



DNDi Helminth Portfolio

*Swiss TPH Winter Symposium
7 December 2017*

Ivan Scandale



Origins of DNDi

1999

- First meeting to describe the lack of R&D for neglected diseases
- MSF commits the Nobel Peace Prize money to the DND Working Group
- JAMA article: 'Access to essential drugs in poor countries - A Lost Battle?'

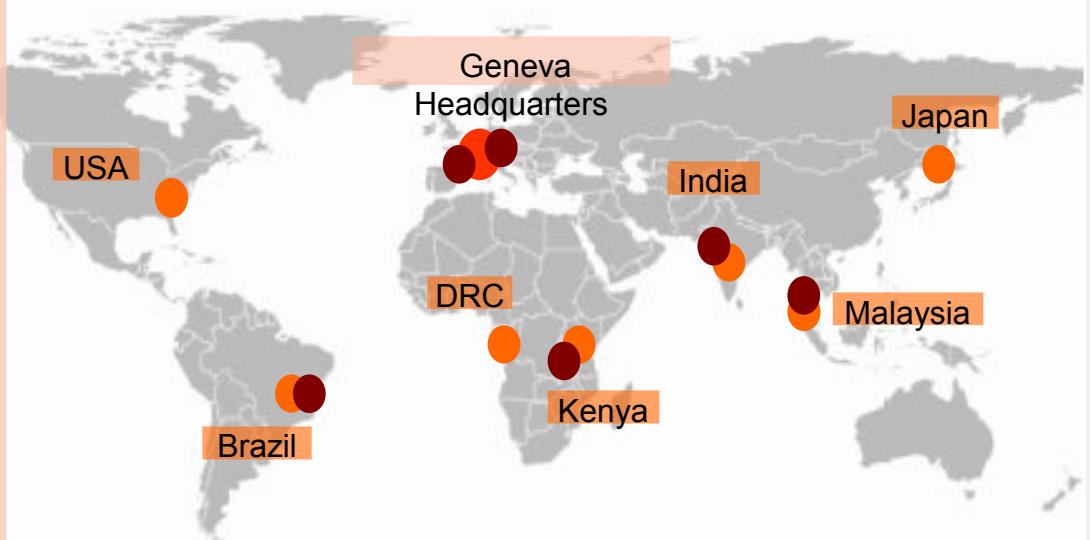
July 2003

- Creation of DNDi



Founding Partners

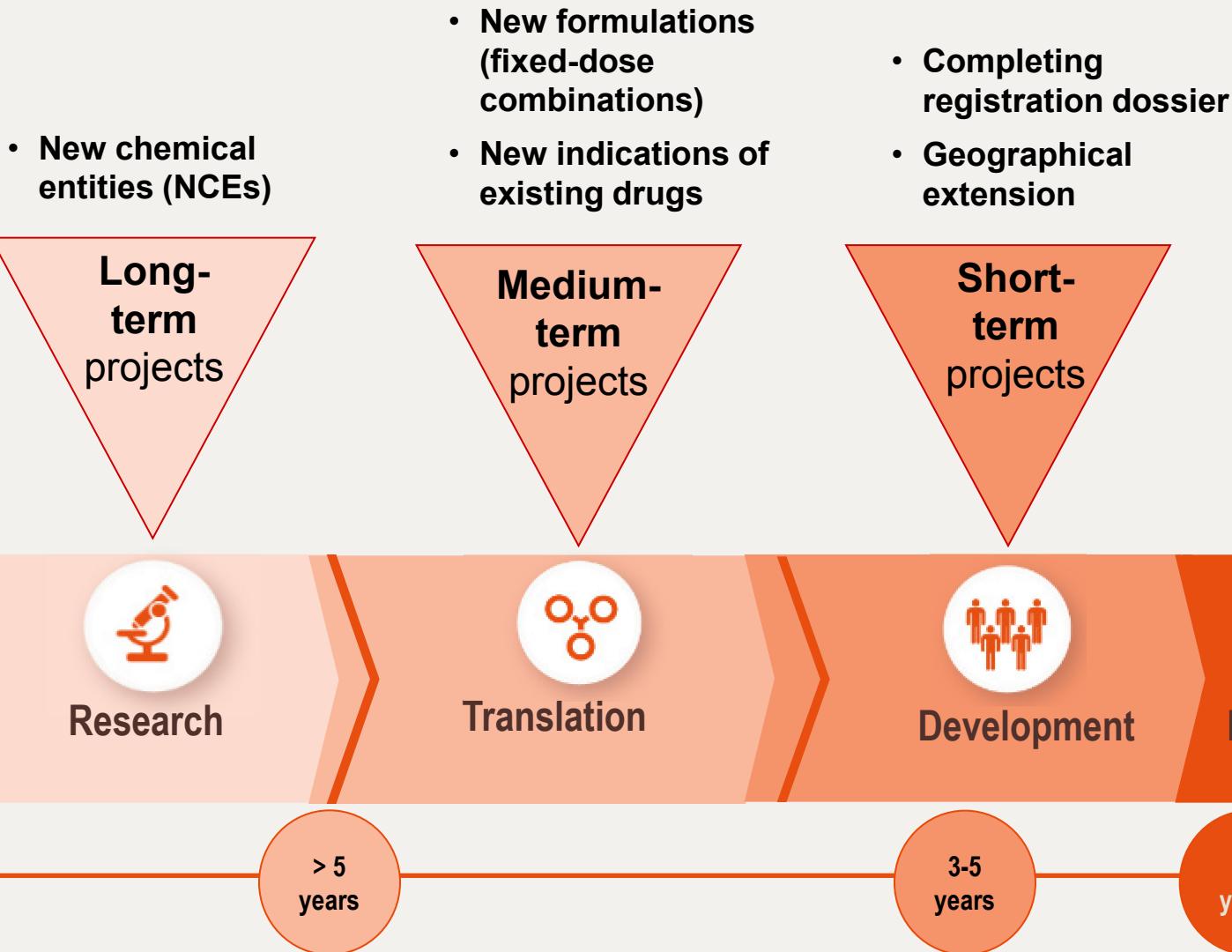
- Indian Council for Medical Research (ICMR)
- Kenya Medical Research Institute (KEMRI)
- Malaysian MOH
- Oswaldo Cruz Foundation, Brazil
- Médecins Sans Frontières (MSF)
- Institut Pasteur France
- TDR (permanent observer)



7 offices worldwide

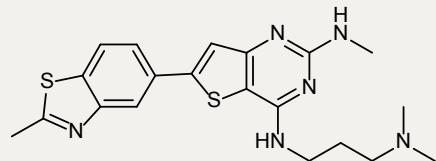
DNDi Portfolio-Building Model:

Address Immediate Patient Needs & Deliver Innovative Medicines

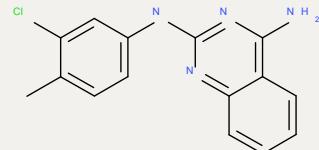


Screening: *S. mansoni* *A. ceylanicum* & *T. muris*

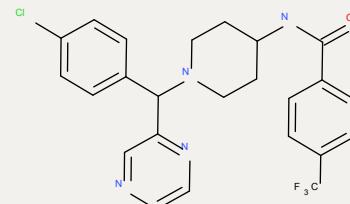
- Sanofi (aprox. 1000 cpds): repositioning library
 - *S. mansoni*: 17 hits with IC₅₀ in micromolar range (structures not disclosed)
- MMV (aprox 400 cpds):
 - *T. muris* & *S. mansoni*: 3 hits with IC₅₀ in micromolar range
- Epichem (aprox 50 cpds): Chagas program (CYP51 inhibitors)
 - *T. muris* & *S. mansoni*: 5 hits with IC₅₀ in micromolar range
- Commercial library of FDA approved drugs
- Several starting points to conduct lead optimization have been identified



MMV668309 *in vivo*:
58% *S. mansoni* reduction

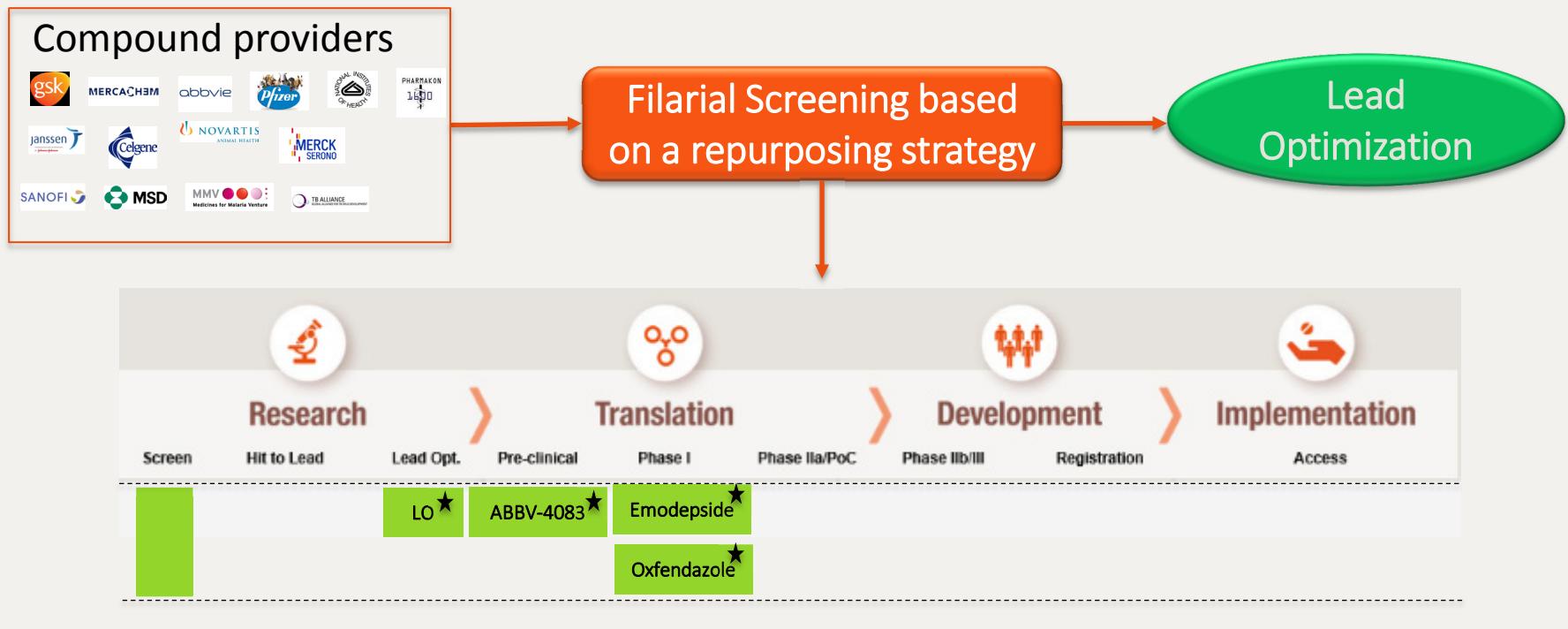


MMV011522 *in vivo*:
100% *T. muris* reduction



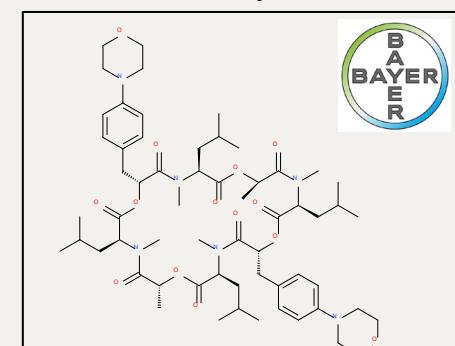
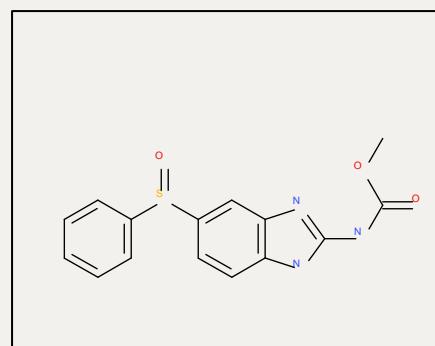
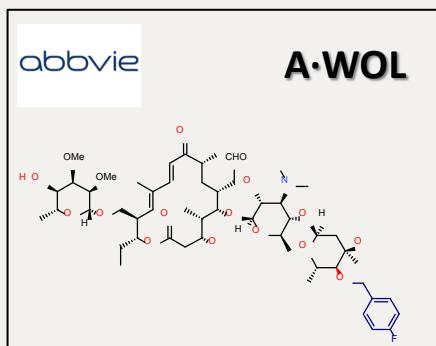
EPL-BS0431 *in vitro*:
IC₅₀ = 6.46 μM *S. mansoni*

Filarial Portfolio



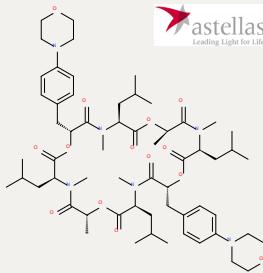
Celgene

1 preclinical candidate
1 back-up



Emodepside

- Anthelmintic veterinary drug for cats and dogs in combination with praziquantel (Profender®) and in combination with toltrazuril (Procox®).



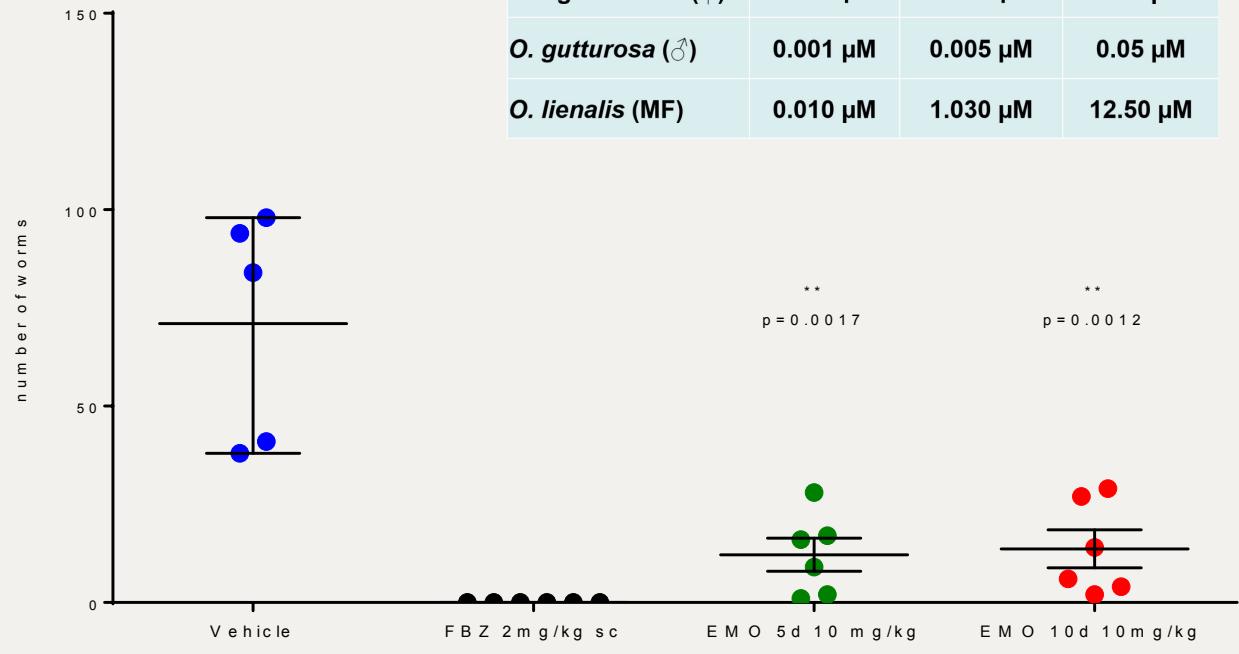
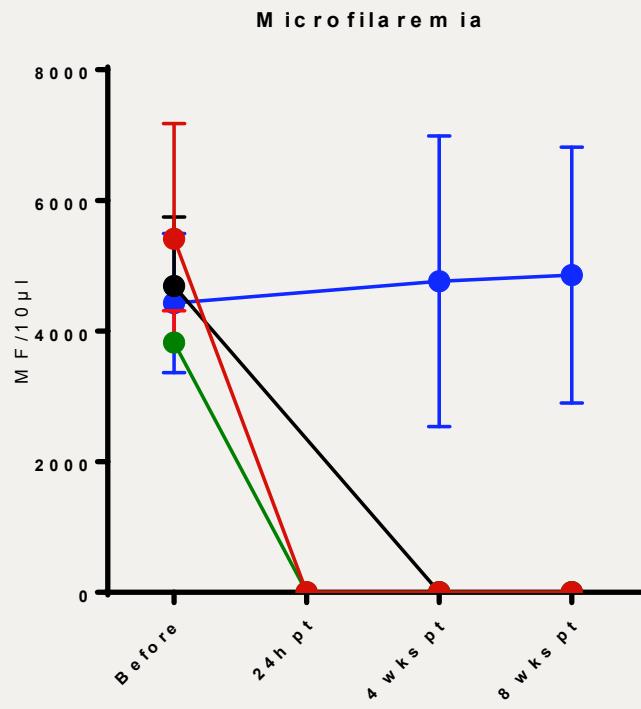
License to Bayer



- Emodepside showed remarkable *in vivo* and *in vitro* activity against a variety of filarial nematodes including *O. volvulus*.
- DNDi has an agreement with Bayer to develop emodepside for the treatment of onchocerciasis

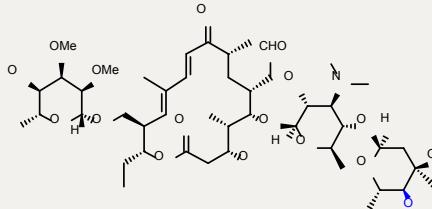
Efficacy emodepside (*L. sigmodontis* in jird)

- Vehicle
- FBZ 2mg/kg sc
- EMO 5d 10 mg/kg
- EMO 10d 10 mg/kg



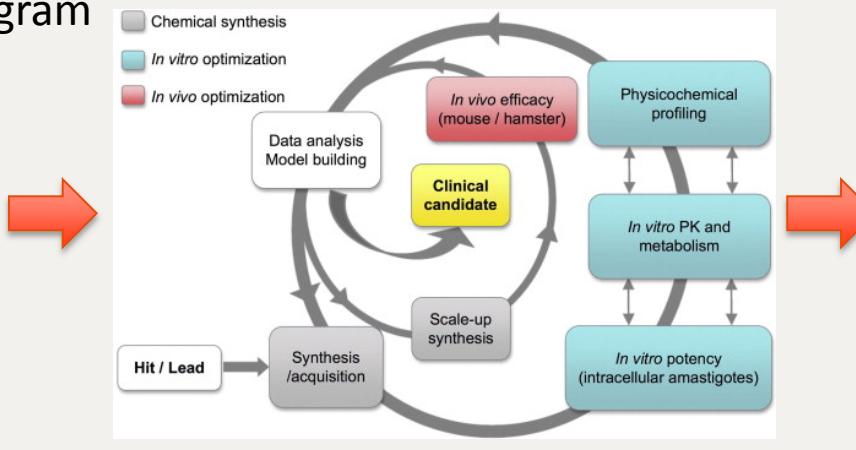
Tylosin Analogue Macrofilaricide ABBV-4083

- Tylosin is a macrolide antibiotic used as food additive in veterinary medicine

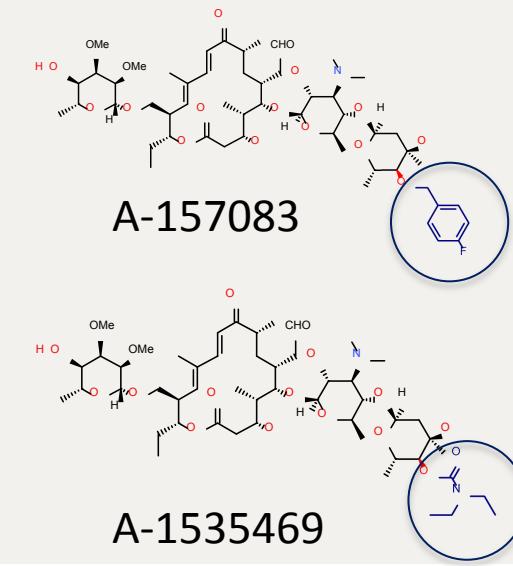


- Tylosin targets the endosymbiont Wolbachia bacterium present in *O. volvulus* and *W. bancrofti*. This causes:
 - Inhibition of fertility (absence of microfilariae)
 - Possible macrofilaricide activity
- Tylosin is poorly bioavailable:

Optimization program
conducted by:

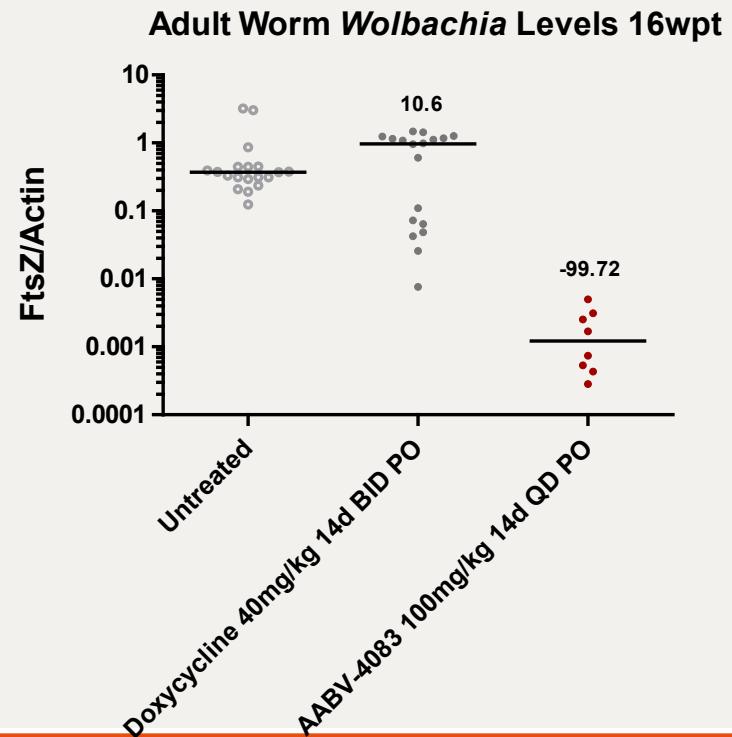
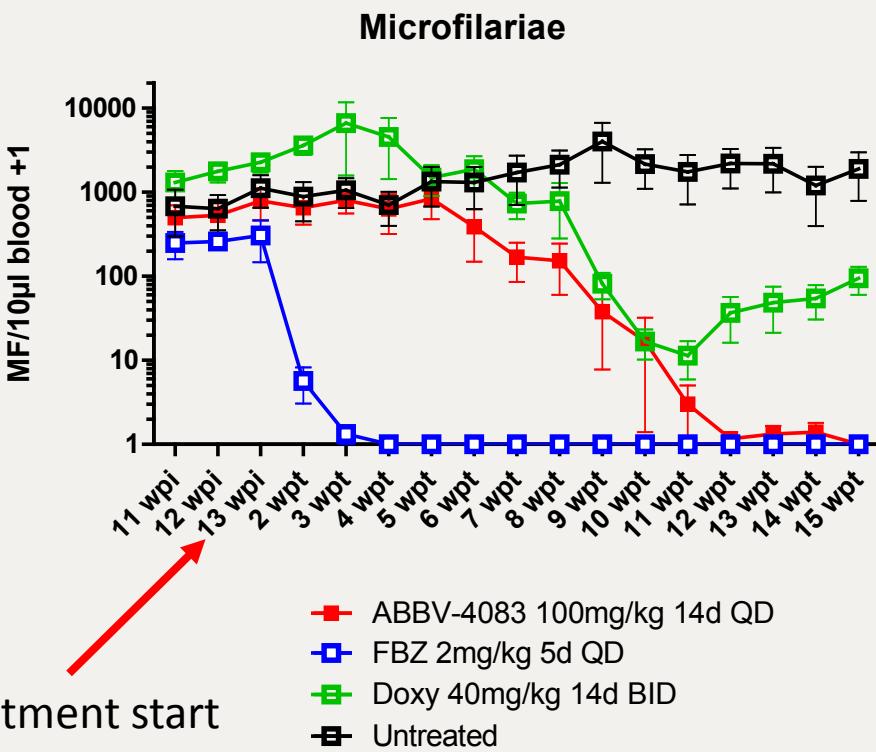


Analogues:



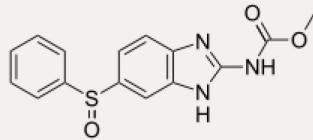
Efficacy ABBV-4083 (*L. sigmodontis* in jird)

Treatment	MF negative animals 15wpt	Treatment	MF negative animals 15wpt
Untreated	0/5	Doxycycline	0/5
FBZ	3/3	A-4083	6/6



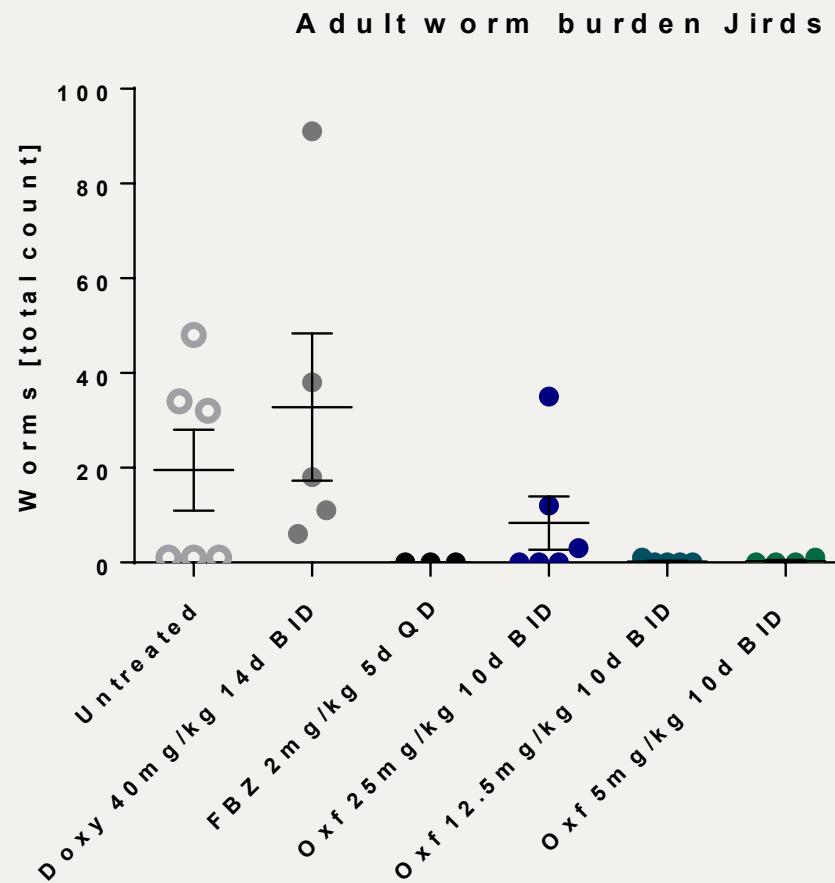
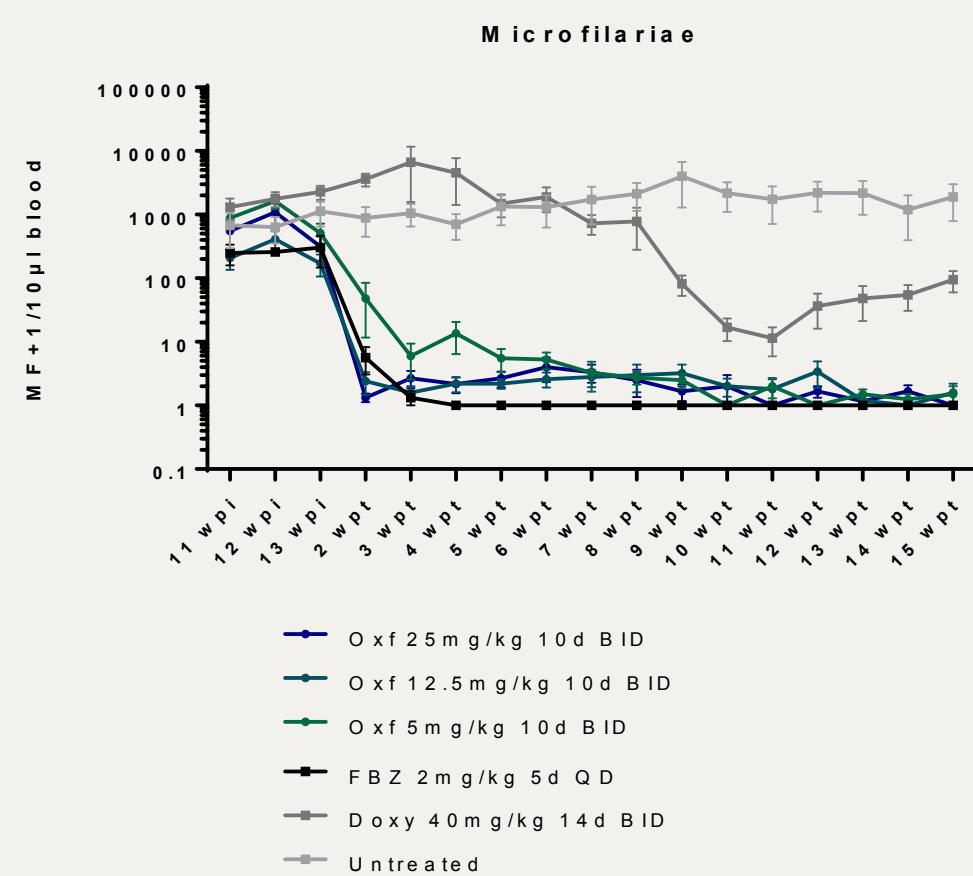
Oxfendazole

- Oxfendazole is a benzimidazole, anthelmintic treatment for farm and domestic animals.



- Oxfendazole is potent *in vivo* against a variety of filarial nematodes (*L. sigmodontis*, *B. malayi*, *A. viteae*)
- A Phase I trial evaluating safety and pharmacokinetics of oxfendazole is ongoing for two inductions:
 - Neurocysticercosis. Sponsor: National Institute of Allergy and Infectious Diseases (NIAID)
 - Tenia Solium Infection. Sponsor: Johns Hopkins Bloomberg School of Public Health

Efficacy oxfendazole (*L. sigmodontis* in jird)



Batch 1

50 mg

in vitro efficacy



O. Gutturosa

Adult worm (male)

Parameters:

- Motility
- MTT

$EC_{50} \leq 1 \mu M$

// Cytotoxicity



L. sigmodontis

Adult worm

Parameters:

- Motility
- MTT

$EC_{50} \leq 1 \mu M$

O. lienalis

microfilariae

Parameters:

- Motility

Monkey kidney cells
Feeder cell layer

No toxicity at 10 μM or
 $SI (cells/worms) > 5X$

in vitro ADME / Chem. Charact.



Solubility, logD, permeability (MDCK-MDR1), protein binding, metabolism in liver microsomes (human + in vivo target species)

Solubility > 0.01mg/ml at pH 7.4

Metabolic Stability: medium or high

Permeability: medium or high

Batch 2

Mouse:
200 mg

Jird:
800 mg

in vivo ADME

In vivo mouse or jird pharmacokinetic profile at ≤ 50 mg/kg



abbvie



Achievable plasma levels above EC_{50} for 24 hours

in vivo efficacy

Mouse or jird model
(*L. sigmodontis*)
 ≤ 50 mg/kg BID

Reduction of adult worms > 70%
No toxicity

Mouse or jird model
(*L. sigmodontis*)
Dose –response
At least three dose groups

Exposure in mouse
Dosing groups overlap with in vivo study

Reduction of adult worms > 70%



In vitro, in vivo safety profiling

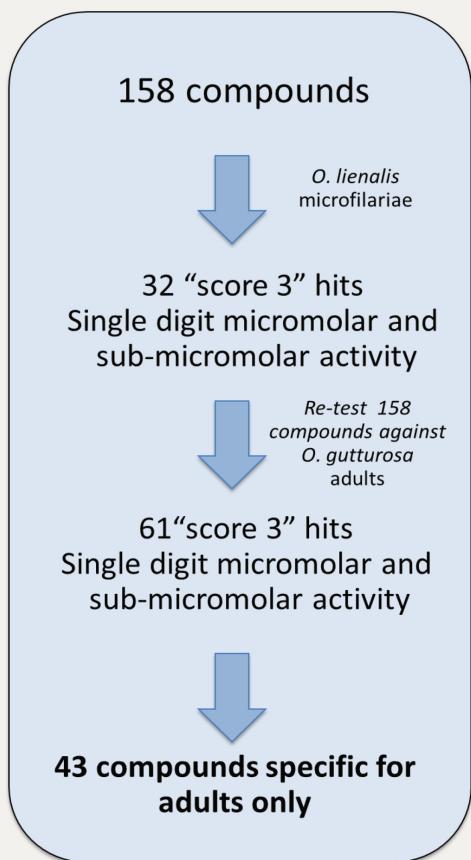
PK/PD established



Celgene program

*In vivo Results (*Litomosoides sigmodontis*)*

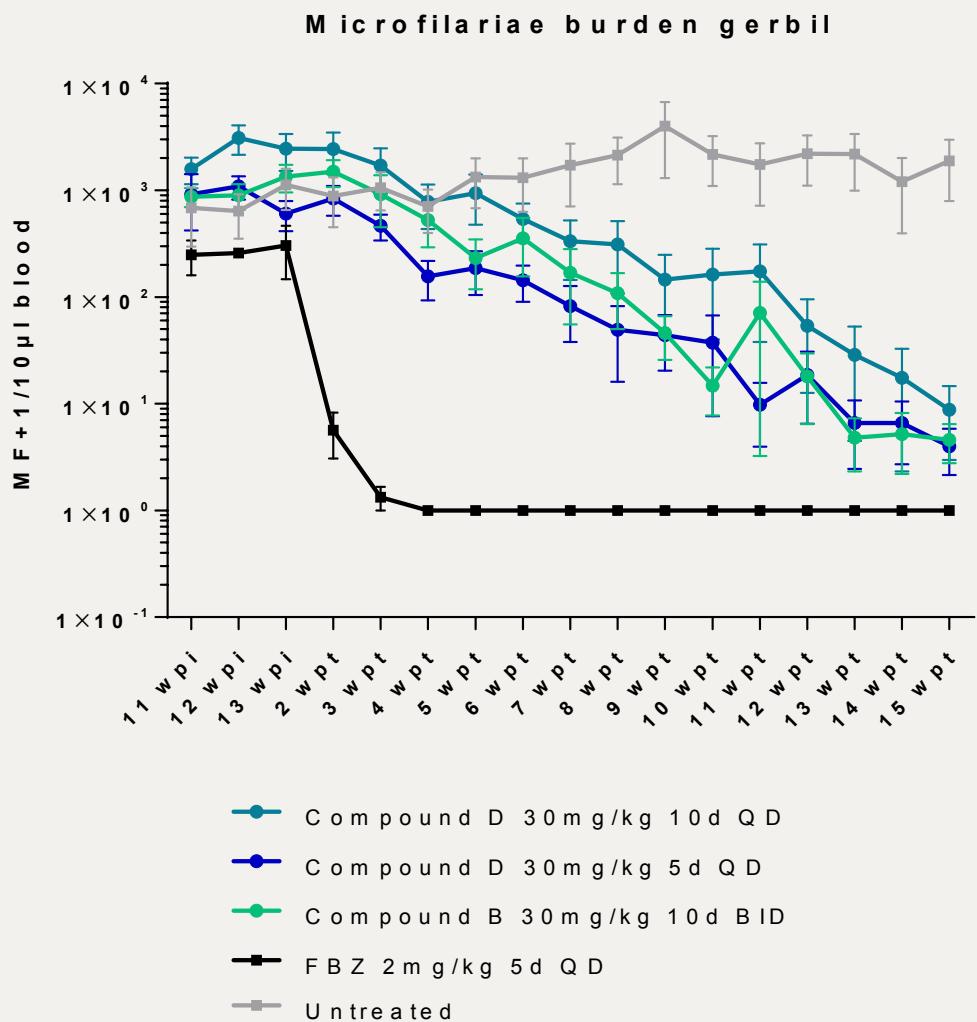
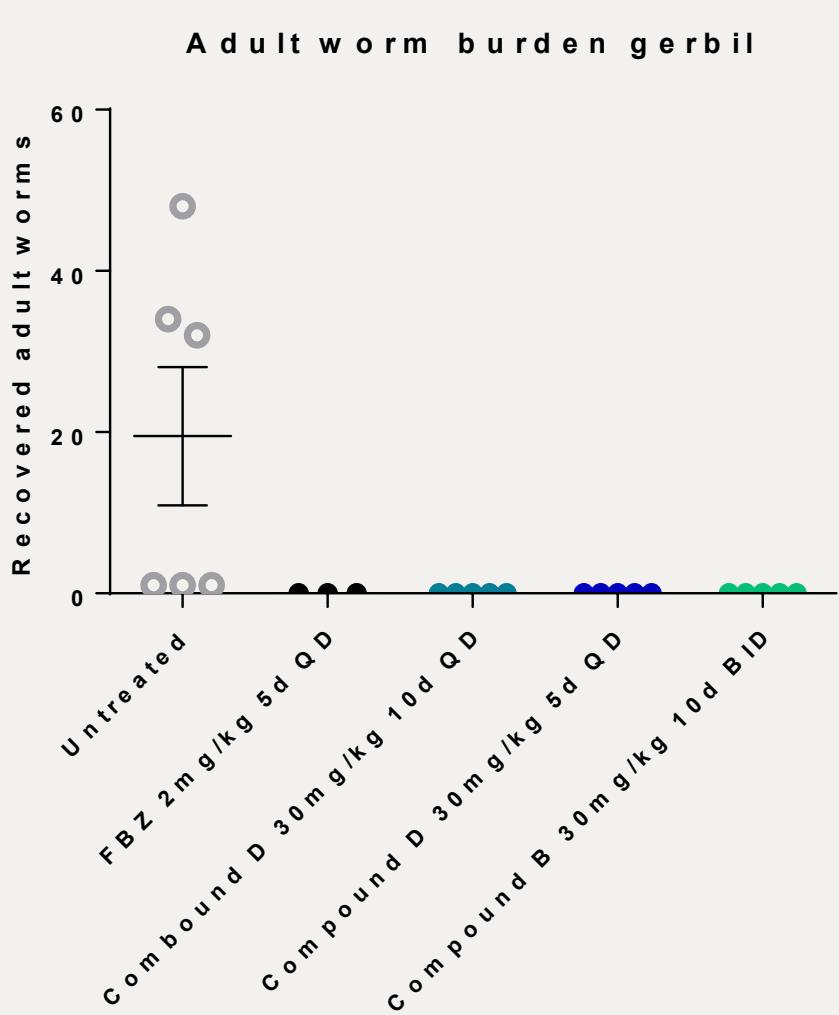
In vitro (Onchocerca species)



Day:	0	Treatment (5 Days)			Worm Recovery and Analysis: • Parasite number • Microfilariae count
	30	Vehicle	FBZ	Compounds	
	1. Injection of L3 2. Natural Infection (<i>L. sigmodontis</i> , BalbC mice)				
Compound	Dose	Average Adult worms	Reduction Adult worms	Reduction Microfilaria	
Vehicle		11 (26)	-	NA	
Flubendazole	2 mg/kg 5 days	0	100 % (P=0.007)	NA	
Compound A	3x30 mg/kg 5 days	2 (1.7)	68 % (p=0.032)	NA	
Vehicle		11 (26)	-	-	
Flubendazole	2 mg/kg 5 days	0.2 (0.5)	98 % (P=0.019)	100 % (P=0.034)	
Compound B	3x30 mg/kg 5 days	2.17 (1.3)	80 % (p = 0.044)	98 % (p = 0.042)	
Compound C	3x30 mg/kg 5 days	5.5 (2.7)	56 % (p = 0.125)	78 % (p=0.078)	
Compound D	3x30 mg/kg 5 days	10.2 (9.4)	18 % (p = 0.685)	86% (p=0.058)	

Values expressed as mean (SD)

Efficacy (*L. sigmodontis* in jird)



Acknowledgments



Stacie S. Canan,
Natalie A. Hawryluk,
Vikram Khetani



Andrew Freeman
Simon Townson
Suzanne Gokool



Nathaly
Coralie Martin



Milan Bruncko
Kevin Cusack
Karla Drescher
Tom von Geldern
Herve Geneste
Paul Jung
Joe Kalcsits
Dale Kempf
Kennan Marsh
Shaun McLoughlin
Marc Scanio
Irini Zanze



Dominique Blömker
Achim Hoerauf
Sabine Specht
Marc Hübner



Hongjuan Liu
Jia Wang
Meijing Wang
Zhongyuan Wang
Songling Yu
Jingyu Zhang
Zhyuan Zhang



Sabine Specht
Frederic Monnot
Ivan Scandale



Gemma Molyneux
Laura Myhill
Gemma Nixon
Nicolas Pionnier
Raman Sharma
Hanna Sjoberg
Andrew Steven
Mark Taylor
Joe Turner
Hayley Tyrer
Stephen Ward
David Waterhouse
Ghaith Alijayyoussi
Andy Cassidy
Ana Castro Guimaraes
Rachel Clare
Darren Cook
Susie Crossman
Jill Davies
Louise Ford
Joanne Gamble
Laura Hayward
Kelly Johnston
Susan Jones



THANK YOU

TO ALL OUR
PARTNERS &
DONORS

DNDi
Drugs for Neglected Diseases initiative



DNDi
BILL & MELINDA GATES foundation



Ministry of Foreign Affairs of the
Netherlands



GHIT Fund

Global Health Innovative Technology Fund



USAID
FROM THE AMERICAN PEOPLE

UBS
UBS Optimus Foundation

The Global Fund
To Fight AIDS, Tuberculosis and Malaria



Regione Toscana



giz
Deutsche Gesellschaft
für Internationale
Zusammenarbeit (GIZ) GmbH

Fundación BBVA

BNDES
Rutaⁿ
MEDELLÍN

Rockefeller Foundation
Innovation for the Next 100 Years



medicorfoundation
GLOBAL INNOVATION

SPF THE SASAKAWA PEACE FOUNDATION

THE STARR FOUNDATION

BILL & MELINDA GATES foundation



Federal Ministry
of Education
and Research
by



MINISTÈRE
DES
AFFAIRES ÉTRANGÈRES

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

wellcome trust



Jird model of filariasis: *Litomosoides sigmodontis*

