

# Oxfendazole against filariae and soil-transmitted helminths

Marc P. Hübner

Second International Workshop on  
Onchocerciasis-Associated Epilepsy

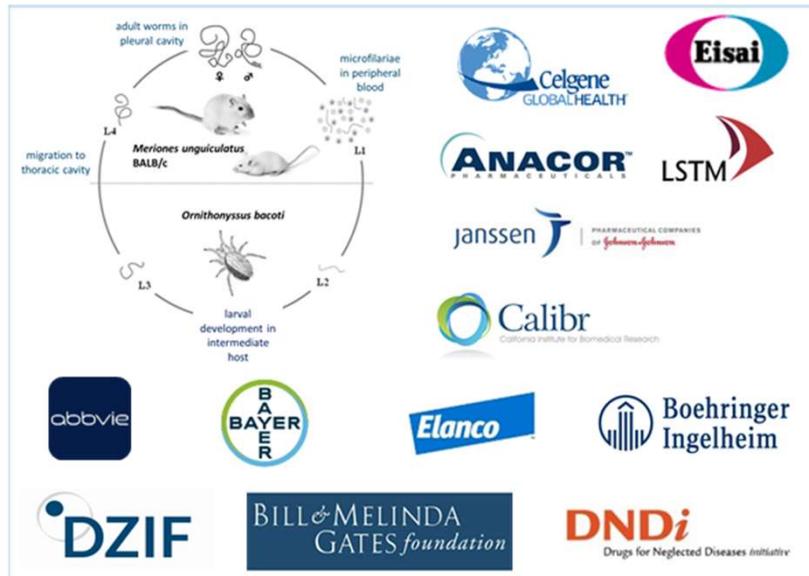
19<sup>th</sup> September 2023

## Preclinic



## Clinical studies

- Intern. hit to lead program (>500K candidates)
- Collaboration with industry & academia
- > 450 candidates tested in the *Litomosoides sigmodontis* rodent model



### Phase 1:

- **CorA** (scheduled for 2025)
- **AWZ-1066**



### Phase 2:

- **Flubentylosin/ABBV-4083**
- **Emodepside**
- **Oxfendazol** (in 2024)

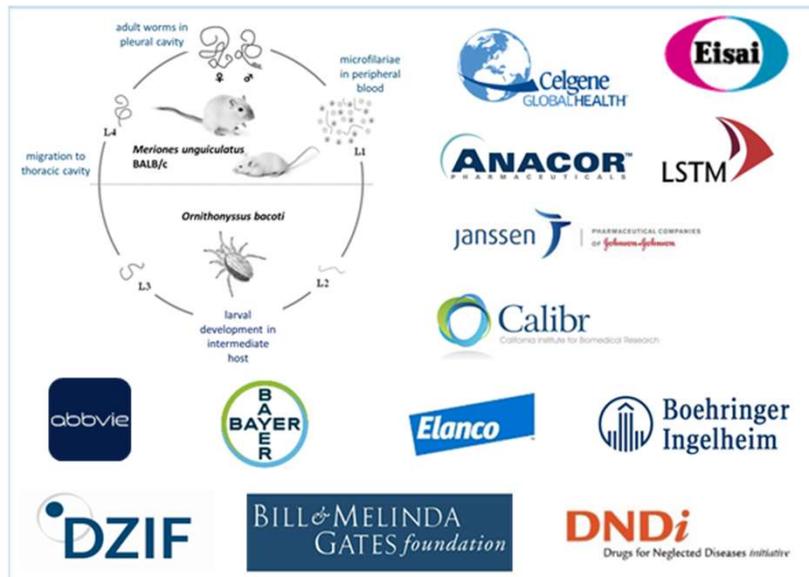


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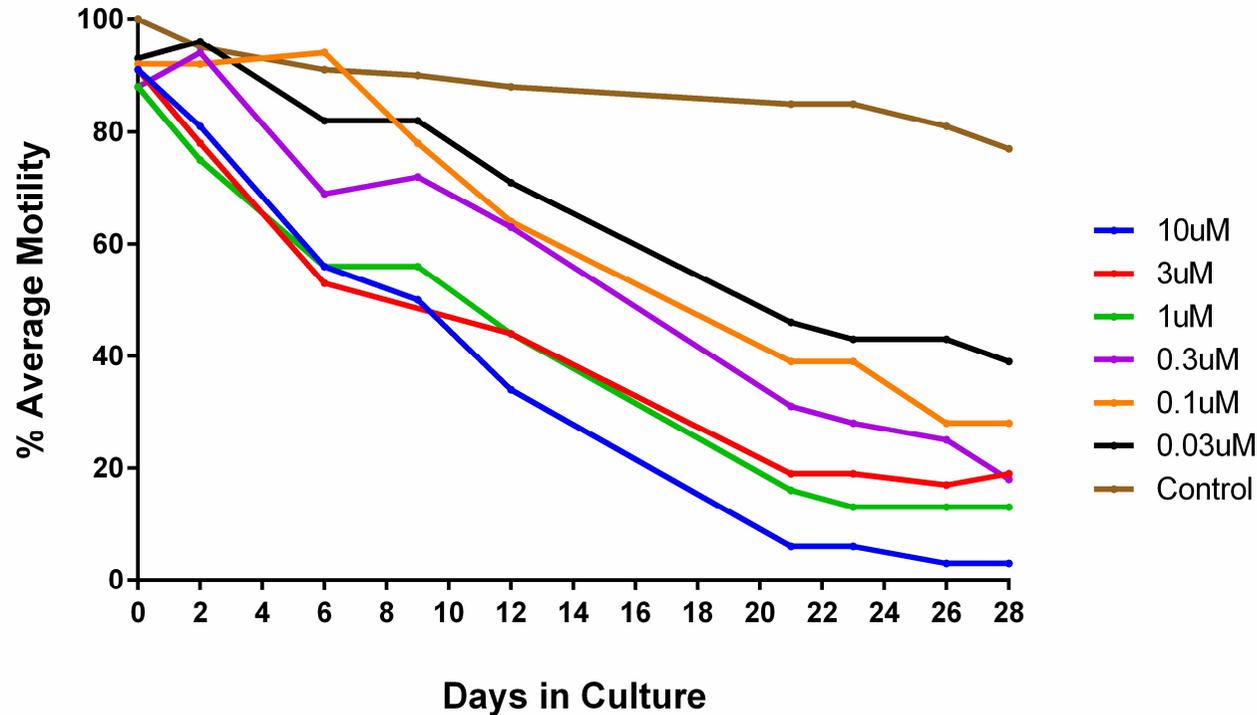
- **Flubentylosin/ABBV-4083**
- **Emodepside**
- **Oxfendazol** (in 2024)



- **Broad spectrum anthelmintic** used as dewormer in the veterinary field
  - **Multiple ascending dose phase 1 studies** using up to 15 mg/kg for 5 days were **completed** (Bach et al. 2020)
  - **Field applicable formulation** developed by DNDi via USAID
  - **Bioavailability study** was performed in Tanzania via HELP
- **Pan-nematode candidate:** efficacy against filariae and STH?



# In vitro assessment of the efficacy of oxfendazole against *O. volvulus* L5s

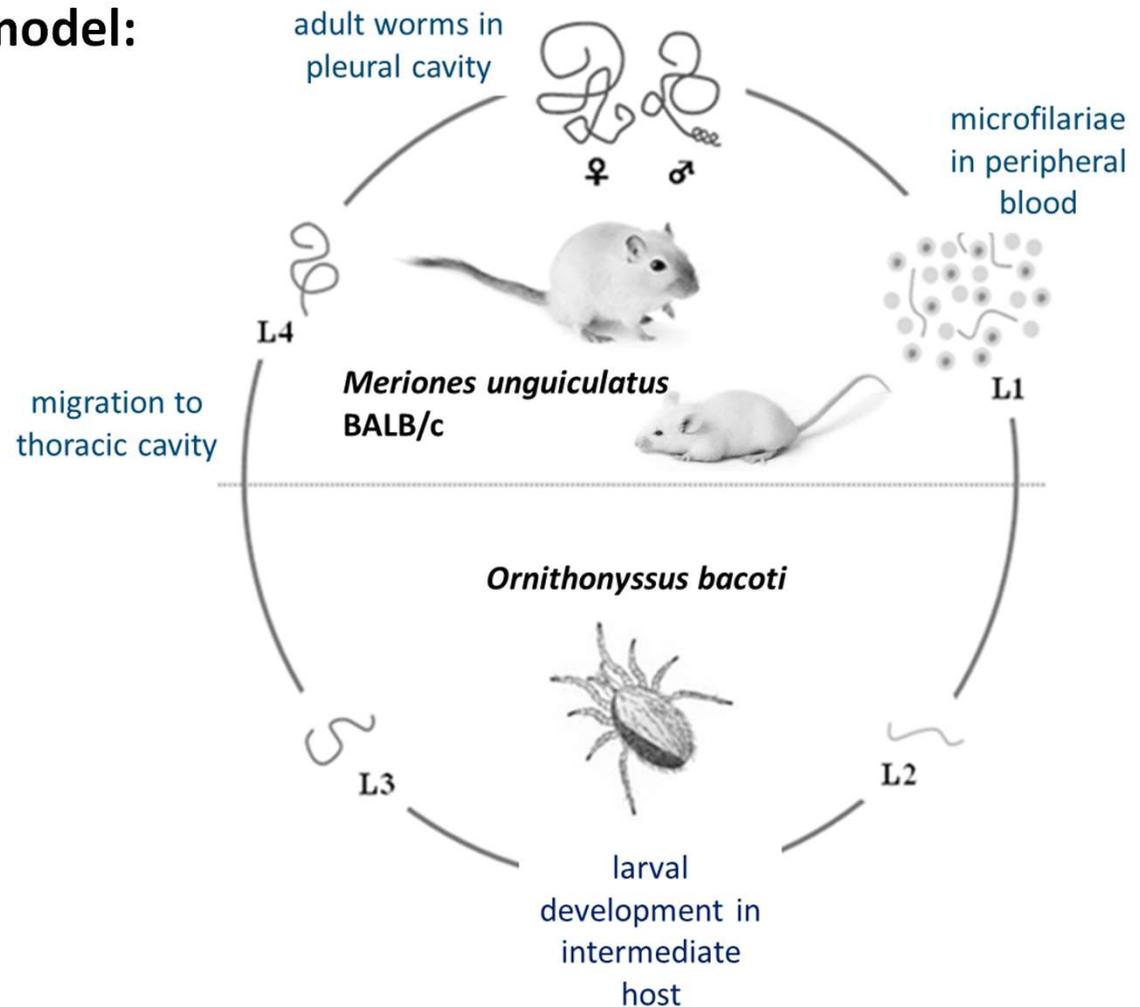


→ Oxfendazole inhibits the motility of *O. volvulus* L5s

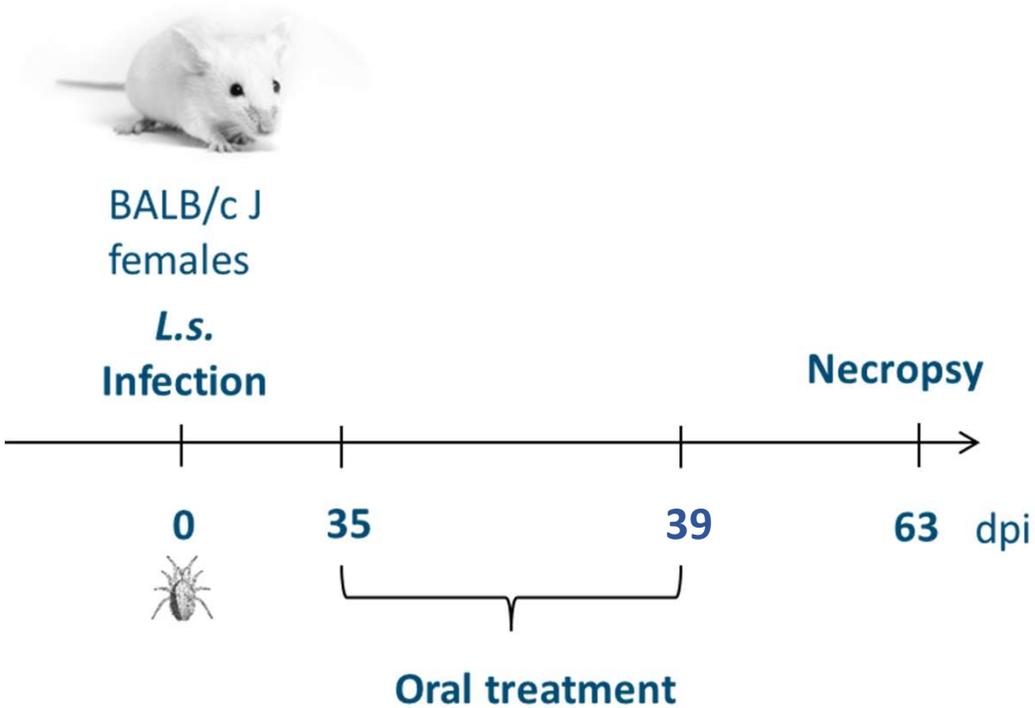
***Litomosoides sigmodontis* rodent model:**

Identification of:

- anti-*Wolbachia* candidates
- direct acting compounds



# Assessment of the oxfendazole efficacy in the *Litomosoides sigmodontis* model



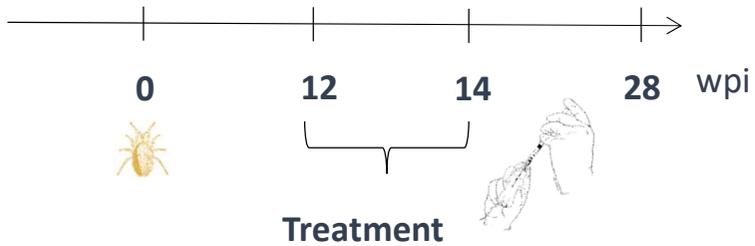




*Meriones unguiculatus*

*L.s.*  
infection

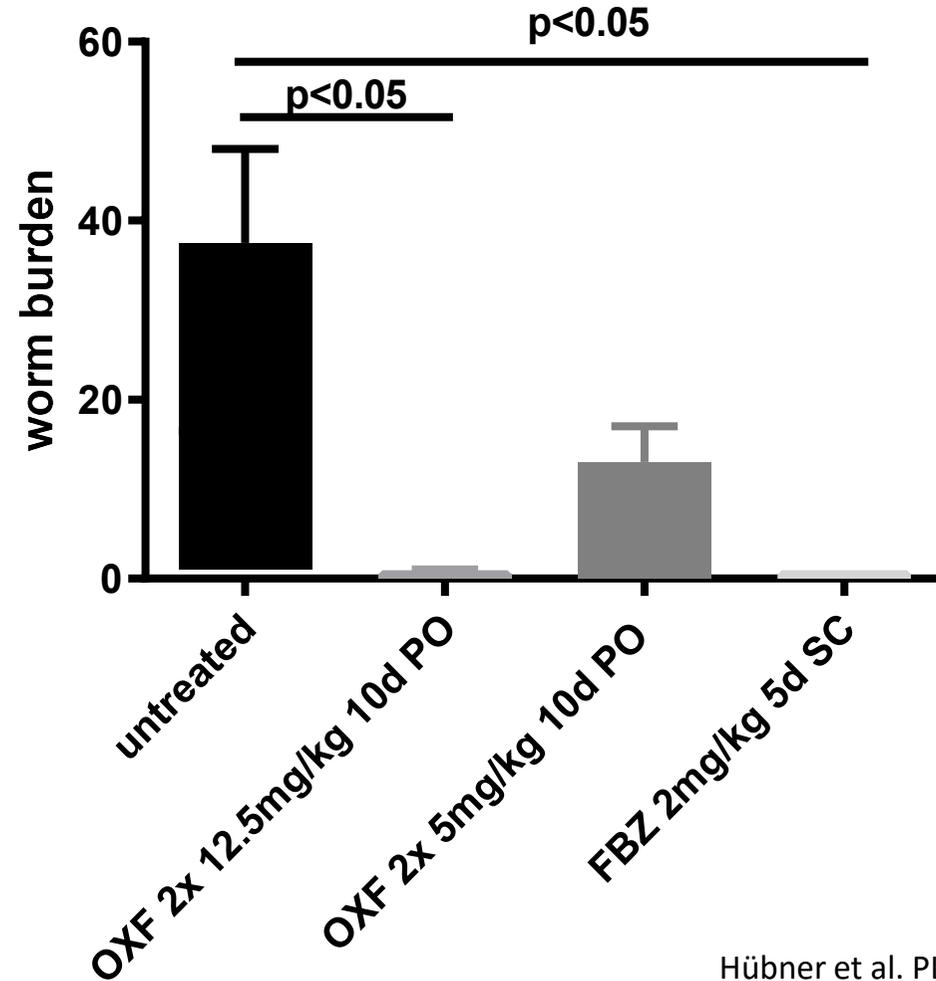
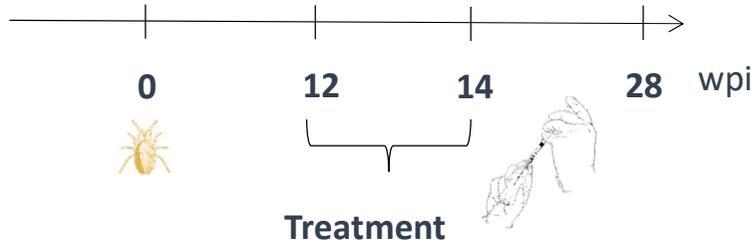
Necropsy





*Meriones unguiculatus*

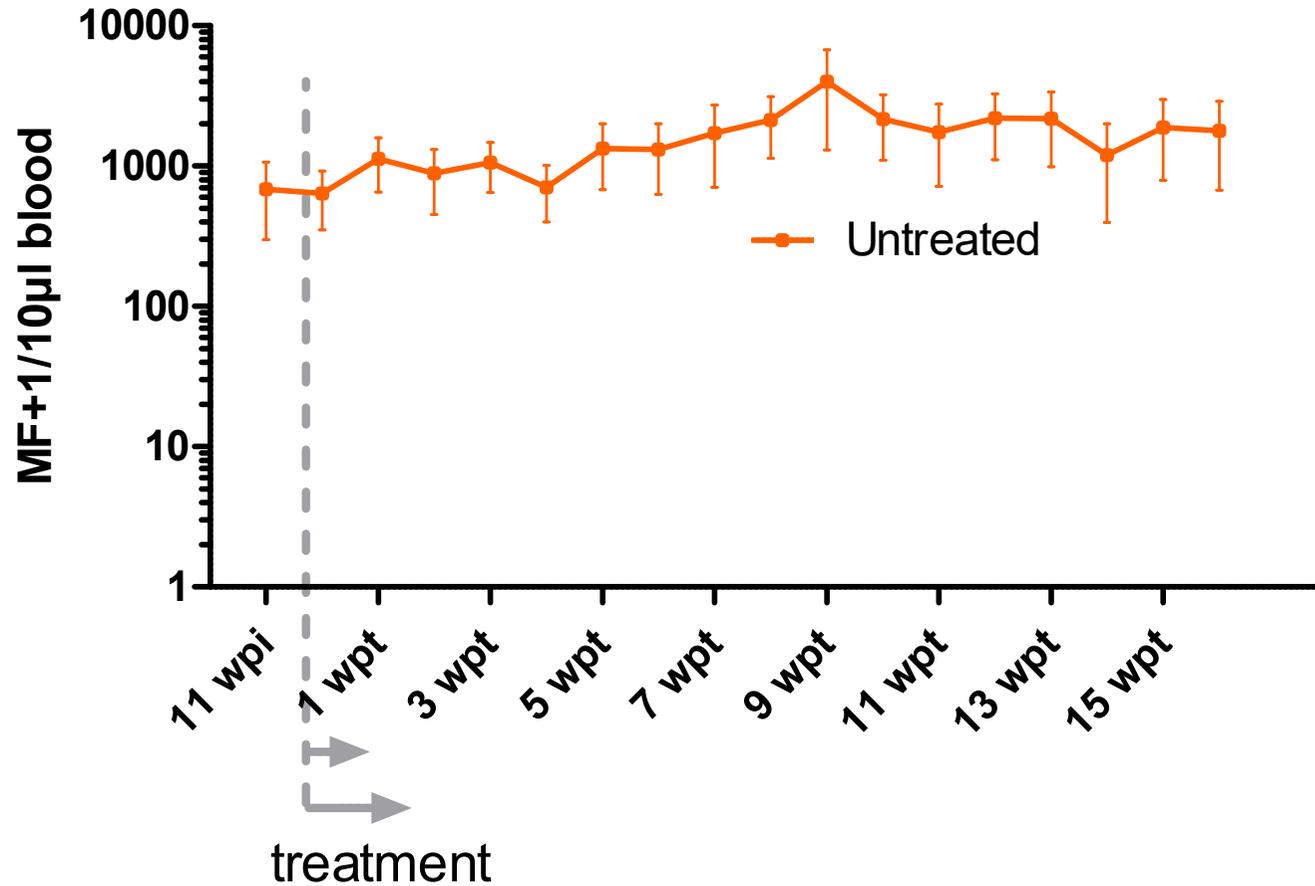
*L.s.* infection



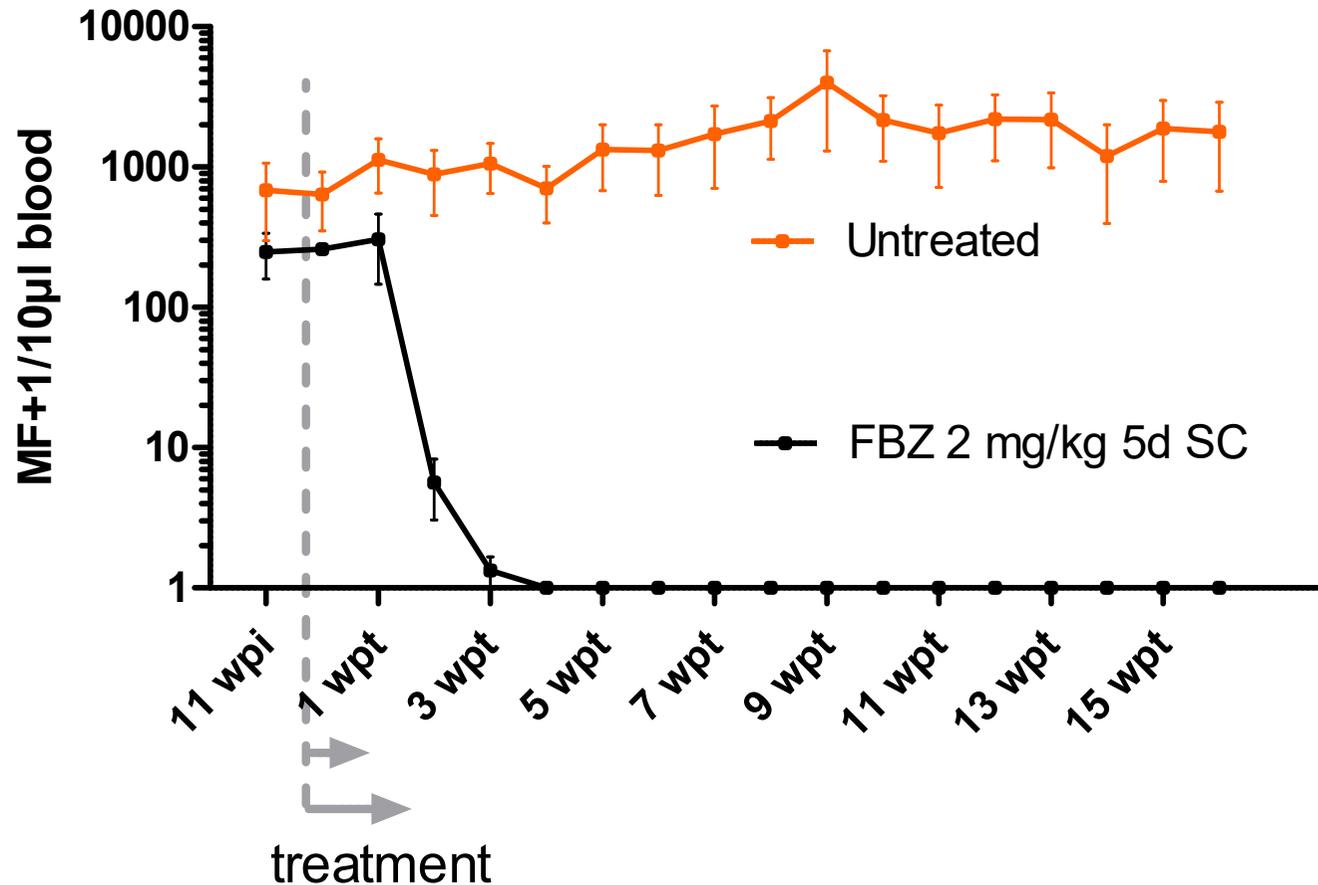
→ Oral oxfendazole treatment is macrofilaricidal

# Assessment of the oxfendazole efficacy on microfilaremia in patentlly *L. sigmodontis*-infected jirds

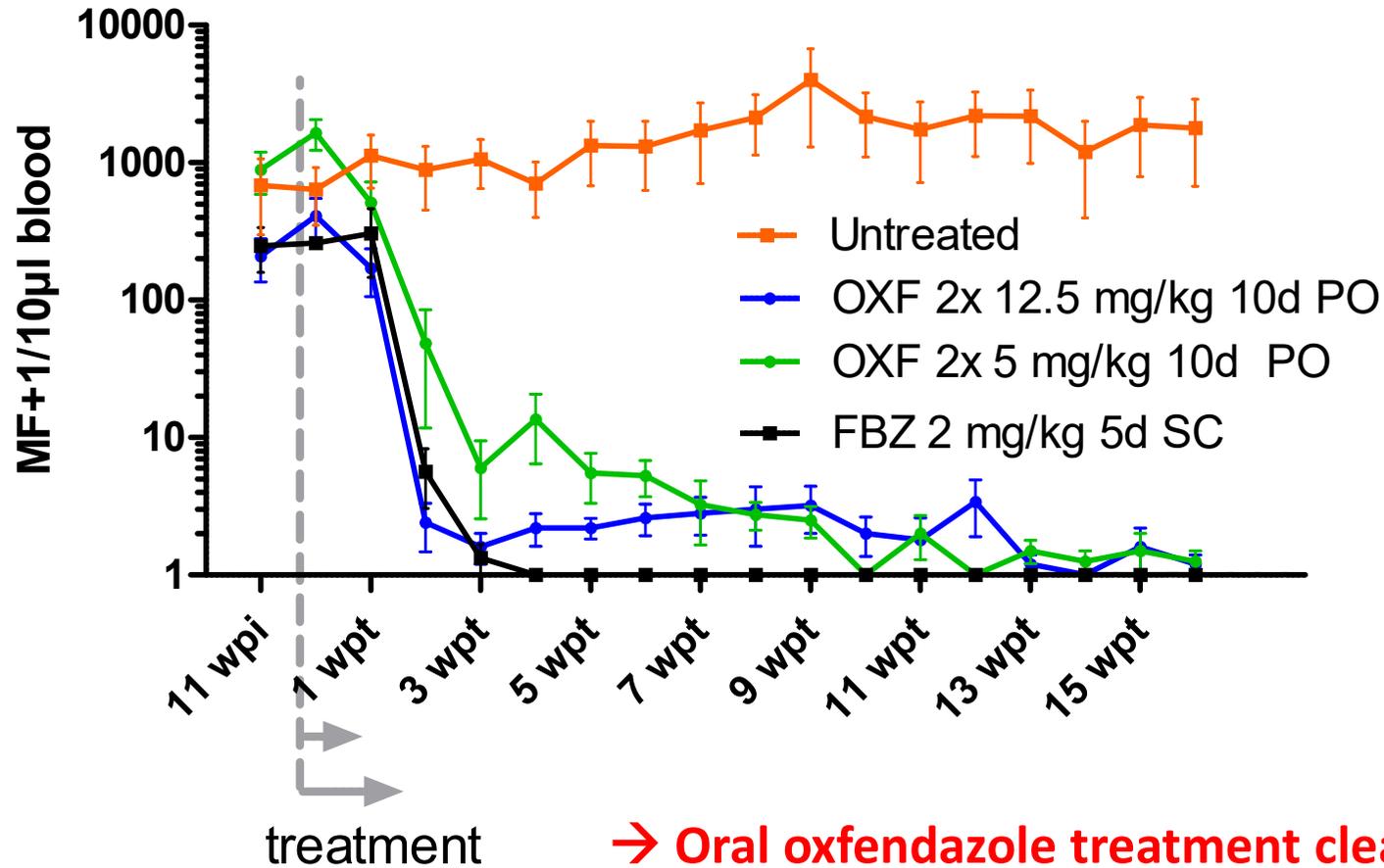
# Assessment of the oxfendazole efficacy on microfilaremia in patently *L. sigmodontis*-infected jirds



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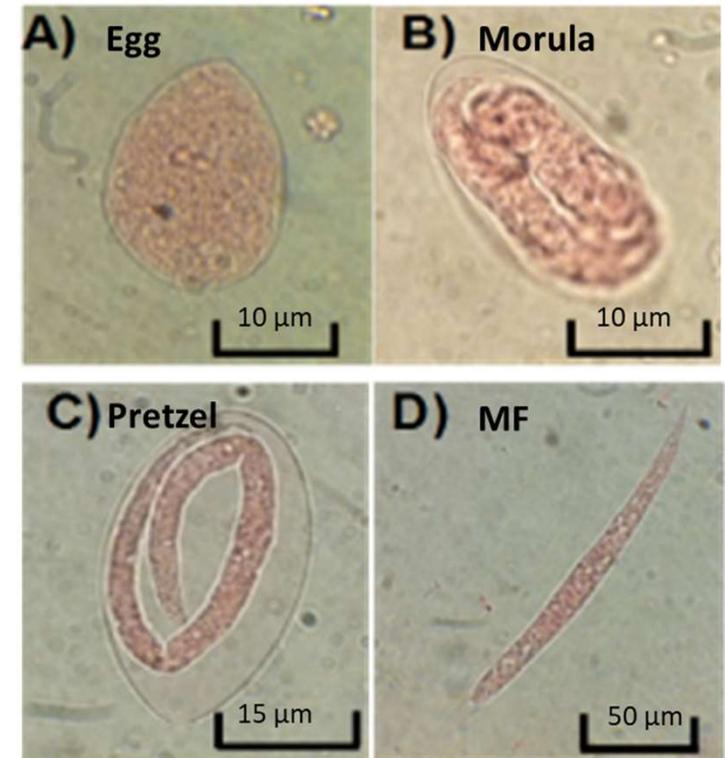


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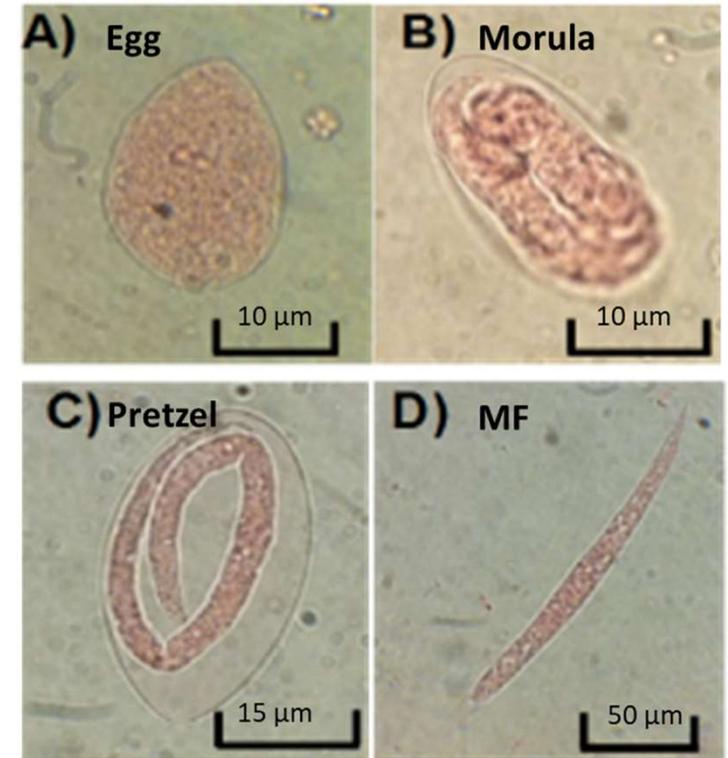
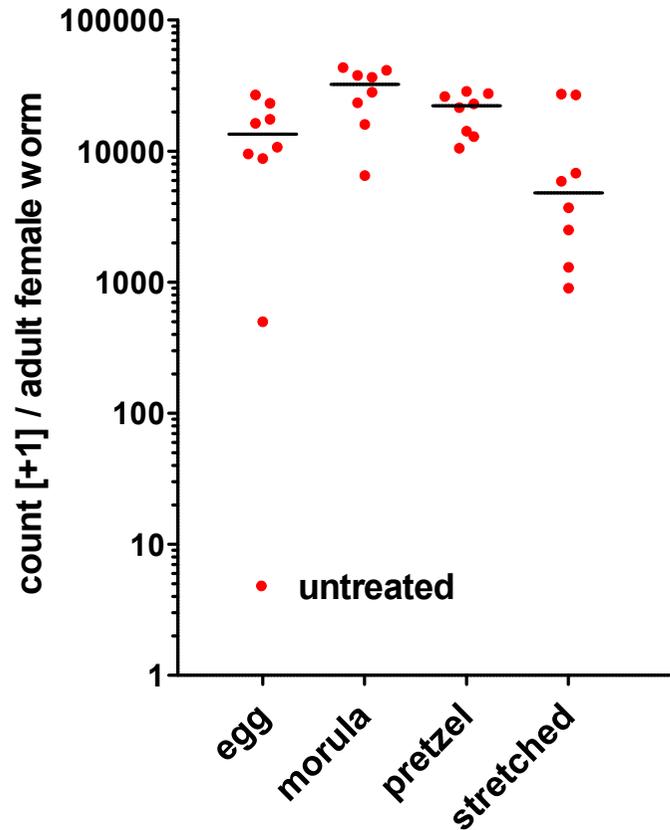


# Impact of oxfendazole treatment on filarial embryogenesis

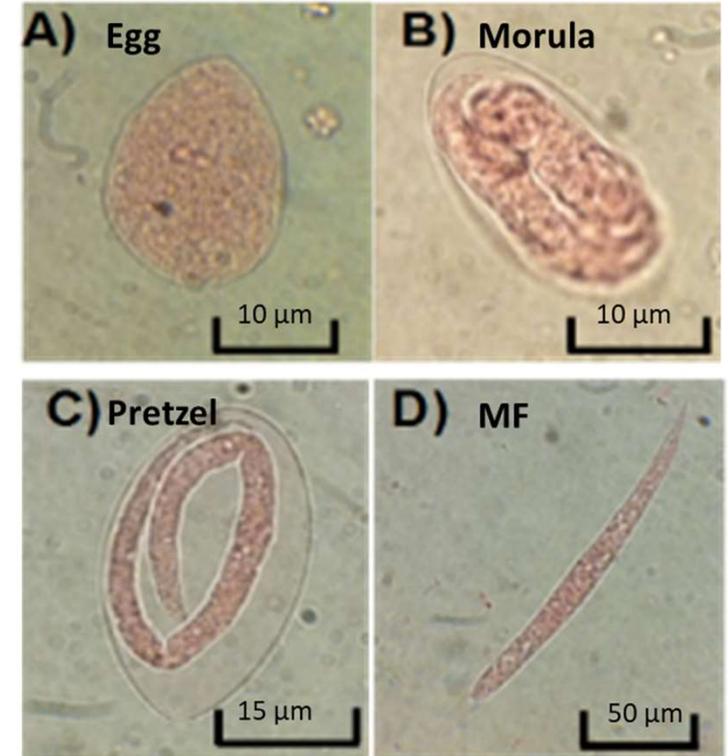
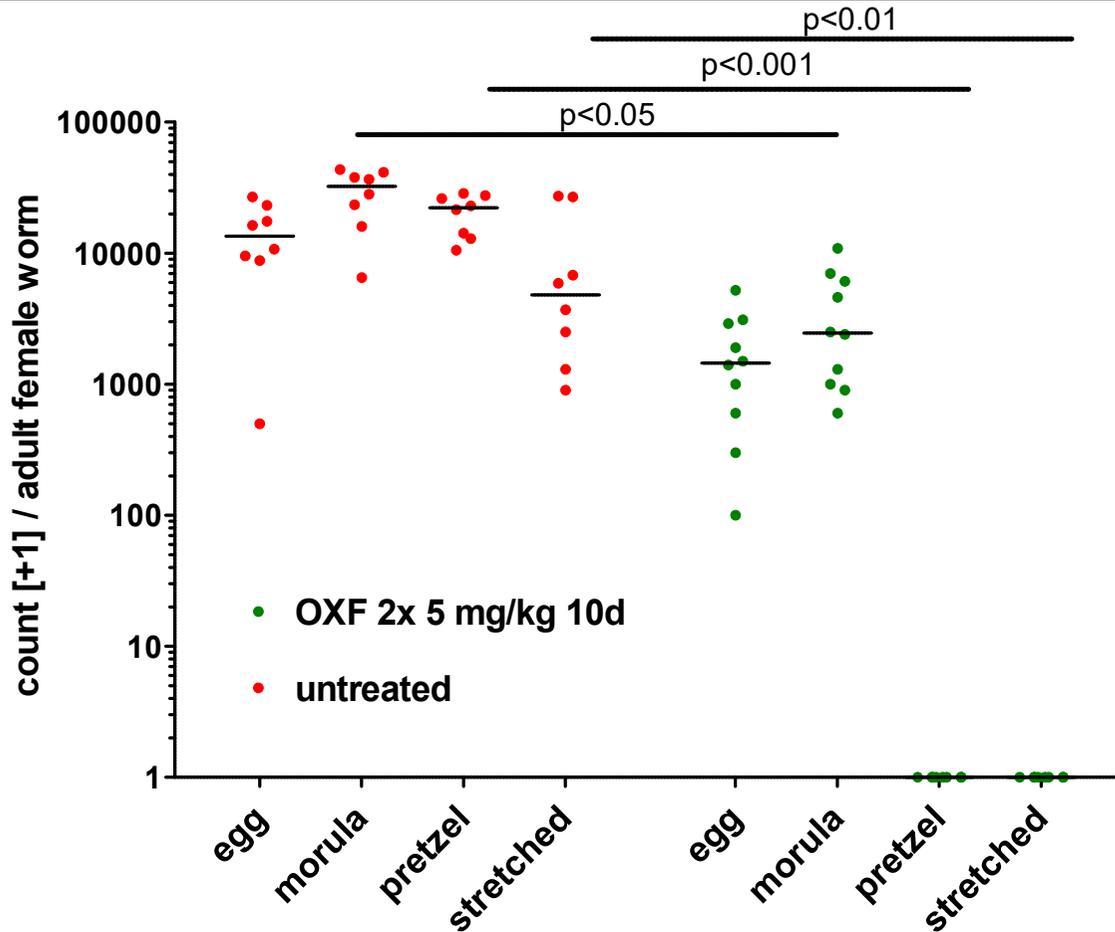
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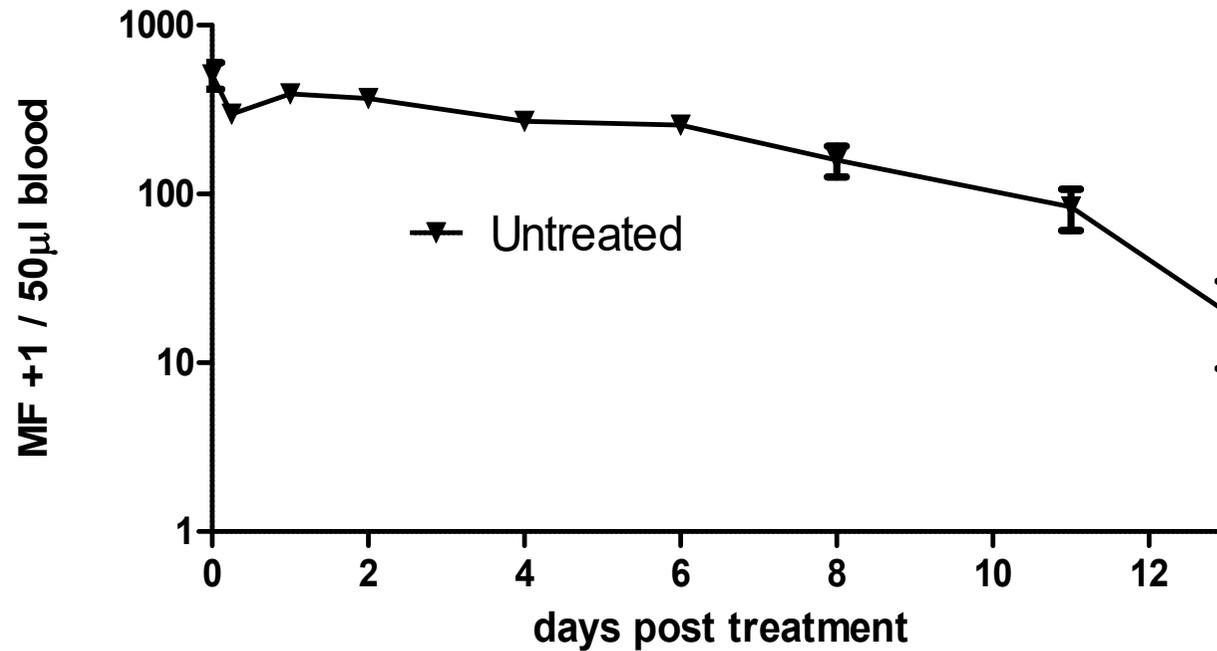


# Impact of oxfendazole treatment on filarial embryogenesis

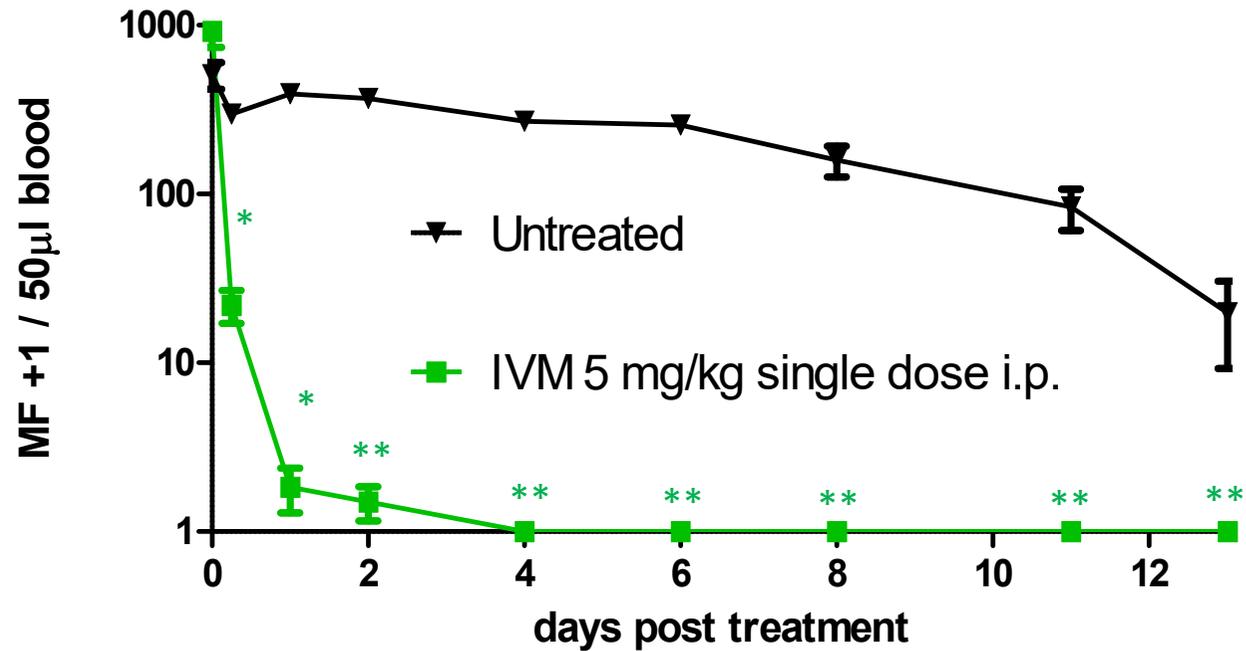


→ Oral oxfendazole treatment inhibits embryogenesis

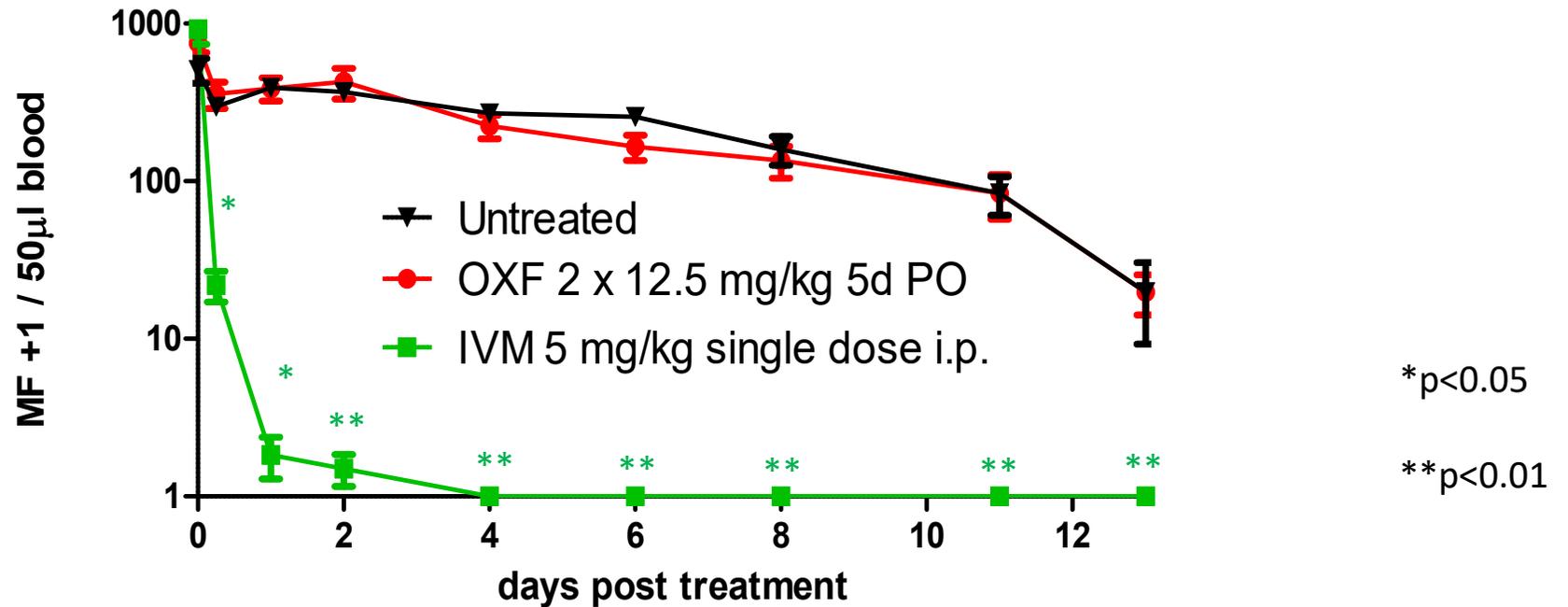
# *In vivo* assessment of the direct microfilaricidal efficacy of oxfendazole



# In vivo assessment of the direct microfilaricidal efficacy of ivermectin

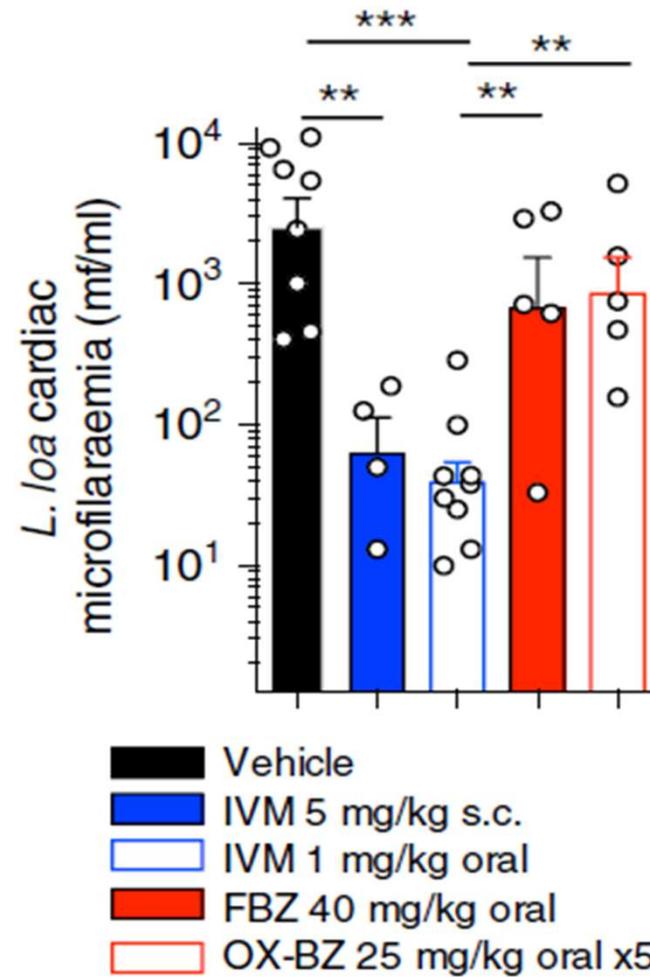


# In vivo assessment of the direct microfilaricidal efficacy of oxfendazole



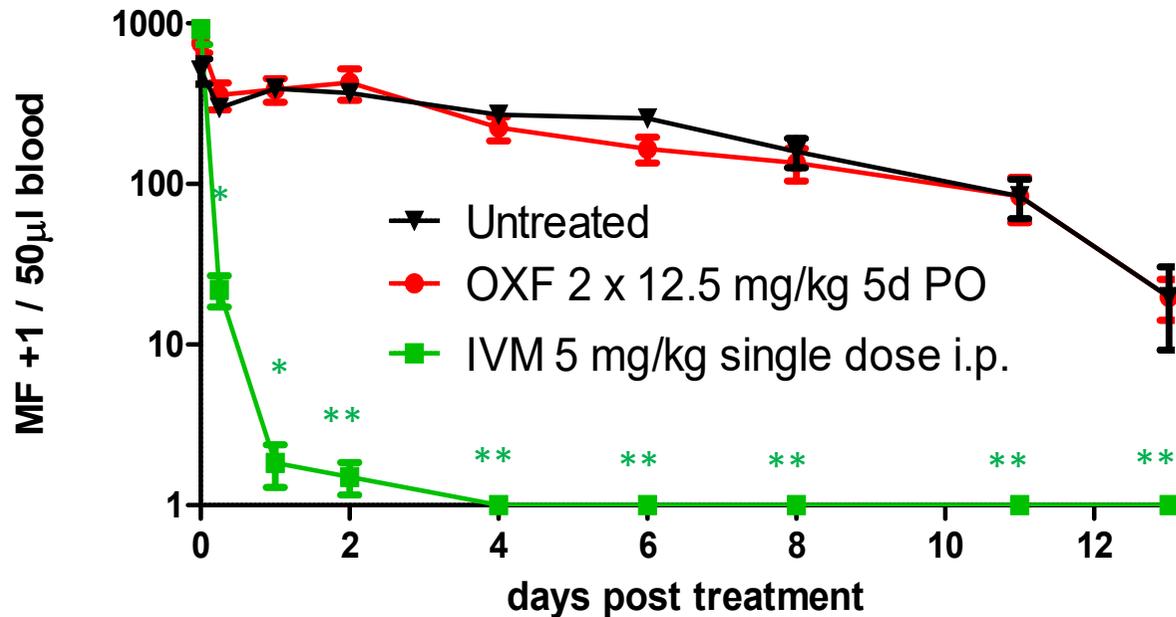
Hübner et al. PLOS NTDs 2020

# In vivo assessment of the direct microfilaricidal efficacy of oxfendazole

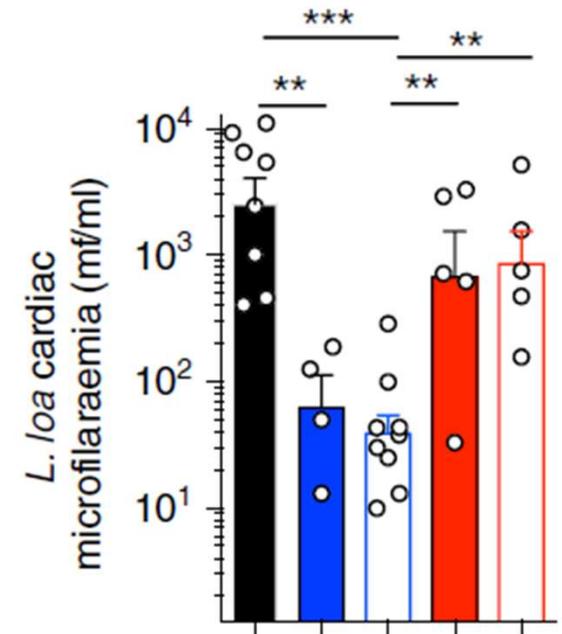


Pionnier et al. Nat Commun 2019

# In vivo assessment of the direct microfilaricidal efficacy of oxfendazole



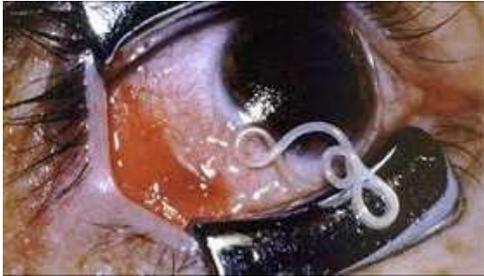
Hübner et al. PLOS NTDs 2020



■ Vehicle  
 ■ IVM 5 mg/kg s.c.  
 □ IVM 1 mg/kg oral  
 ■ FBZ 40 mg/kg oral  
 □ OX-BZ 25 mg/kg oral x5

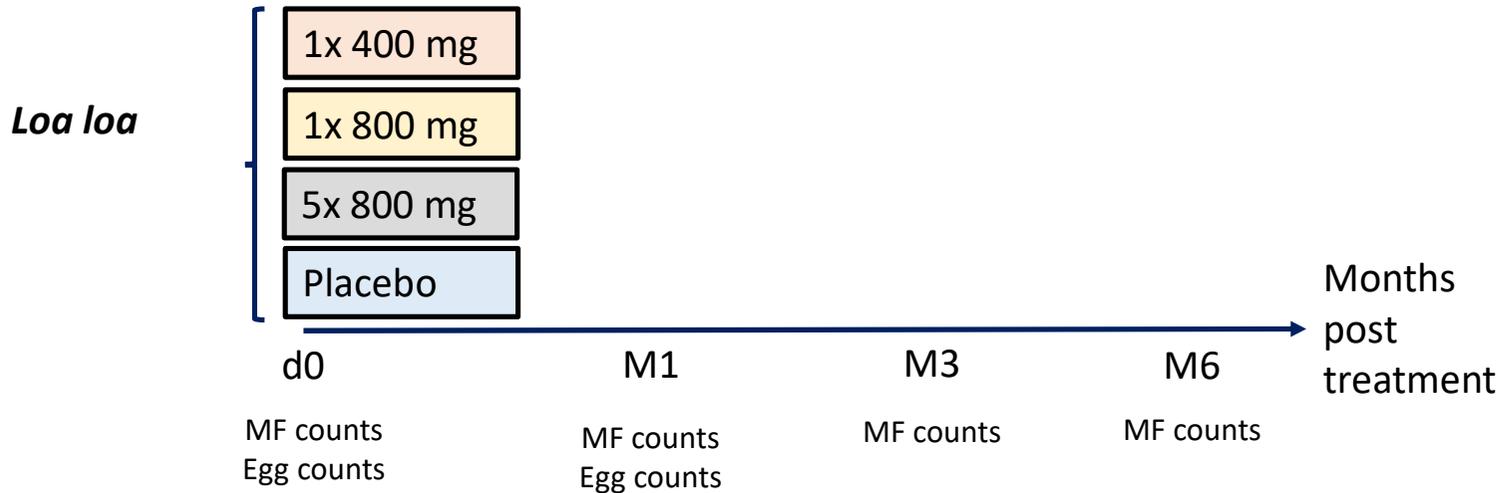
Pionnier et al. Nat Commun 2019

→ Oral oxfendazole treatment has **no strong direct microfilaricidal efficacy**  
 → **No microfilariae-induced SAE** in onchocerciasis & loiasis patients **expected**  
 → **Potential macrofilaricidal candidate for loiasis**



**Primary endpoint:**

- Occurrence of **drug related adverse events** during first 28 days post treatment



Michael Ramharter  
Lidwine Badjna



Rella Zoleko Manego  
Ghyslain Momba Ngoma



Sabine Specht  
Frédéric Monot





[www.ewhorm.org](http://www.ewhorm.org)

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Confederazione Svizzera  
Confederaziun svizra



Disease Pathogen	Pathology	Treatment & Limitations	Endemic in study site of
<b>Onchocerciasis</b> <i>O. volvulus</i> ~ 21 Mio infected	Blindness, severe dermatitis	<u>Ivermectin, Moxidectin</u> : do not kill the adult worms <u>Doxycycline</u> : daily 5-6 week treatment to kill adult worms; children and pregnant women excluded	DRC, Cameroon
<b>Loiasis</b> <i>L. loa</i> ~ 13 Mio infected	Eye worm, angioedema, Calabar swelling	<u>DEC, Ivermectin</u> : may cause life-threatening adverse events; daily 2-4 week treatment, currently not within MDA programs <u>Albendazole</u> : limited efficacy against mf (twice daily 3-week treatment to reduce mf load) -> not on the NTD list!	DRC, Gabon, Cameroon
<b>Mansonellosis</b> <i>M. perstans</i> ~ 120 Mio infected?	Mainly asymptomatic	<u>DEC, Ivermectin</u> : MDA treatment (single dose) not efficacious; twice daily 3-week DEC or twice daily 4-week albendazole treatment reduces mf load, currently not within MDA programs -> not on the NTD list!	DRC, Gabon, Cameroon
<b>Trichiuriasis</b> <i>T. trichiura</i> >600 Mio infected	Delayed child development, anemia	Albendazole, mebendazole, levamisole and pyrantel pamoate: all with poor efficacy at single dose; Emodepside promising candidate for Phase 3	DRC, Gabon, Cameroon, Tanzania

## Common problems across helminthiases

- A profound **lack of drug pipeline**
- **Drug development** has become more **complex** it is **risky** and **expensive**
- Current model: **testing one target, one drug at a time**

## Common problems across helminthiases

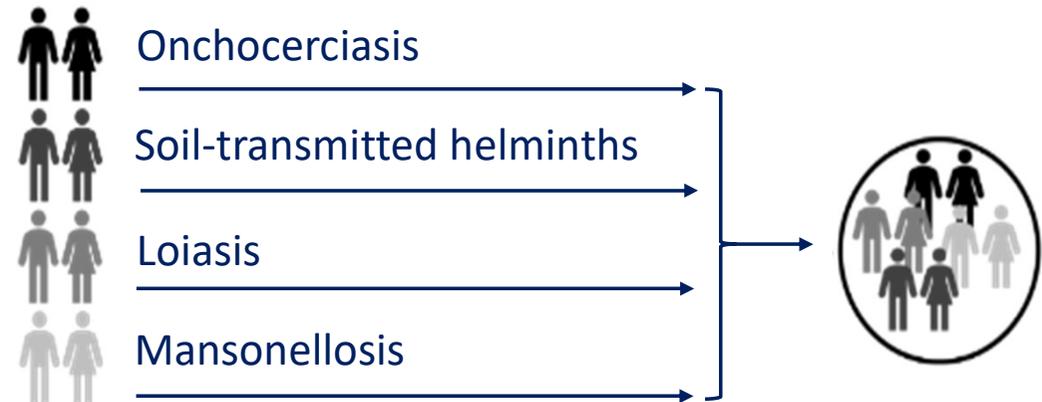
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- **Drug development** has become more **complex** it is **risky** and **expensive**
- Current model: **testing one target, one drug at a time**

## Adaptive basket trial design: A collaborative approach to R&D

- **One candidate – multiple indications** at the same time (!)
- **Minimizing number of trial participants**
  - **Reduce** the need of **redundant trials**
  - **Patient centricity** (coinfection)
  - **Mid-course adaptations** to avoid repetition
  - Detection of **country-specific drug differences**

- Allow academics/pharma/NGO to **collaborate**
- Expedite drugs to market and more **quick decisions** overall
- Likely to be valuable in complex and rare diseases

## Oxfendazole – multiple indications at the same time



**Adaptive clinical trial platform** in Gabon, Cameroon and Democratic Republic of the Congo

Proof of concept for **pan-nematode** drug candidate **oxfendazole**



**Trichuriasis – Tanzania (+ Cameroon, DRC, Gabon)**



**DNDi**

**Onchocerciasis – DRC (+ Cameroon)**



**Loiasis – Gabon (+ Cameroon, DRC)**



ukb universitäts  
klinikumbonn

**Mansonellosis – Cameroon (+ DRC, Gabon)**

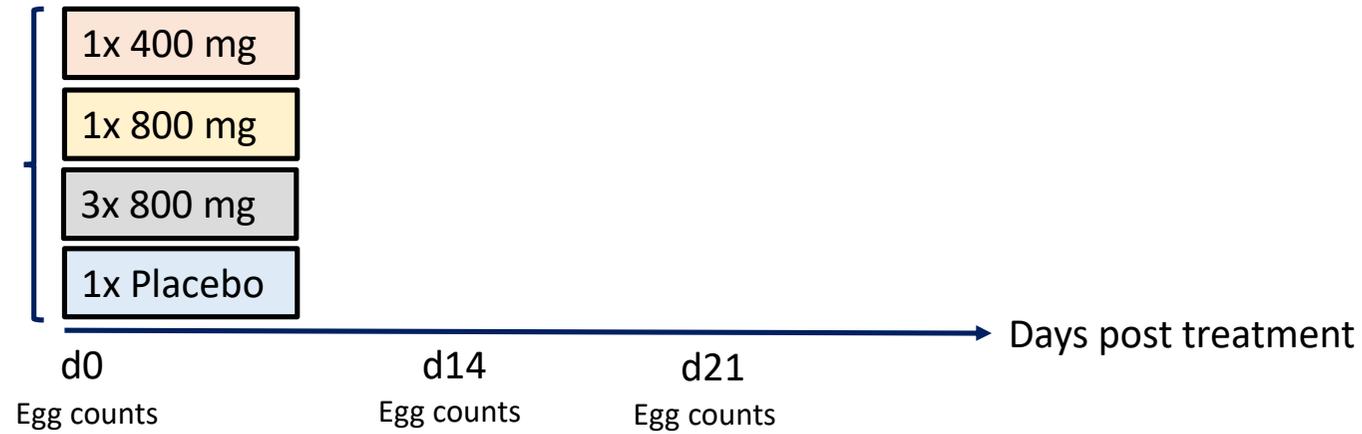


	d0	d14	d21	M3	M6	M12	Days/ Months
	Egg & MF counts	Egg counts	Egg counts	MF counts	MF counts	MF counts	

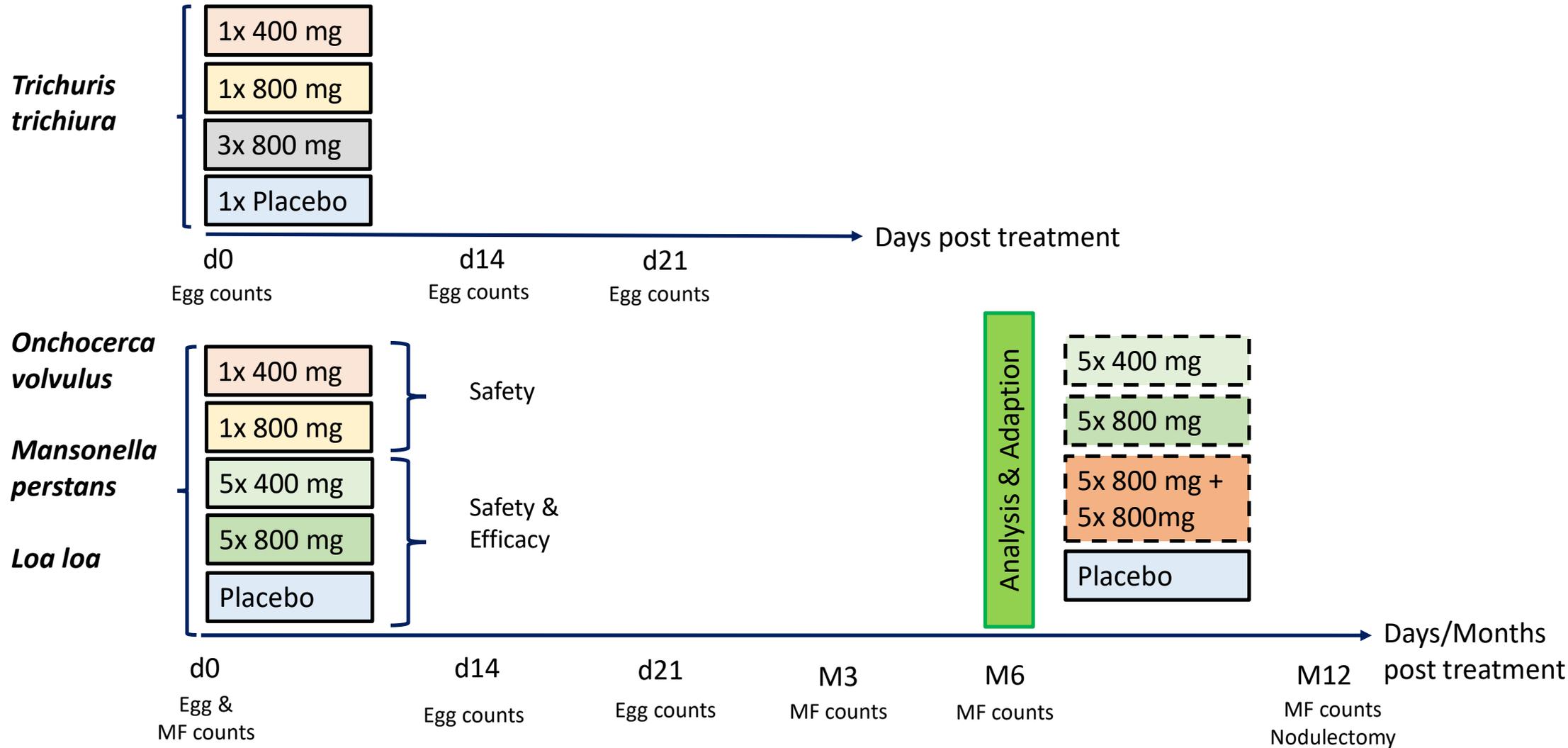
**Include data from co-infected participants**

# Oxfendazole basket trial

*Trichuris  
trichiura*

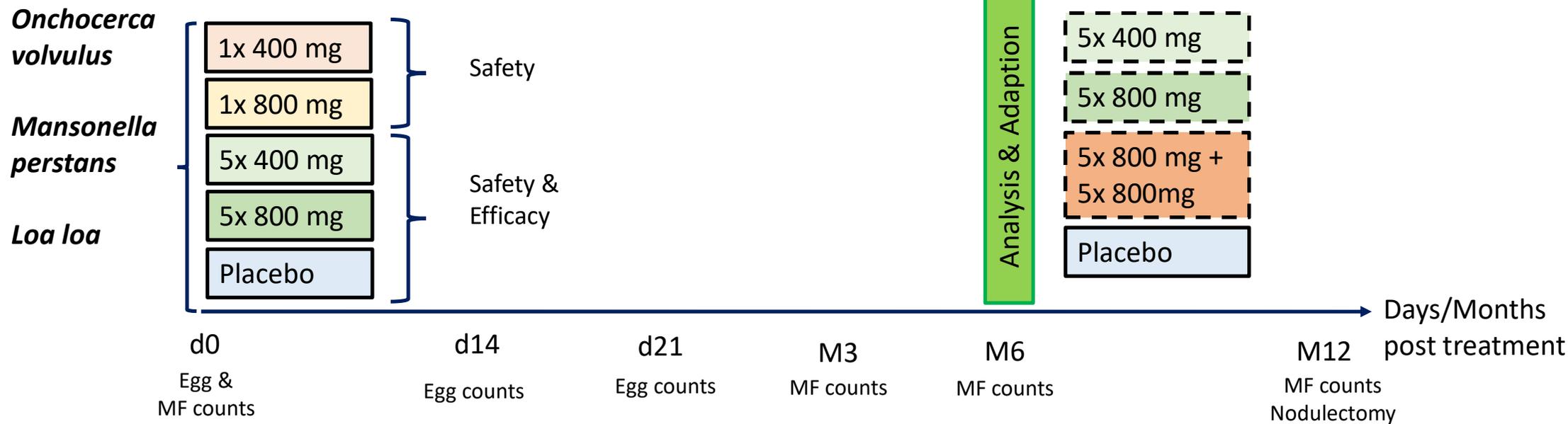


# Oxfendazole basket trial



Co-infected will be included

75% randomized, Adaptation  
 If no effect visible: Recruitment into 5x800 mg+ 5x800 mg  
 If effective: continue with effective arm



- Oral oxfendazole treatment is **macrofilaricidal** against *L. sigmodontis* (Hübner et al. PLOS NTDs 2020)
- Oral oxfendazole treatment **inhibits embryogenesis**, but has **no strong direct microfilaricidal efficacy**  
→ no microfilariae-induced SAE in onchocerciasis and loiasis patients expected
- **Oxfendazole isomers display similar anti-filarial activity** and our data do not support the development of a single isomer for future use in human patients (Risch et al. 2022 Front Trop Med)
- **Oxfendazole efficacy is dependent on immune responses** (Risch et al. 2023 Front Microbiol)
- **Predicted human efficacious dose (1.5 and 4.1 mg/kg) is within the range of previously tested multiple ascending phase 1 studies** (Hübner et al. PLOS NTDs 2020)

## Conclusions oxfendazole

- Oxfendazole is the only drug candidate with a **predicted selective adulticidal efficacy for human filariae** and the **only macrofilaricidal candidate** available for *Loa loa*
- Oxfendazole is a **pan-nematode candidate** to treat **STH** and **filarial infections**
- **Phase 2 clinical trials in loiasis patients** are scheduled for **early 2024**
- **Phase 2 clinical trials in STH, onchocerciasis, loiasis and manonsellosis patients** are scheduled for **late 2024**



Co-funded by  
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Jesuthas Ajendra  
Celia Nieto Perez  
Linda Bart  
Pia Schumacher



Sara Lustigman



Sam Hoefman  
Sonja Bergner



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[huebner@uni-bonn.de](mailto:huebner@uni-bonn.de)



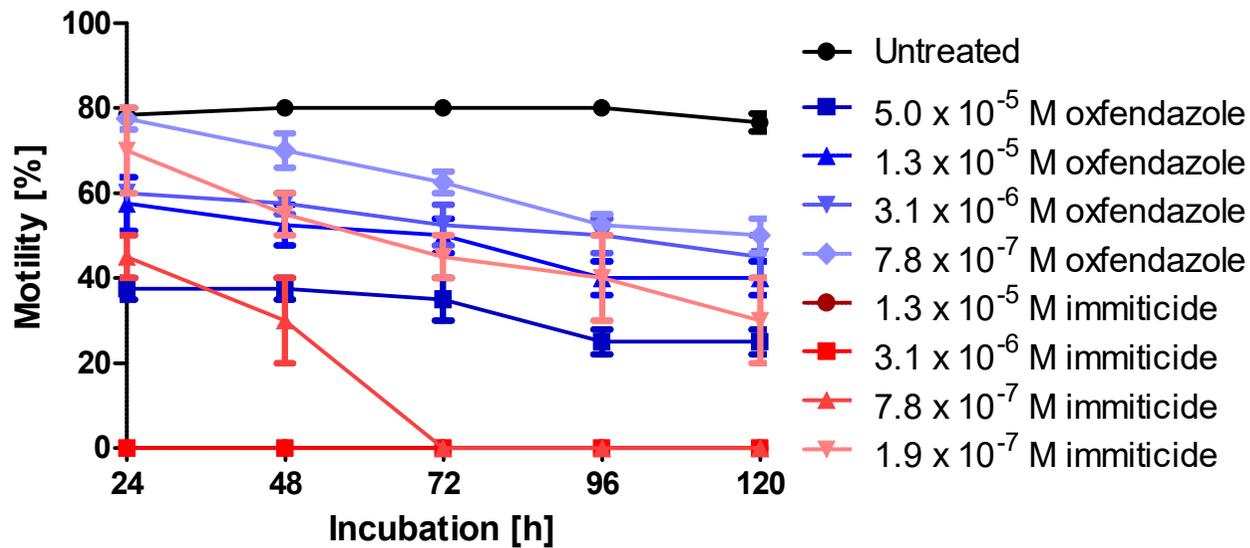
Human PK Prediction for Oxfendazole <sup>a</sup>		
Clearance (CL)	(mL/min/kg)	Comments <sup>b</sup>
rat-dog allometry	8.0	$CL = \alpha \times BW^\beta$
rat-dog allometry (+PPB <sup>c</sup> )	0.4	unbound CL = $\alpha \times BW^\beta$
hepatocyte CL scaling	0.4	well-stirred model using $f_u \times CL_{int}$
<b>Final</b>	<b>0.4</b>	
Vol. of Distribution (V <sub>ss</sub> )	(L/kg)	Comments <sup>b</sup>
rat-dog allometry	1.2	$V_{ss} = \alpha \times BW^\beta$
via rat (with PPB <sup>c</sup> )	0.2	$V_{ss,h} = \text{mean } f_{u,h} \times (V_{ss,y}/f_{u,y})$
via dog (with PPB <sup>c</sup> )	0.1	
<b>Final</b>	<b>0.5</b>	
Half-Life (HL)	(h)	Comments
via predicted V <sub>ss</sub> /CL	14.4	$T_{1/2} = \ln 2 \times (V_{ss}/CL)$
rat-hum correlation	12.1	$\log(T_{1/2} \text{ human}) = 0.906 \log(T_{1/2} \text{ rat}) + 0.723$
dog-hum correlation	4.2	$\log(T_{1/2} \text{ human}) = 0.934 \log(T_{1/2} \text{ dog}) + 0.433$
<b>Final</b>	<b>10.2</b>	
Bioavailability (F)	(%)	Comments
rat/sheep/cattle	>50	published data <sup>37</sup>
rat	~35	Published data <sup>22</sup>
dog	~10	in-house data at high dose of 25 mg/kg
<b>Final</b>	<b>30</b>	

The resulting daily doses needed to reach all assumed **target concentrations** for these scenarios in humans were calculated to be **between 1.5 and 4.1 mg/kg** (average all methods: 2.7 mg/kg assuming a 70 kg subject).

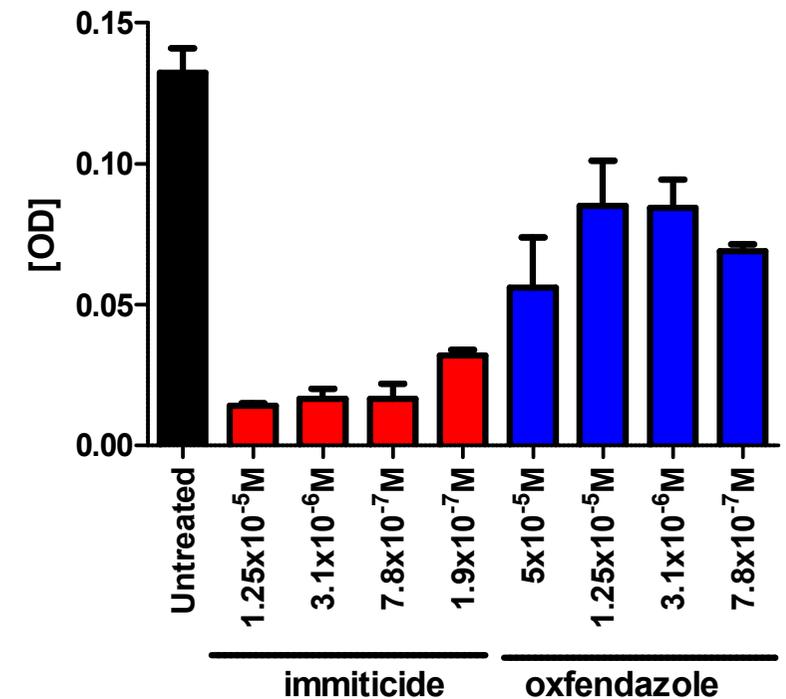
→ **Reasonable dose with an acceptable range.**

# In vitro assessment of the efficacy of oxfendazole against *O. gutturosa* adult worms

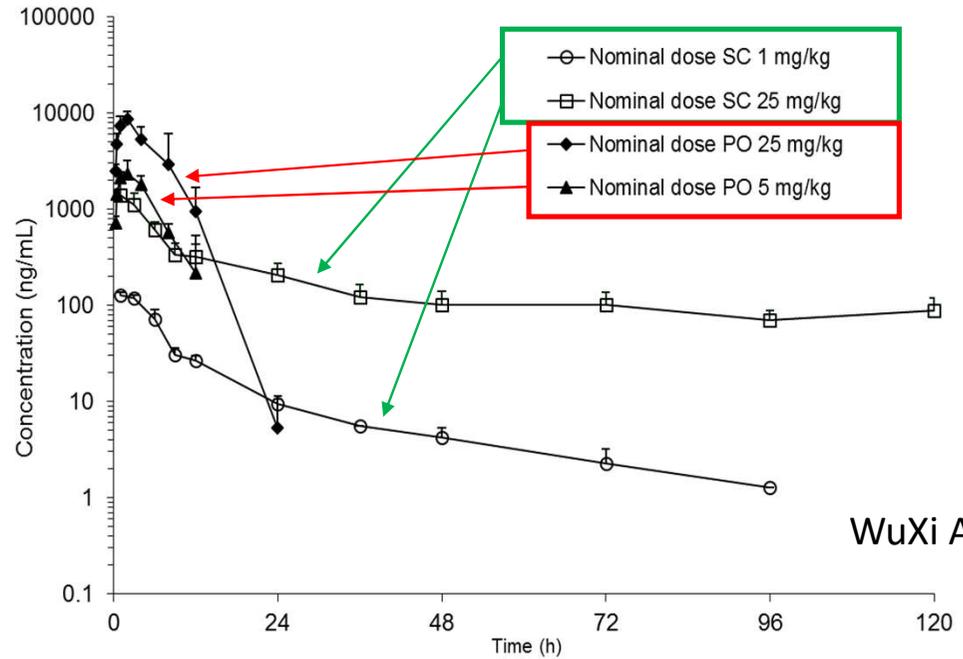
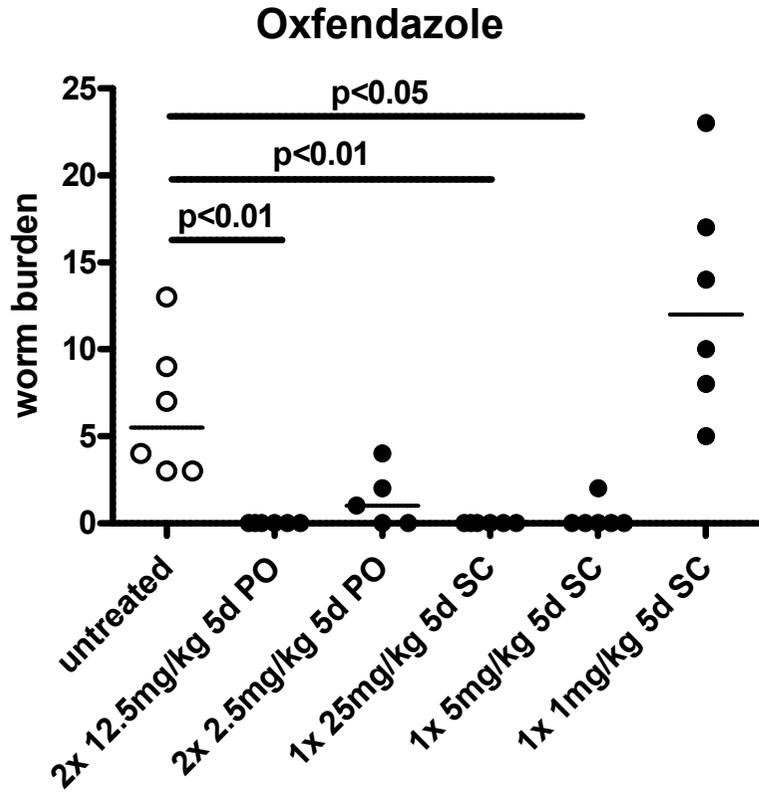
*O. gutturosa* adult worm motility



*O. gutturosa* MTT



→ Oxfendazole is macrofilaricidal for *O. gutturosa*

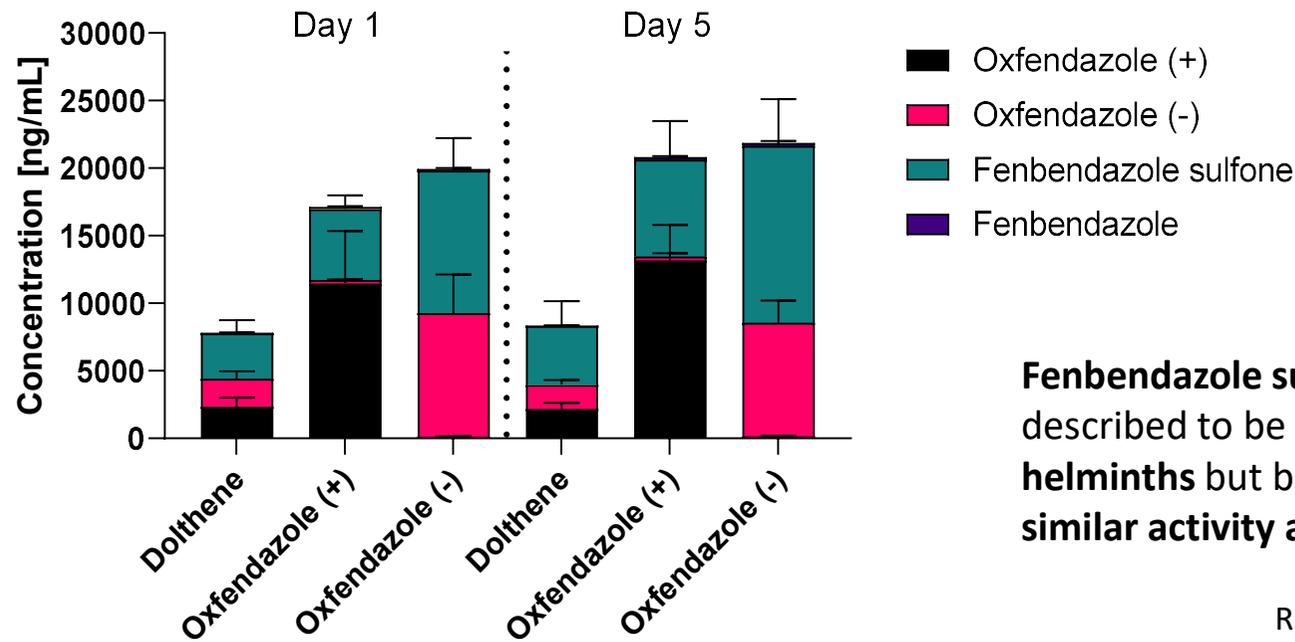
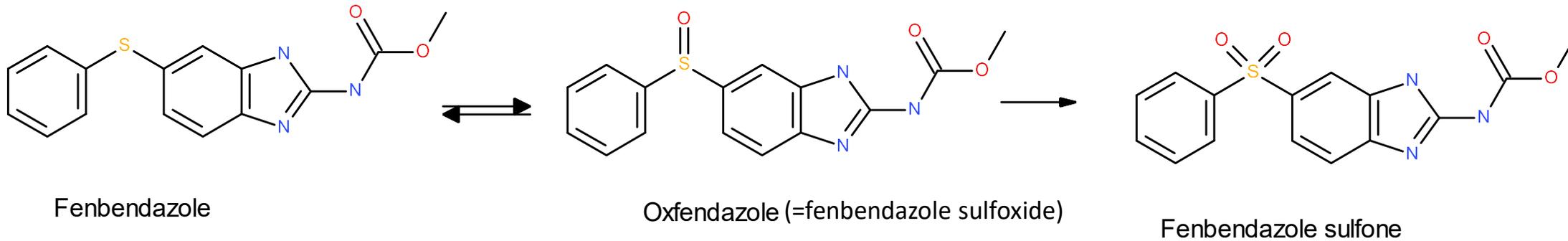


WuXi AppTec LTD

oxfendazole	PO (5mg/kg)	PO (25mg/kg)	SC (1mg/kg)	SC (25mg/kg)
$C_{max}$ (ng/ml)	2530	8593	131	1447
$T_{max}$ (h)	1,67	2,00	1,67	2,33
$T_{1/2}$ (h)	2,87	1,87	24,8	76
$AUC_{0-last}$	14673	50311	1284	20817

→ Maintenance of  $C_{min}$  determines efficacy

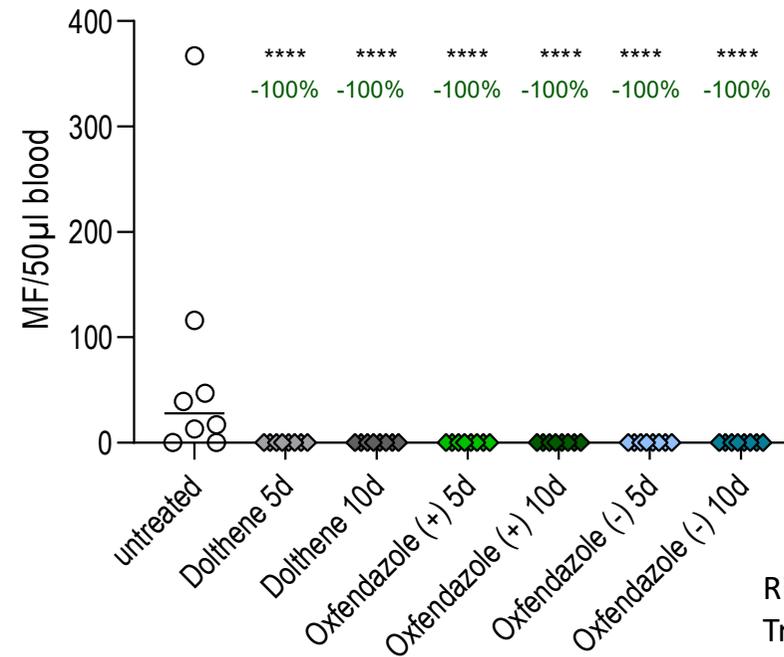
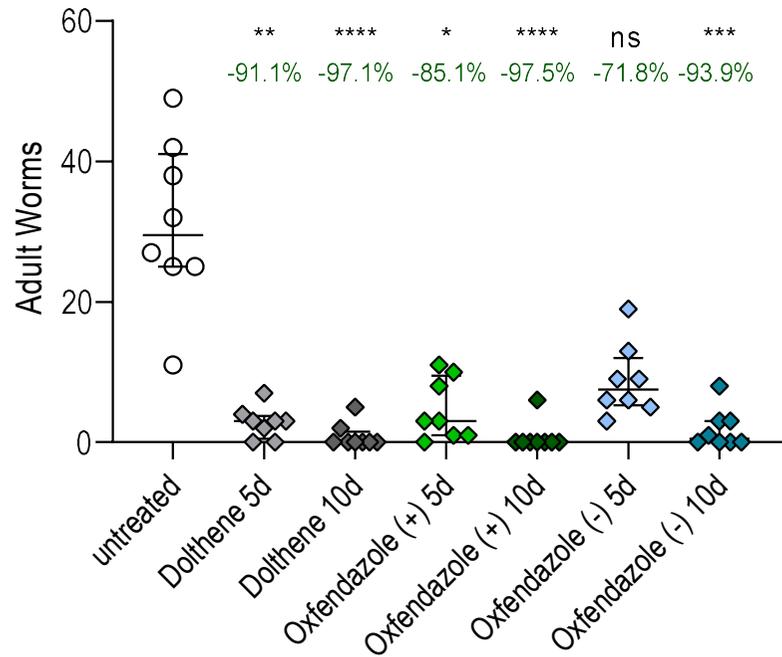
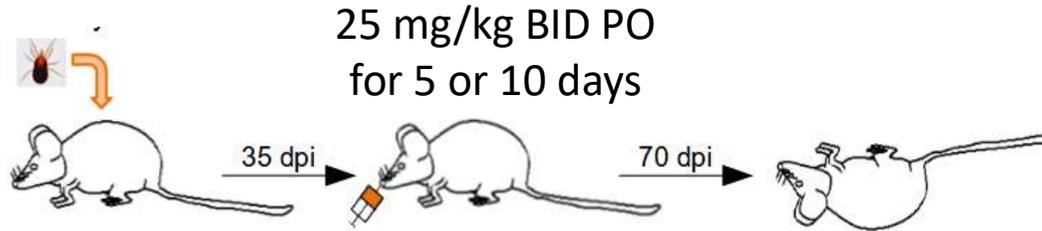
# Oxfendazole isomers are metabolized at different rates into fenbendazole sulfone



**Fenbendazole sulfone** has been described to be **inactive against several helminths** but both isomers have **similar activity against *L. sigmodontis***

Risch et al. submitted

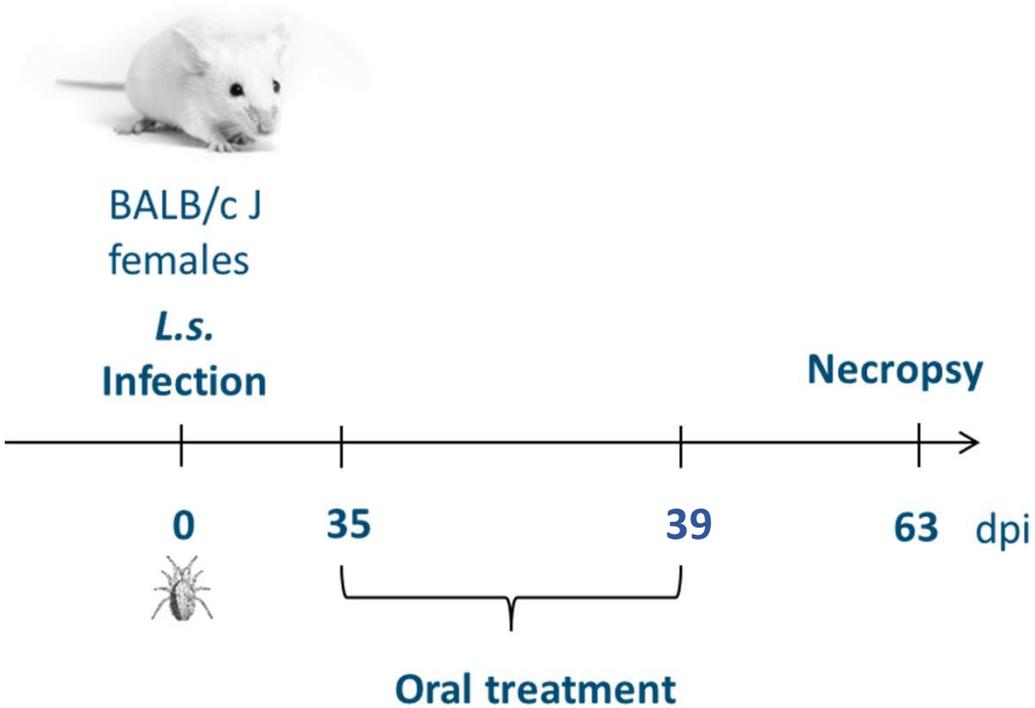
# In vivo assessment of the efficacy of oxfendazole isomers



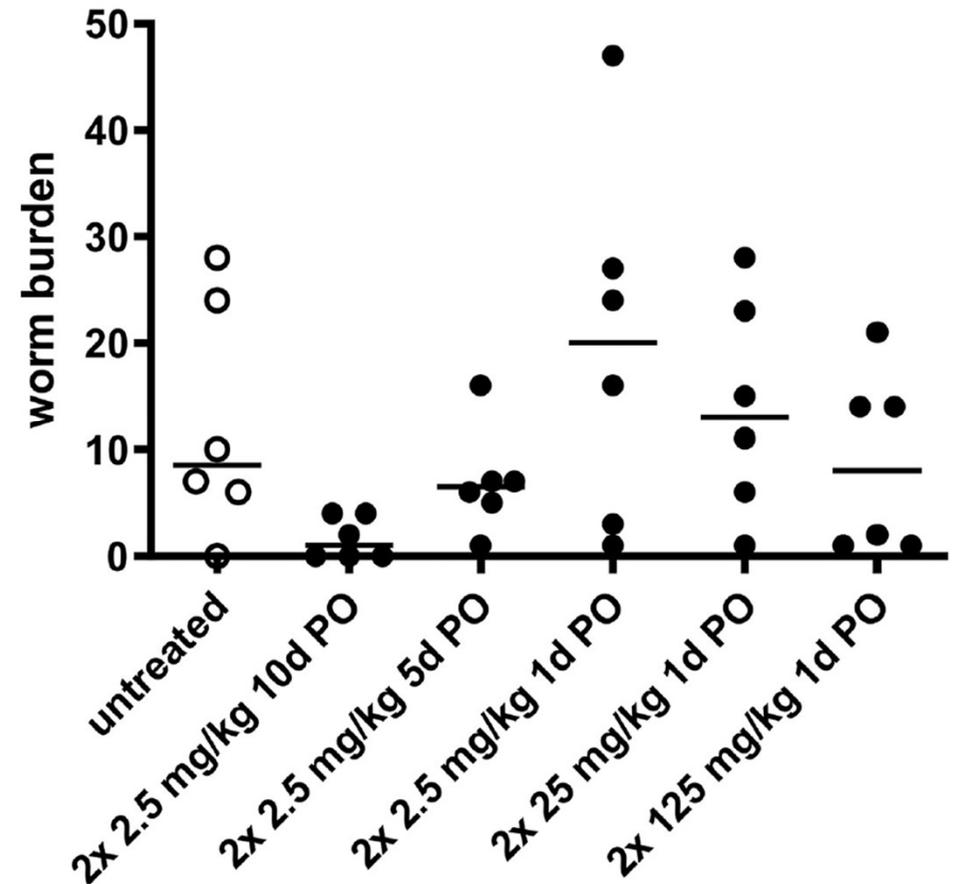
Risch et al. Froniters in Tropical Diseases 2022

→ Oxfendazole isomers have a similar macrofilaricidal efficacy as the racemic formulation (Dolthene)

# Assessment of the oxfendazole efficacy in the *Litomosoides sigmodontis* model



→ Maintenance of minimal efficacious dose determines efficacy



Hübner et al. PLOS NTDs 2020