Drug discovery and development for the treatment and control of filariasis: repurposing emodepside

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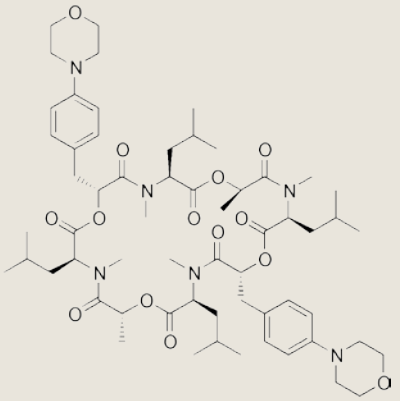
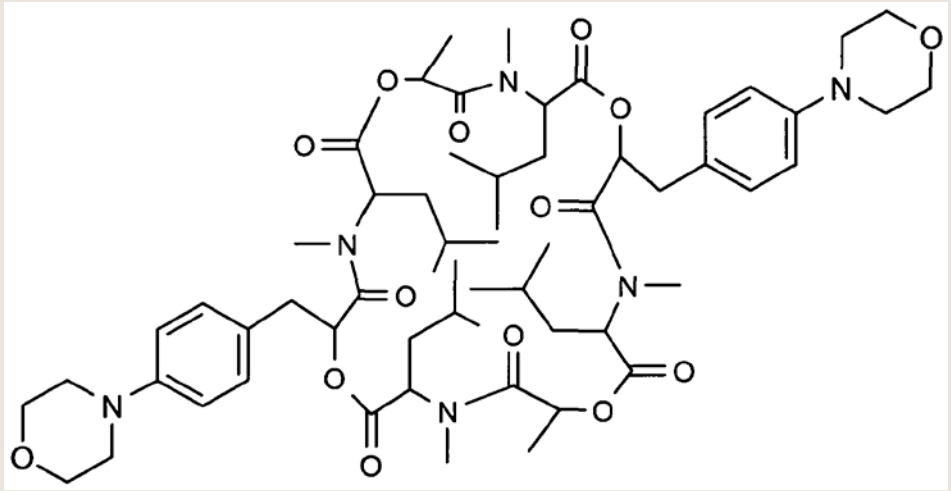


DNDi
Drugs for Neglected Diseases *initiative*

Emodepside (+ praziquantel) is used in topical solutions



DNDi
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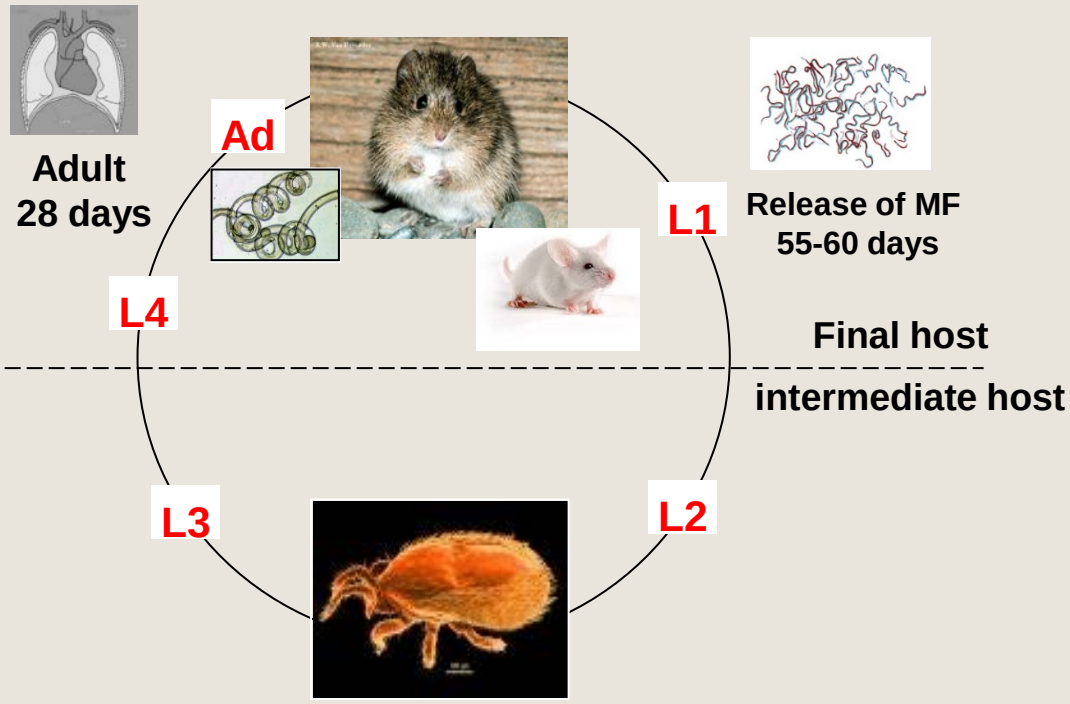
Animal Model of filariasis:

Litomosoides sigmodontis

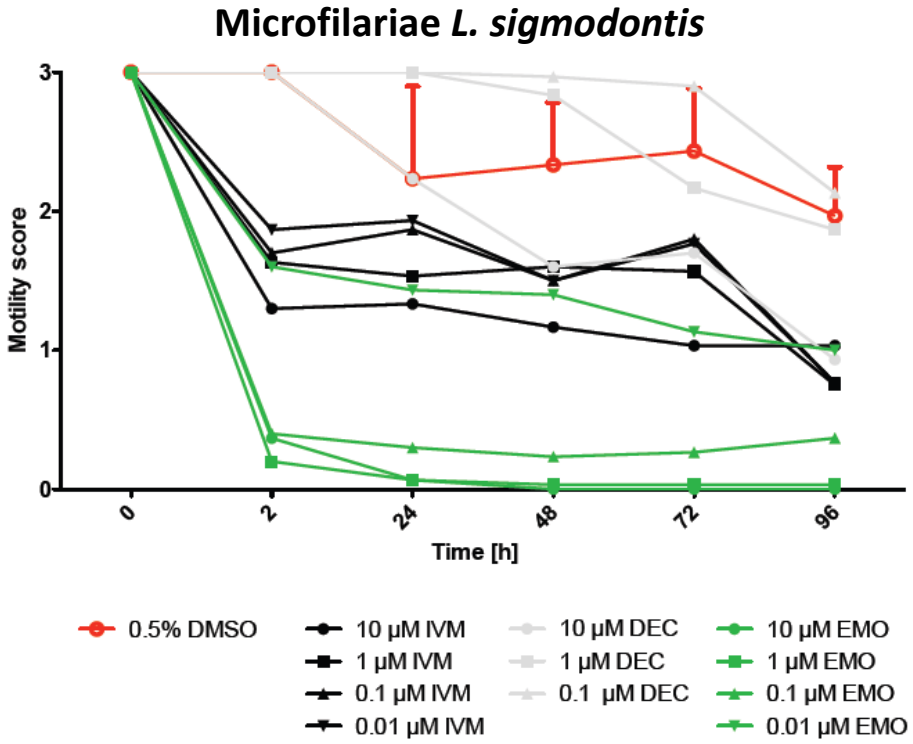


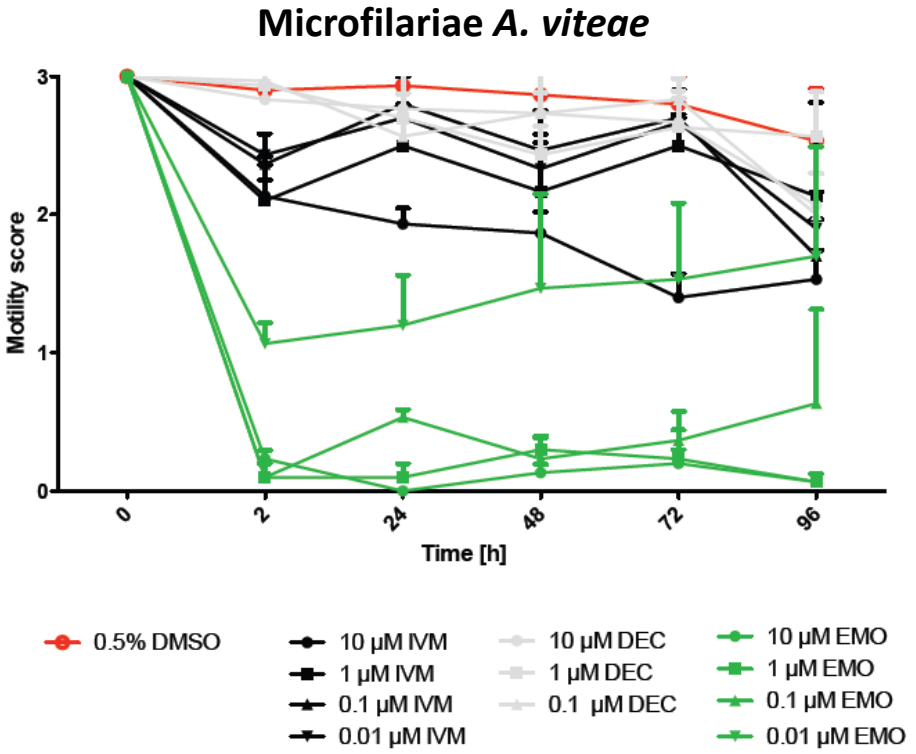
The only fully permissive model for filarial infections

- *Litomosoides sigmodontis* is transmitted by a mite, *Onithonyssus bacoti*.
- The parasitized mite transmits third stage larvae (L3) during a blood-meal
- The larvae then migrate from the skin, through the lymphatics, to the thoracic (pleural) cavity where they mature and breed.
- The adult female worms release their microfilariae in the pleural cavity from where they make their way to the blood circulation, ready to be taken up by a mite feeding on the skin.

In vitro efficacy: microfilariae

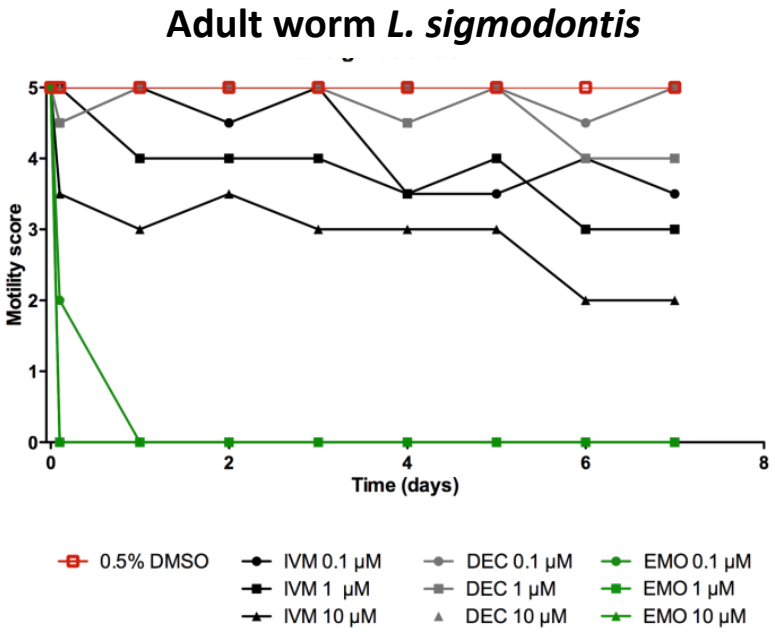
- Minimum inhibitory concentration (MIC) = 0.1 µM (~112 ng/ml)
- MIC is defined as the minimum concentration producing 100% reduction of motility

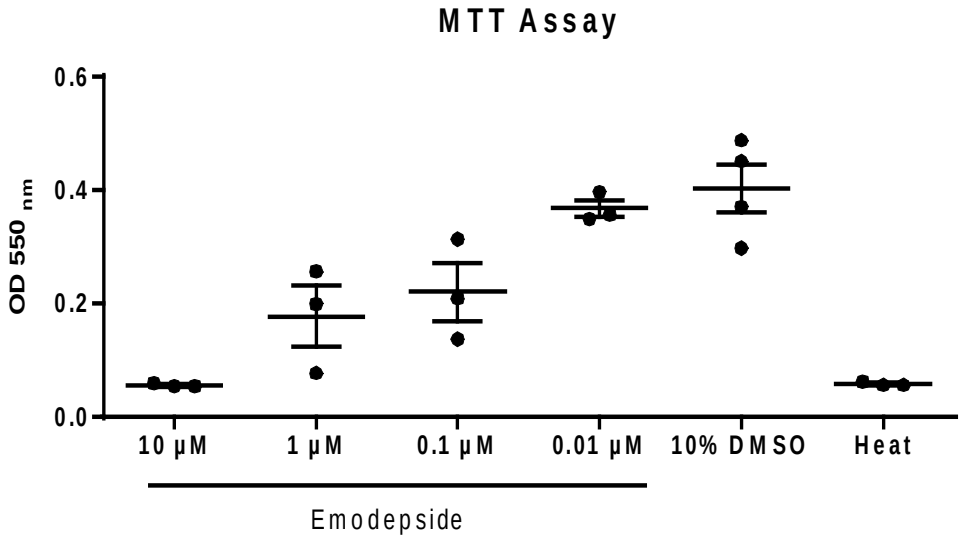




In vitro efficacy: adult worms

- **MIC for *L. sigmodontis* adult worms is below 0.1 µM** (~112 ng/ml) (minimum concentration producing 100% reduction of motility)
- **MIC for *O. gutturosa* adult worms was measured at 0.048 µM** (S. Townson *et al.* ASTMH 54th annual meeting 2005 abstract 280)





Jird model of filariasis:

Litomosoides sigmodontis in jird

3 months pi

D0

9-12 weeks pt

Natural infection

Patency

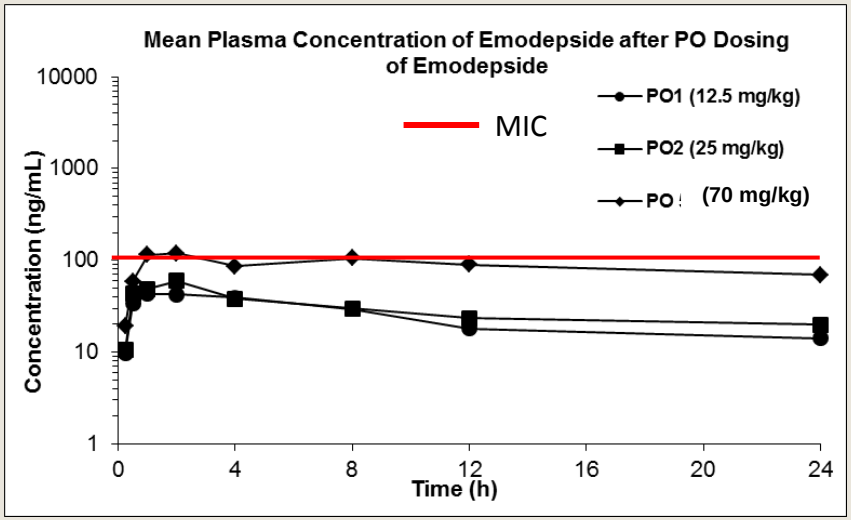
Randomization (weight, MF)

Treatment's start

Worm recovery & analysis

Analysis:
- parasite numbers
- length of females/males
- microfilariae counts

Exposure in jird

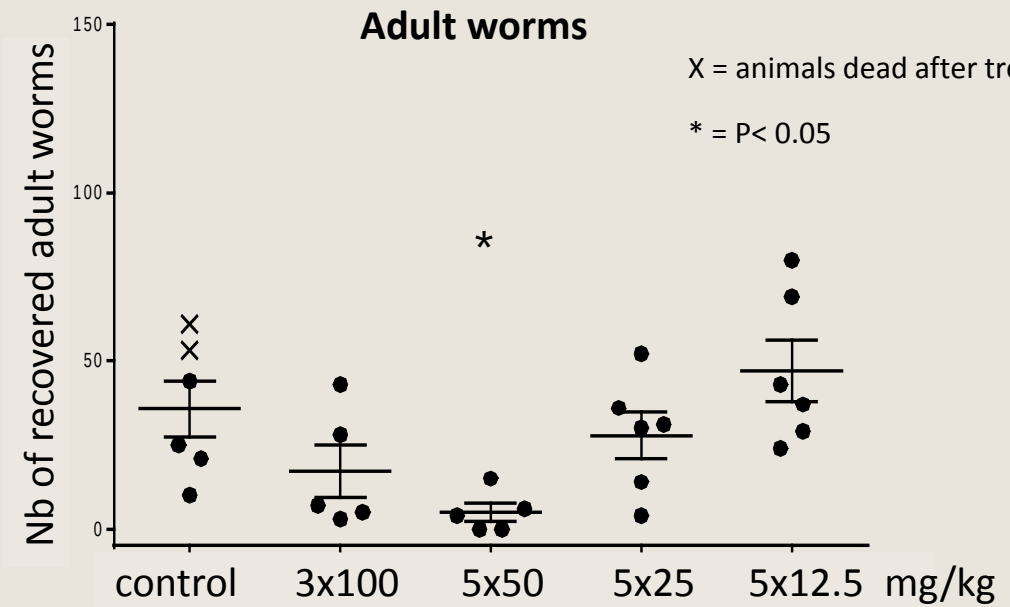


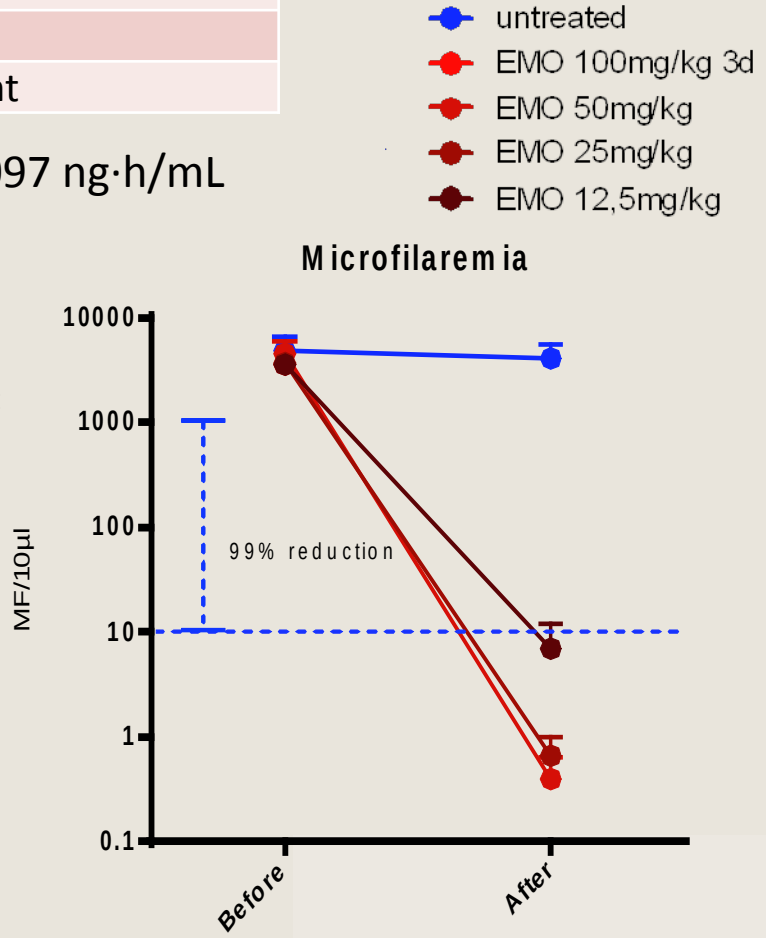
Dose mg/kg	12.5	25	70
formulation	Suspension 2% Cremophor EL in saline		
C_{max} (ng/mL)	59	58.6	145
T_{max} (h)	2	2.33	3.33
$T_{1/2}$(h)	22	22	19.7
$AUC_{0\text{-last}}$ (ng·h/mL)	567	567	2097

Efficacy in Jird

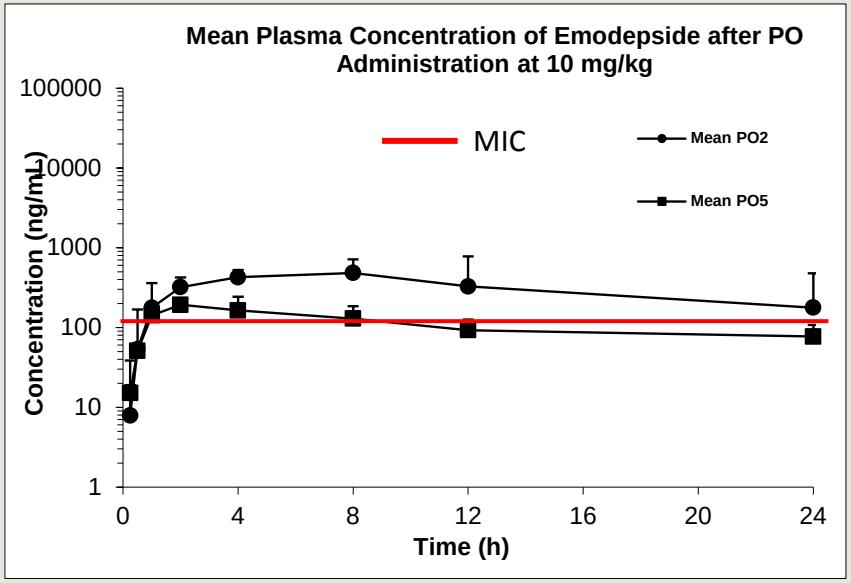
Jirds infected with *L. sigmodontis*	100 mg/kg (3 days)	50 mg/kg (5 days)	25 mg/kg (5 days)	12.5 mg/kg (5 days)
Reduction of adult worms compare to control group	55 %	86 %	22 %	0 %
Formulation	Suspension in 2% Cremophor EL			
Route of administration	Oral gavage			
Readout	9 weeks post treatment			

- 5 x 50 mg/kg dose : C_{max} = 145 ng/mL $AUC_{0\text{-last}}$ = 2097 ng·h/mL
- 5 x 100 mg/kg dose was not tolerated





Exposure in jird

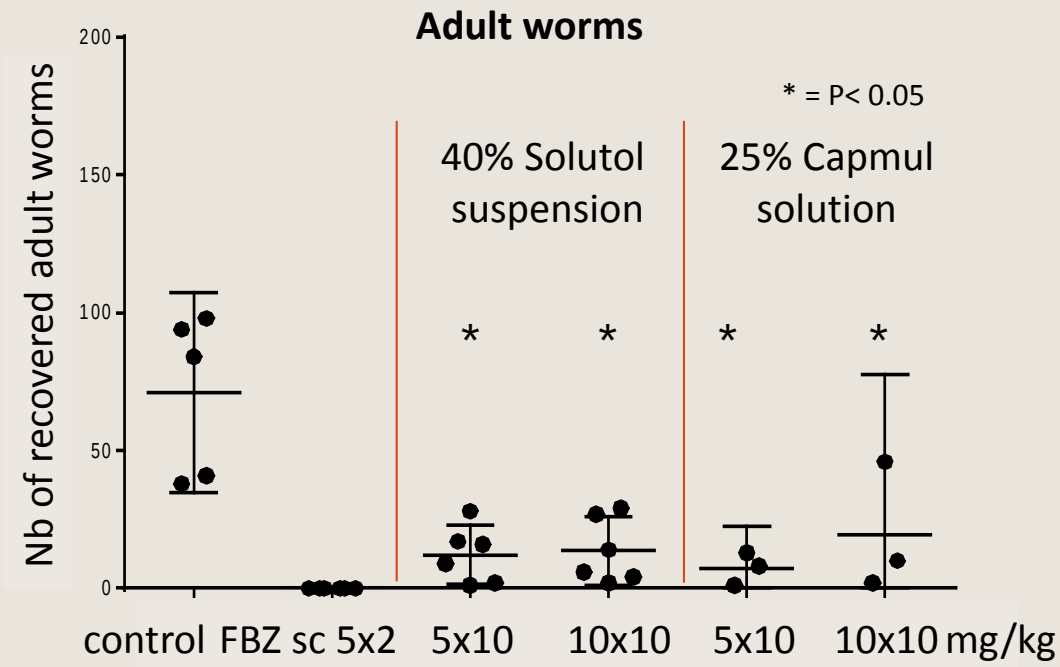


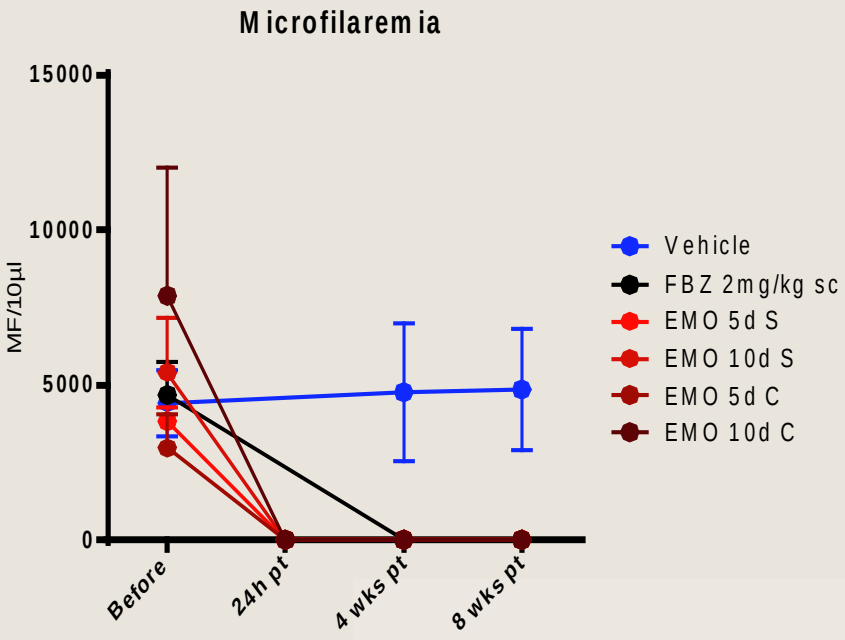
Dose mg/kg	10	10
formulation	clear solution 25% Capmul MCM in Corn oil	suspension 10% EtOH/40% Solutol/50% H_2O
C_{max} (ng/mL)	530	195
T_{max} (h)	5	1.67
$T_{1/2}$(h)	14	21.9
$AUC_{0\text{-last}}$ (ng·h/mL)	7390	2612

Treatment duration comparison

Jirds infected with *L. sigmodontis*	5 mg/kg (5 days)	10 mg/kg (10 days)	5 mg/kg (5 days)	10 mg/kg (10 days)
Reduction of adult worms compare to control group	82.9	80.8	89.7	72.8
Route of administration	Oral gavage			
Readout	9 weeks post treatment			

- The excipient Capmul MCM was not well tolerated in jirds



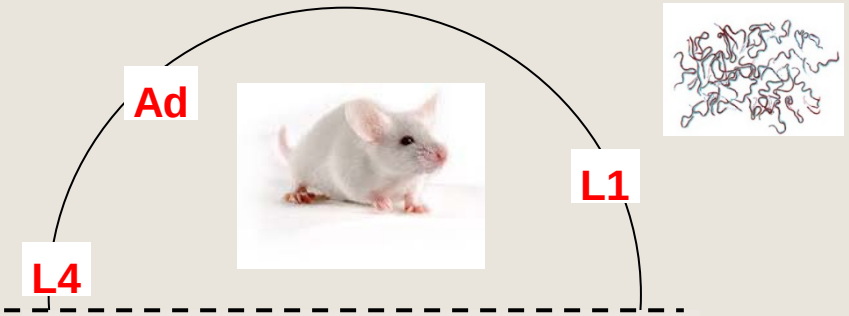


Conclusions

- Exposure of emodepside depends on the formulation
- Reduction > 80% of adult worms is obtained when plasma levels are close to the *in vitro* MIC (~ 112 ng/ml); fulfills efficacy TPP requirements for a macrofilaricide
- Longer treatment regimens don't seem to improve the pharmacological response

Murine model of filariasis:

Litomosoides sigmodontis in mouse



30 days pi
Treatment start

D0

75 days pt

Patency

Worm recovery & analysis

Natural infection

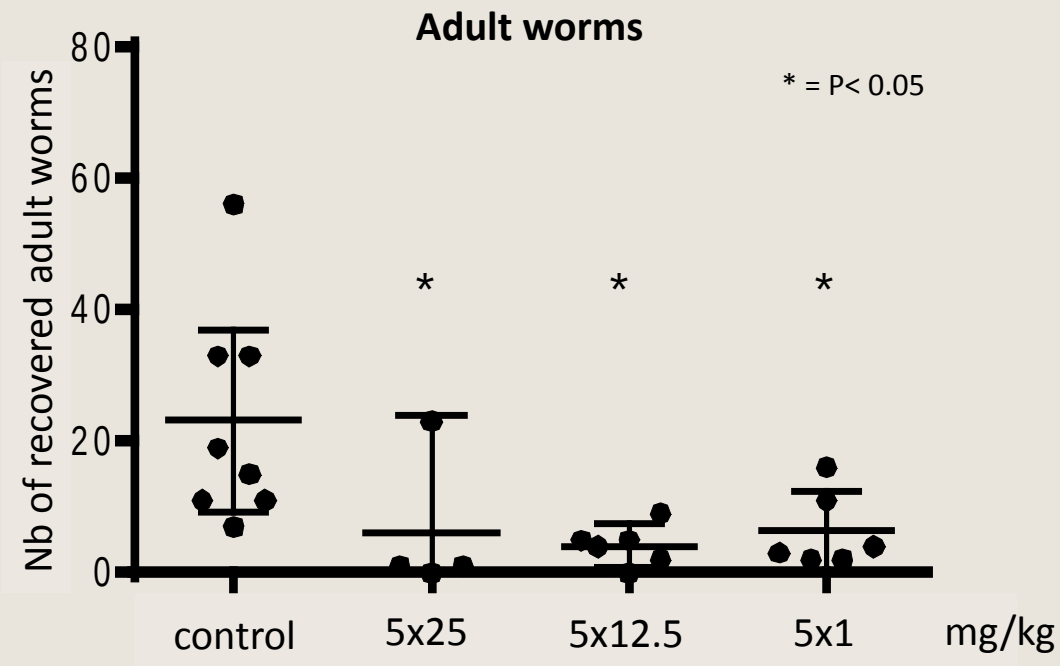
Randomization (weight, MF)

Begin of treatment

Analysis:
parasite numbers
length of females/males
microfilariae counts

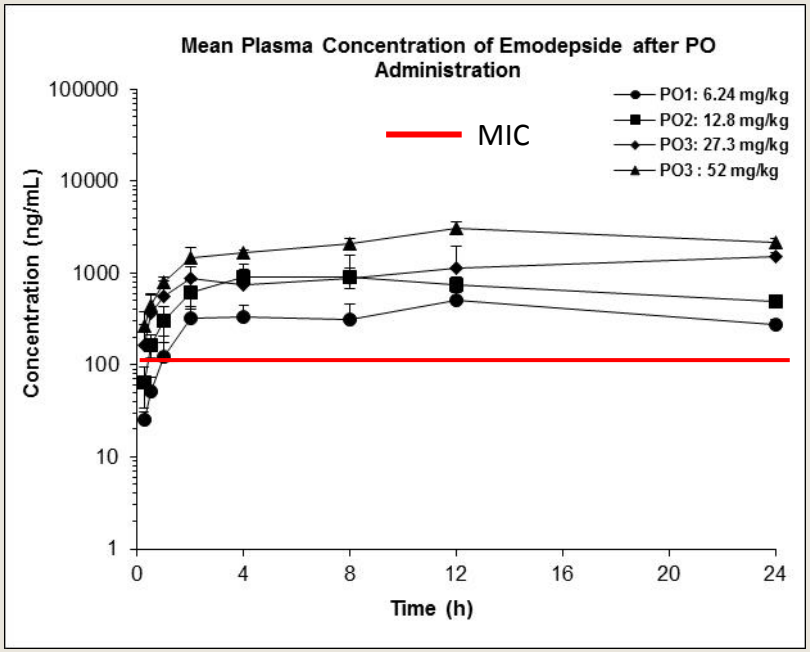
Efficacy in mice

Mice infected with *L. sigmodontis*	25 mg/kg (3 days)	12.5 mg/kg (5 days)	1 mg/kg (5 days)
Reduction of adult worms compare to control group	73 %	82 %	72 %
Formulation	Solution 100% capmul MCM		
Route of administration	Oral gavage		
Readout	75 days post treatment		



- 5 x 50 mg/kg dose was not tolerated
- 5 x 25 mg/kg was partially tolerated: 2 animals died
- Linearity of the pharmacokinetic profile allows extrapolating key PK parameters for 1 mg/kg dose:
  - C_{max} = 84 ng/ml
  - $AUC_{0\text{-}last}$ = 1399 ng·h/ml

Exposure in mouse



Dose mg/kg	6	12.5	25	50
formulation	100% Capmul MCM clear solution			
C_{max} (ng/mL)	508	1038	1553	3093
T_{max} (h)	12	5.33	20	12
$T_{1/2}$(h)	ND	35.1	ND	ND
$AUC_{0\text{-last}}$ (ng·h/mL)	8396	16354	25775	53594

Conclusion

- Comparable efficacy was obtained at all tested doses (25, 12.5 and 1 mg/kg)
  - Reduction of adult worms is about 80%
- Exposure of emodepside depends on the formulation

- PK parameters of efficacious doses in both mouse and the jird model are approximatively in the same ballpark:
- Mouse
  - 1 mg/kg (capmul solution)
  - C_{max} = 84 ng/ml
  - $AUC_{0\text{-last}}$ = 1399 ng·h/ml
- Jird
  - 10 mg/kg (solutol suspension)
  - C_{max} = 195 ng/ml
  - $AUC_{0\text{-last}}$ = 2612 ng·h/ml

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THANK YOU