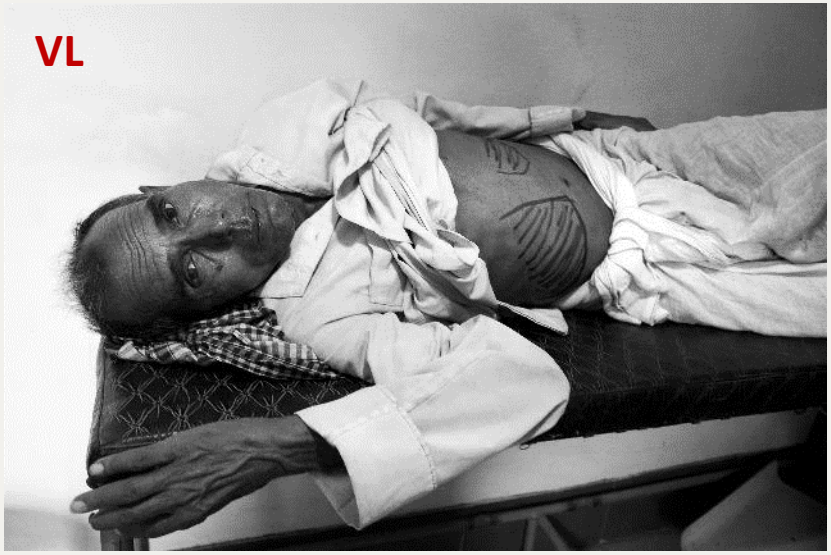
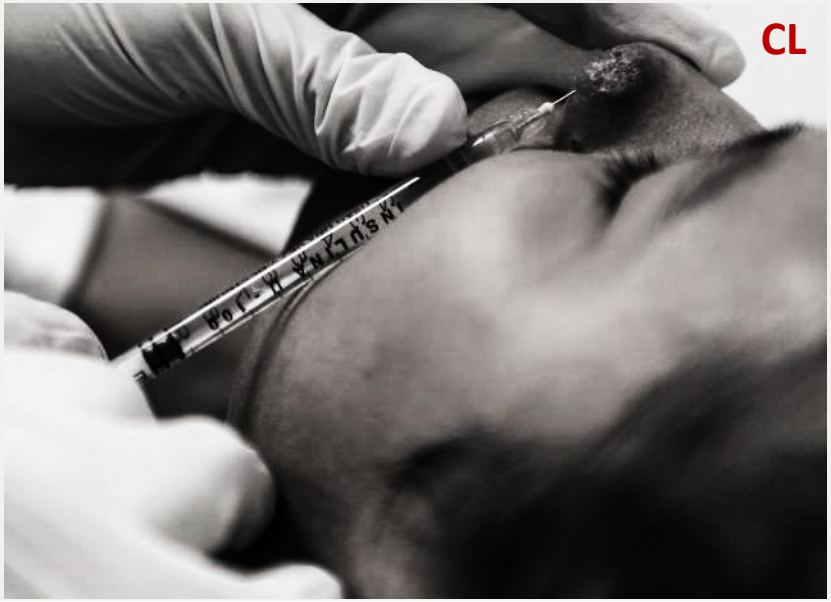
Visceral Leishmaniasis Strategy

Kampala, 03rd October 2018

DNDi
Drugs for Neglected Diseases *initiative*

Leishmaniasis: unmet medical needs





- Disease of poverty
- Multiple manifestations
- Inadequate treatments
- Targeted by WHO and SDGs

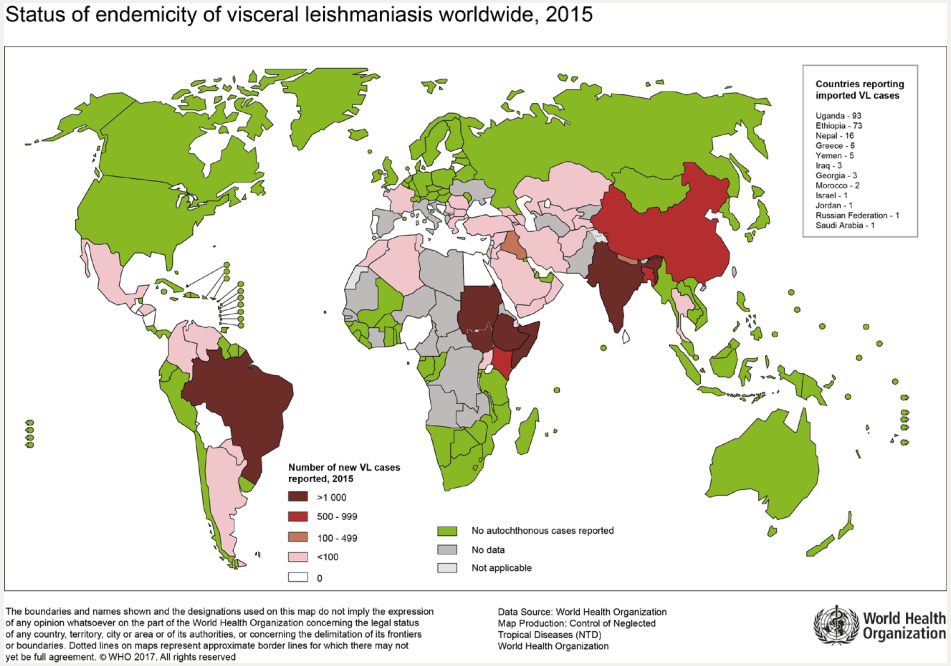
Visceral Leishmaniasis (VL)

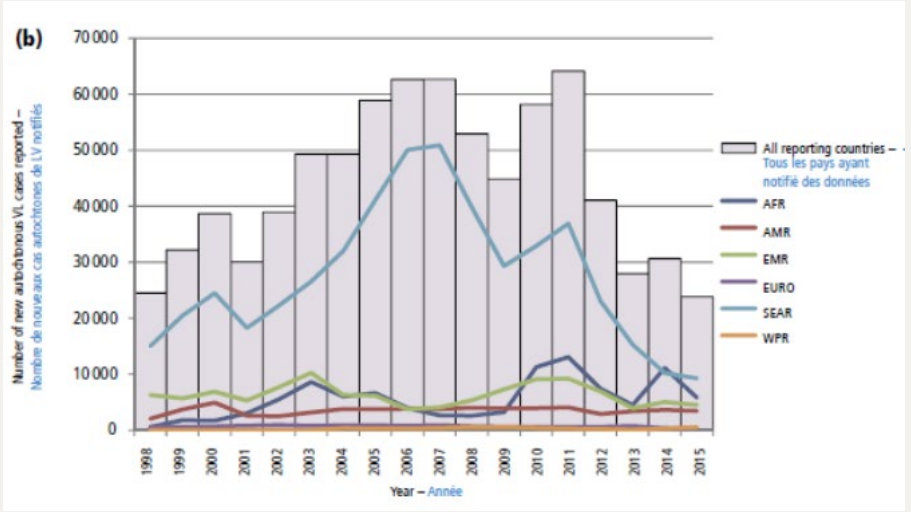
- 50,000 – 90,000 cases/year
- > 50% are children
- 82 countries worldwide
- 20,000 - 30,000 deaths/year
- 556 million at risk in high burden countries

Cutaneous Leishmaniasis (CL)

- 900,000 –1,200,000 cases/year
- 91 countries worldwide
- 399 million at risk in high burden countries
- Social stigmatization

Three epidemiological hot-spots for VL

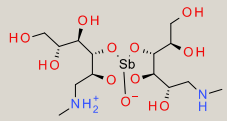
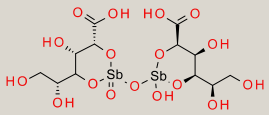
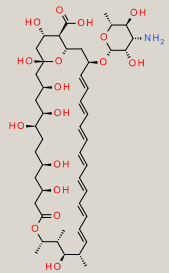
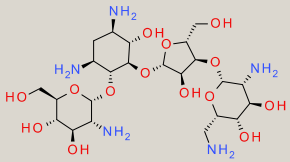
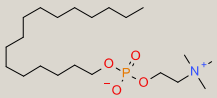




	WHO country profile, 2004-2008		WHO report, high-burden countries, 2014	
Region	Cases reported/year	Estimated annual	Cases reported/year	Estimated annual
Latin America	3,661	5,000 to 7,000	3,571	not informed
Eastern Africa	8,569	30,000 to 40,000	16,413	24,157 to 41,813
Indian subcontinent	42,619	160,000 to 320,000	10,311	12,373 to 13,015
	Alvar et all, 2012; PLOS One 7(5): e35671		WHO WER (38) 2017, 92: 557-572	

Current drugs for leishmaniasis

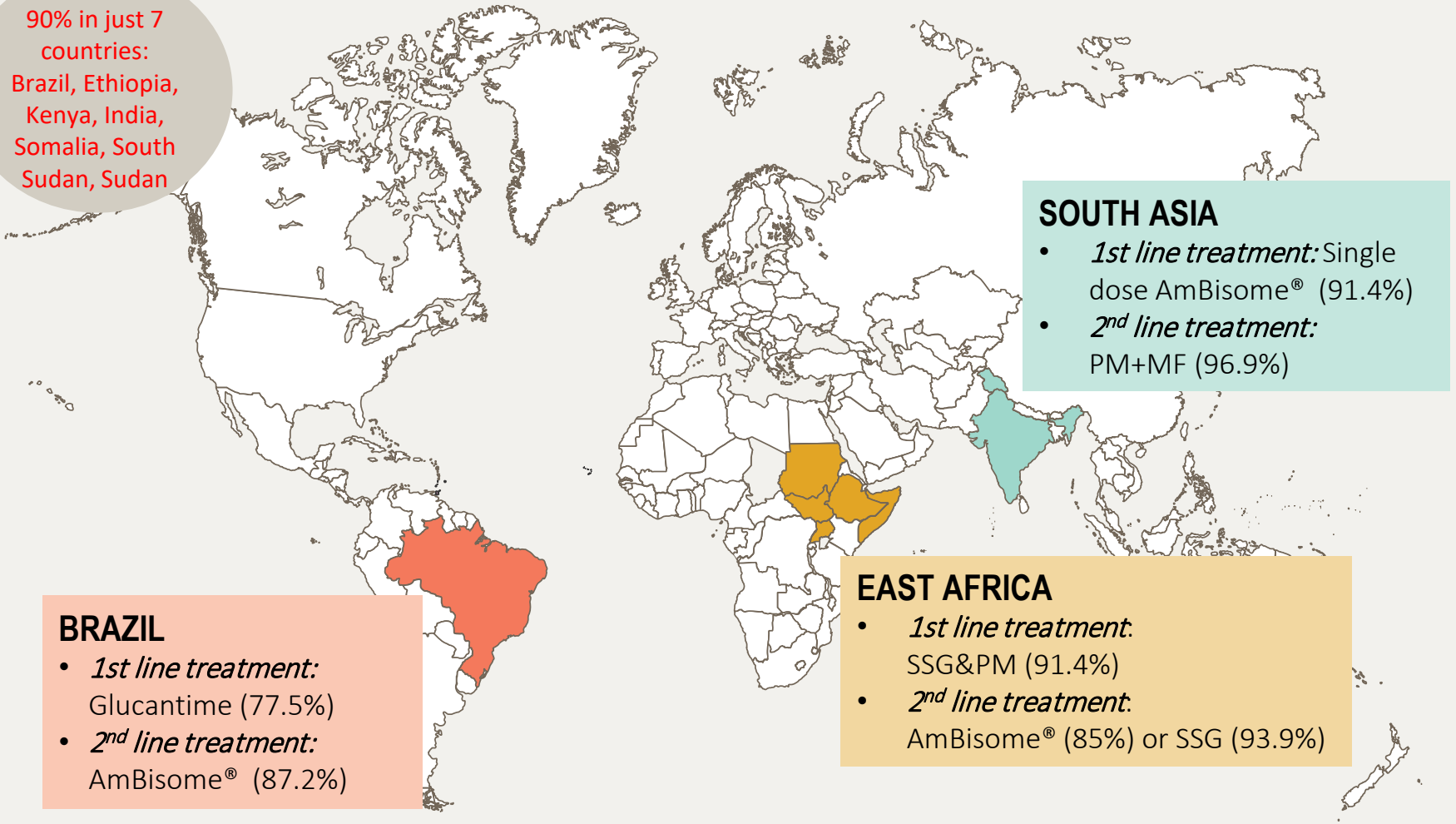
- Variable efficacy, serious toxicities, only one is oral & rest are painful iv/im
- Urgent need for new effective, safe, and convenient treatments

				
MW 525, clogP -3.8	MW 664, clogP -4.2	MW 924, clogP -2.3	MW 616, clogP -6.1	MW 409, clogP +1.3
Meglumine antimoniate	**Sodium Stibogluconate (SSG)**	**Liposomal Amphotericin B**	**Paromomycin sulfate**	**Miltefosine**
Slow iv or im infusion	Slow iv or im infusion	2h iv infusion	im	po
20mg/kg/day, 30 days	20mg/kg/day, 30 days	10-30mg/kg total, 1-10 days	15-20mg/kg/day, 21D	1.5-2.0mg/kg/day, 28D
35-95% depending on area, resistance in India	35-95% depending on area, resistance in India	>95% efficacy in India, variable response in Africa	93-95% India 64-85% Africa	94-97% India 60-80% Africa
• painful injections • cardiotoxicity • hepatotoxicity • Pancreatitis	• painful injections • cardiotoxicity • hepatotoxicity • Pancreatitis	• rigor & chills • nephrotoxicity • hypokalemia • Anaphylaxis	• painful injections • nephrotoxicity • hepatotoxicity • Ototoxicity	• teratogenic • gastrointestinal toxicity • hepatotoxicity

Current treatments/region

Efficacy at 6 months post-treatment is indicated

90% in just 7 countries: Brazil, Ethiopia, Kenya, India, Somalia, South Sudan, Sudan



SOUTH ASIA

- *1st line treatment:* Single dose AmBisome® (91.4%)
- *2nd line treatment:* PM+MF (96.9%)

EAST AFRICA

- *1st line treatment*: SSG&PM (91.4%)
- *2nd line treatment*: AmBisome® (85%) or SSG (93.9%)

BRAZIL

- *1st line treatment:* Glucantime (77.5%)
- *2nd line treatment:* AmBisome® (87.2%)

Large variations in efficacy of the same treatment from region to region

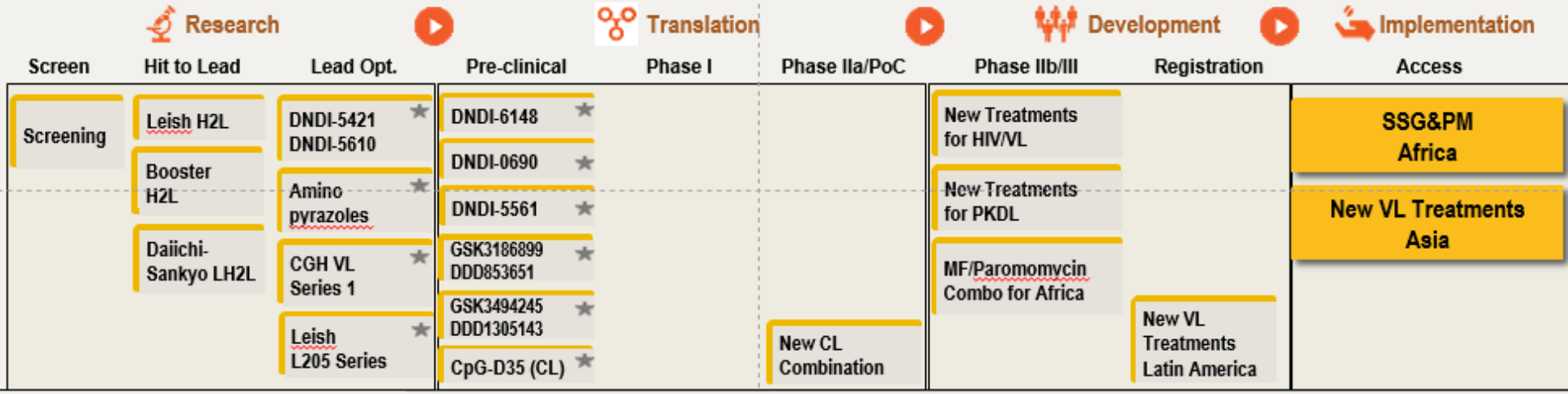
	Monotherapies					Combination therapies				
	SSG or MA	LAB (20-21 mg/Kg)	LAB (SD, 10 mg/Kg)	MF (2.5mg/Kg/d x 28 days)	PM (15mg/Kg/d x 21 days)	SSG-PM	LAB + SSG or LAB+MA	LAB + MF	PM + MF	LAB + MF
Asia	35 - 95%	> 95%	≥ 95%	90-94%	94.6%	NA	NA	> 97%	> 97%	> 97%
Eastern Africa	93.7%	85% (71-100%)	58% (33-100%)	72%	63.8% (14 - 96%)	91%	87%	77%	Phase III trial ongoing	NA
Latin America	77.5%	87.2%	NA	43% (67% for 42d)	NA	NA	83.9%	NA	NA	NA

SSG: *sodium stibogluconate*
MA: *meglumine antimoniate*
LAB: *liposomal amphotericin B*
PM: *paromomycin*
MF: *miltefosine*

DNDi R&D Portfolio, Leishmaniasis — June 2018

Long-term strategy:
Development of new field-adapted oral combination treatments with NCEs

Short-term strategy:
Improving treatments with existing tools



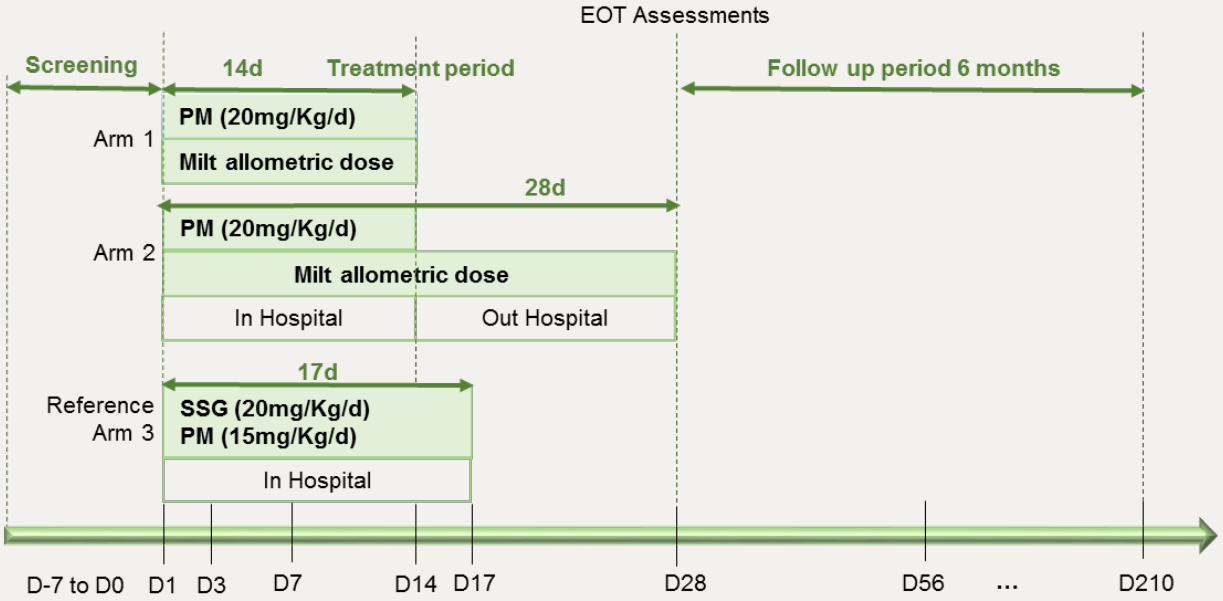
To develop a safe, efficacious and field-adapted combination therapy for VL in eastern Africa by 2020

Phase III MF/PM clinical trial:

An Open Label, Phase III, Randomized Controlled, Multicentre Non-Inferiority Trial to Compare Efficacy and Safety of Miltefosine and Paromomycin with SSG and PM Combination for Treatment of Primary Visceral Leishmaniasis (VL) Patients in Eastern Africa

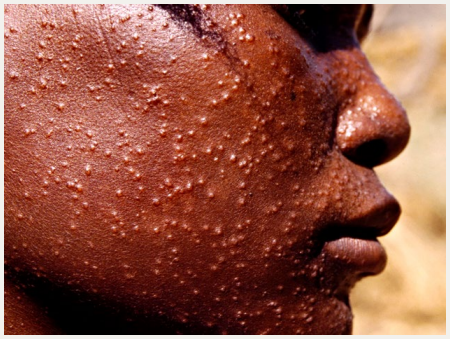
Secondary objectives: safety, PK, PD, compliance to oral treatment in outpatient settings

- Countries: Ethiopia (1), Kenya (2), Sudan (2) and Uganda (1); 6 sites + 2 MSF sites
- Patient population: confirmed primary VL patients 4-50y old, HIV neg, signed ICF
- Sample size: 192/arm, total of 576 VL patients



PKDL clinical trial in Sudan

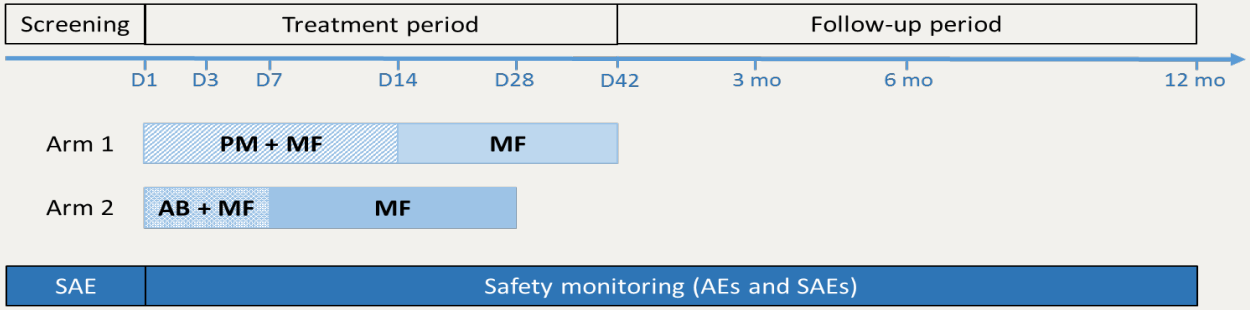
Open label, non-comparative, randomised, multicentre phase II clinical trial to assess new regimens for PKDL Rx in Sudan



Target population: Confirmed PKDL case by clinical presentation and demonstration of parasites by microscopy in a skin smear or by PCR, with documented stable or progressive disease for at least 6 months or grade 3 PKDL

Objectives:

- to assess safety, efficacy of the 2 regimens MF/PM and Amb/MF
- To assess PK, parasitological and immunological parameters before and after treatment



Infectivity studies in Bangladesh showed PKDL is a reservoir of the disease. Study to be replicated in Sudan.

DNDi's leishmaniasis program goal

- *To deliver a combination of two co-administered, orally acting drugs for the treatment of both visceral and cutaneous leishmaniasis by 2026/7*

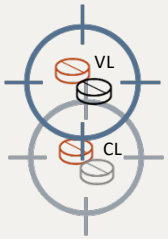
Anticipated public health impact

- Sustainable elimination of VL in Asia; disease control in Africa and Latin America
- Control of CL
- Support WHO's VL Elimination Framework & WHO's objective of detection and treatment of CL patients

Target Product Profile for VL Combination Therapy

	Optimal Target Profile	Minimal Target Profile
Target Label	VL and PKDL	Primary VL
Species	All species	*L. donovani*
Distribution	All areas	Eastern Africa
Target Population	Immunocompetent and immunosuppressed	Immunocompetent
Clinical Efficacy	≥ 95%	≥ 90%
Safety and Tolerability	No AEs requiring monitoring	1 monitoring visit in mid/end - point OR Baseline assessment to exclude high risk groups (dependent on the profile of the drug) and self-report if AEs
Contraindications	None	Pregnancy/lactation
Interactions	No interactions between the drugs to be combined for VL Rx, and also for other common co-morbidities (malaria, TB, ART)	No interactions between the drugs to be combined for VL Rx
Formulation	Oral / oral	Oral / IM IV could be acceptable
Treatment Regimen	Single dose Rx or fixed combo tablet/paed formulation up to 7 days	Bid for ≤ 28 days po; and IM injections over ≤ 14 days Oral NCEs: 14 days
Stability	3 years in zone 4	2 years in zone 4
Cost	To be defined	To be defined

TPP is focused on IMPACT for leishmaniasis patients



Current treatments
Largely injectable
With some toxicity
Variable efficacy
Limited spectrum
Hospitalization, cold chain
Expensive

New oral short-course combination treatment

New combination(s)
Oral
Well tolerated
Improved efficacy
Wide spectrum
Lower level health systems
Affordable

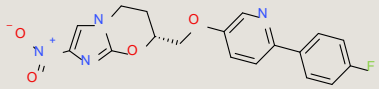
Turning innovation into impact

SUSTAINABLE DEVELOPMENT GOALS
17 GOALS TO TRANSFORM OUR WORLD

RESEARCH | TRANSLATION | DEVELOPMENT | IMPLEMENTATION

- Nitroimidazole — DNDI-0690
- Oxaborole — DNDI-6148
- Aminopyrazole — DNDI-5561

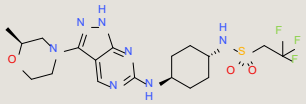
SAD Q4 2018



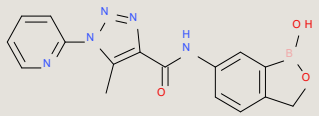
DNDI0690

- CGH VL series 1 (DNDi/Celgene)
- Pyrazolopyrimidine — GSK-3186899
- Imidazopyridine — GSK-3494245

SAD Q1 2019

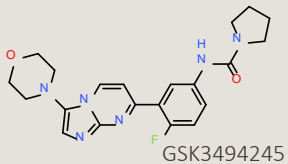


GSK3494245
DDD1305143



DNDI6148

- CF Series (DNDi/GSK/DDU)
- '205 series (DNDi/GSK/DDU)

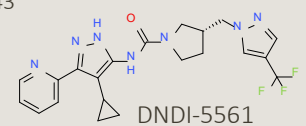


GSK3494245
DDD1305143

- Triazolopyrimidine — GNF-3408

SAD Q4 2018

- GNF Cytochrome B inhibitor series
- Other lead opt. partners

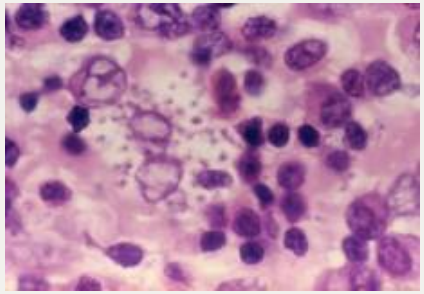


DNDI-5561

NOVARTIS | gsk do more feel better live longer | Drug Discovery Unit | Celgene | Pfizer | Takeda | GHIT Fund Global Health Innovative Technology Fund


Thank You

Leishmaniasis



THE PARASITE: Leishmaniasis is caused by a protozoa parasite
>20 ***Leishmania*** species

THE VECTOR: Transmitted to humans by the bite of infected female **phlebotomine sandflies**
> 90 sandfly species are known to transmit *Leishmania* parasite

THE DISEASE: An estimated **900,000–1.3 million** new cases yearly. 3 main forms of the disease (**visceral, cutaneous, mucocutaneous**)

1 in 7 people
worldwide live in leishmaniasis endemic areas
at risk of infection
> 616 million for visceral leishmaniasis (VL)
> 431 million for cutaneous leishmaniasis (CL)

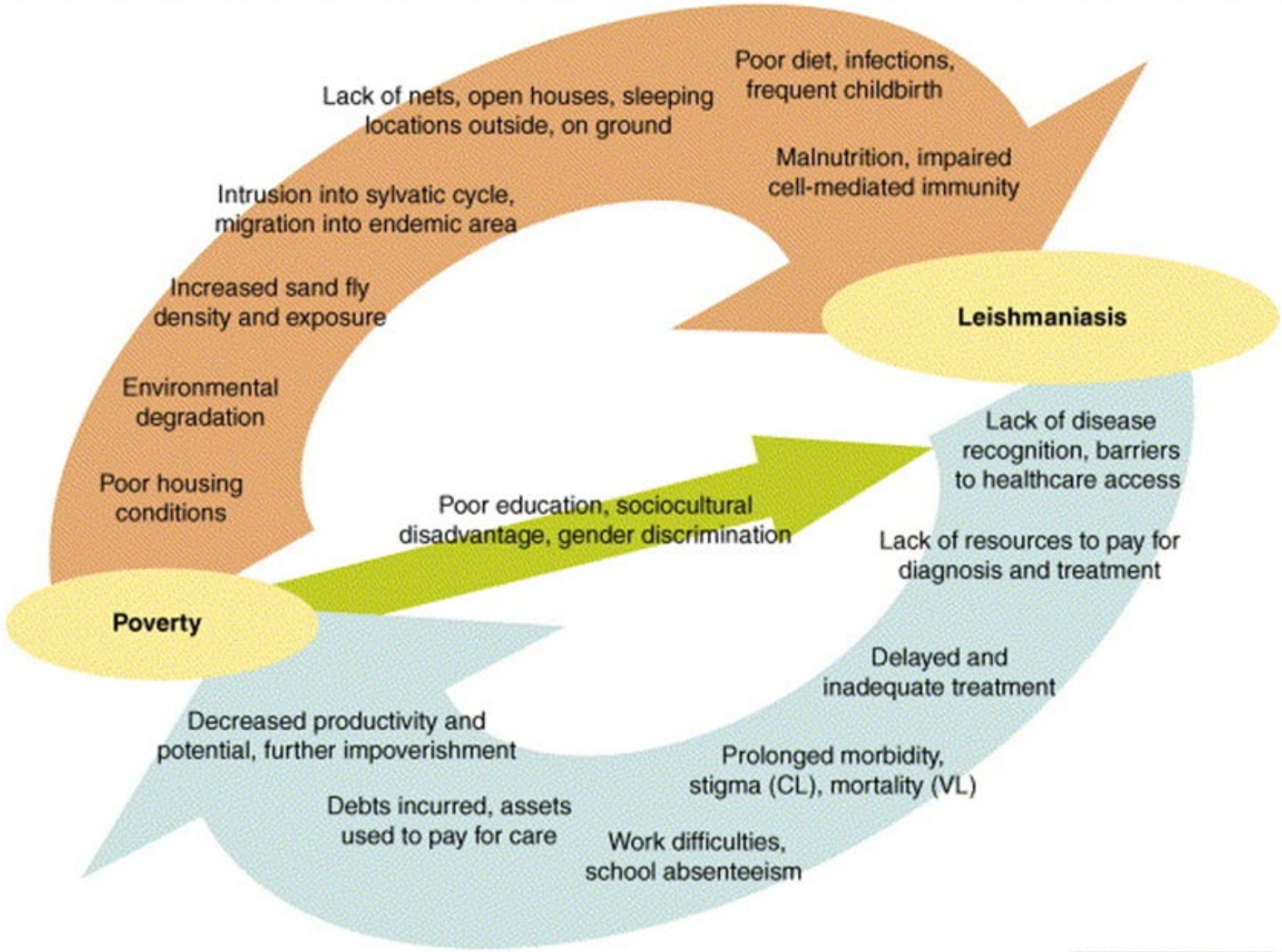
The disease: *kala-azar*

- The parasite multiplies within macrophages throughout the reticuloendothelial system; it affects the spleen, liver, bone marrow and lymph nodes.

- The typical manifestations of VL include:
  - fever for more than 2 weeks
  - weight loss (cachexia; wasting)
  - hepatosplenomegaly
  - pancytopenia—i.e., anemia, leukopenia, and thrombocytopenia
  - a high total protein level and a low albumin level, with hypergammaglobulinemia
  - Lymphadenopathy may be noted, particularly in some geographic regions, such as Sudan
- Poor prognosis: signs of bleeding, jaundice, oedema, co-morbidities, HIV co-infection

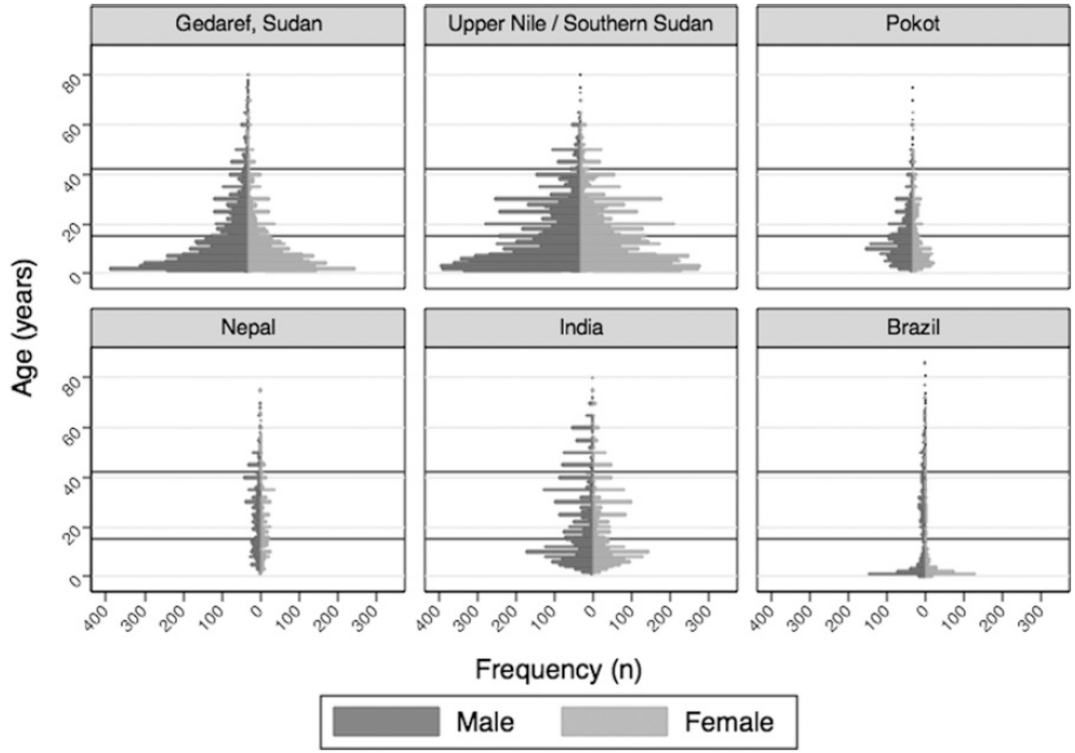
Kala-azar is fatal if untreated → 20,000-30,000 deaths/year

The vicious cycle of leishmaniasis



Trends in Parasitology 2006 22, 552-557DOI: (10.1016/j.pt.2006.09.004)

Who is a typical VL patient?



Harhay *et al*, 2011. *AJTMH* 84 (4): 543-550. doi:10.4269/ajtmh.2011.10-0321

Majority of patients are children living in rural areas

- **At least 50% of VL cases are < children 15years**

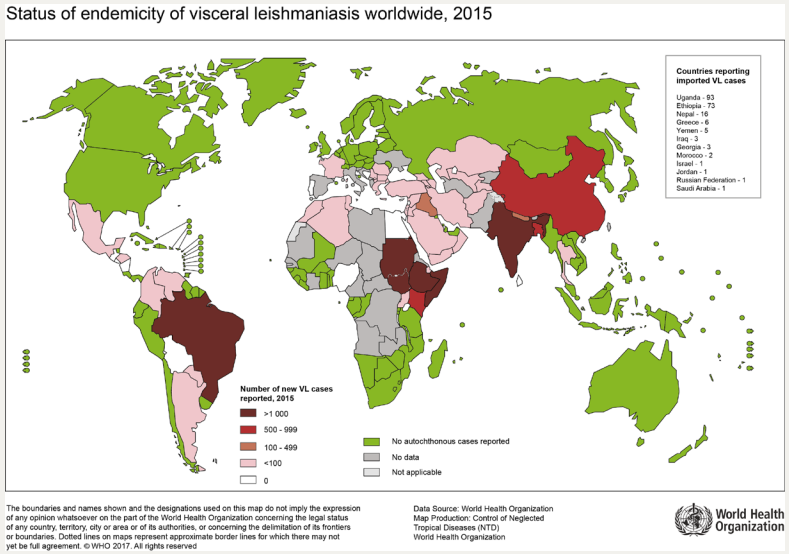
- Males predominate (ratio male:female 1.2 – 2.2)

~ 6 to 18% are women in reproductive age

The need: *an efficacious, safe, field adapted treatment to be deployed in remote areas where VL affects the rural communities.*

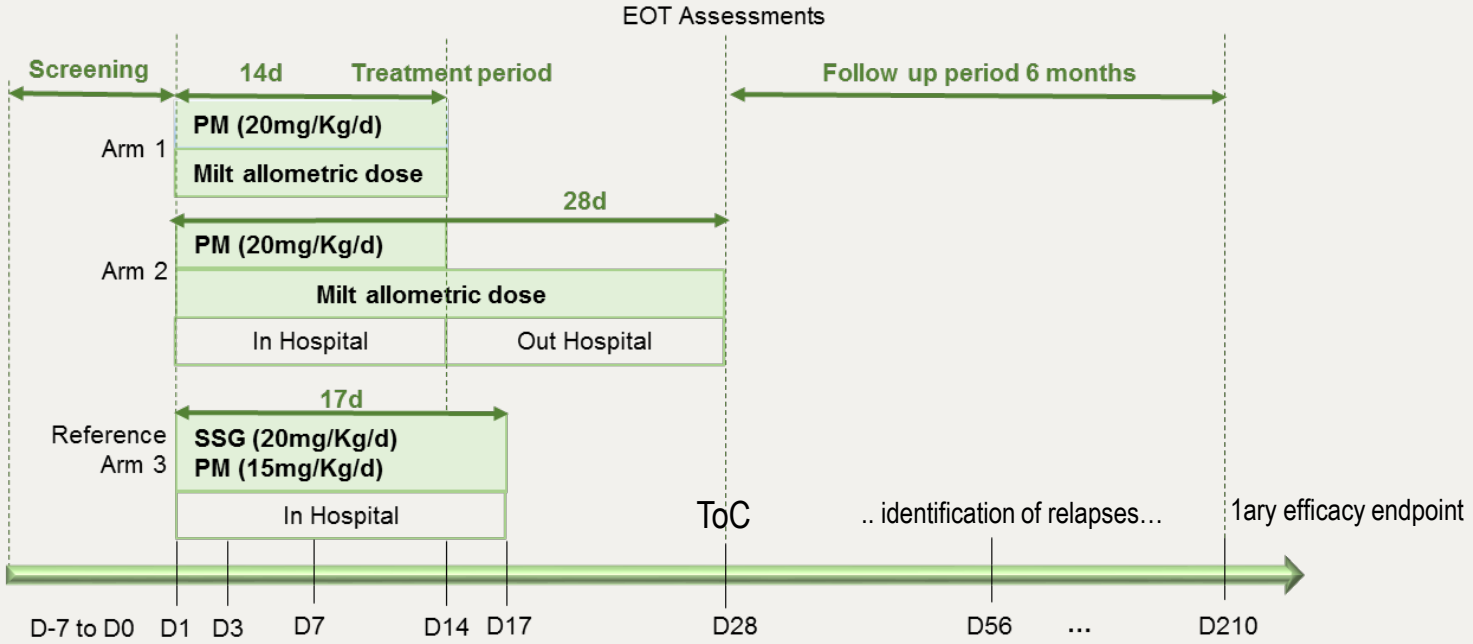
Endemic countries for VL and CL, 2015

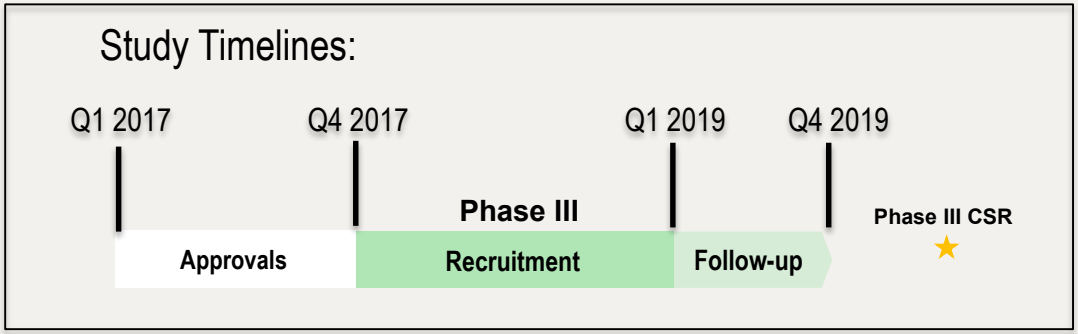
- 75 countries are endemic for VL
  - 14 are ‘high-burden countries’ (> 100 cases in 2013)
  - 54 countries reported to WHO with data from 2015 (low reporting from Africa)
- 87 countries are endemic for CL
  - 12 are ‘high-burden countries’ (> 2,500 cases in 2013)
  - 57 countries reported to WHO with data from 2015



WHO WER, 2017. 38 (92): 557-572

MF/PM phase III clinical trial





- Submissions ongoing in the 4 countries
- Joint regulatory and national EC review through WHO/AVAREF

Leishmaniasis treatment: Oral NCEs required to move away from old drugs & their limitations

> 13 years ago : **SSG**

Treatment limitations:

- Toxic
- Painful
- Resistance
- Expensive
- Long duration
- Not field adapted

Since 2010

SSG & PM for VL in **Africa**

Since 2011

SD Ambisome®, and **Paromomycin + Miltefosine** combination for VL in **Asia**

2018

A new first-line treatment for VL in **Latin America**

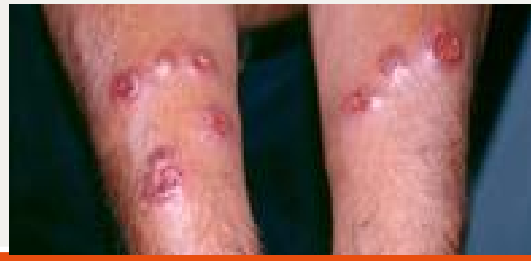
AmBisome® + miltefosine combination for **HIV/VL**

2025/6

New oral combination treatment for leishmaniases

Patients' needs for cutaneous leishmaniasis

- ✓ A safe, topical or oral well tolerated, and affordable treatment
- ✓ which could cure the lesions quickly without leaving deep scar
- ✓ can be deployed within primary healthcare systems for self-treatment without requiring follow up by health workers.

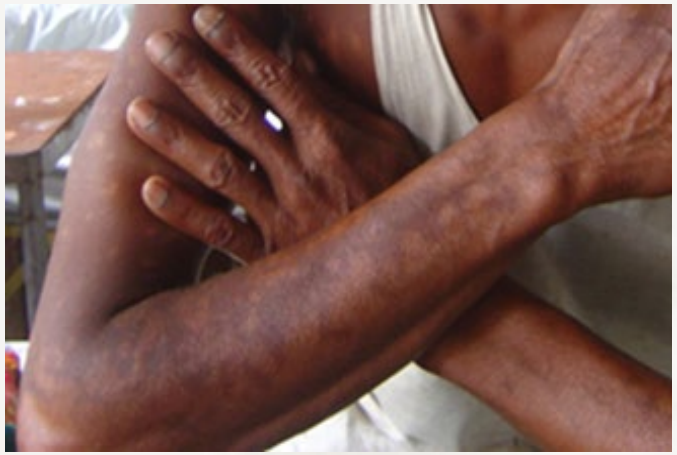


Target product profile for CL

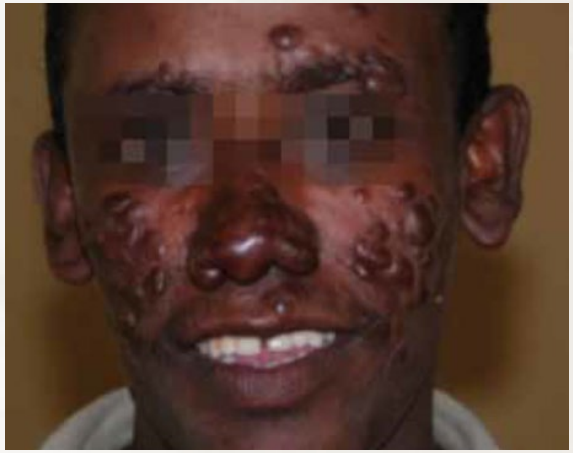
ATTRIBUTE	TARGET (IDEAL)	MINIMALLY ACCEPTABLE	COMMENTS
Target Species	All Leishmania species	*L. tropica* or *L. braziliensis*	Speciation not required for treatment
Safety monitoring requirement	None	PHC. No major safety concerns.	No supervision for at least 60% of the pop.
Tolerability	Well tolerated; All AR's < grade 1	Systemic AR > grade 2 in <5%. Local AR ≤ grade 2 in <30%. No Tx mortality	
Contra-indications	None	Lactation, Pregnancy Cat B	
Efficacy (3M)	>95% patients	60% for *L. tropica*, 70% *for L. braziliensis*	Natural cure rates: 10-20 M, or +
Improved scar formation	Minimal scar	No worse than natural healing	Young female facial scars of highest impact
Prevention of relapse and recidivans	No relapse or recidivans/ML	<5% rate of relapse or recidivans/ML at 1 year	Natural relapse and recidivans rate 2-8%; ML 2-5%
Route of administration	Topical / oral	Non-parenteral, or few doses, if parenteral	Combination can be considered
Topical	14 days	28 days	
Oral	< 7 days	Oral: bid for 28 days	
Parenteral	No	3 injections	
Age / Gender	No restrictions	> 9 months of age	With a good safety profile: <9 M
Use in Pregnancy	Yes	No	Any risk to fetus should disqualify Tx
Efficacy in immuno-compromised patients	Yes	No	Immune stimulation may be applicable under certain conditions.
Stability	No cold chain, at least 3 years at 37ºC	2 years at 4-8ºC	

Current therapies for Post Kala-azar Dermal Leishmaniasis (PKDL)

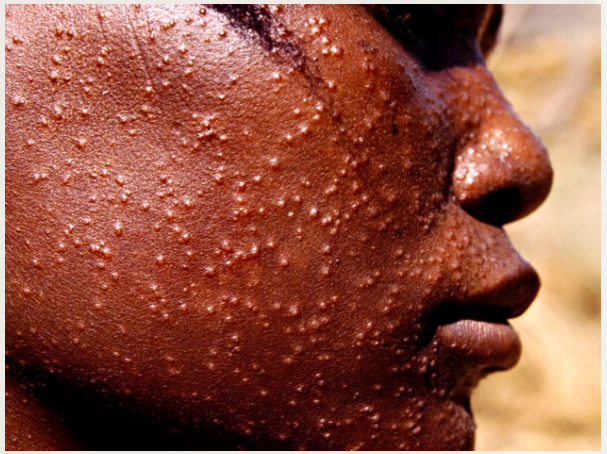
- PKDL patient is 'healthy' other than the skin rash



macular



nodular



papular

South Asia

- Predominanty macular lesions
- It does not self-heal
- All patients are treated, but it may take long time for patient to reach service in a specialized treatment center
- Rx: miltefosine 2.5mg/Kg/day for 12w; Ambisome 30mg/Kg/d total dose

Eastern Africa (mainly Sudan)

- Predominanty papular lesions
- ~ 40-50% will develop PKDL within 6 months, but 85% self-heals
- Only grade 3, severe grade 2 and chronic patients (> 6mo) are treated
- Rx: SSG 20mg/Kg/d for 40-60d; Ambisome 50mg/Kg total dose

PKDL Target Product Profile

	Target (ideal) Profile	Minimally Acceptable Target Profile
Target Species		
L. donovani	One treatment for all PKDL patients	*P*KDL treatment regimen adapted by region (Asia or Africa)
Safety		
Safety monitoring requirement	None	No major safety concerns Acceptable for patient to come for 1 follow-up visit during treatment
Tolerability (CTCAE v4.3)	Well tolerated All AR's ≤ grade 1	Well tolerated in > 90% of patients treated. Systemic AR > grade 2 in < 5%. No treatment induced mortality. No irreversible AEs.
Contraindications	None	Assessed by qualified person at PHC/DH, as per local context
Efficacy		
Complete clinical cure: - 100% disappearance of papules or nodules by 12 weeks - 80% improvement in macular lesions with re-pigmentation by 12 months	≥ 90% efficacy *[PK of the NCEs: penetration in the skin should also favor development for PKDL]*	≥ 80% efficacy

	Target (ideal) Profile	Minimally Acceptable Target Profile
Drug / treatment schedule		
Route of administration	Oral	Oral or combo oral-parenteral
Oral	≤ 4 weeks treatment OD	BID for up to 6 weeks (regardless of PKDL presentation)
Parenteral	None	Up to 2 weeks if IM Up to 7 injections if IV
Target population		
PKDL type	All	All in South Asia Persistent (> 6mo) or grade 3 PKDL in Eastern Africa + grade 2 severe presentation
Use in pregnancy	Yes (delay treatment after delivery)	No studies done in the population
Efficacy in immuno-compromised patients (especially HIV co-infected patients)	Yes	Yes, with regimen adapted for this population
Product characteristics		
Stability	At least 3 years in zone 4 (hot and humid)	2 years in 4-8ºC Stable under storage at ≤ 30° C in case of self-administered
Cost		
Cost of products/procedures per treatment	≤ 60 Euros	≤ 100 Euros for treatment (MoH) (minimal price for the manufacturer) Africa: cheaper than SSG treatment (100 – 140 Eu for 40-60d) Asia: cheaper than MF treatment preferential price (160 – 270 Eu for 12w)

DNDi has a track record in developing drug combinations

7 new treatments delivered, of which **6** are combinations, and **2** for VL

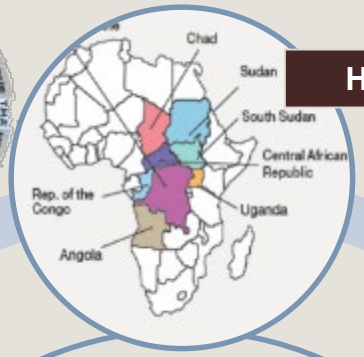
- ✓ Easy to use
- ✓ Affordable
- ✓ Field-adapted

- **Sleeping sickness**
  - **NECT -** improved combination therapy since 2009
  - **Fexinidazole – NCE** short-course oral treatment
  - **Acoziborole – NCE** single dose oral treatment
- **Leishmaniasis**
  - **SSG & PM** approved for **VL in E. Africa**
  - **2 treatments** approved for **VL in Asia**
  - Specific **clinical trial platforms/ networks**
    - LEAP (VL)
    - redeLEISH (CL) platforms
  - Defined **TCPs, TPPs**
  - **Network** of industrial and academic partners
  - **Regulatory experience**

redeLEISH

LEAP
LEISHMANIASIS
EAST AFRICA PLATFORM

Using & Strengthening research capacities in endemic regions



HAT

A Key Role for Regional Disease Platforms

Defining patient needs and Target Product Profile (TPP)

Strengthening local capacities

Conducting clinical trials (Phase II/III studies)

Facilitating Registration of new therapies

Accelerating implementation of new therapies, ensure therapies reach patients

redeLEISH

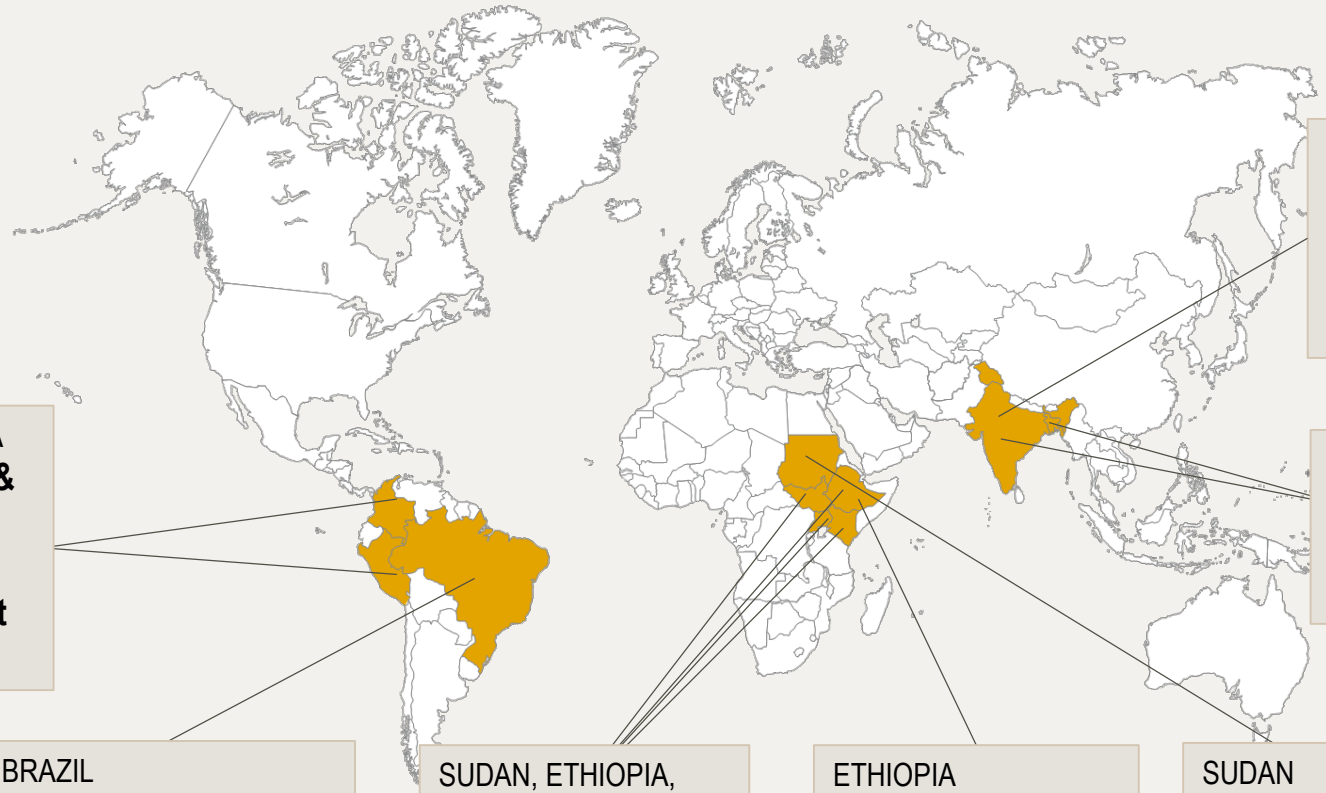
LEISHMANIASIS

CHAGAS

LEISHMANIASIS

LEAP
LEISHMANIASIS
EAST AFRICA PLATFORM

DNDi clinical trial and capacity building for leishmaniasis



PERU + COLOMBIA
Thermotherapy & miltefosine combination proof-of-concept
(Phase II) for CL

BRAZIL
Created **5 research sites for VL providing data evidence for policy change**

SUDAN, ETHIOPIA, KENYA, UGANDA
Non-inferiority trial of miltefosine & paromomicin
(Phase III) for VL

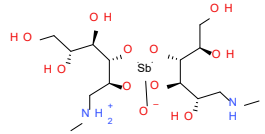
ETHIOPIA
New treatments for HIV/VL co-infection
(Phase III) for VLC

INDIA
Prevalence study of PKDL in VL patients
(Phase IV)

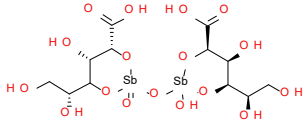
INDIA + BANGLADESH
Infectivity studies for PKDL patients
(Phase III)

SUDAN
PKDL clinical trial
(Phase II)

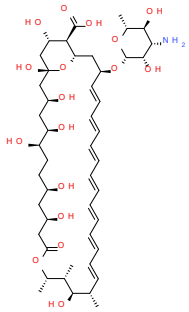
Replacing old therapies with modern treatments



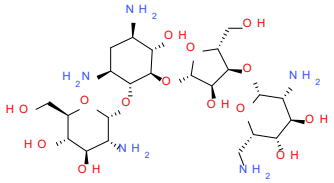
Meglumine antimoniate



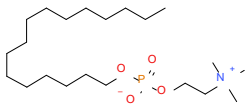
Sodium Stibogluconate (SSG)



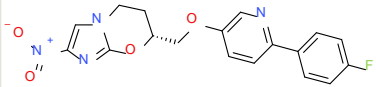
Liposomal Amphotericin B



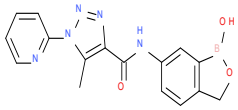
Paromomycin sulfate



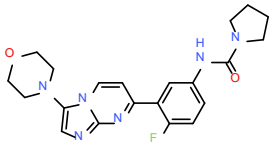
Miltefosine



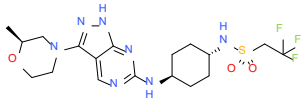
DNDI0690



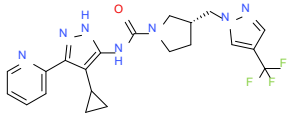
DNDI6148



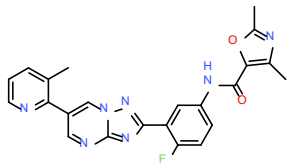
GSK3494245 DDD1305143



DDD853651 / GSK-3186899



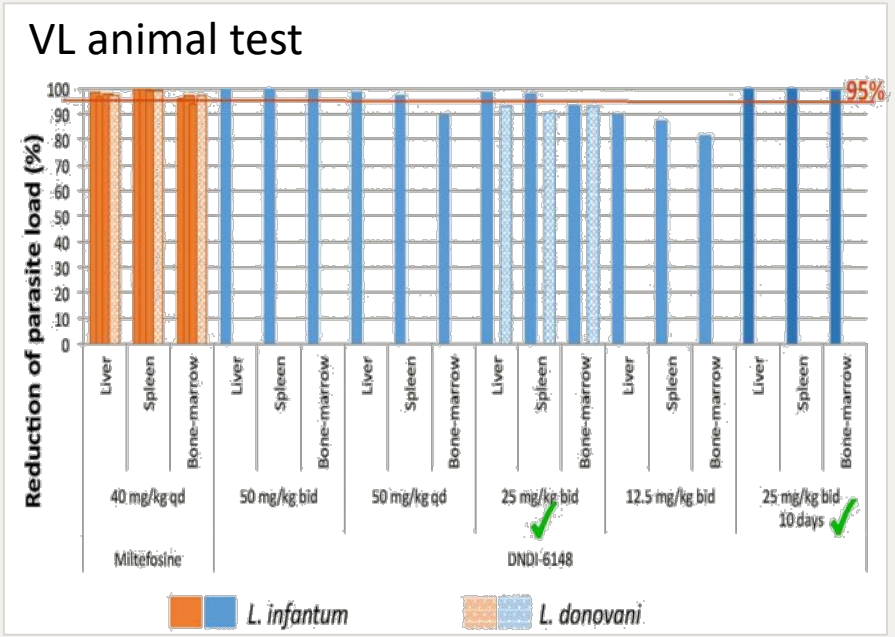
DNDI-5561

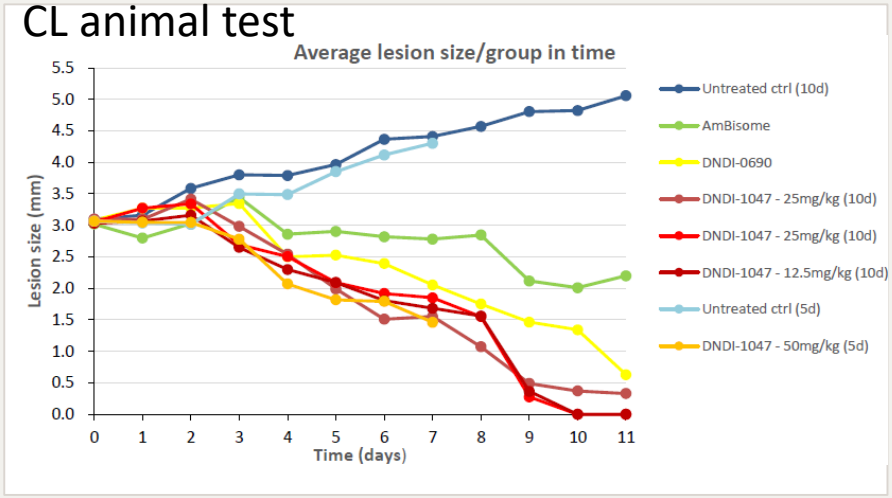


LXE408

Portfolio of NCEs specially optimized for treatment of leishmaniasis

- **Unprecedented numbers of developable NCEs**
  - > 6 novel chemotypes entering Phase 1 in next 12 months
- **NCEs designed to meet the TPP**
  - Oral dosing, short course, affordable
  - Broad spectrum of action on leishmaniasis strains
- **Cure in animal tests**
  - Potent in VL tests
  - Lesion-resolving action in CL tests
- **Options to overcome attrition in development**





A strong case for oral combination treatments

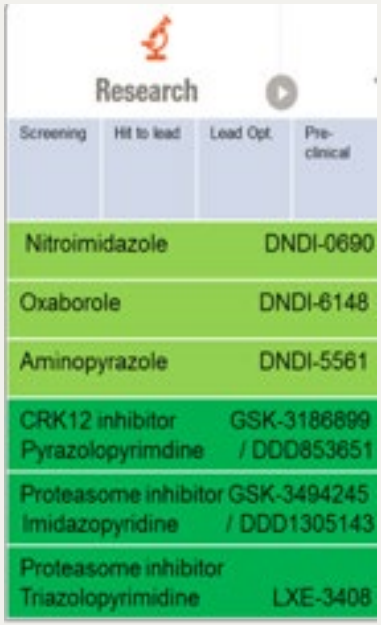
Shorten treatment course & address potential for resistance

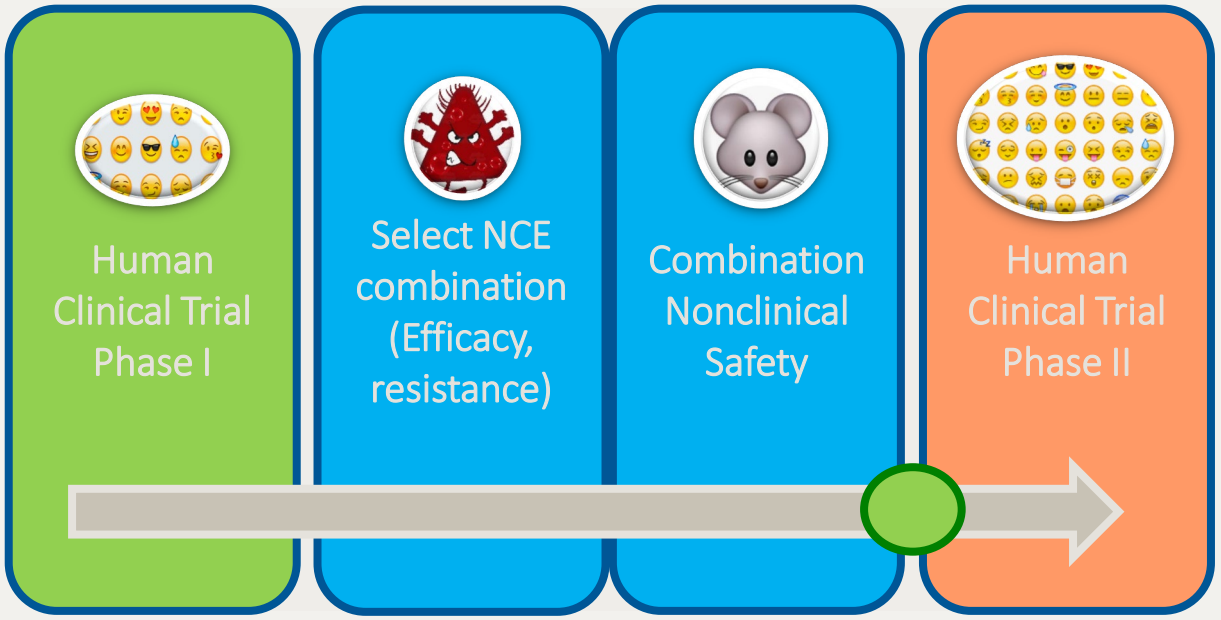
1. **Maximize efficacy**
   - Faster parasiticidal effect & reduced risk of relapse
   - Monotherapy has largely failed in patients (except Ambisome® in some regions), although more and more reports of reduced efficacy

2. **Minimize treatment duration and dose**
   - Adapted for use in resource-poor settings
   - Optimize safety

3. **Long-term protection against resistance**
   - Avoid use of monotherapies

Development of NCE combinations





Precinical data

- Efficacy in models
- Acceptable safety profile
- Dosing convenience
  - ✓ o.d. *vs* b.i.d.
- No cross resistance
- Affordability / CoG

In man data

- FIM, SAD, MAD, FE
- Pharmacokinetics
- Safety: AEs, ECGs, vital signs, clinical chemistry, coagulation, haematology
- DDI

In patient data

- Safety, tolerability
- Pharmacodynamics
- Pharmacokinetics
- Combo *vs* monotherapy (A+B *vs* A *vs* B)