



The Future of Global Treatment of Cutaneous Leishmaniasis

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DNDi
Drugs for Neglected Diseases initiative

Current treatment recommendations for CL

Diseases Severity



No treatment

Small lesion, *L. major* or *L. mexicana*, not in face or joint

Topical

≤ lesions, ≤ 4 cm diameter, not in face or joint

- Thermoherapy
- Liquid Nitrogen
- IL SSG

Systemic

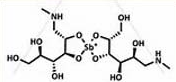
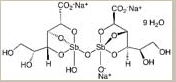
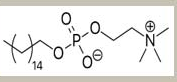
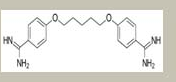
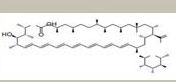
Those who failed with a topical, > 4 lesions, or lesions > 4 cm diameter, any anatomical location.

- Antimonials
- Miltefosine
- Pentamidine
- Amphotericin B deoxycholate
- AmBisome

Combinations

- Antimonials + allopurinol for *L. recidivans*
- Antimonials + paromomycin for *L. aethiopica*
- Antimonials + Pentoxifiline for MCL

Current Treatment Options for CL





				
Meglumine antimonate	Sodium Stibogluconate	Miltefosine	Pentamidine	Liposomal Amphotericin B
IM or IV or IL	IM or IV or IL	PO	IM or IV	IV
20 mg / kg / day / 21 days	20 mg / kg / day / 21 days	1.5- 2.0 mg /kg / day / 28 days	4 mg/kg/ 3 doses in 7 days	3.0mg /kg /day /7 doses
OW~53%; NW~78% Variable depending on species and region		55-90%. Depending on species and region	<i>L. guyanensis</i> ~75-90%. <i>Others</i> 35% - 75%	Mainly for complicated forms
Painful injections Nephro & Cardio toxicity Hepatotoxicity Pancreatitis		Teratogenic GI toxicity Nephro-Hepatotoxicity	Painful injections Renal and cardiac toxicity, Hyperglycaemia, B/P alterations	Rigors Childs Hypokalaemia Anaphylaxis

Systemic

Variable efficacy, serious toxicities, only one is oral & rest are painful IV/IM

Topical

Variable efficacy, some times lengthily, painful, only for non-complicated cases

			
Liquid Nitrogen	Intralesional antimonials	Liquid Nitrogen + IL antimonials	Thermotherapy
1-2 applications per week	3-10 applications	3-10 applications	1-3 applications
50-85%	~53% OW ~75% NW	75-82% in OW	55-90%
Nitrogen supplies, multiple applications	Painful injections, several applications, difficult to standardized	Multiple applications, painful,	Requires local anesthesia, AE Grade II (2 nd grade burns)

Room for improvement the treatment for CL

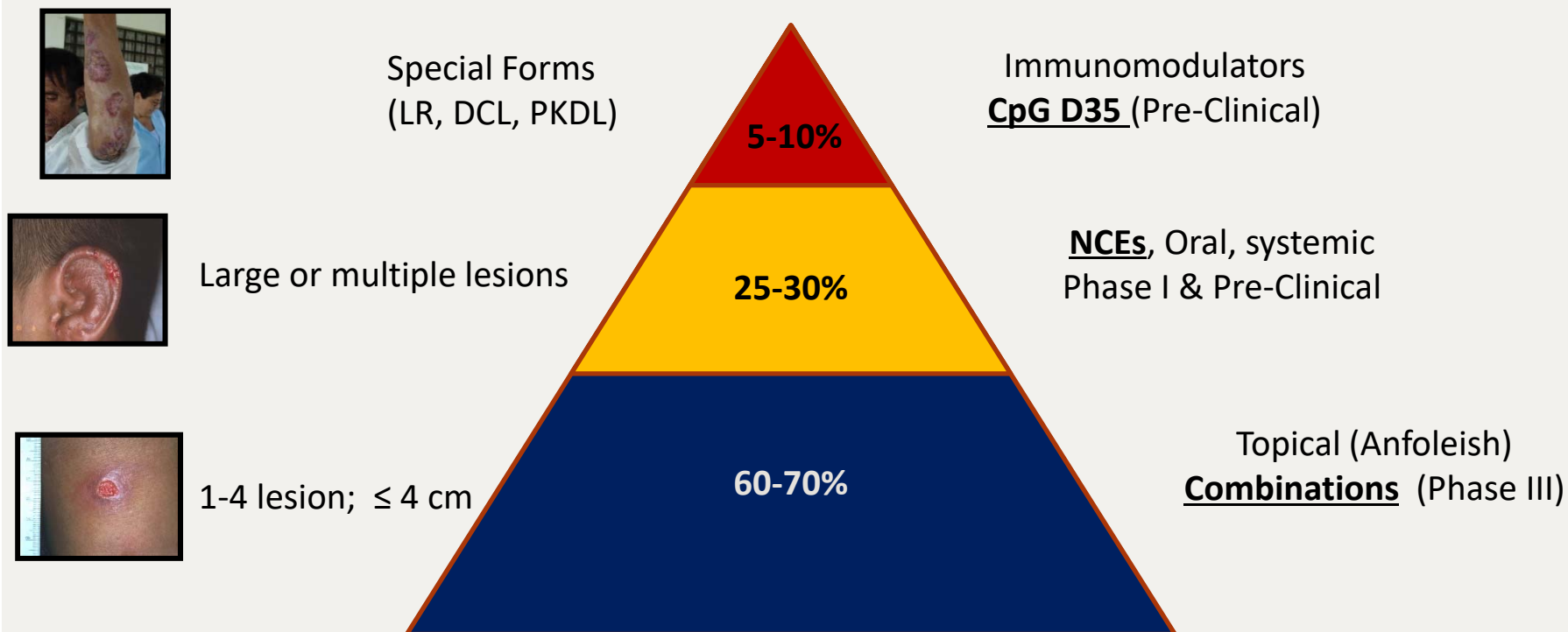
- Improve efficacy from ~53-70% to $\geq 90\%$
- Reduce AEs rate from ~40-75% to $\leq 30\%$
- Reduce length of Tx from ~21-84 d to 14 -21 d
- Increase compliance from ~50% to $\geq 90\%$
- Speed of healing from ~6-17 W to 6-13 W

DNDi's CL Strategy

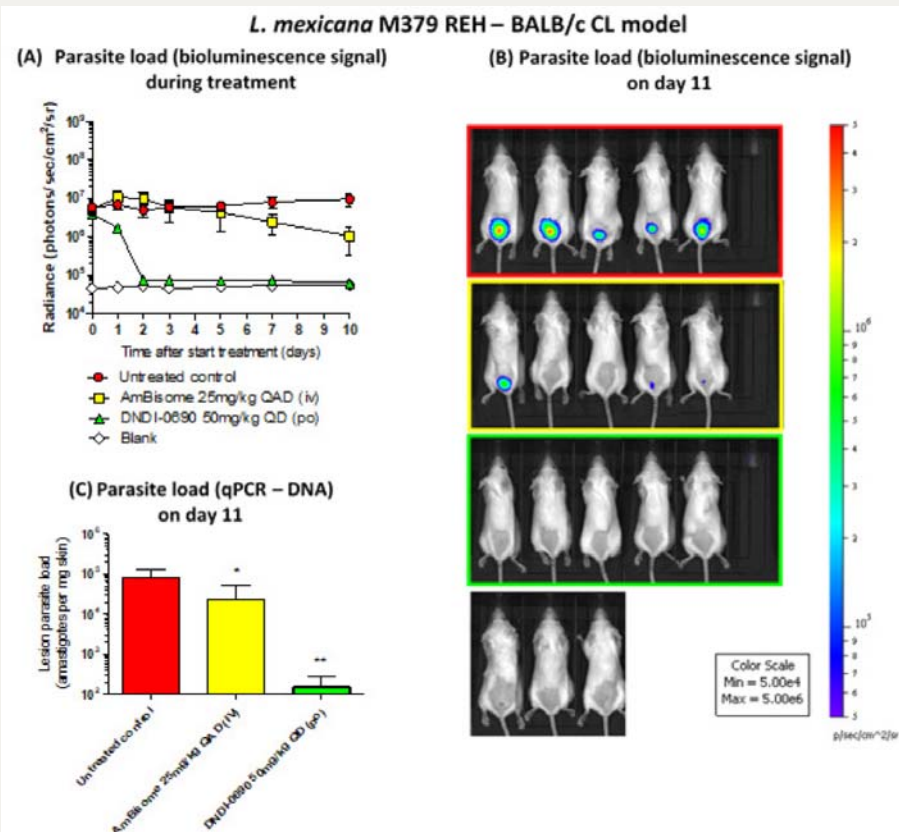
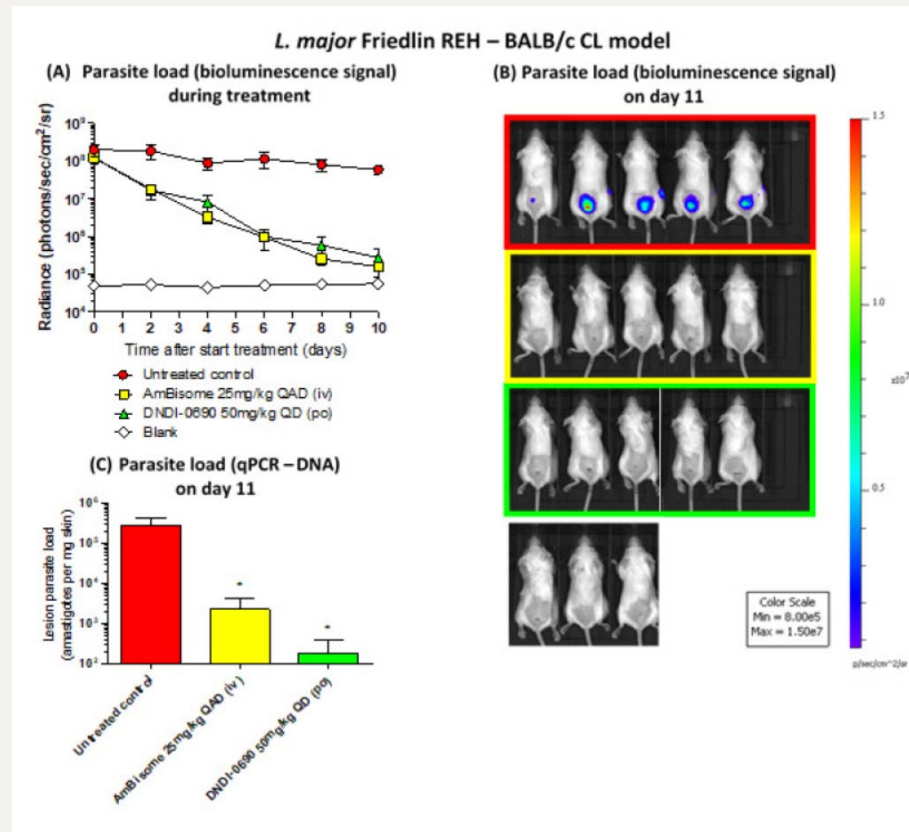
To achieve short, safe, non-invasive, efficacious, affordable and field-friendly treatments for CL or at least for lesions caused by *L. tropica* and *L. braziliensis*.

Disease presentation

Activity / Project

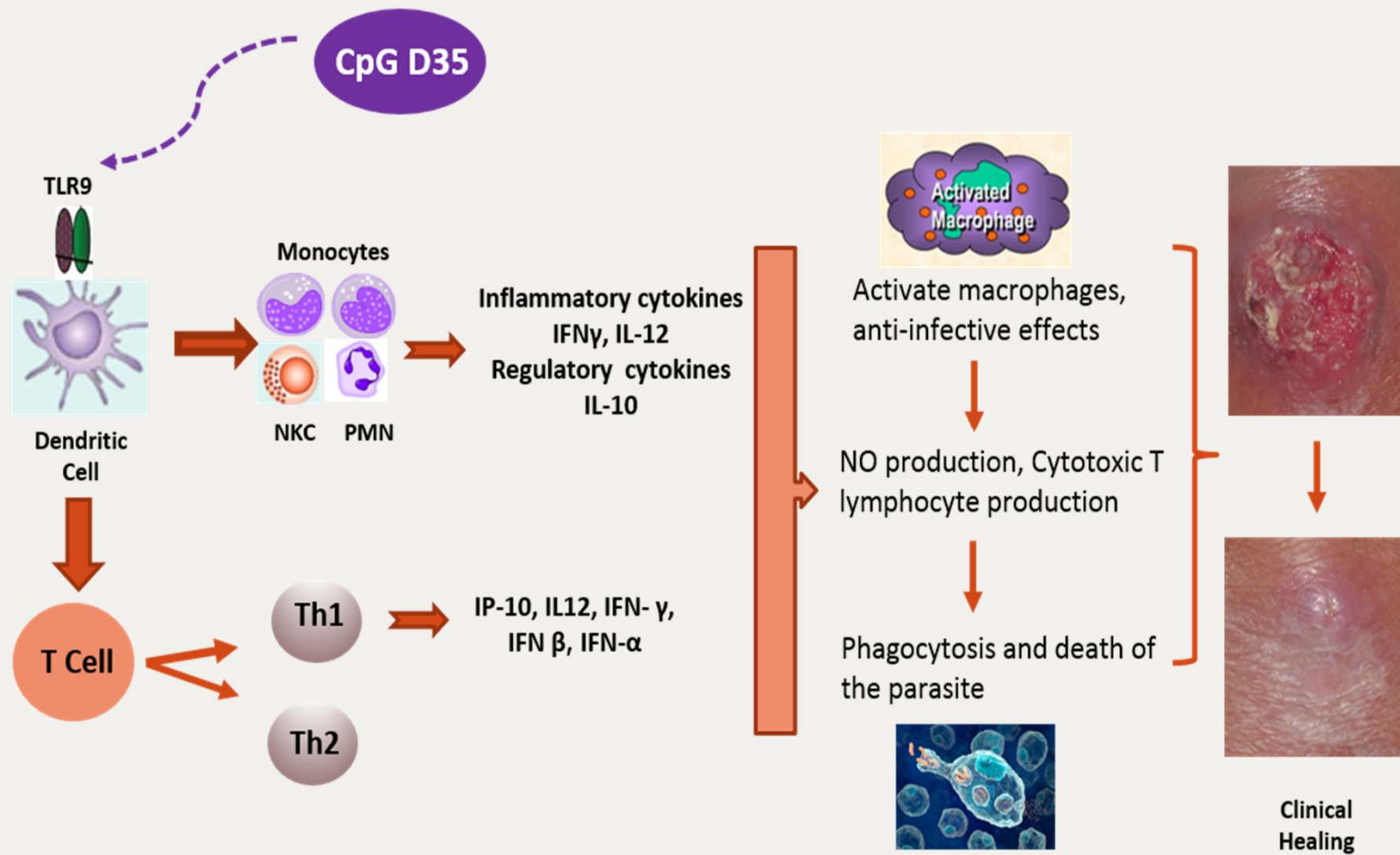


Anti-leishmanial efficacy of oral DNDI-0690 (50 mg/kg, once daily for 10 days) in an OW and NW CL model infection of BALB/c mouse

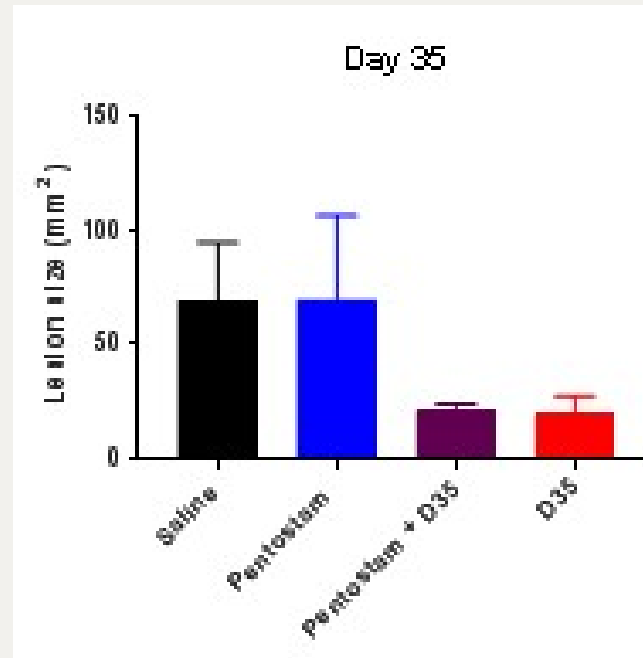
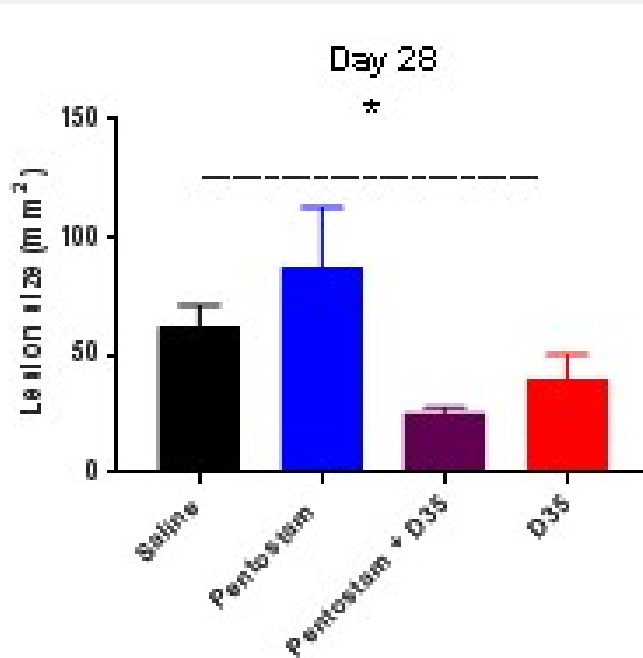


Wijnant GJ, et al. 2019. Pharmacokinetics and pharmacodynamics of the nitroimidazole DNDI-0690 in mouse models of cutaneous leishmaniasis. Antimicrob Agents Chemother. Jul 1. pii: AAC.00829-19. doi: 10.1128/AAC.00829-19.

CpG D35



Lesion size in infected Rhesus monkeys by treatment group



* p < 0.05; ** p < 0.01

Time to re-epithelization (Mean # of days) per treatment group

	Saline	Sb ^V 5mg/kg	CpG D35	CpG D35 + Sb ^V 5mg/kg
Mean (# days)	28.5	23.7	17.5	14.3
SD	7.6	2.3	4.0	7.4
SEM	3.8	1.3	2.0	3.7

Combination Study

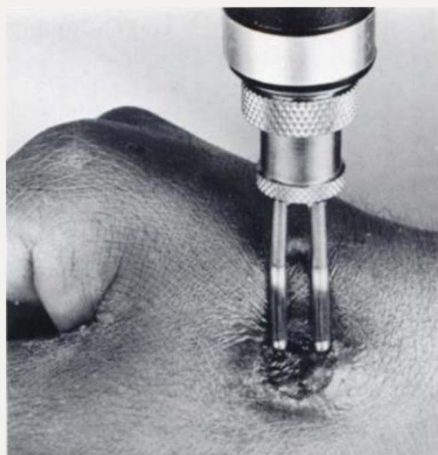
Rationale

It will take 5-10 more years to develop a new Tx for CL.

Our best option right now is to better use the existing approved treatments in combination.

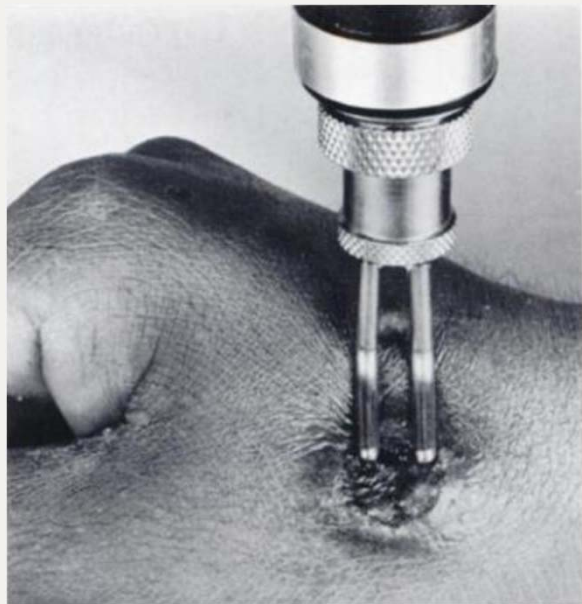
DNDi proposal

To test the efficacy and safety of a combined therapy using thermotherapy (TT) (one application, 50°C for 30") + miltefosine (2.5 mg/kg/day for 21 days) for the treatment of uncomplicated CL in NW



Background information

The ThermoMed™ device, which produces heat utilizing radio-frequency technology remains the most tested local heat modality. Its safety and efficacy have been demonstrated in multiple clinical trials. It is WHO recommended and FDA approved its use for the treatment of CL, among other skin conditions



- ❖ Miltefosine is the only oral treatment currently available for treatment of leishmaniasis.
- ❖ In 2014, was registered at FDA for the treatment of infections due to *L. braziliensis*, *L. guyanensis* and *L. panamensis*.
- ❖ Included in PAHO treatment guidelines and PAHO strategic fund list of medicines in 2015



Combination (TT + MLT) Study in Peru and Colombia

- PoC study completed on January, 2019
- The Combination of TT + MLT showed to be significantly better than TT alone for the treatment of uncomplicated CL in NW (**PP at D180: TT 64.3%; Combination 84%**).
- Subjects with lesions due to *L. braziliensis* and/or *L. peruviana* responded better to the Combination (22 out 27 = 74.1%) than to TT alone (7 out 19 = 36.8%).
- **Next Step:** Conduct a phase III study comparing the non-inferiority of the Combination against the current recommended treatment (SSG) and miltefosine. FV/FP expected by Q2-2020

Other Potential New Treatments for CL

Topical

SinAmpholeish
PMM – WRAIR
Simvastatin

Orals

Extend the label of Miltefosine (OW)
D-121 (Oblitas)
18-MC (Hebron)

Combinations

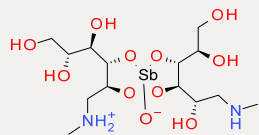
GM-CSF + Miltefosine

Immunomodulators

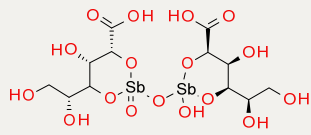
GM-CSF
Canakinumab (Ilaris)

Drugs for Cutaneous Leishmaniasis

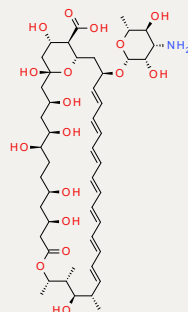
Promising new series for a brighter future



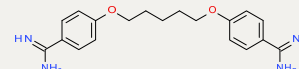
**Meglumine
antimonate**



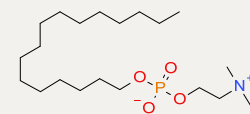
**Sodium
Stibogluconate**



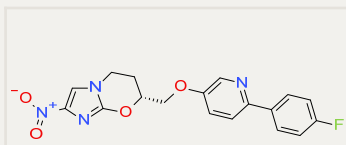
Miltefosine



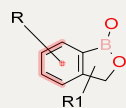
Pentamidine



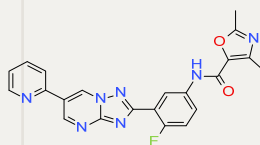
**Liposomal
Amphotericin B**



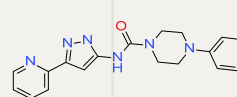
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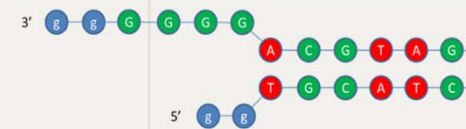
DNDI-6148



GNF6702



Aminopyrazoles



CpG D35



Thank You

DNDi
Drugs for Neglected Diseases *initiative*