Swiss TPH
Swiss Tropical and Public Health Institute
Schweizerisches Tropen- und Public Health-Institut
Institut Tropical et de Santé Publique Suisse

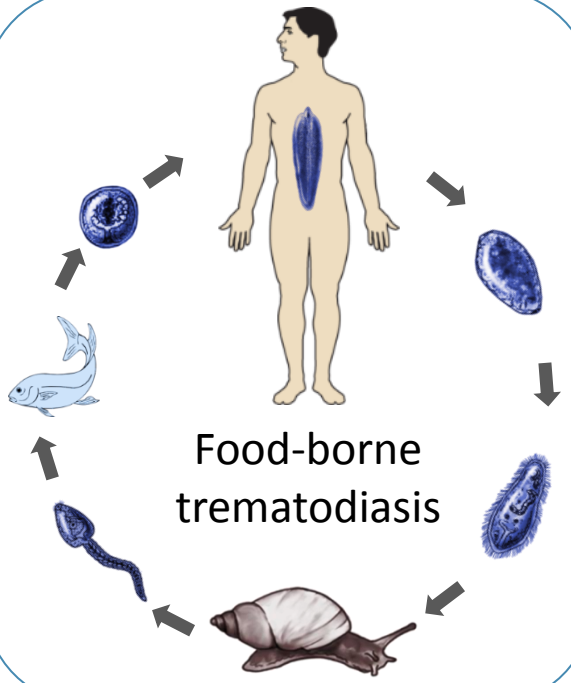
Jennifer Keiser
Helminth Drug Development Unit
Department of Medical Parasitology and Infection Biology

# Tribendimidine for the treatment of liver fluke infections

Weimar, 17.10.2014

# Background – Opisthorchiasis and Clonorchiasis

*Opisthorchis viverrini*




Cyprinoid fish

Raw fish dish

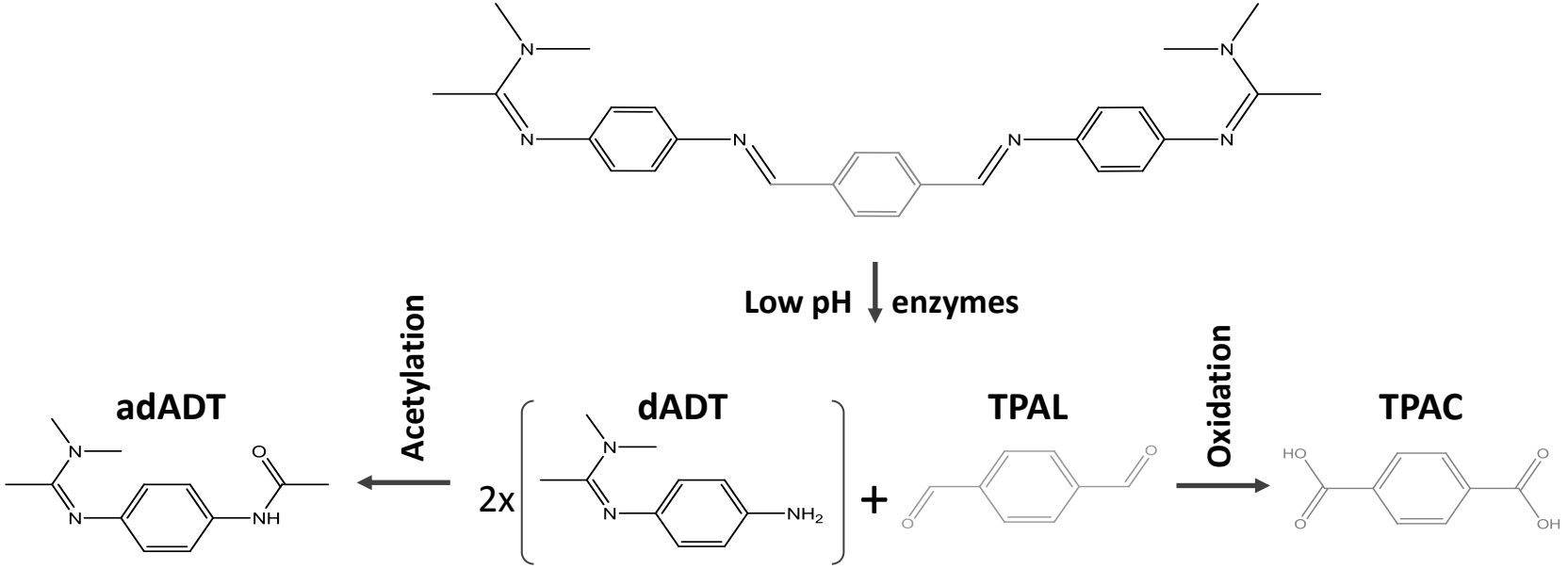
**>15 million** people infected in Southeast Asia

Huge public health burden → Development of malignant **cholangiocarcinoma**

Single drug available: **praziquantel**

# Tribendimidine

- Derivative of amidantel, an anthelminthic discovered by Bayer, with broad anthelminthic activity
- Discovered by the Institute of Parasitic Diseases, CDC Shanghai, China
- Marketed in China since 2004 for the treatment of hookworm, *Ascaris lumbricoides* and *Enterobius vermicularis* infection
- Efforts ongoing to develop tribendimidine outside China

# *In vitro* and *in vivo* studies with tribendimidine



**Tribendimidine tested *in vivo* and *in vitro***

**A. *In vitro* against *O. viverrini***

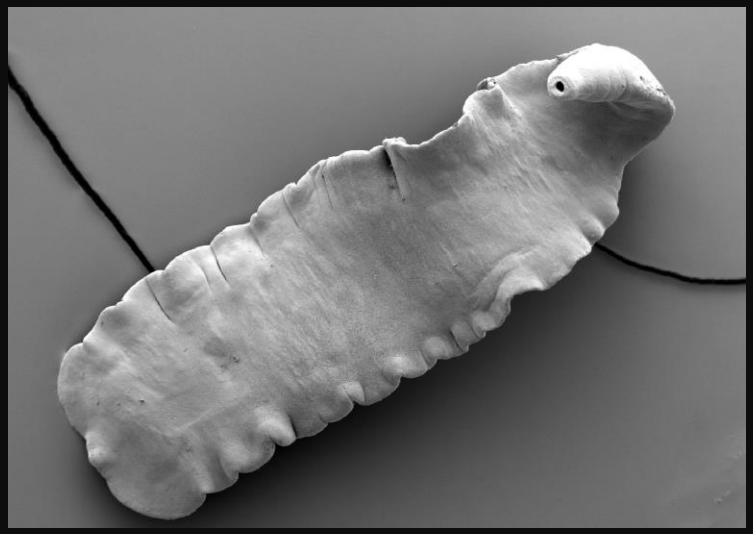
Fast acting: $EC_{50}$ = 225 nM (≙ 40 ng/ml) after 3 h of incubation

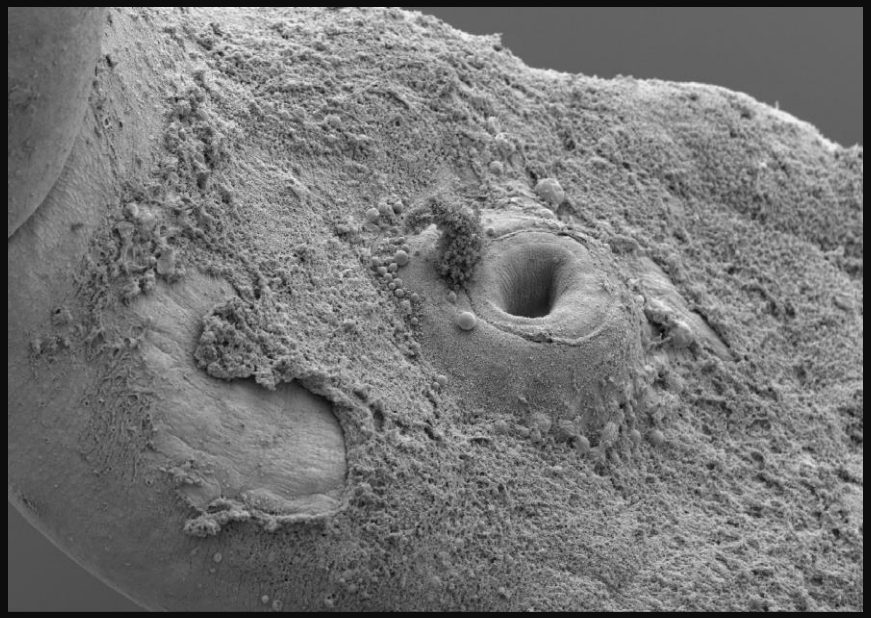
**B. *In vivo***

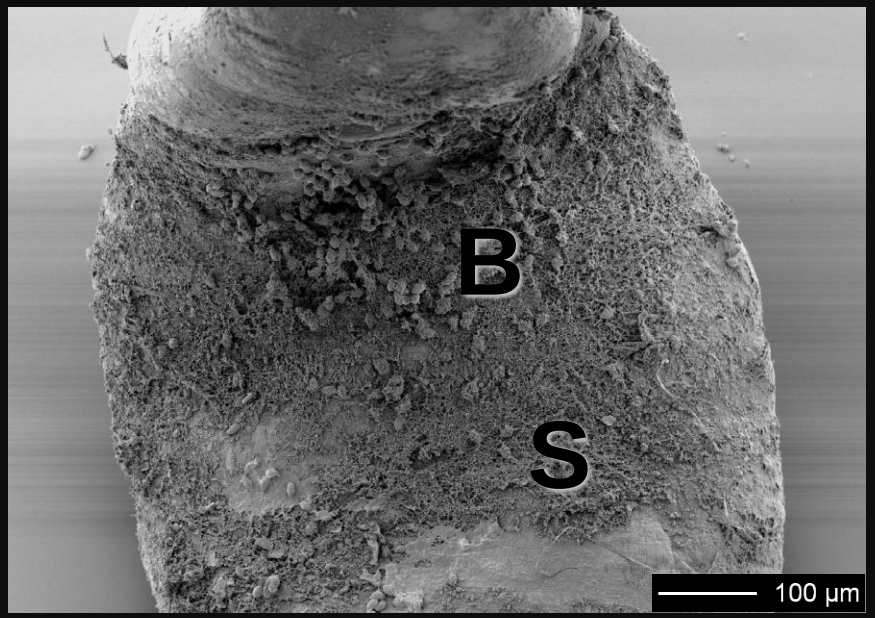
| Liver fluke | Dose (mg/kg) | No. of rodents investigated | Total worm burden reduction (%) |
|---|---|---|---|
| ***C. sinensis*** | 150 | 5 | 99.0 |
| ***O. viverrini*** | 400 | 5 | 62.9 |

# *In vitro* and *in vivo* studies with tribendimidine









Swiss TPH

## Efficacy and safety of mefloquine, artesunate, mefloquine–artesunate, tribendimidine, and praziquantel in patients with *Opisthorchis viverrini*: a randomised, exploratory, open-label, phase 2 trial

*Phonepasong Soukhathammavong, Peter Odermatt, Somphou Sayasone, Youthanavanh Vonghachack, Penelope Vounatsou, Christoph Hatz, Kongsap Akkhavong, Jennifer Keiser*

# Proof of concept trial tribendimidine against *O. viverrini*

125 children (age 10-15 years) infected with *O. viverrini*

Randomly assigned to praziquantel (75 mg/kg), **tribendimidine (400 mg)**, mefloquine (25 mg/kg), artesunate (10 mg/kg), mefloquine-artesunate (100/250 mg x 3)

2x2 Kato-Katz and 1 FECT at baseline and follow up (21 days post-treatment)

Mefloquine, artesunate, mefloquine-artesunate: **no effect**

**Tribendimidine**: cure rate: **70%**, egg reduction rate: **99.3%** *versus* **praziquantel**: cure rate: **56%**, egg reduction rate: **98.4%**

# Exploratory trial against *Clonorchis sinensis*

# Exploratory trial against *Clonorchis sinensis*

Swiss TPH

## Tribendimine (TBD) versus Praziquantel (PZQ)

| Parameters | TBD 400 mg once (n=25) | TBD 400 mg once daily for 3 days (n=24) | PZQ 75 mg/kg divided in 3 doses (n=25) |
|---|---|---|---|
| **No. of patients cured (%)** | 11 (44) | 14 (58) | 14 (56) |
| **No. of patients cured light infection (%)** | 5 (100) | 4 (100) | 4 (100) |
| **No. of patients cured moderate infection (%)** | 6 (54) | 10 (59) | 7 (54) |
| **No. of patients cured heavy infection (%)** | 0 | 0 | 3 (38) |
| **Egg reduction rate (%)** | 97.6 | 98.8 | 98.8 |

- Tribendimidine well tolerated

# Tribendimidine-study design

Swiss TPH

Efficacy and Safety

Pharmacokinetics

## Phase 2a Trial – Dose finding

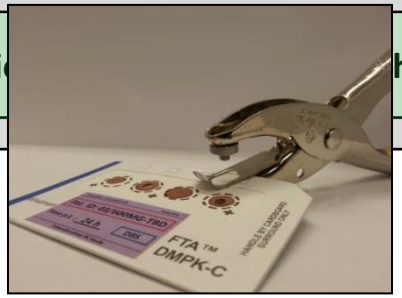
Tribendimidine
(n = 40 / dose)

| 25 mg | 50 mg | 100 mg |
|---|---|---|
| 200 mg | 400 mg | 600 mg |
| N = 10 | N = 10 | N = 10 |

**Blood sampling for PK study**
Venous and capillary blood

+

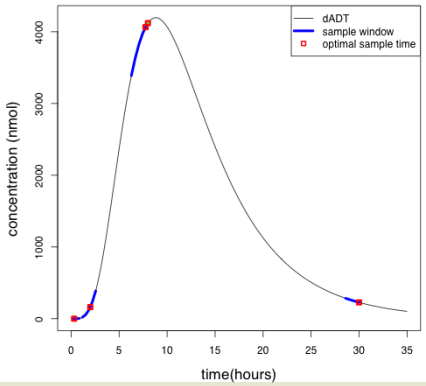
Validati… …hod




## Phase 2b Trial – Efficacy and Safety

| Tribendimidine | Praziquantel |
|---|---|
| 400 mg<br>N = 300 | 75 mg/kg<br>N = 300 |

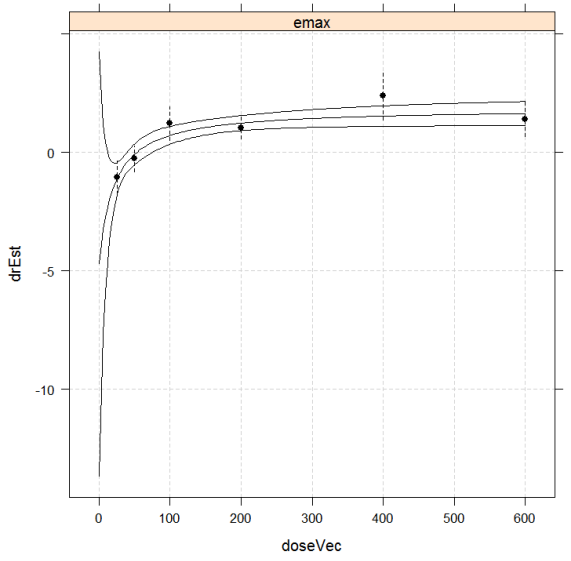
**Population Pharmacokinetic Study**
Dried blood spot analysis



# Phase 2a trial- results adults

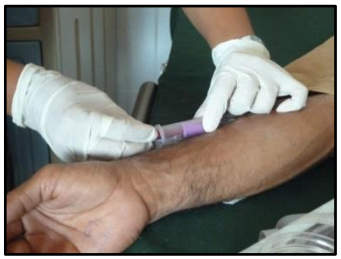
| Dose | N | № Cured (%) | ERR (%) |
|---|---|---|---|
| 25 mg | 39 | 10 (25.6) | 62 |
| 50 mg | 47 | 20 (42.6) | 91 |
| 100 mg | 44 | 34 (77.3) | 94 |
| 200 mg | 47 | 40 (85.1) | 94 |
| 400 mg | 47 | 43 (91.5) | 88 |
| 600 mg | 45 | 36 (80.0) | 95 |

- Best efficacy observed with 400 mg tribendimidine

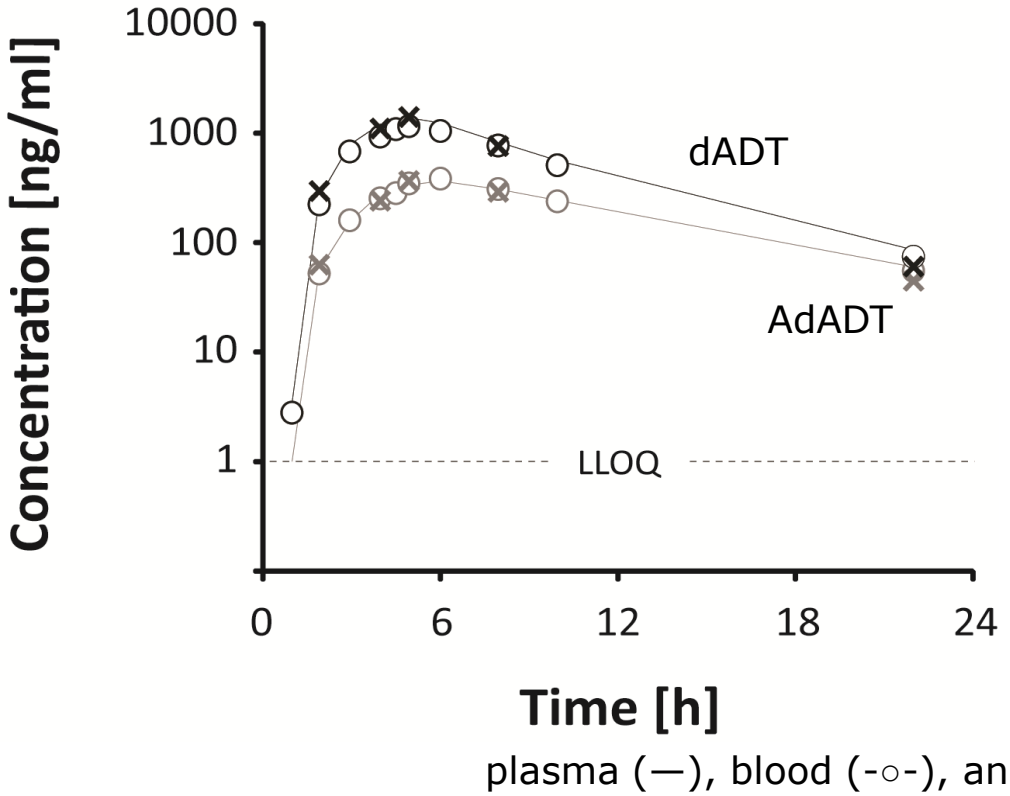



ERR: Egg reduction rate

# Pharmacokinetic studies

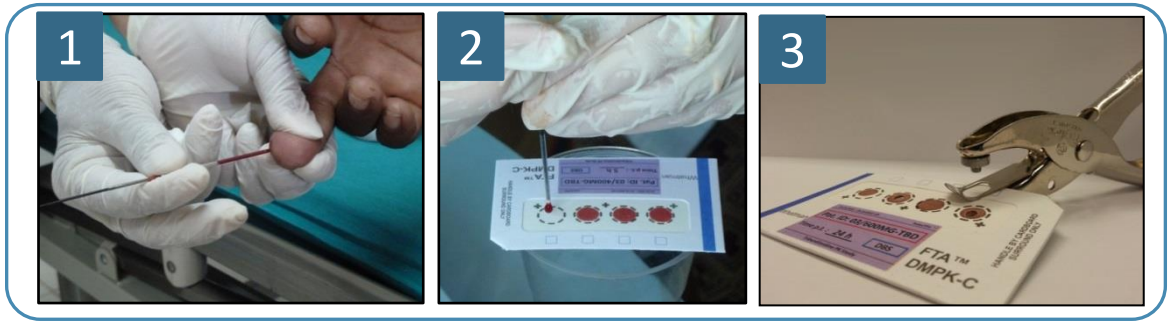


Venous blood sampling




plasma (—), blood (-○-), and DBS (X)

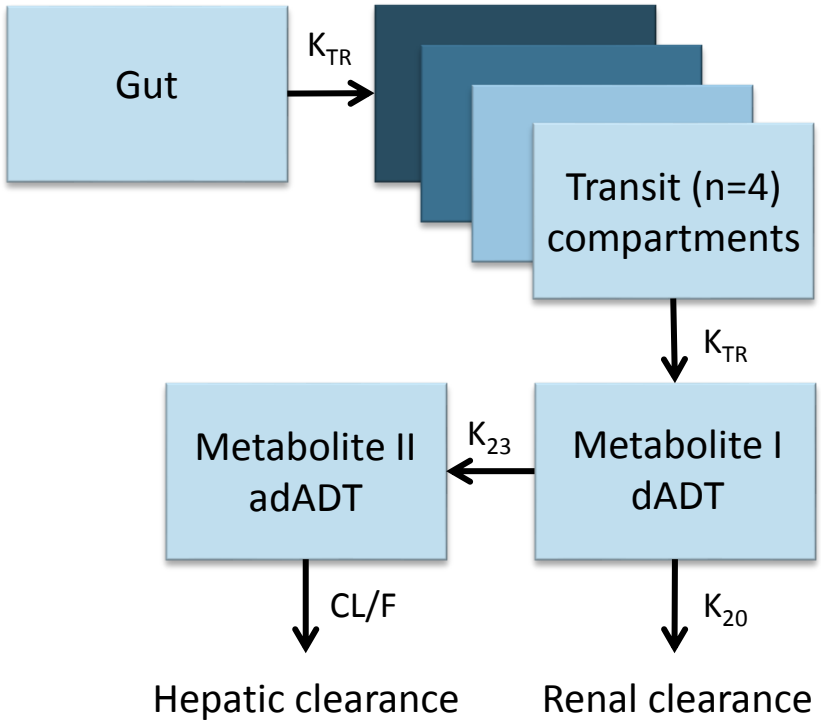
**Dried blood spots technique**



# Tribendimidine – Optimal PK model structure

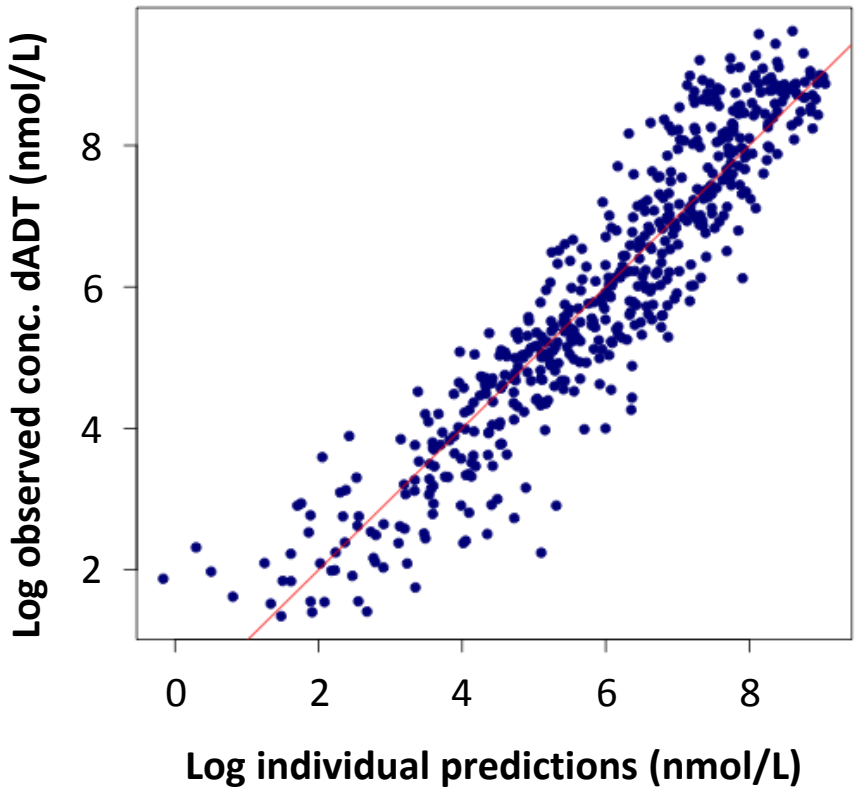
Swiss TPH

## PK compartmental model




- Iterative process to optimised final model
- least squares objective function
- $K_{20}$ = 0.35 CP / V and $K_{23}$ = 0.65 CP / V [1]

## Model diagnostics




[1] Drugs in R&D (Guiyan Yuan et al, 2010)

# Tribendimidine – Pharmacokinetic Results Plasma dAdT 400 mg

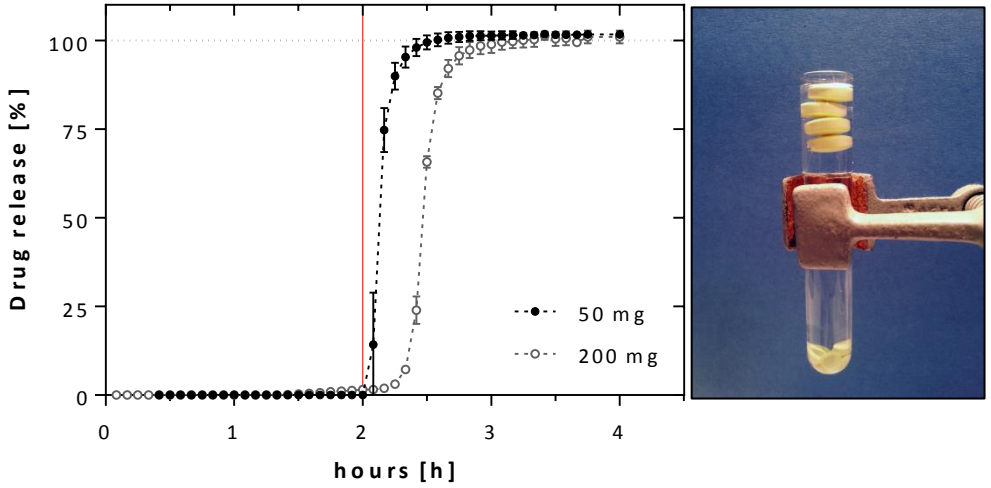
Swiss TPH

| | AUC (hr*nmol/L) | Cmax (nmol/L) | T1/2 (hr) | Tmax (hr) |
|---|---|---|---|---|
| Blood | 47800 (18000-51100) | 4040 (1690-6030) | 4.9 (2.9-16.7) | 9.9 ( 4.3-12.9) |
| Plasma | 44400 (19900-53700) | 4090 (3260-6030) | 4.1 (3.8-4.4) | 9.3 ( 3.8-12.9) |
| DBS | 35300 (6870-46200) | 3400 (2100-5010) | 4.6 (4.4-5.1) | 9.6 ( 3.6-13.8) |

- PK/PD relationship to be determined
- The observed $C_{max}$ are higher than the $EC_{90}$ determined *in vitro* (± 430 nM)

**Large PK-variability in $T_{max}$ were observed**

- Produced by the gastroretentive drug formulation (immediate floating tablets)
- A reduced intestinal pH might delay drug release but cannot explain the large variability
- 50 mg tablets exhibit improved pharmaceutical properties (non-floating, fast release)



# Acknowledgements


Swiss National Science Foundation

UKaid from the British people

wellcome trust

MRC Medical Research Council

**National Institute of Public Health**
Dr. S. Sayasone, Dr. P. Soukhathammavong

DIVISION OF PHARMACEUTICAL TECHNOLOGY

**Pharmaceutical Technology**
Prof. Dr. J. Huwyler

**National Institute of Parasitic Diseases, Chinese Center for Disease Control and Prevention**
Qian Men-Bao, Zhou Xiao-Nong

**SwissTPH**
Dr. U. Duthaler, I. Meister, Dr. P. Odermatt, Dr. M. Penny