeutics Group, University College London, London, UK
[2]Kinetoplastid Discovery Performance Unit, GlaxoSmithKline, Tres Cantos, Spain
[3]Clinical Pharmacology Modelling & Simulation, GlaxoSmithKline, Uxbridge, UK

Chagas Disease

(American trypanosomiasis)

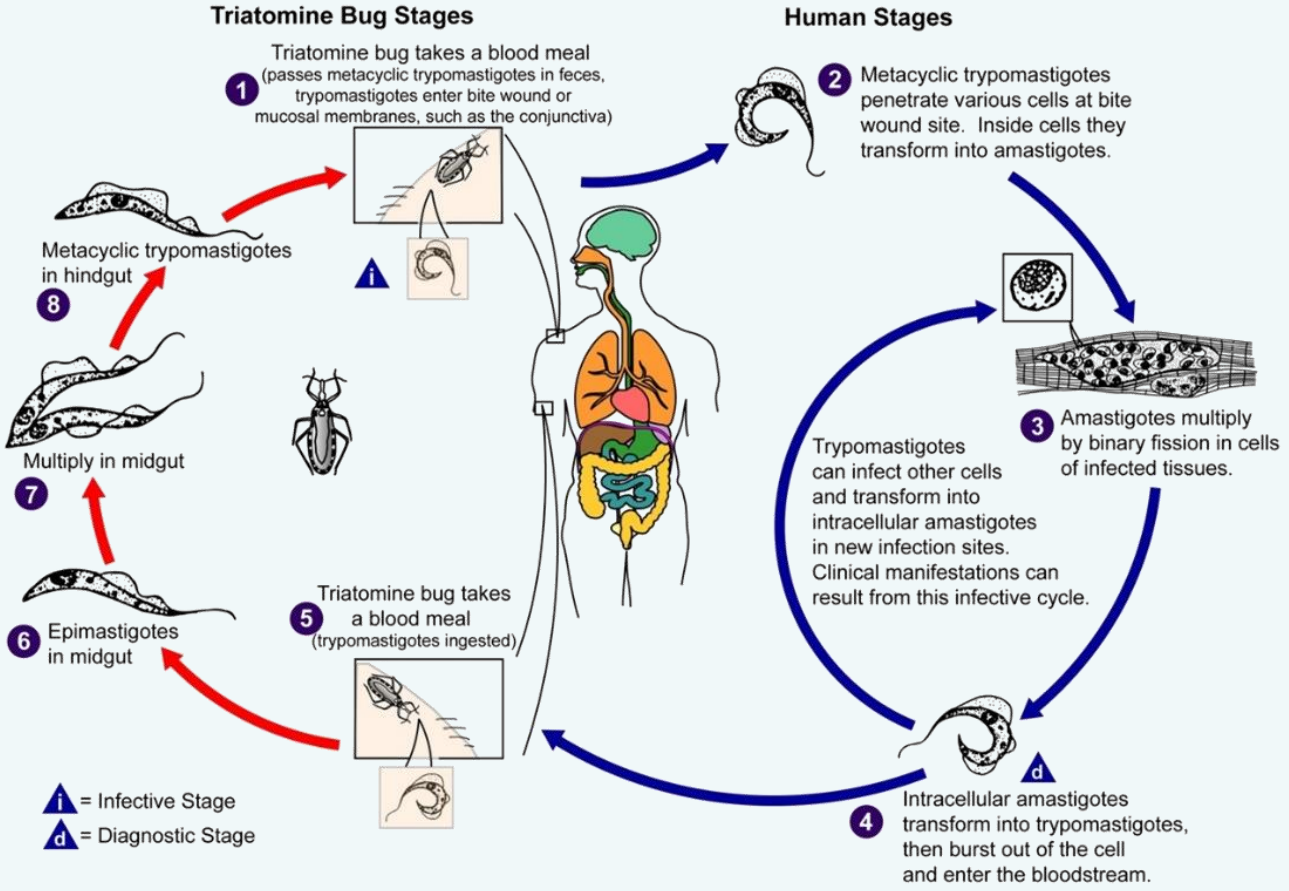


Data Source: World Health Organization
Map Production: Control of Neglected Tropical Diseases (NTD)
World Health Organization



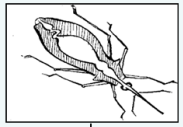
World Health Organization

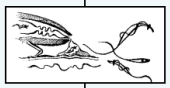
Trypanosoma cruzi



Trypanosoma Cruzi life cycle summarised (CDC. CDC - DPDx - Trypanosomiasis, American. In: DPDx.).

Chagas Disease



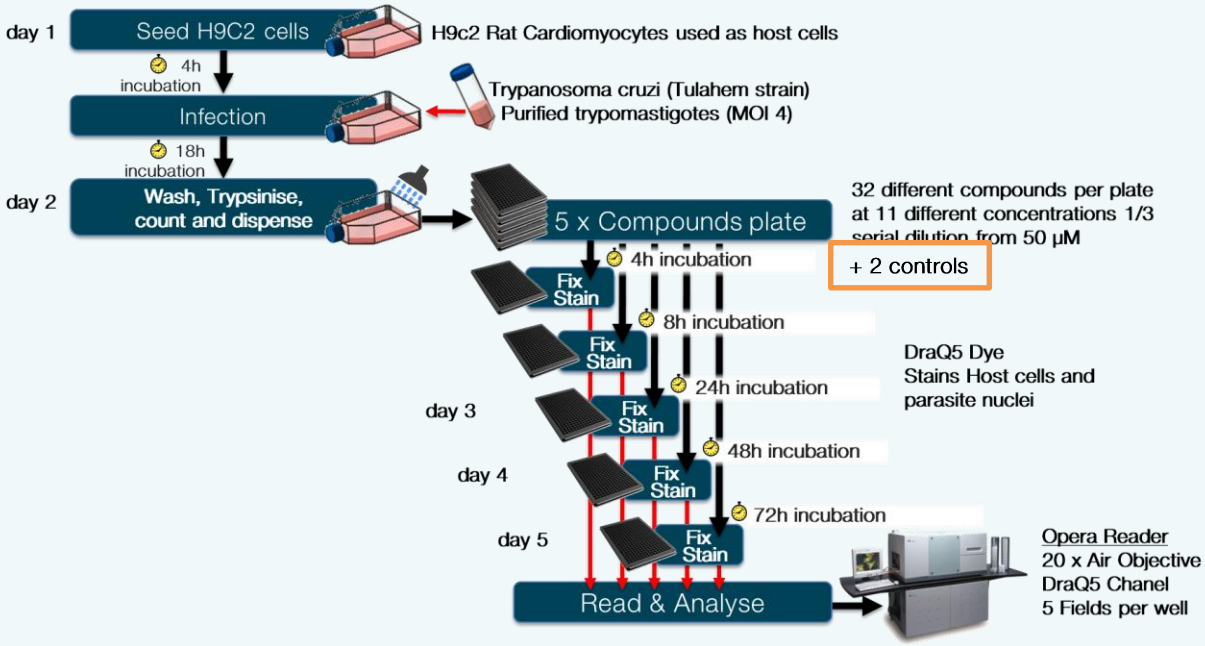


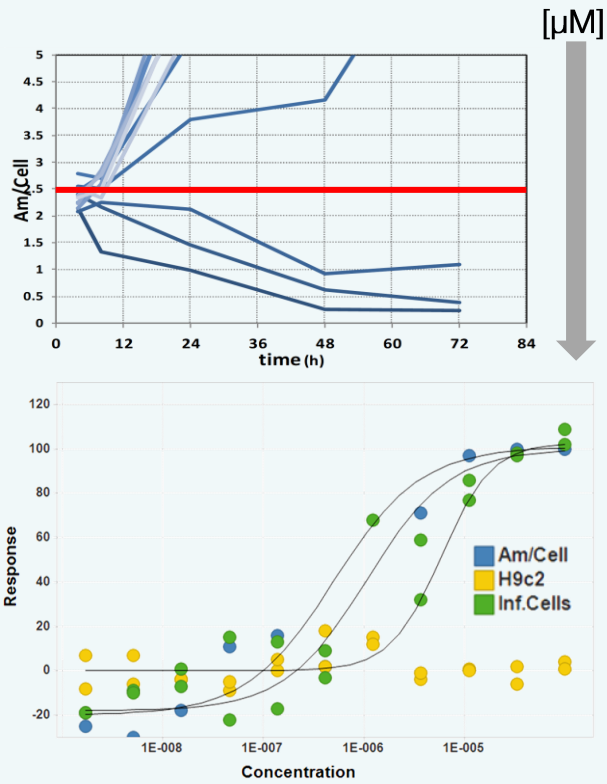
FEVER
HEADACHE
ANOREXIA
WEAKNESS
NAUSEA
VOMITING
DIARRHOEA
CHAGOMA
ROMAÑA'S SIGN

DRUG	AGE GROUP	DOSAGE AND DURATION
BENZNIDAZOLE	< 12 years	5-7.5 mg/kg/day p.o. b.i.d. for 60 days
	12 years or older	5-7 mg/kg/day p.o. b.i.d. for 60 days
NIFURTIMOX	≤ 10 years	15-20 mg/kg/day p.o. t.i.d./q.i.d. for 90 days
	11-16 years	12.5-15 mg/kg/day p.o. t.i.d./q.i.d. for 90 days
	17 years or older	8-10 mg/kg/day p.o. t.i.d./q.i.d. for 90 days

Courtesy of Dr Patricia Paredes, Guadalajara, Jal., Mexico.

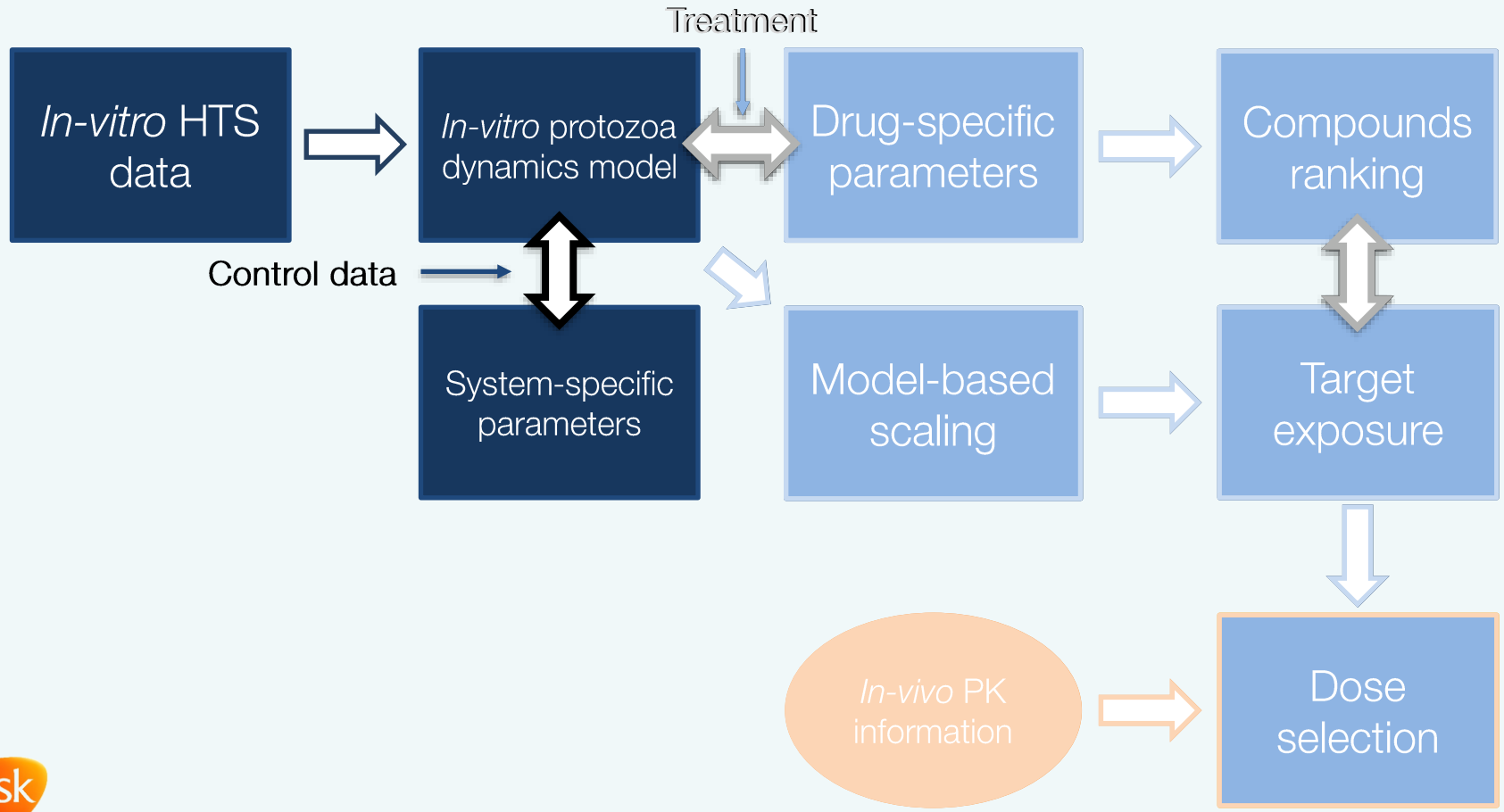
Materials - experimental protocol[1]





1. Alonso-Padilla et al. PLoS neglected tropical diseases 2015; 9: e0003493.

Aims of the current investigation



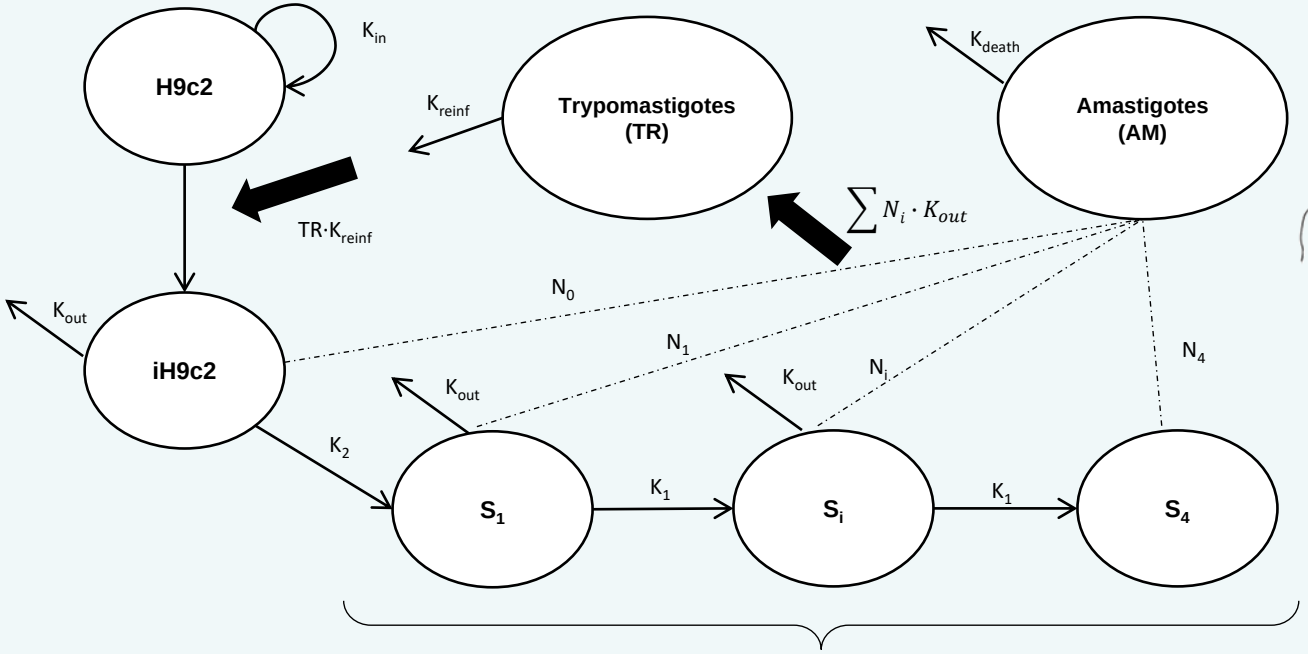
Methods - model development

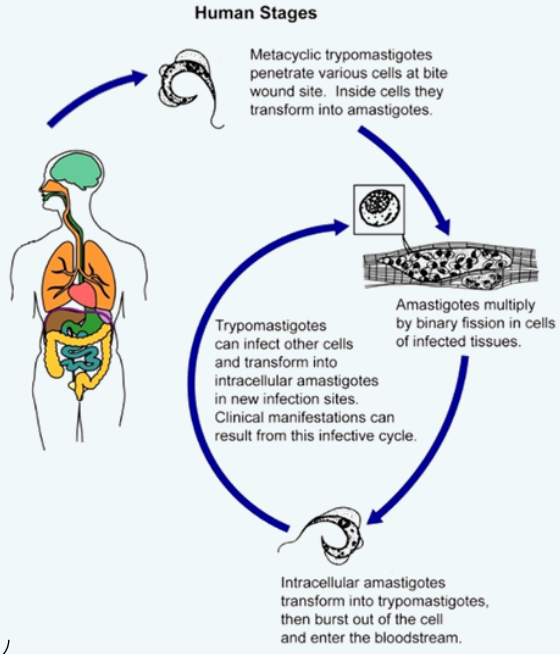
- Semi-mechanistic model parameterisation, aimed at disentangling drug-specific from system-specific parameters.
- Compartmental model describing protozoa growth and infection processes.

- Sequential PK/PD modelling approach:
  1. Control data used for the estimation of system-related parameters,
  2. Compound data used for the estimation of drug-related parameters.

- All analyses were carried out in NONMEM V7.3 using first-order conditional estimation with interaction (FOCE-I);
- Goodness of fit assessed by graphical methods, visual predictive check and bootstrap techniques.

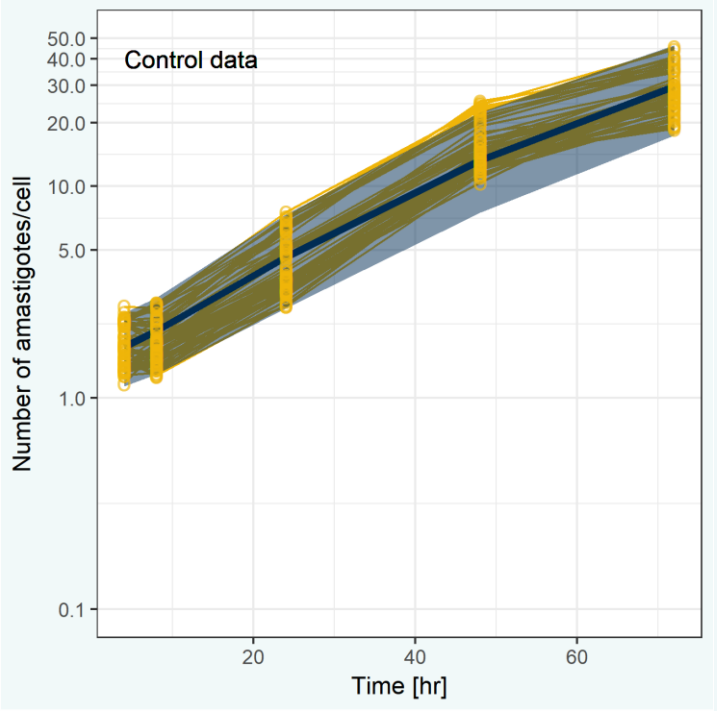
Methods – Protozoa dynamics





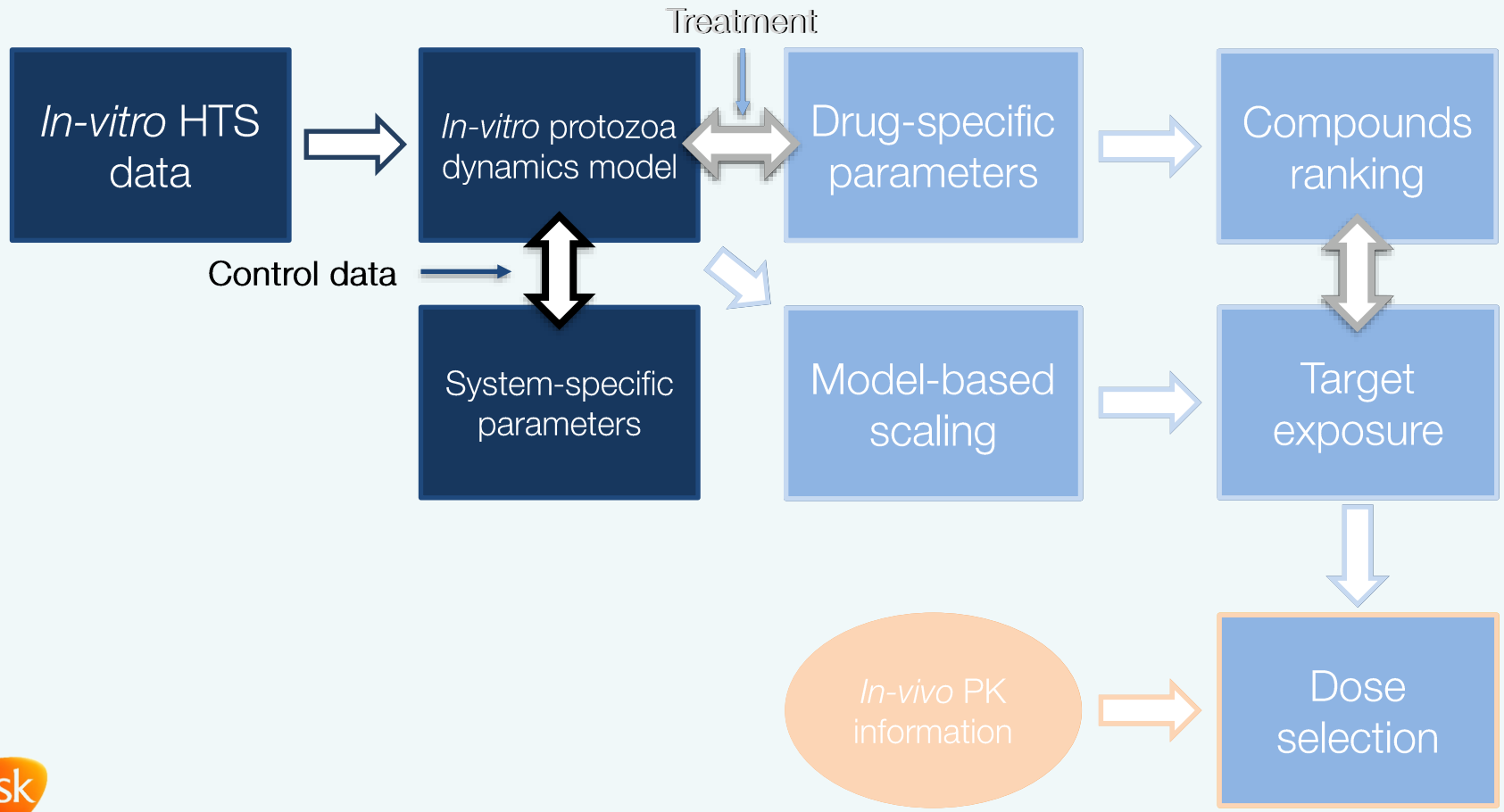
Visual predictive checks/Protozoa dynamics

Parameters of interest	Estimate
Reinfection rate (h^{-1})	0.0012
Premature host cell lyse (h^{-1})	0.0046
Initial number of amastigotes/cell	3.303
Parasite replication rate (h^{-1})	0.0716

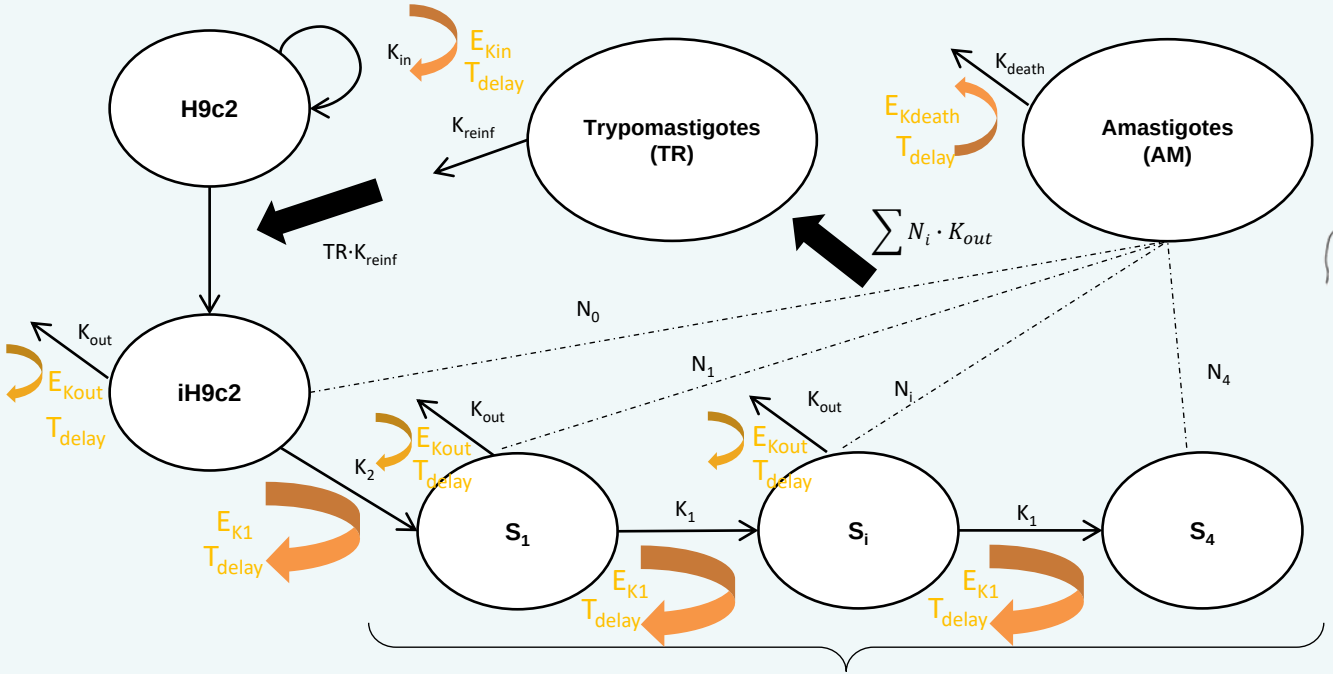


Data from control wells ($N_{samples}$=310) were used in the model building process.

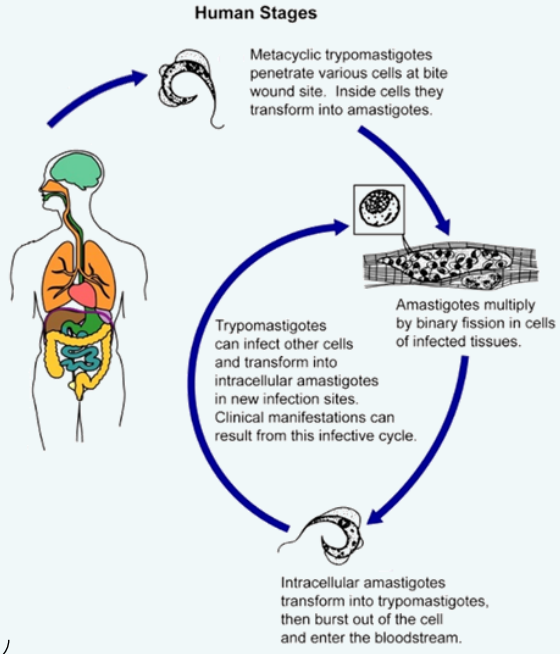
Aims of the current investigation



Methods - final model



Intracellular parasite growth



$$E = 1 - \frac{I_{max} \cdot C(t)}{IC_{50} + C(t)} \cdot D \text{ or } E = \frac{E_{max} \cdot C(t)}{EC_{50} + C(t)} \cdot D \text{ and } D = \frac{t}{T_{delay} + t}$$

Drug-specific parameters

$$E = 1 - \frac{I_{max} \cdot C(t)}{IC_{50} + C(t)} \cdot D \text{ or } E = \frac{E_{max} \cdot C(t)}{EC_{50} + C(t)} \cdot D \text{ and } D = \frac{t}{T_{delay} + t}$$

- IC_{50K1} ⇨ inhibitory effect on the parasite replication rate
- EC_{50KD} ⇨ direct effect on the death rate of the parasite
- IC_{50KIN} ⇨ inhibitory effect on the host cells growth rate
- IC_{50KOUT} ⇨ inhibitory effect on the premature lysis of host cells

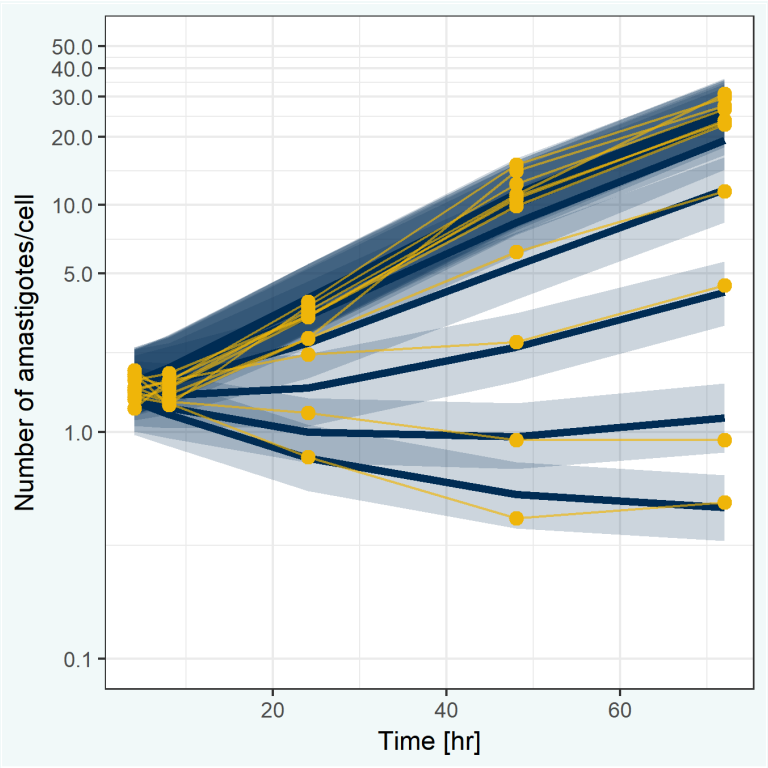
Compound analysis

- Screening data:
  - 2 reference drugs (benznidazole, nifurtimox);
  - 44 new compounds

- Experimental protocol:
  - Exposure-response curves for each compound include 11 levels, ranging from 0.85 nM to 50 μM.

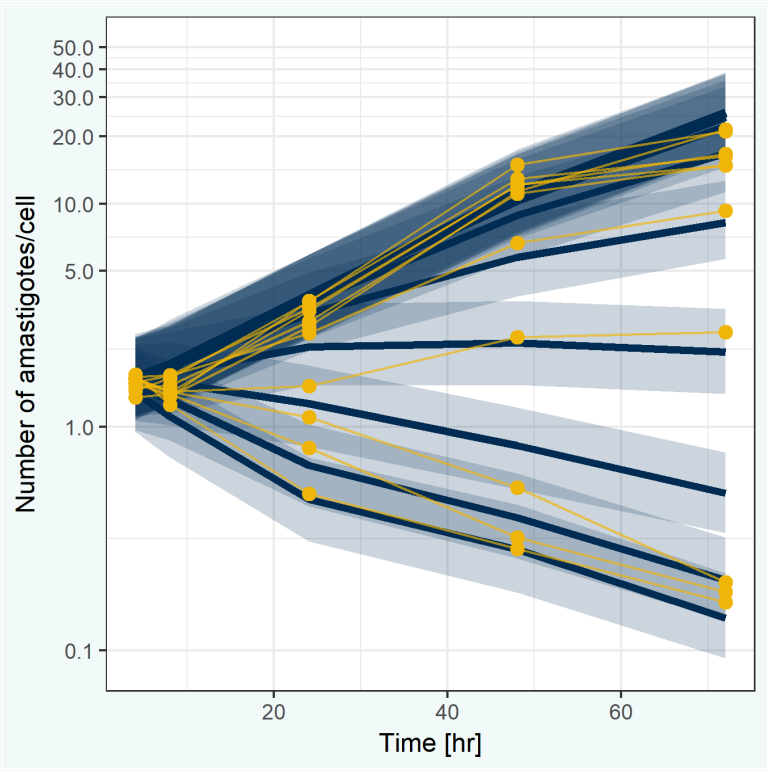
Visual predictive checks/Drug effect

Benznidazole



IC_{50K1} = 4.26 µM
EC_{50KD} = 14.73 µM

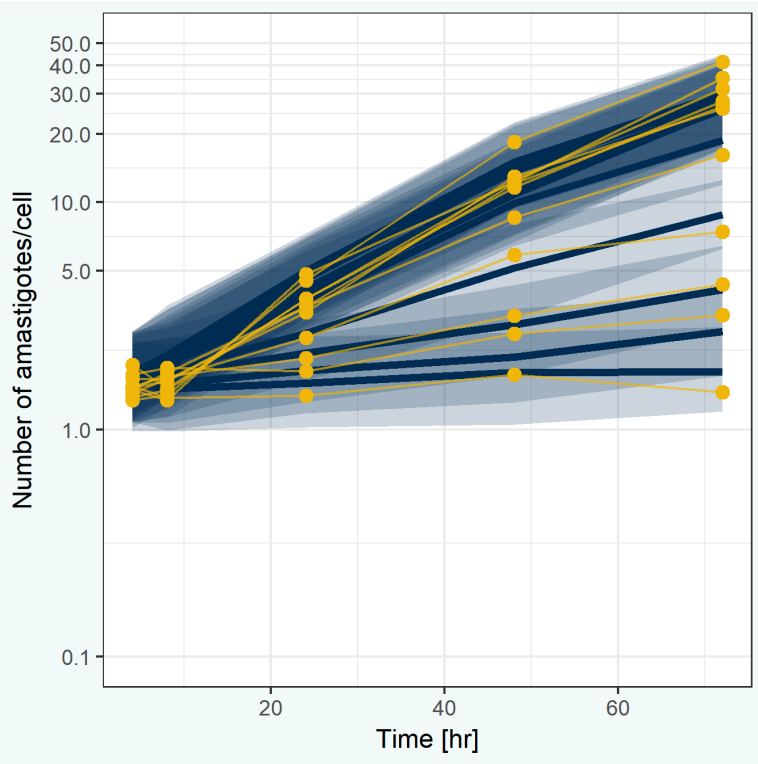
Nifurtimox



IC_{50K1} = 1.59 µM
EC_{50KD} = 13.01 µM

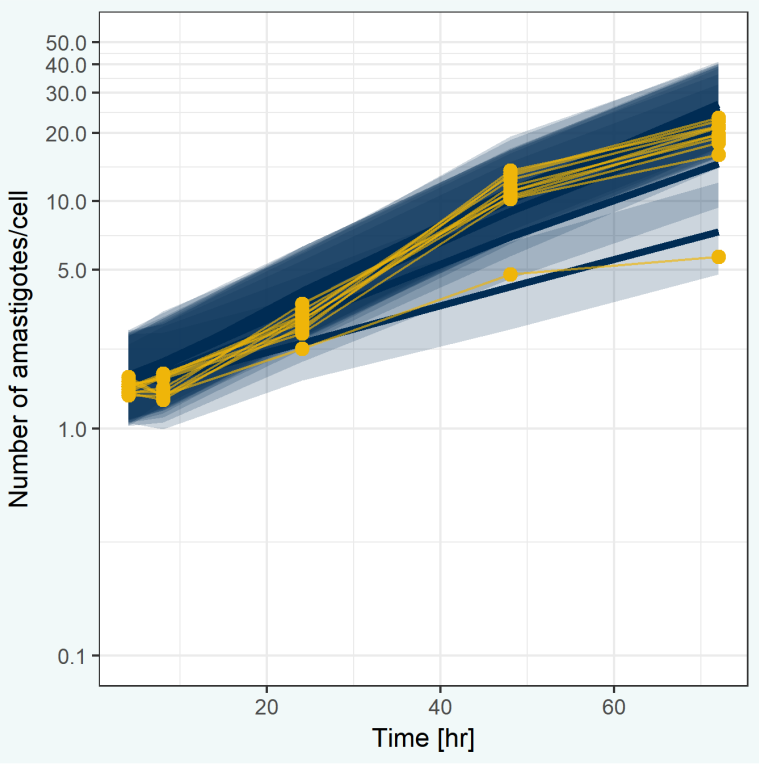
Visual predictive checks/Drug effect

GW358625X



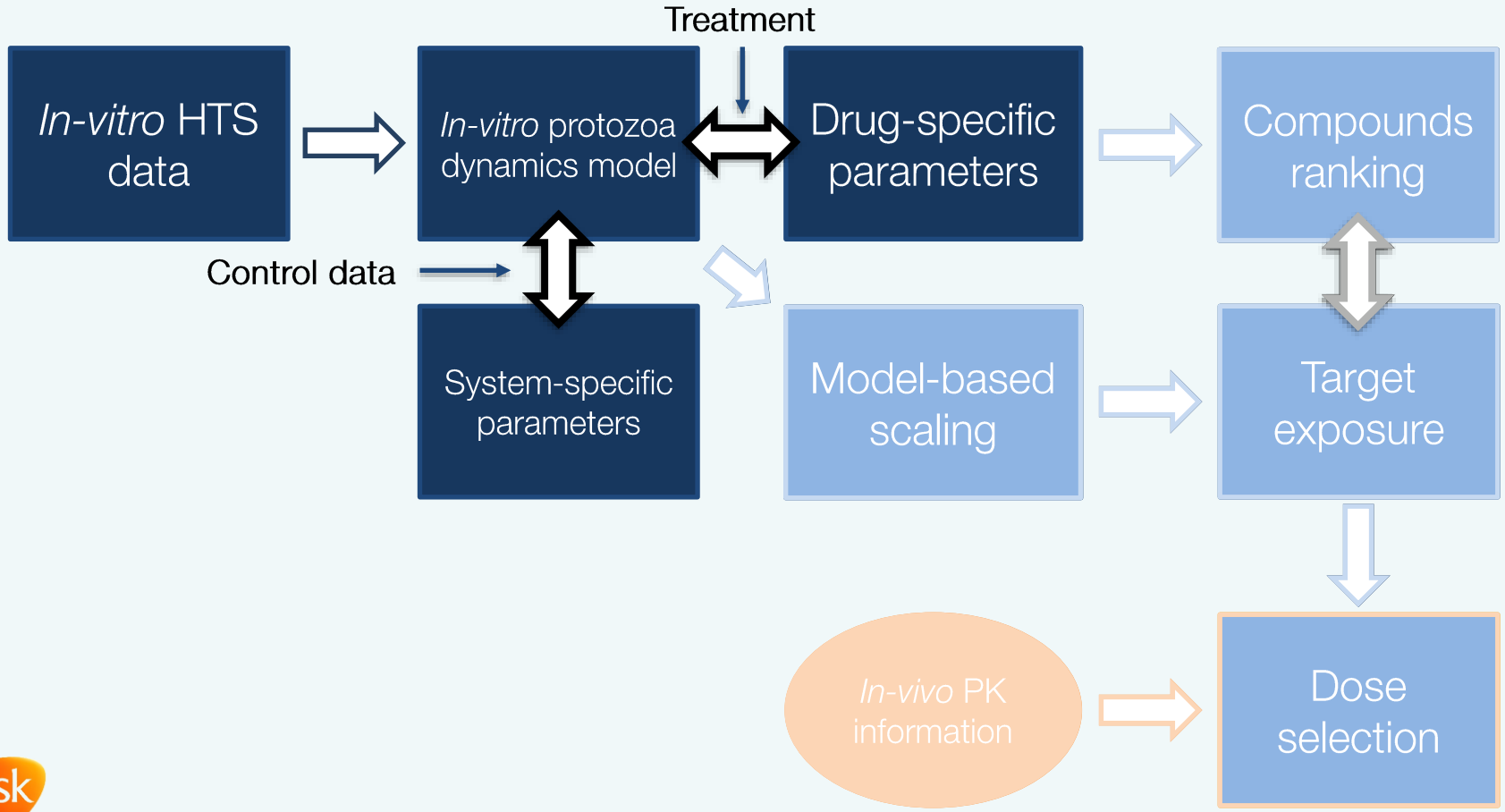
IC_{50K1} = 0.93 μM

GW332909A



IC_{50K1} > 50 μM

Aims of the current investigation



Compound ranking

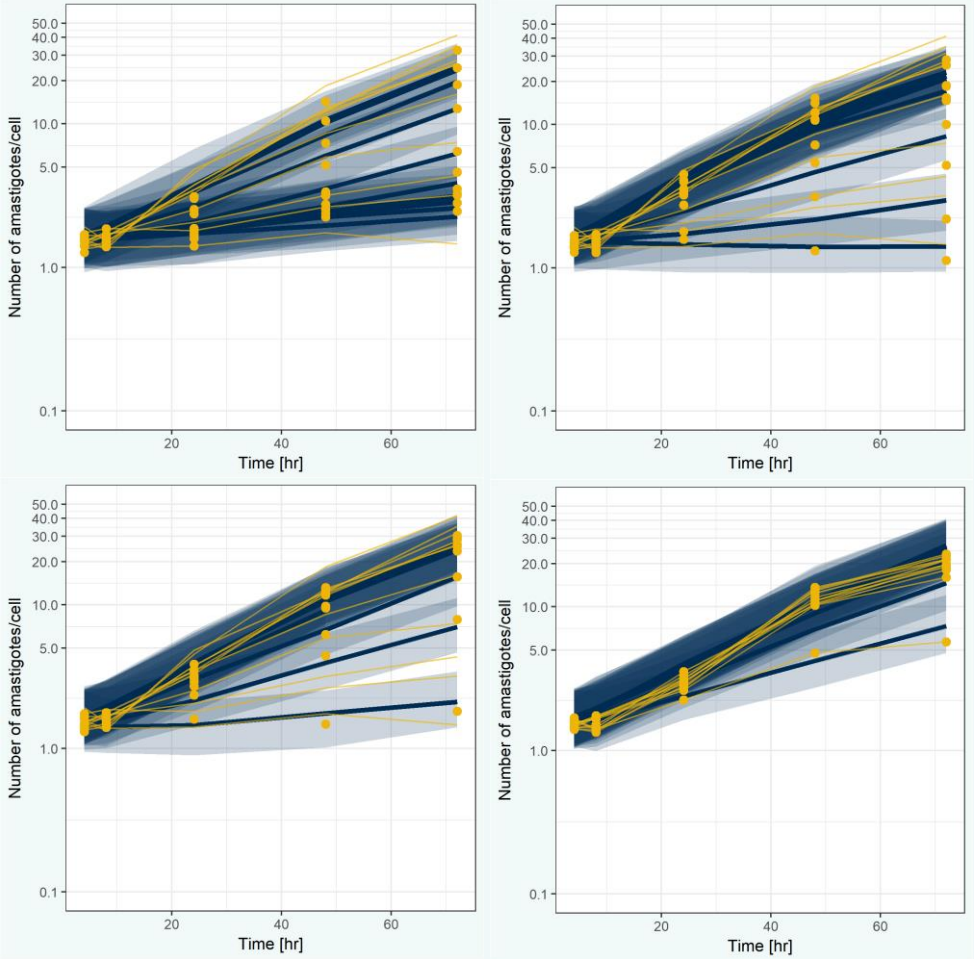
- Sensitivity analysis was performed to identify the most sensitive parameter describing parasiticidal and parasitostatic effects;

- IC_{50K1} represents the drug effect on parasite replication rate (parasitostatic);

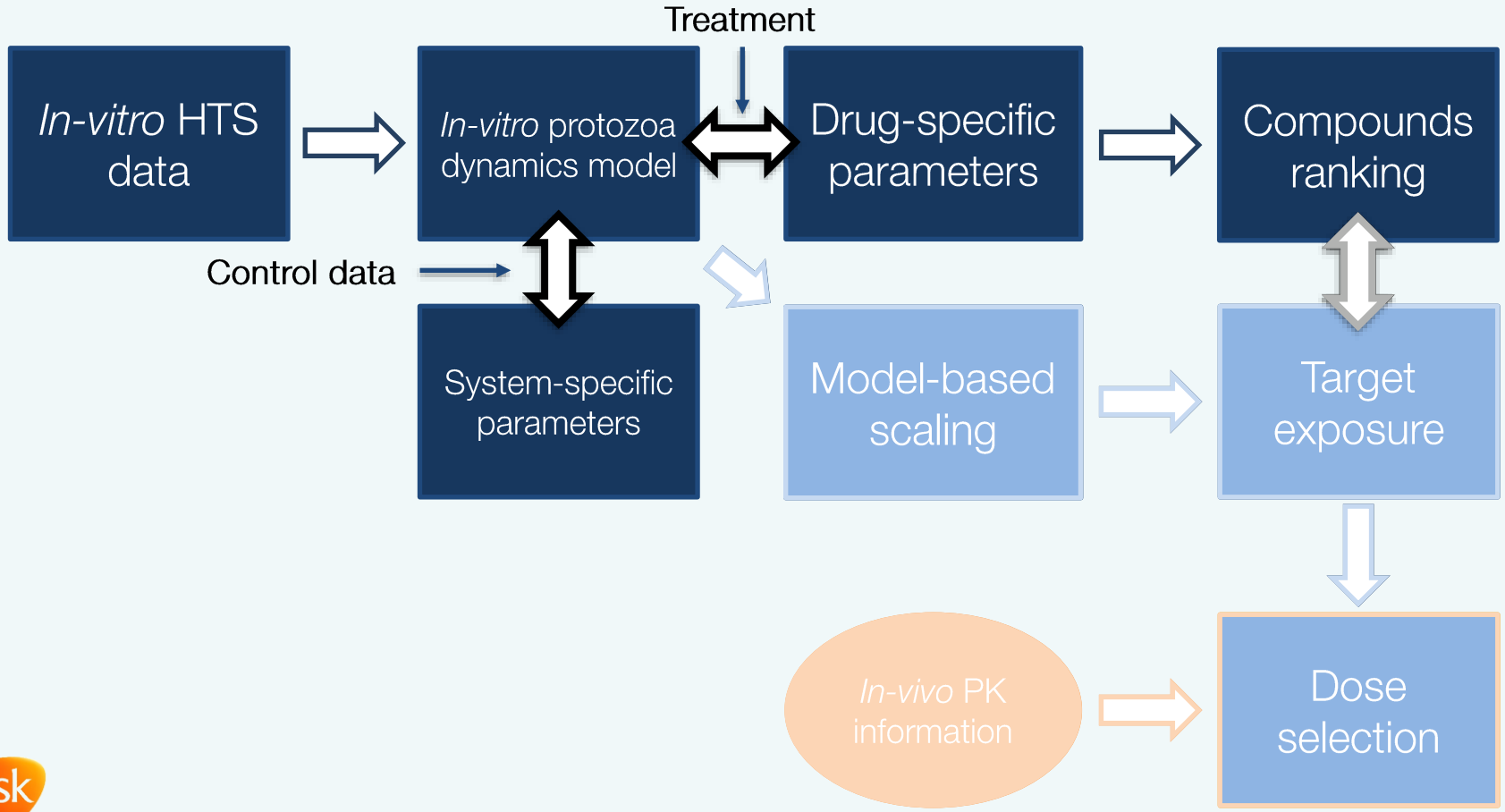
- EC_{50KD} represents the drug induced increase in parasite clearance (parasiticidal).

Compound ranking

Compound	IC_{50K1} (μM)
GW380944A	0.037
GSK2249069A	0.066
GSK503900A	0.071
Posaconazole	1.26
Nifurtimox	1.59
GW368548X	1.61
GW866668A	1.67
GSK2960477A	1.71
GSK1172530A	2.16
GW368763X	2.63
Benznidazole	4.26
GSK121884A	16.96
GW332909A	>50



Aims of the current investigation



Dose rationale in humans

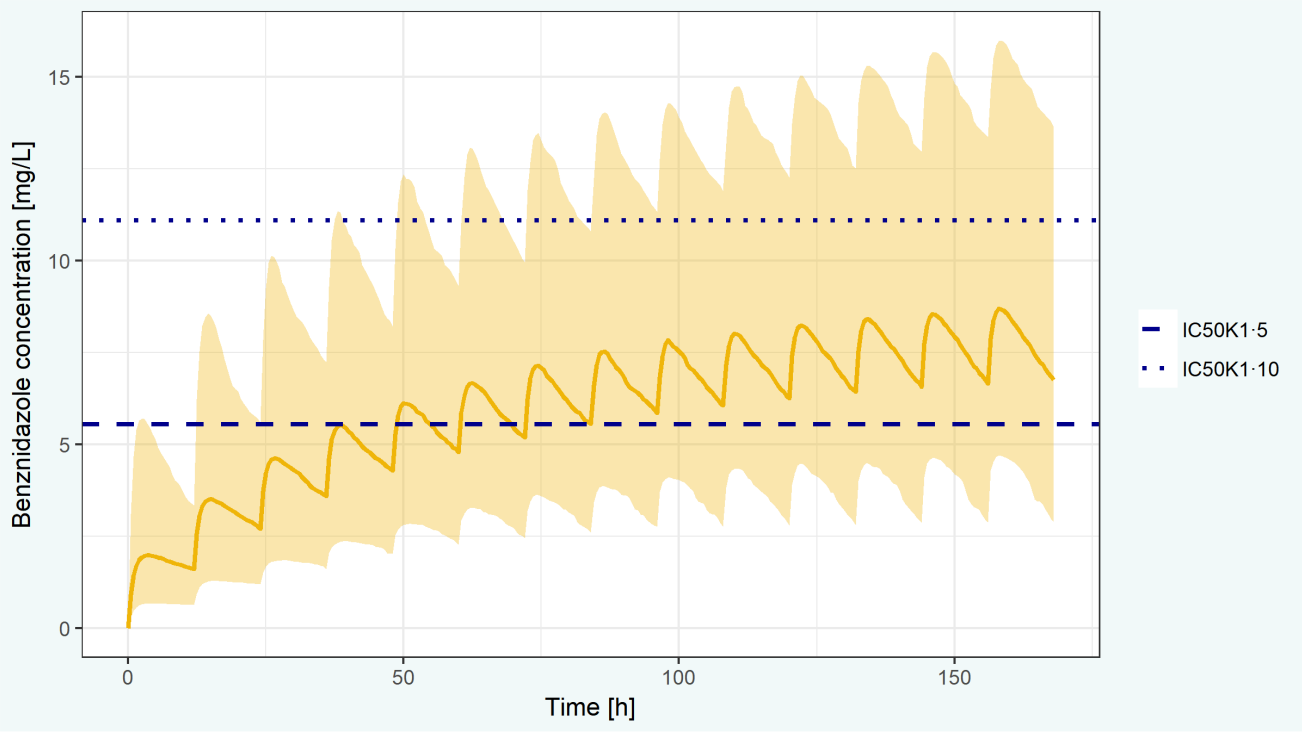
- Benznidazole and posaconazole were used to exemplify how model derived parameters can support the dose rationale for first-time-in humans and proof-of-concept studies.

- Target exposure corresponding to >IC80 and >IC90 values were assumed to be required for the therapeutic effect.

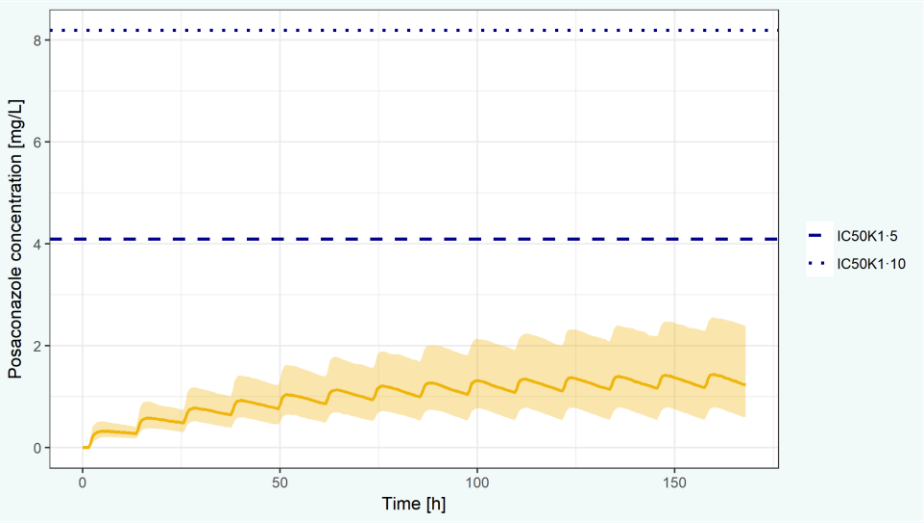
- Predicted exposure (plasma concentrations) were derived using allometric scaling principles and/or available pharmacokinetic data[2]. Results were then compared to currently used/tested clinical doses.

2. Soy D. et al. Antimicrob Agents Chemother 2015;59:3342–3349.

Target exposure - benznidazole



Target exposure - posaconazole



A Study of the Use of Oral Posaconazole (POS) in the Treatment of Asymptomatic Chronic Chagas Disease (P05267) (STOP CHAGAS)

This study has been completed.

Sponsor:
Merck Sharp & Dohme Corp.

Information provided by (Responsible Party):
Merck Sharp & Dohme Corp.

ClinicalTrials.gov Identifier:
NCT01377480

First received: May 13, 2011
Last updated: April 17, 2017
Last verified: April 2017
History of Changes

Full Text View | Tabular View | Study Results | Disclaimer | How to Read a Study Record

Purpose

This is a study to compare the efficacy of oral **posaconazole** to placebo for the treatment of asymptomatic **Chagas** disease. The primary hypothesis of the study is that **posaconazol** mg twice daily improves therapeutic response compared to placebo in participants with a diagnosis of asymptomatic chronic **Chagas** disease.

Condition	Intervention	Phase
Chagas Disease	Drug: **Posaconazole** Drug: Placebo for **posaconazole** Drug: Benznidazole	Phase 2

Conclusions

- We have shown that model-based approach can be used to describe parasite growth dynamics *in-vitro*;
- The model was parameterised using system and drug-specific parameters, enabling more precise estimates of the parameters of interest (IC_{50});
- Most compounds appear to have a predominant parasitostatic, rather than parasiticidal effect, which potentially explains the failure of some compounds in clinical trials;
- Given that target exposure can be derived from model parameters, our approach also allows a more robust dose rationale for proof of concept in Chagas disease.

Acknowledgements

Tres Cantos Open Lab Foundation

Nadia Terranova

References

[1] Benzekry S, Lamont C, Beheshti A, Tracz A, Ebos JM, Hlatky L, Hahnfeldt P. Classical mathematical models for description and prediction of experimental tumor growth. PLoS computational biology 2014; 10: e1003800.

[2] Nielsen EI, Friberg LE. Pharmacokinetic-pharmacodynamic modeling of antibacterial drugs. Pharmacol Rev 2013; 65: 1053-90.

[3] Alonso-Padilla, J., et al. (2015). "Automated high-content assay for compounds selectively toxic to Trypanosoma cruzi in a myoblastic cell line." PLoS Negl Trop Dis **9**(1): e0003493.

[4] Soy, D., et al. (2015). "Population pharmacokinetics of benznidazole in adult patients with Chagas disease." Antimicrob Agents Chemother 59(6): 3342-3349.

[5] N. Terranova, M.B Jiménez-Díaz, I. Angulo-Barturen, P. Magni, O. Della Pasqua. Modelling of protozoa dynamics and drug effects in a murine model of malaria infection. PAGE. Abstracts of the Annual Meeting of the Population Approach Group in Europe. ISSN 1871-6032. PAGE 21 (2012) Abstr 2574.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