BEST SCIENCE FOR THE MOST NEGLECTED

CUTANEOUS LEISHMANIASIS: DNDi STRATEGY

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Drugs for Neglected Diseases *initiative*

1st International Conference on Cutaneous Leishmaniasis,

10 to 13 August 2015; Manaus, Brazil

Drugs for Neglected Diseases Initiative, DNDi

DNDi is a collaborative, patients' need-driven, non profit drug research and development organization that is developing new treatments for neglected diseases.

HQ in GVA, Regional offices in Rio de Janeiro, Nairobi and New Delhi, Japan, USA, Malaysia.

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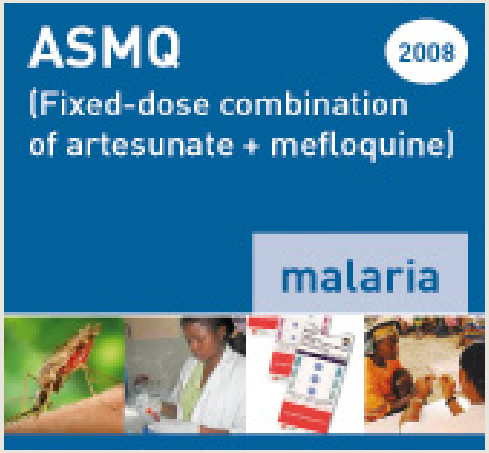
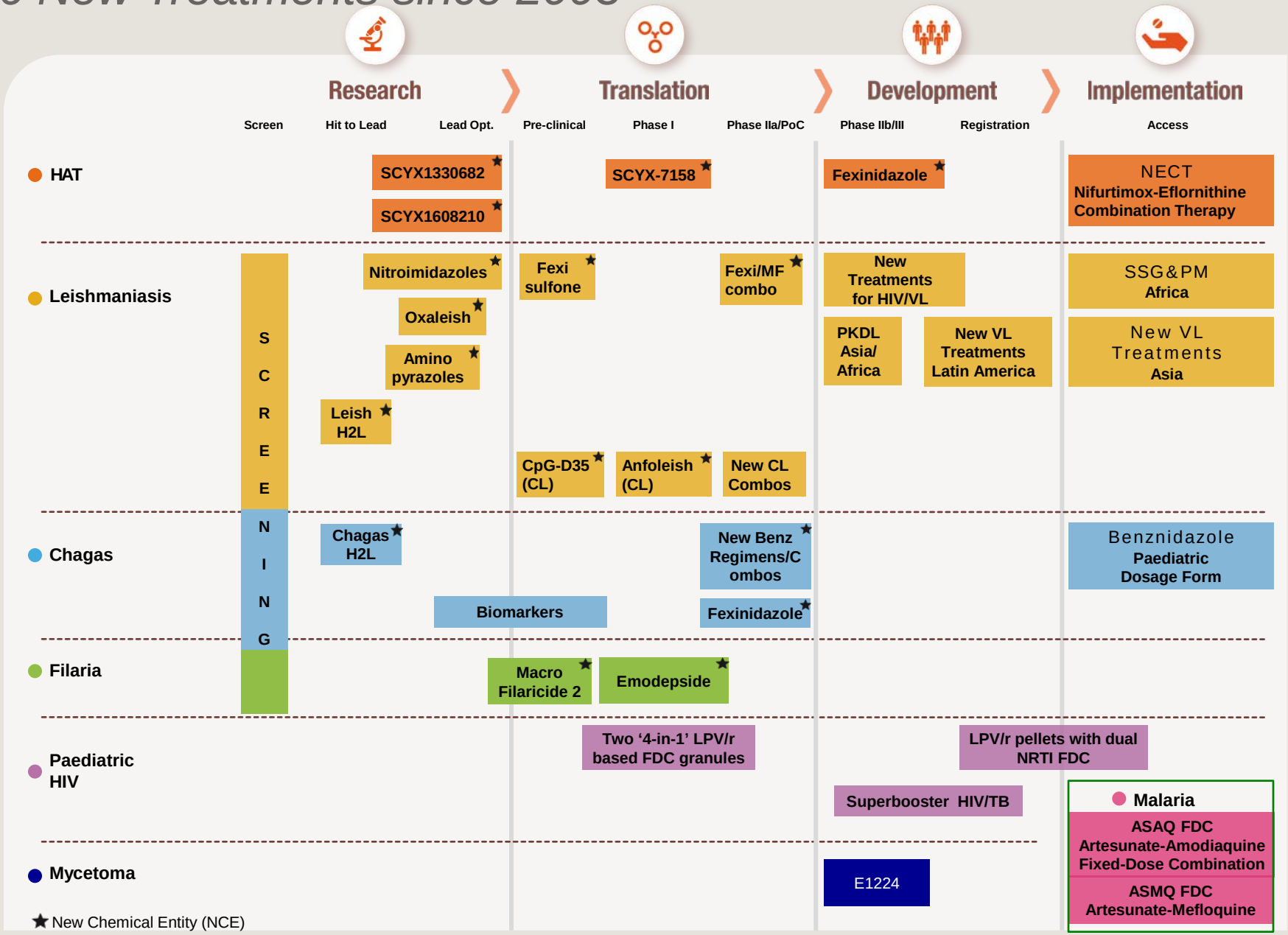
6 New Treatments Developed Since 2007



☑ Easy to Use ☑ Affordable ☑ Field-Adapted ☑ Non-Patented

DND*i* Portfolio June 2015

6 New Treatments since 2003



Cutaneous Leishmaniasis Program

2010	CL included in DNDi portfolio
2011	CL strategy approved and endorsed by SAC and BoD
Q1 2012	Anfoleish selected for its clinical development
Q1 2014	Enrolment of first patient
Q2 2015	Enrolment of first 30 patients completed. DSMB met and recommended continuation of the enrolment.
Q2 2015	Combinations approach approved by R&D and SAC
2012	Literature review completed
Q1 2013	In vitro – in vivo studies of selected compounds (none selected for further studies)
Q4 2014	Inclusion of CL strains in the screening of VL compounds
Q2 2015	Firsts orals compounds identified (in vitro and in vivo studies)
Q1 2014	CpG D35 approved by SAC and Q2 2014 by BoD
Q4 2014	CpG D35 Demo project merged with VL Demo project
Q3 2015	Licence agreement with NIH and CRADA with FDA completed
Q3 2015	Initiation of CMC and Tox package studies

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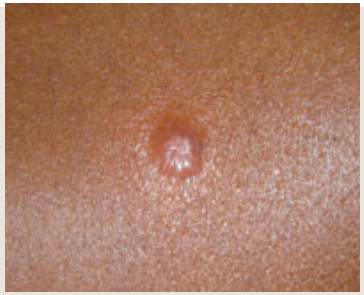
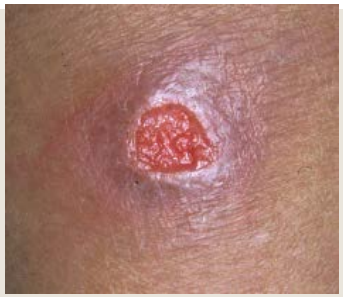
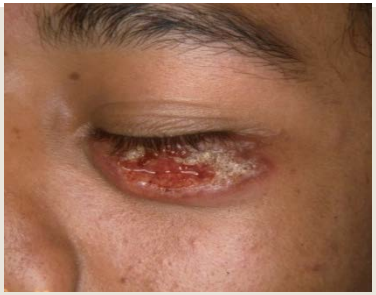
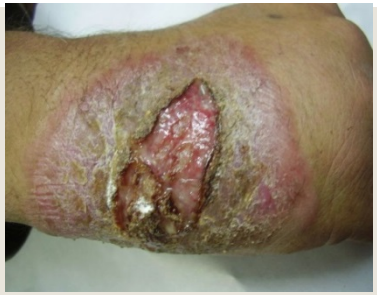
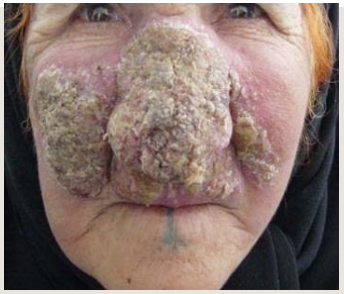
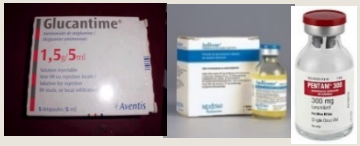
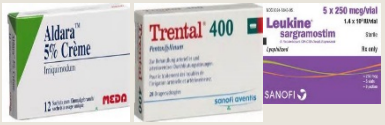
Spectrum of the disease, current treatment options and gaps

Diseases Severity

No Tx	Topical	Syst oral	Syst parenteral	Combinations
Variable self healing rate (0-40% at 6M) Might take long time Transmission in ACL	Multiple applications Painful Equipment Access Cosmetic problems	Variable efficacy Teratogenic GI and renal problems Availability Cost	Toxicity Painful Difficult to administrate Compliance Efficacy is ⬇	Limited information Variable efficacy

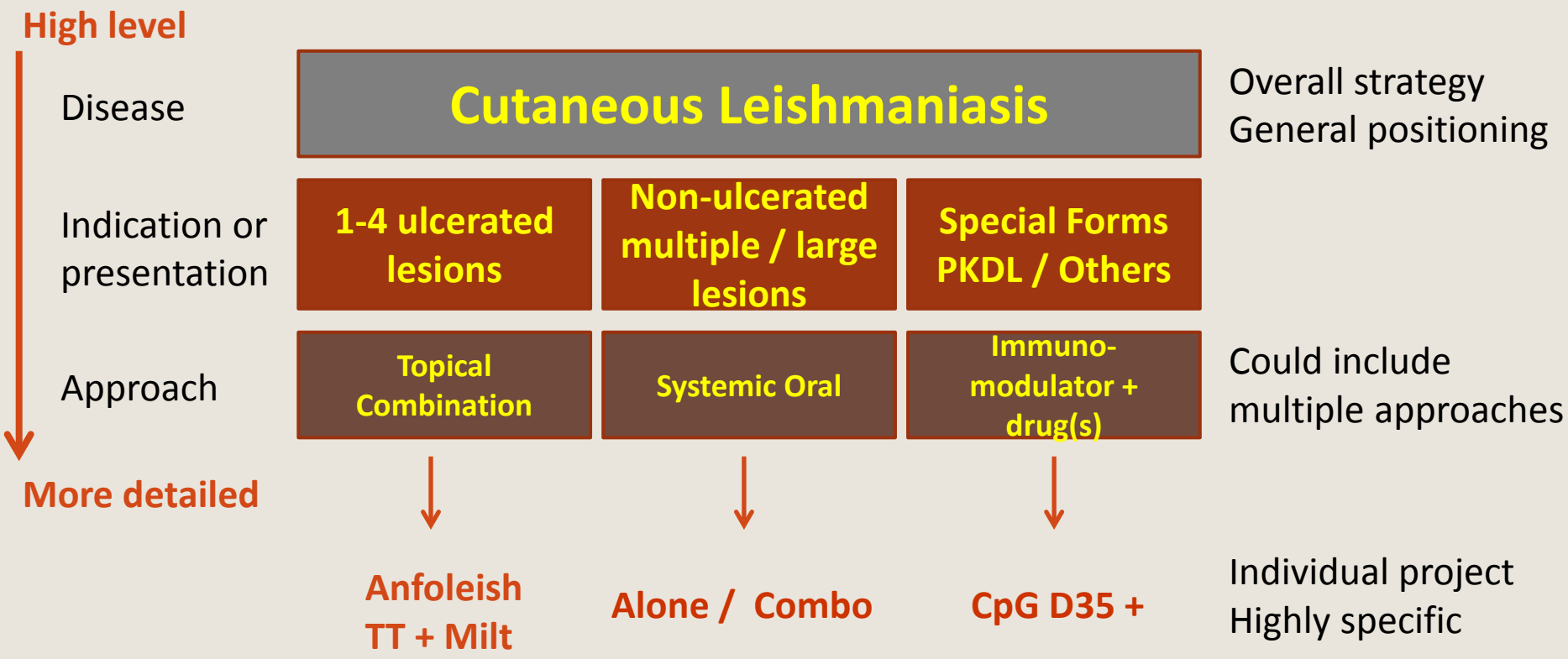


The “gap”

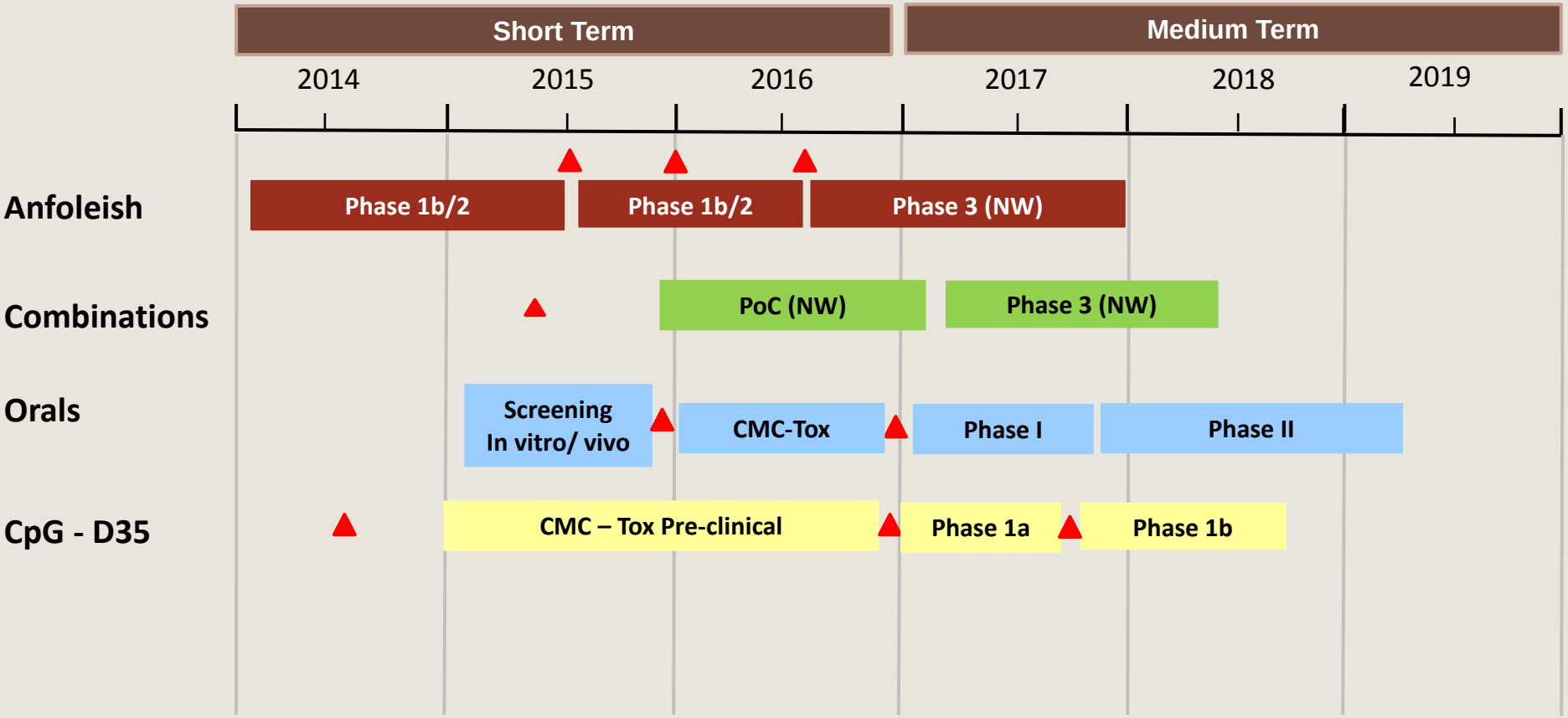
Topical & oral drugs, safe, effective against all forms of CL, with superior cosmetic results, at a low-cost and easy to use in rural areas

DNDi CL Strategy: Objective

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.*



CL Roadmap



▲ Go / No Go decisions

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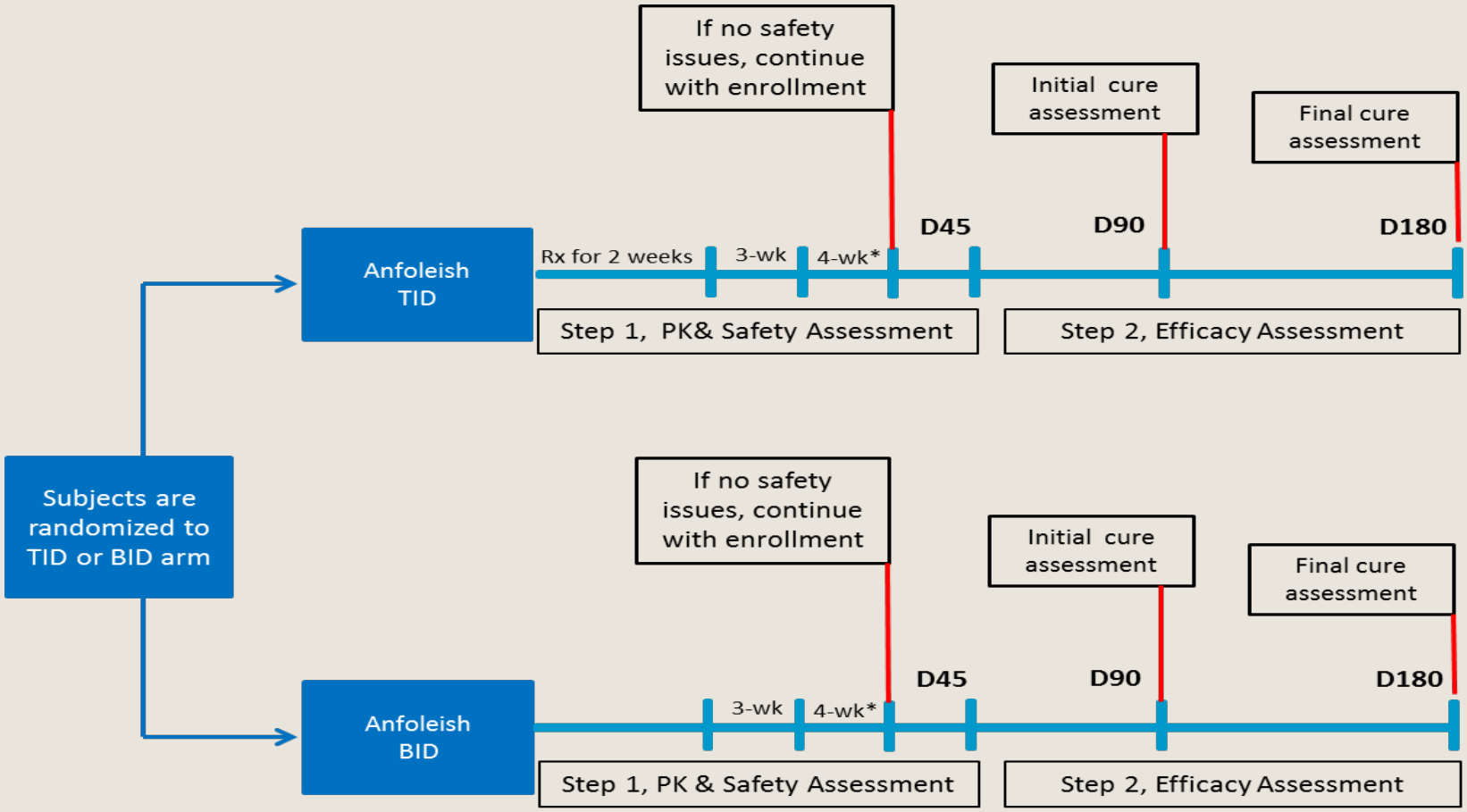
Topical →Anfoleish

- Anfoleish is a topical formulation containing 3% of AmB
- The 3% concentration was based on previously available AmB topical products in the market (Fungizone cream, which is no longer available).
- Formulations in the range 0.3%-3% w/w were evaluated and was found that Amphotericin B concentrations at 3% offered the best option.
- Pre-clinical studies showing encouraging results in animal models.
- Open label study in humans shows to be very efficacious (10 out 11)

Safety, PK, and Efficacy of topical 3% Amphotericin B cream (Anfoleish) for the treatment of uncomplicated cutaneous leishmaniasis in Colombia



* Enrollment will be paused after enrolling 15 subjects per arm.

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Systemic → Oral Drugs

- Literature review (DNDi Brazil)
- Screening of drugs/compounds against cutaneous leishmaniasis *in vitro* (Imperial College London)

  ~ 50 compounds already in the market or in late stage of development were screened against *L. tropica* and *L. braziliensis*
- Effect of ravuconazole (E1224) in BALB/c mice infected with *L. tropica* (Pasteur Institute, Iran) and in gold hamster model infected with *L. braziliensis* (PECET, Medellin, Colombia)
- *In vitro and In vivo* evaluation of fexinidazole against CL *Leishmania* strains (FIOCRUZ)

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Literature Review

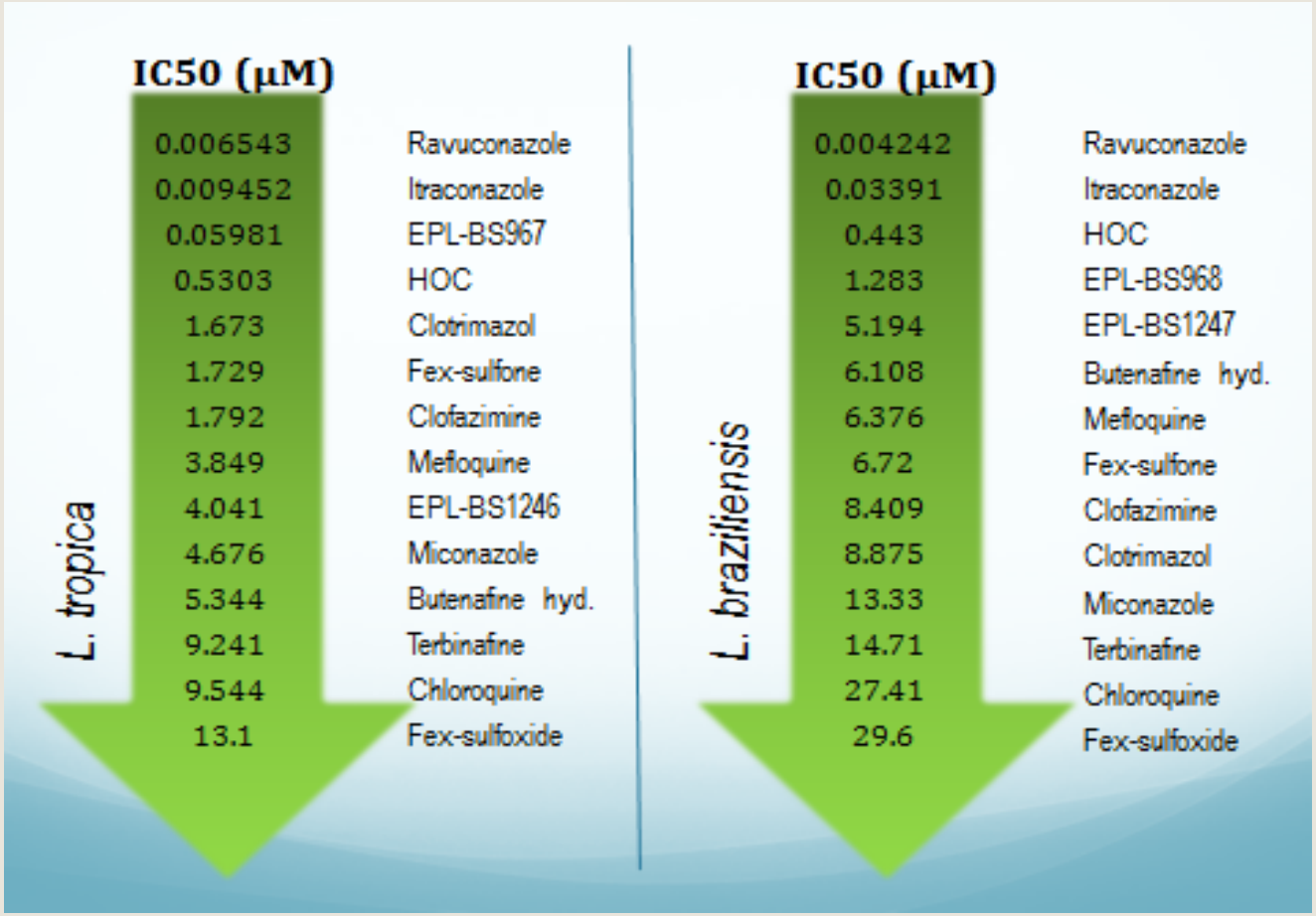
Drug	Clinical Trials	# CT	In Vivo studies	#	In Vitro studies	#
Azithromycin	Weak OW & NW (45% - 83%	8	La, Lb, Lm (Weak)	3	Lm, La, Lb (Strong)	3
Chloroquine	Weak	1	No evidence	0	No evidence	0
Chlorpromazi	Weak (Case report)		Lm, L mex, L aeth (Weak)	2	Lt, L mex, Lm, L aet (Strong)	3
Cimetidine	Weak	1	La, L mexicana (Strong)	2	No evidence	0
Ciprofloxacine	Weak	1	No evidence	0	Lp (Strong)	2
Clofazimine	Weak	1	La, Lm (Weak)	1	La, Lm, Lb, Lt, L. mex (Strong)	2
Clotrimazole	Weak	1	La, Lm (Weak)	1	Lt (Weak)	1
Dapsone	Strong to weak	5	L?	1	Lm (Strong)	1
Furazolidone	Weak	1	No evidence	0	Lm, La, Lb, L chagasi (Strong)	3
Itraconazole	Strong - Controversial	10	Strong	1	Lm (Weak)	1
Mefloquine	Weak - Controversial	7	La (Weak)	1	No evidence	0
Miconazole	Weak	3	La, Lm (Weak)	1	Lt (Weak)	1
Omeprazole	Strong (in combination)	2	Lb (Weak)	1	No evidence	0
Rifampicin	Strong to weak	13	Lm (Weak)	3	La, Lm, Lt (Weak-Controversial)	4
Terbinafine	Weak	1	La, Lm (Weak)	2	Lb, La, Lm, L mex. Sinerg. w Ketc	4
Flucoanzole	Strong but methodol prob	2	No evidence	0	No evidence	0
Posaconazole	Case report (Strong)		La (Strong)	1	La, Lm, Lb, Lp, L mexicana (Weak	1
Zinc Sulphate	Weak	1	?		Lm (Weak)	1

WEAK: efficacy < 60% and/or < standard treatment; Efficacy range variable but < 60% and/or < standard treatment in RC trials

CONTROVERSIAL: efficacy range variable according to clinical trials and methodological issues (nC, nR trials, small number of patients, < 3mFU)

STRONG: efficacy > or = 60%, or > or = standard treatment

Oral Drugs: IC50 of the most active compounds against *L. braziliensis* and *L. tropica*



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CpG ODN D-35

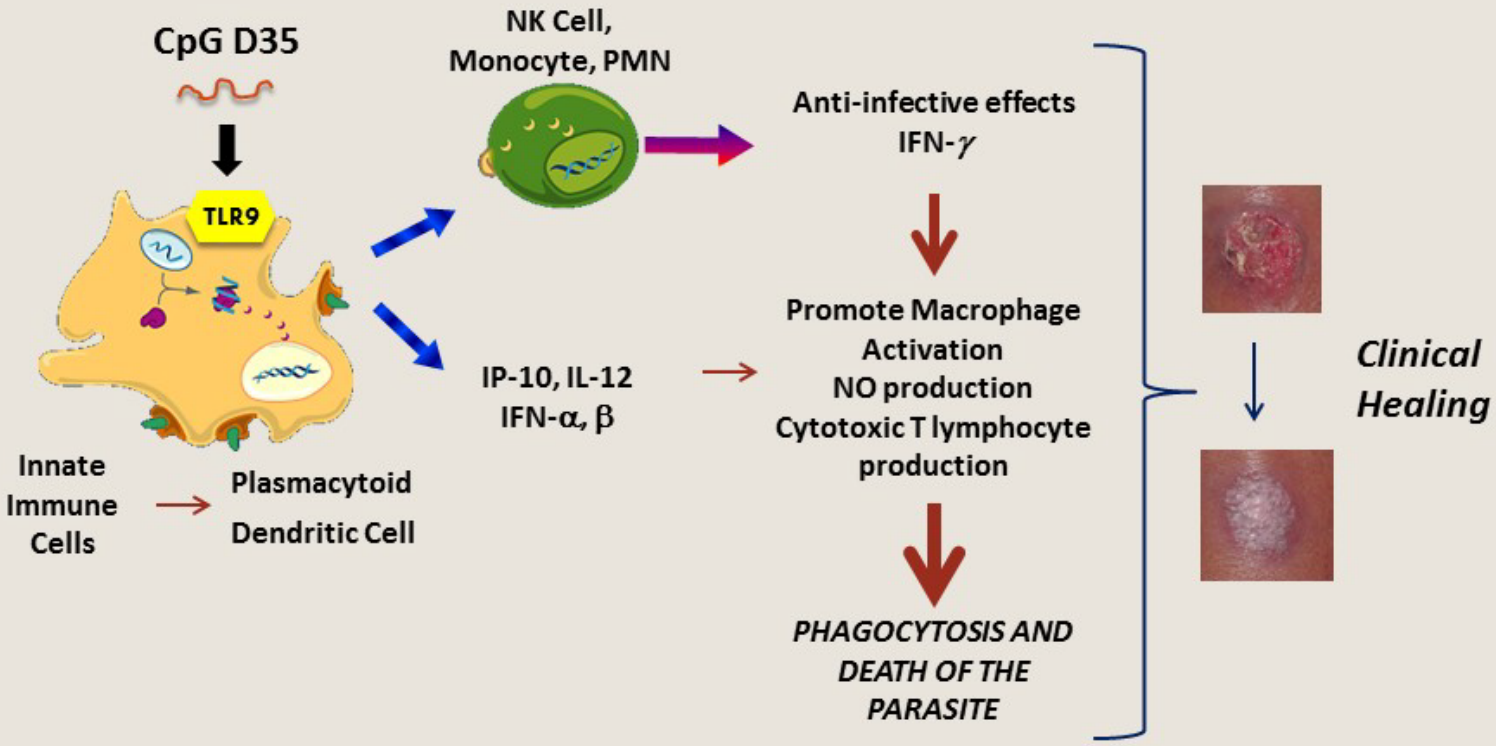
Class D CpG ODN D35 was selected based on its activity profile, the results on animal studies, the quality of the studies and the willingness for collaboration of the patent's owner

Favorable characteristics includes:

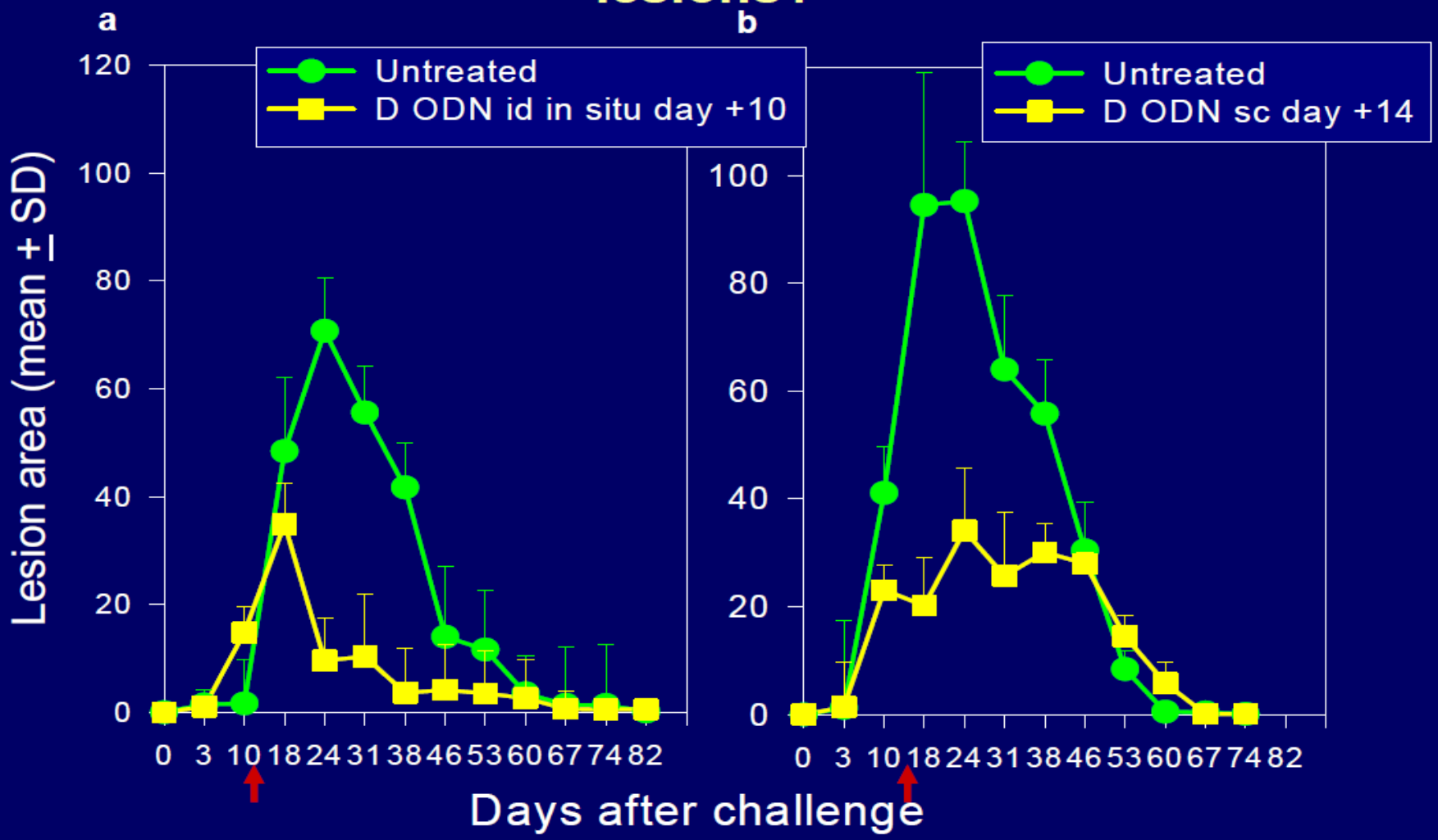
- Structure optimized for humans
- *In vitro* stimulation profiles of cells from monkey and human are similar
- Tested in a monkey CL model (with *L. major*) with encouraging results (reduction of pathogenicity, enhanced healing - even without a drug)
- No apparent toxicity
- Single or two low doses required
- Simple production amenable to large scale manufacturing at affordable cost (depending on needed dose for humans – to be reviewed further)
- Should results be favorable, D35 could be applicable for treatment of other disease forms.

CpG D35 Mode of Action

- Tested in a monkey CL model (with *L. major* and *L. amazonensis*) with encouraging results (reduction of pathogenicity, enhanced healing - even without a drug).
- No apparent toxicity in animal models.
- One dose of 100 µg/kg produce the desired immune response and efficacy in animal models.
- Effect evident even when administrated therapeutically (10-15 d after lesion development)



Can CpG ODN be used to treat established L.major skin lesions?



- 4-6 macaques per group challenged with 10^6 metacyclic promastigotes
- Treated 15 days after challenge with 500 ug CpG ODN ID or SC (0.5mg/kg).

Improve Current Treatment Strategies → Combinations

- **Thermotherapy (1 application, 50^{0}C x 30") + Miltefosine for 3 weeks.**

  - Even though progress has been made for VL treatment, for CL it seems that what is currently available will probably represent almost the entire therapeutic arsenal for the coming years. *(Filling the gap with other formulations: CR-RCT: Sb^v 53-78%; Milt 78%, LH 71%)*

  - Multiples treatment combinations have been tested in the past and at least two are currently in use, specially in the EMRO region (*SOP for TT dev. by WHO available*)

  - Theoretically, combining a topical with a systemic treatment offers the best chances to increase efficacy and reduce the length of treatment. *(Efficacy from ~75% to ≥ 90%; Length of Tx from 28d – 14-21d and GII AEs from ~10% to ≤5%)*

  - A combination which requires the less contact with health providers and easily to implement in the field. *(Fits TPP)*

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Annex 4.
Standard operating procedure for thermotherapy

Thermotherapy is an available technique for the treatment of cutaneous leishmaniasis patients by application of local heat at the site of lesion with a portable, battery-operated, localized current field radiofrequency generator (ThermoMed 1.8; Thermo-surgery Technologies).

Indication

- Papule, nodule or ulcer <4 cm.
- Number of lesions <4 cm.
- Location of the lesion should not be close to the eyes, nose or lips.

Method

A single thermotherapy treatment (one or more applications of localized heat of 50°C for 30 seconds, depending on lesion size). The area between the electrodes covers 49–73 mm^2. Therefore, several thermotherapy applications may be required to cover a lesion.

Procedure

- Disinfect the lesion and 2 cm border of healthy skin around the lesion with antiseptic (e.g. 0.1% chlorine dioxide solution).
- Anaesthetize the lesion with 1% lidocaine HCl.
- Moisturize the lesion with sterile saline solution.
- Apply the heat locally for 30 seconds.
- Apply chlorine dioxide gel to the lesions and then cover them after treatment.

Patient follow-up

To evaluate the outcome of thermotherapy, follow-up after completion of treatment should be scheduled at 14, 30, 45 and 180 days. It will be important to explain to patients that in case the lesion does not improve they should return to the health facility at any time.

WHO, 2014. Series 35,

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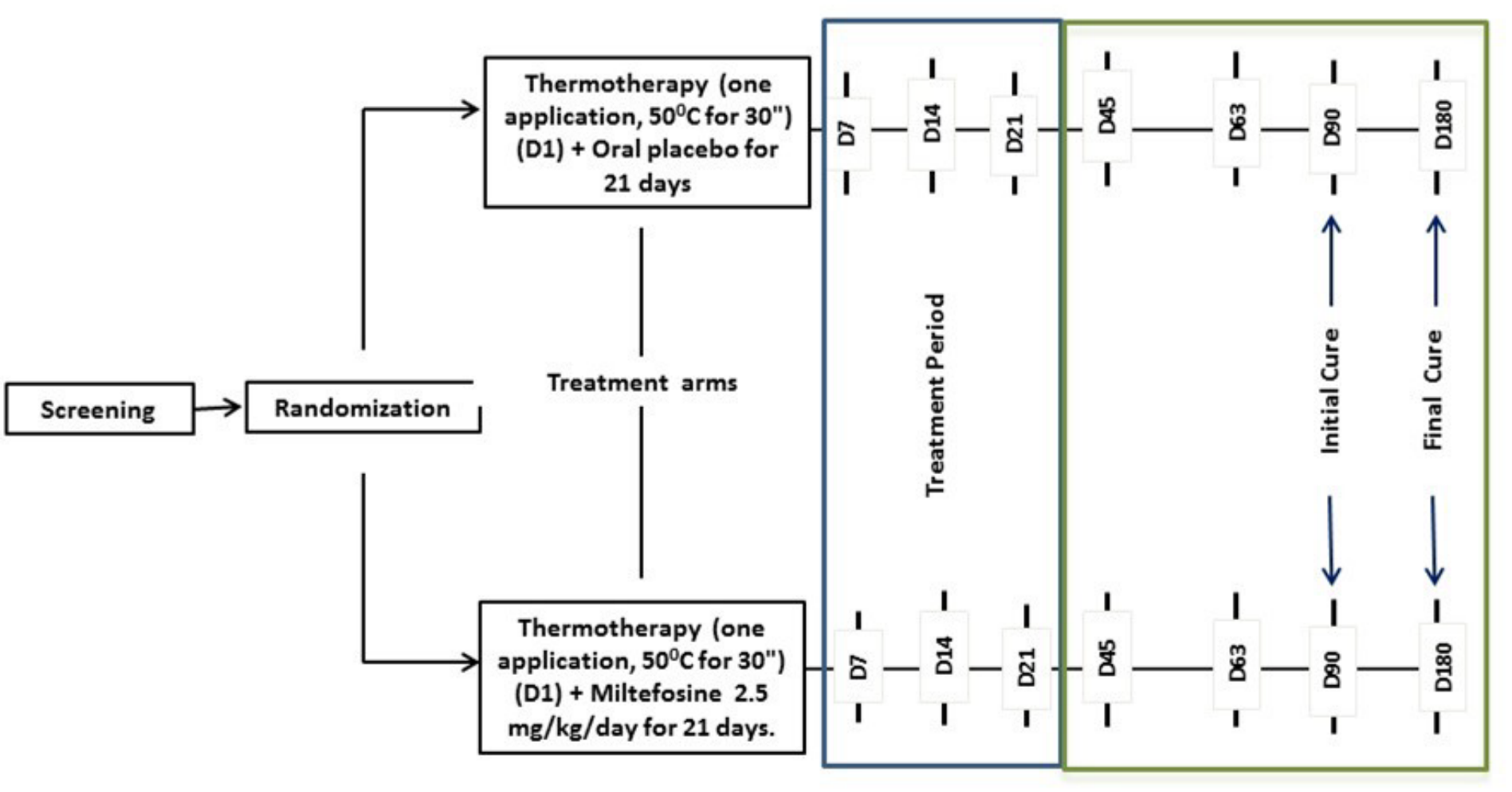
A randomized, double blind, multicenter study to determine the efficacy and safety of combining thermotherapy and a short course of Miltefosine for the treatment of uncomplicated cutaneous leishmaniasis in the New World'



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Thank You

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