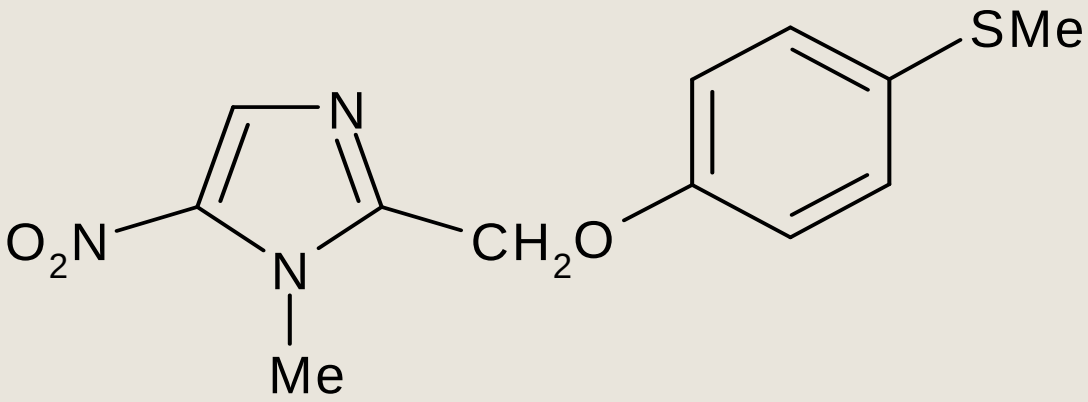

NITROIMIDAZOLES FOR VISCERAL LEISHMANIASIS – FEXINIDAZOLE AND VL-2098

SHYAM SUNDAR

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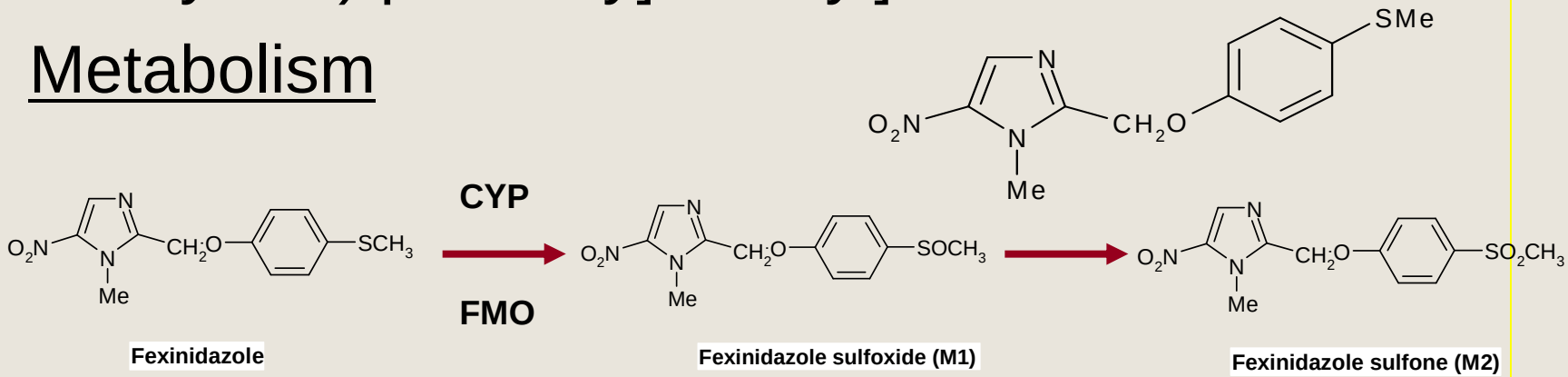
Target Product Profile for a NCE

	Optimal Target Profile	Minimal Target Profile
Target Label	VL and PKDL	VL
Spp	All species	L. donavani
Distribution	All areas	Either India or Africa
Target Population	Immunocompetent and immunosuppressed	Immunocompetent
Clinical Efficacy	> 95%	> 90%
Resistance	Active against resistant strains	
Safety and Tolerability	No AEs requiring monitoring	1 monitoring visit in mid/end - point
Contraindications	None	Pregnancy/lactation
Interactions	None - Compatible for combination therapy	None for malaria, TB, and HIV concomitant therapies
Formulation	Oral / im depot	Oral / im depot
Treatment Regimen	1/day for 10 days po/ 3 shots over 10 days*	bid for <10 days po; or >3 shots over 10 days
Stability	3 yrs in zone 4	Stable under conditions that can be reasonably achieved in the target region (> 2 yr)
Cost	< $10 / course	<$80 / course

Fexinidazole

- Discovery : 1970 HOE 239, discontinued 1980
- Chemical Name: 1H-imidazole,1-methyl-2-[[4-methylthio) phenoxy] methyl] 5-nitro-imidazole
- Metabolism



- PM FEXI = 279 g/mol
- PM M1 = 295g/mol
- PM M2 = 311g/mol

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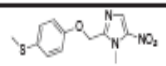
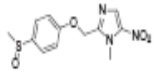
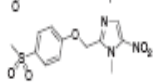
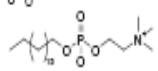
In vitro data of fexinidazole and metabolites on **L donovani**

Table 1. Key physicochemical properties and in vitro leishmanicidal activity of fexinidazole and its metabolites.

Compound	Structure	Molecular weight*	cLogP*	Polar surface area (Å^2)*	Unbound fraction (Fu)†	*L. donovani* EC_{50},‡ µM (Hill slope)		
						Promastigote	Axenic amastigote	Amastigote (in macrophages)
Fexinidazole		279	2.5	73	0.15	5.6 ± 0.2 (4.1)	2.8 ± 0.1 (4.5)	>50
Fexinidazole sulfoxide		295	1.3	90	0.86	3.1 ± 0.1 (4.4)	4.5 ± 0.3 (3.5)	5.3 ± 0.1 (2.4)
Fexinidazole sulfone		311	1.0	107	0.73	4.8 ± 0.1 (5.0)	1.6 ± 0.1 (3.8)	5.3 ± 0.2 (2.4)
Miltefosine		366	6.0	56	0.002	6.1 ± 0.3 (4.0)	4.4 ± 0.2 (3.1)	3.3 ± 0.3 (1.8)

Science Translational Medicine AAAS

The Anti-Trypanosome Drug Fexinidazole Shows Potential for Treating Visceral Leishmaniasis
Susan Wyllie, *et al.*
Sci Transl Med **4**, 119re1 (2012);

In vivo data in mice infected with L *donovani*

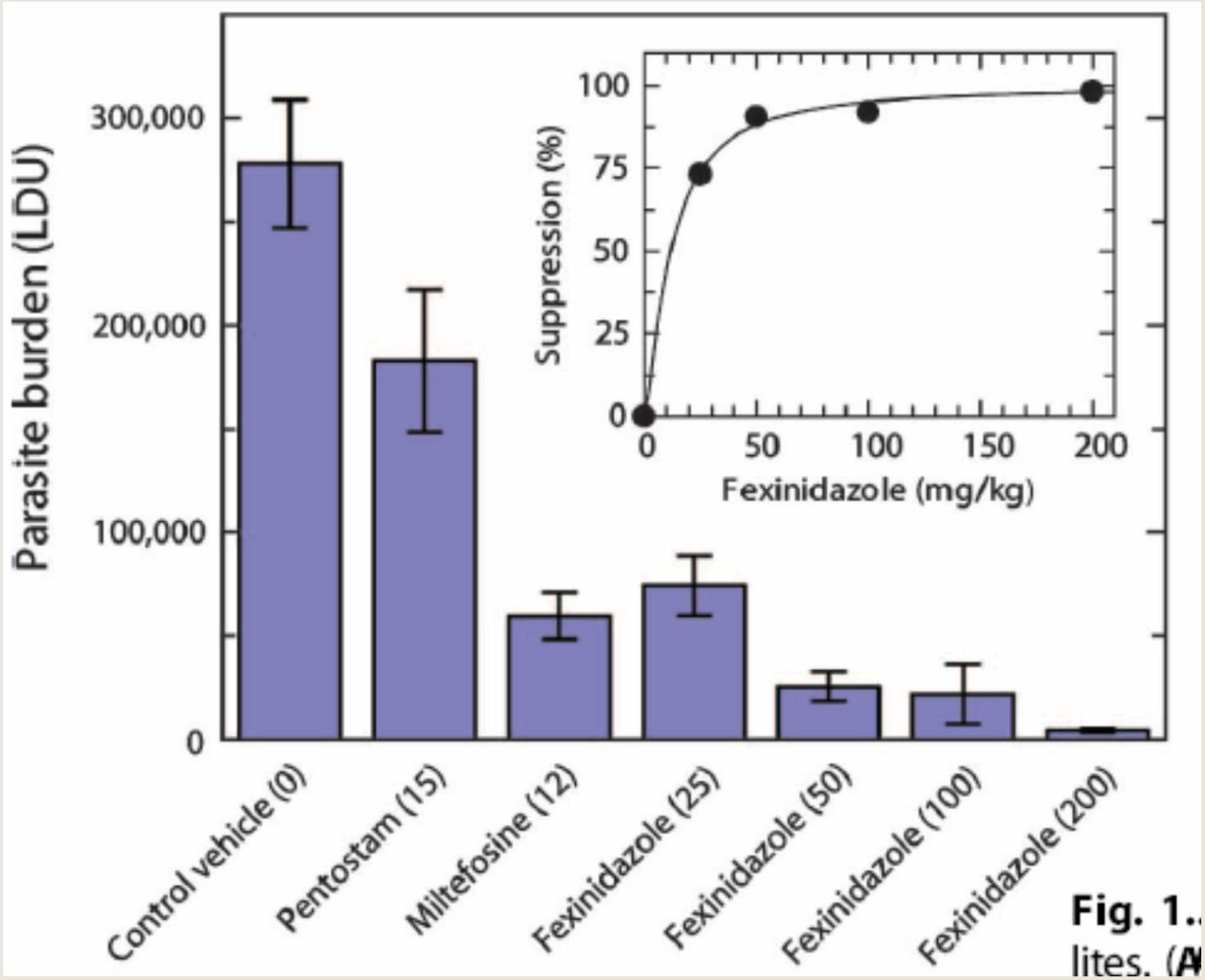


Fig. 1.
lites. (A

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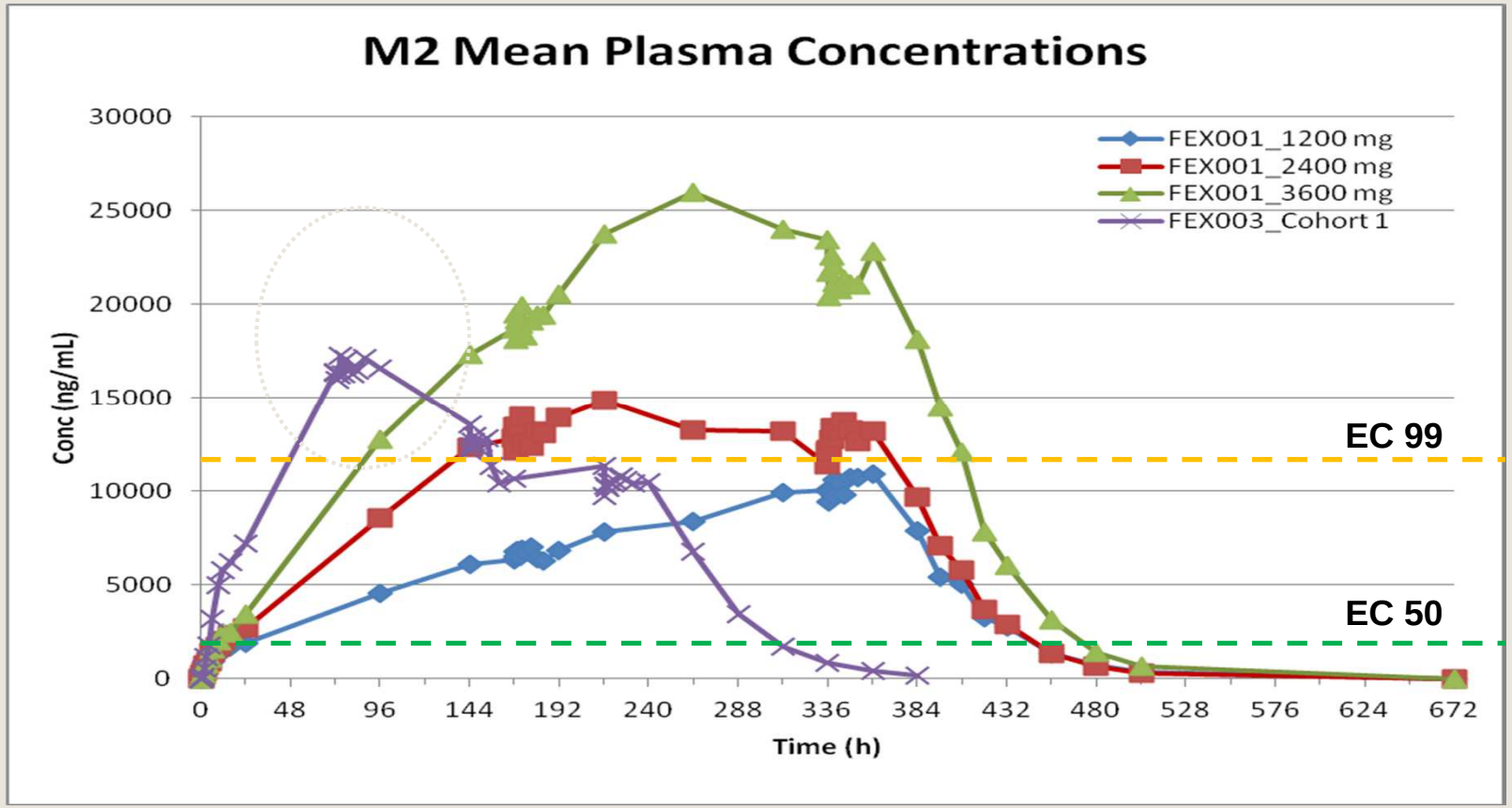
PK summary

- Bioavailability
  - Fexi : rapidly absorbed: median Tmx: 3 – 4 H; mean T1/2: 9-15H
  - M1 : occured rapid : median Tmx: 2-5 H; mean T1/2: 18-20H
  - M2 : occurred slowly: median Tmx: 18-24 H; mean T1/2: 18-25H
- Exposure increased linearly, but not proportional to dose administered
- No saturation of the metabolism
- Steady state in fasted condition :
  - D4 for fexi and M1,
  - D9 for M2
- Free fraction in human : fexi 3 % M1 and M2 > 40%

Rationale for therapeutic dose PK population calculation

Repeated dose under fed condition



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Fexinidazole - Metabolites

- Fexi solfoxide and fexi sulfone, in combination, are
  - Equipotent
  - Additive
- There is accummulation of the drug in liver and spleen
- Their cumulutive blood conc. Exceeds EC_{99} for 30 hours
- These findings underscores the potential of of fexi as a once-daily treatment for VL
- 2 mg/kg human equivalent dose is likely to be effective
- A single oral dose of 1200 mg has been successfully give to human volunteers

Wyllie et al, Sci Trans Med 2010

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Phase I program

118 male subjects of sub-saharian African origin have been exposed to fexinidazole

- Part 1 (SAD) Study Design
  - oral suspension escalation from 100 up to 3600 mg
- Part 2 Cross-over bioequivalence and food effect Study
  - 1200 mg single dose
- Part 3 (MAD) Study Design
  - Three cohorts of 8 subjects (6 active, 2 placebo)
  - Oral tablet (600 mg) *once a day for 14 days 1200mg,2400mg &3600mg*
- Field food effect study (cross-over study)
  - Three cohorts of 12 subjects
- Multiple dose in fed condition
  - Randomized , double- blind versus placebo
  - Two cohorts of 18 subjects (12 active, 6 placebo/ cohort)

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Fexinidazole - To date

- Fexinidazole tested in vitro and in vivo for efficacy in late stage HAT as well as VL
- A dose regimen that should be well tolerated and providing the appropriate exposure was identified after 3 phase 1 studies
- Fexinidazole is entering clinical evaluation in late stage HAT patients in DRC
- Fexinidazole Proof of Concept study for VL is planned to be conducted concomitantly in a small no. of patients in Sudan

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Fexinidazole for VL – Phase II

- Open-label, non comparative, proof of concept study
- Population: max 66 adult hospitalised patients
- Efficacy Primary endpoint: patients cured at D 28 (initial cure)
- Safety
  - Clinical AEs & SAE's
  - ECG (centralised) – Baseline, D4 and 11
  - Extensive Laboratory parameters (Hb, RBC, WCC +diff, Plts – BL, D3, 5, 8, 11, 14 and ALT, AST, Bil, ALP, Na, K, Urea, Cre, - BL, D3, 5, 8, 11, 14)
- PK/PD
- Interim analyses every 10 patients

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Conclusion

- In vitro and vivo data show favorable profile for fexinidazole both in HAT and VL at 200mg/kg for 5 days
- Human dose of 1800mg for 4 days followed by 1200mg for 6 days should provide sufficient exposure for VL
- No safety issue identified. Liver function and QTc will be closely monitored in early clinical studies with patients
- If efficacious and well tolerated, fexinidazole, as an oral treatment, would fill a significant unmet medical need for neglected patients

DNDI-VL-2098
A NITROIMIDAZO-OXAZOLE PRECLINICAL CANDIDATE FOR VL

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DNDI-VL-2098: background

- DNDI-VL-2098 is a nitroimidazo-oxazole identified from a screening campaign containing about 1000 molecules.
- The compound is stable in powder form and as a solution in various media.
- Its anti-leishmanial activity has been assessed *in vitro* and in two animal models

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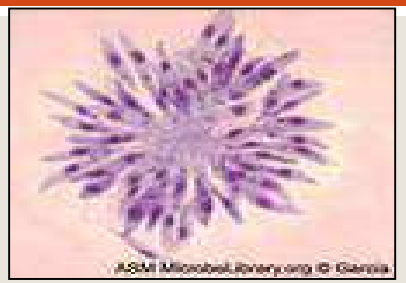
Anti-leishmanial Screening Models

Parasite : ***Leishmania donovani***

Strains : MHOM/ET/67/HU3 (LSHTM)

MHOM/IN/80/DD8 (CDRI)

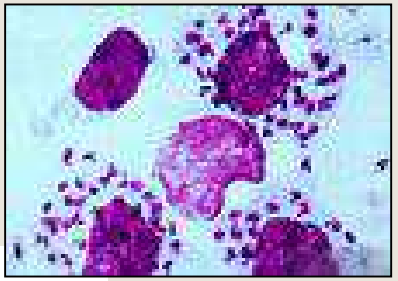


***In vitro* :**

L. donovani amastigote - macrophage model

a) GIEMSA staining technique

b) Luciferase reporter gene based assay



***In vivo* :**

L. donovani - BALB/c Mouse model

L. donovani - Golden Hamster model

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In vitro efficacy

L. donovani strain ID	**DNDI-VL-2098 IC_{50}-µM**	SbV IC_{50}-µM	Amphotericin B IC_{50}-µM	Miltefosine IC_{50}-µM	Paromomycin IC_{50}-µM
BHU1	**0.29**	>150	0.007	0.42	>30
GR265	**1.17**	14.5	0.05	4.6	>30
SUKA001	**<0.74**	10.6	0.053	2.13	>30

BHU1: clinical strain from India, resistant to pentavalent animonials (kindly donated by Prof. S. Sundar
GR265: clinical strain from Ethiopia
SUKA001: clinical strain from Sudan

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In vivo efficacy in the acute mouse model

	Dose mg/kg	% Inh set 1	% Inh Set 2	% Inh Set 3	ED Set 1 mg/kg	ED Set 3 mg/kg
Miltefosine mg/kg p.o. x5 day	12		60.1	47.3		
AmBisome mg/kg i.v. x3 day	1	99.5	90.3	96.1		
sbV mg/kg s.c. x5 day	15	88.7				
DNDI-VL-2098 mg/kg p.o. x5 day	0.78	10.9				
	1.56	48.3				
	3.125	87.5		82.6	ED50=1.5	ED50=2.6
	6.25	99.7		99.9	ED90=3.7	ED90=3.4
	12.5		99.2	98.8		

Dose (mg/kg)	Regimen	Effect
6.25	5 days	99.9/99.3
6.25	3 days (D1, 2, 3)	99.37
6.25	2 days	91.84
12.5	1 day	99.88

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In vivo efficacy in the chronic hamster model

Group	Dose x days	% Inhibition D12	% Inhibition D35
DNDI-VL-2098	50mg/kg x 5	100 ± 0.1 (n=06)	100 ± 0.1 (n=08)
DNDI-VL-2098	**25mg/kg x 5**	**100 ± 0.2 (n=06)**	**97± 4 (n=05)**
DNDI-VL-2098	12.5mg/kg x 5	84 ± 11 (n=05)	71 ± 7 (n=04)
Miltefosine	30mg/kg x 5	100 ± 0.1 (n=05)	99 ± 1. (n=05)

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Absence of relapse (chronic hamster model)

Dose regimen x 5 days, once daily	1st Biopsy - Day 12 Mean % Inhibition ± SD	2nd Biopsy- Day 35 Mean % Inhibition ± SD	3rd Biopsy-Day 50 Mean % Inhibition ± SD
DNDI-VL-2098 (50mg/kg)	(i) 99±0.4 (n=06)	(i) 91± 14 (n=04)	ND
	(ii) 100 ± 0(n=06)	(ii) 100±0 (n=03)	ND
	(iii) ND	(iii) 100±0 (n=05)	(iii) 100 ± 0(n=03)

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In vivo efficacy in overinfected hamsters

Compound	Grade of infection	% Inhibition at Day 12	% Inhibition at day 35
DNDI-VL-2098	2+	100 ± 00(n=08)	100 ± 00(n=04)
Miltefosine	2+	100 + 00 (n=05)	100 + 00 (n=03)
DNDI-VL-2098	3+	100 ± 00 (n=04)	100 ± 00 (n=03)
Miltefosine	3+	100 ± 00 (n=03)	100 ± 00 (n=02)
DNDI-VL-2098	4+	100 ± 00 (n=05)	100 ± 00 (n= 03)
Miltefosine	4+	99.91 ± 0.05 (n=05)	100 ± 00 (n= 04)

Grade 2+: 10-50 amastigotes per 100 cells
Grade 3+: 50-300 amastigotes per 100 cells
Grade 4+: >300 amastigotes per 100 cells
Normal infection produced by 5-10 amastigotes per 100 cells

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Safety Profile

- **Secondary Pharmacology**
  - On a panel of 68 receptors and channels, DNDI-VL-2098 did not show significant binding affinity at 10 μM.
- **Safety Pharmacology**
  - moderate inhibitor of the hERG channel (IC_{50}=10 μM)
  - No effect on CNS and respiratory functions was observed up to the highest dose tested (500 mg/kg)
- **Toxicology**
  - non genotoxic and non clastogenic
  - MTD>2000 mg after single dose administration in mice and rats and > 250mg/kg in dogs after 14 days of treatment (NOAEL=250mg/kg).
  - No ECG effects observed in dogs up to 250 mg/kg
  - 14 day studies on going

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Conclusions

- DNDI-VL-2098 is active against *L. donovani in vitro* and *in vivo*. *In vitro*, no differential strain sensitivity has been observed from a large panel of VL strains and selected CL strains.
- *In vivo*, DNDI-VL-2098 is potent:
  - in the acute mouse model of VL with a minimal effective dose of 6.25 mg/kg over 3 days.
  - In the chronic hamster model, DNDI-VL-2098 is active from the 25 mg/kg dose and no relapses are observed up to 50 days post treatment.
  - The compound is as efficacious in overinfected animals (grade 2+ and 3+). No adverse events have been observed regardless of doses
- Not genotoxic or clastogenic, no ECG signal
- Full safety evaluation on going

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