

Latest drug development and innovation for kinetoplastid diseases



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Medical Director

DNDi

Drugs for Neglected Diseases *initiative*

Iniciativa Medicamentos para Enfermedades Olvidadas

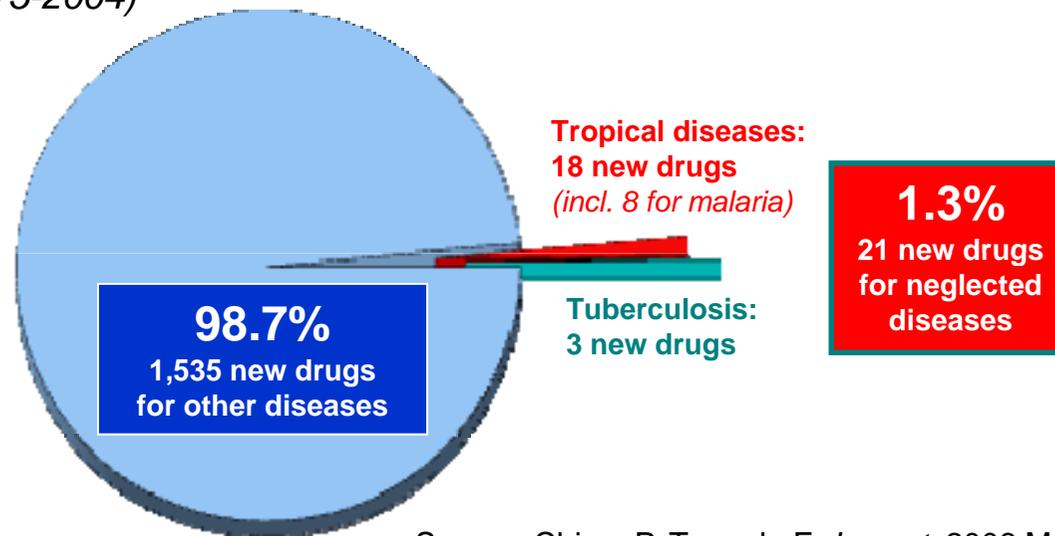
A Fatal Imbalance

Tropical diseases (including malaria) and tuberculosis account for:

- 12% of the global disease burden
- Only 1.3% of new drugs developed



(1975-2004)

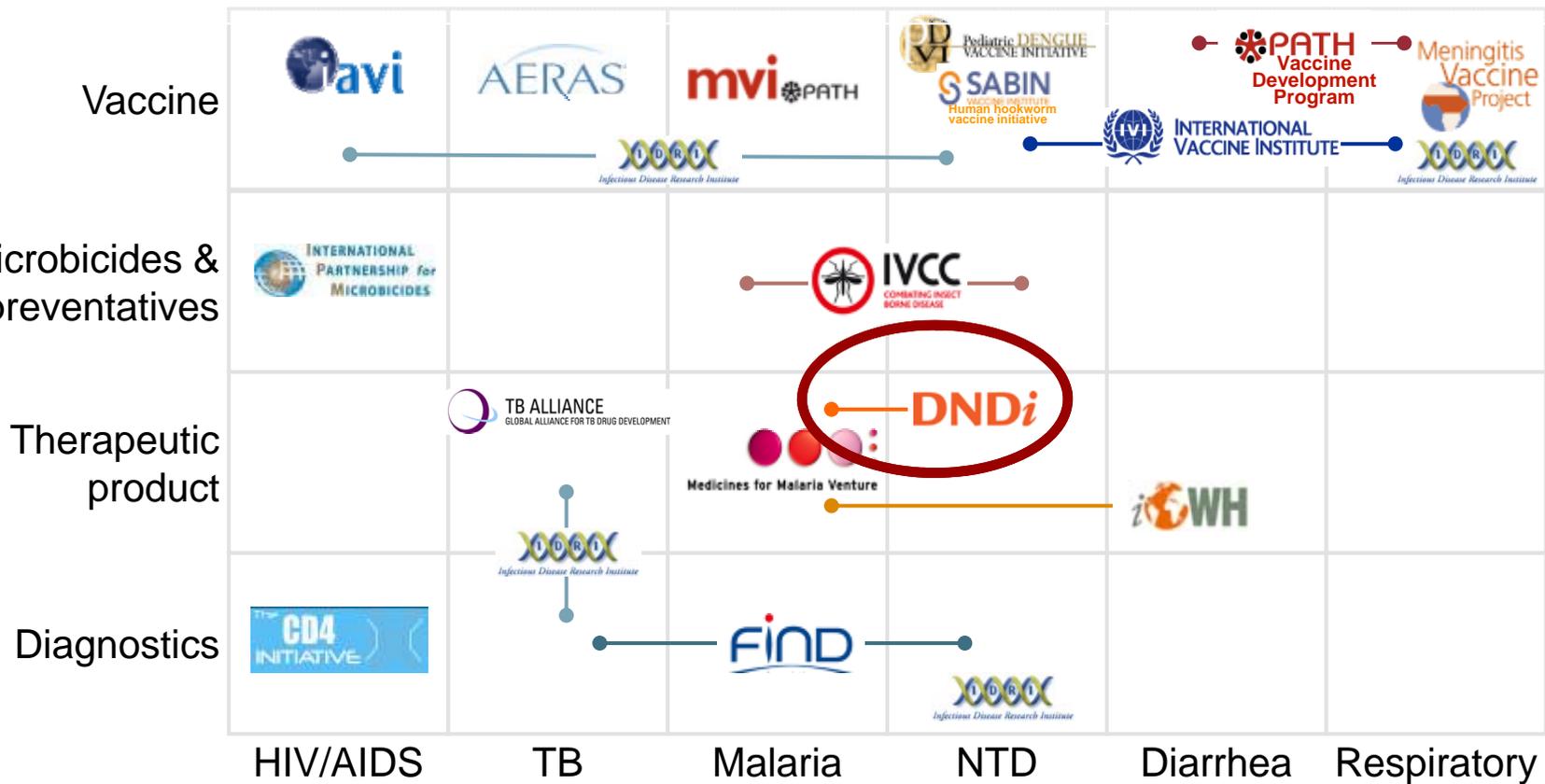


Source: Chirac P, Torrele E. *Lancet*. 2006 May 12; 1560-1561.

Product Development Partnerships (PDPs): Filling the Gaps in Translational Research and Product Development

PDPs work across different diseases and modalities

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Source:

BILL & MELINDA GATES foundation

&

BCG
THE BOSTON CONSULTING GROUP

DNDi: An innovative R&D model

- Non-profit drug research & development (R&D) organization founded in 2003
- Addressing the needs of the most neglected patients
- Harnessing resources from public institutions, private industry and philanthropic entities

● 7 Founding Partners

- Indian Council for Medical Research (ICMR)
- Kenya Medical Research Institute (KEMRI)
- Malaysian MOH
- Oswaldo Cruz Foundation Brazil
- Medecins Sans Frontieres (MSF)
- Institut Pasteur France
- WHO/TDR (permanent observer)



Kinetoplastid diseases / Protozoan Infection: most NTDs

Essentially represented by:

- African Trypanosomiasis (HAT) or sleeping sickness
- American Trypanosomiasis or Chagas Disease
- Leishmaniasis
 - Visceral (and PKDL) or Kala-Azar
 - Cutaneous

DNDi Portfolio-Building Model

- Existing chemical libraries
- New lead compounds

Long-term projects

- New formulations (fixed-dose combinations)
- New indications of existing drugs

Medium-term projects

- Completing registration dossier
- Geographical extension

Short-term projects

Discovery
S LS LO

Preclinical

Clinical

Access to Patients

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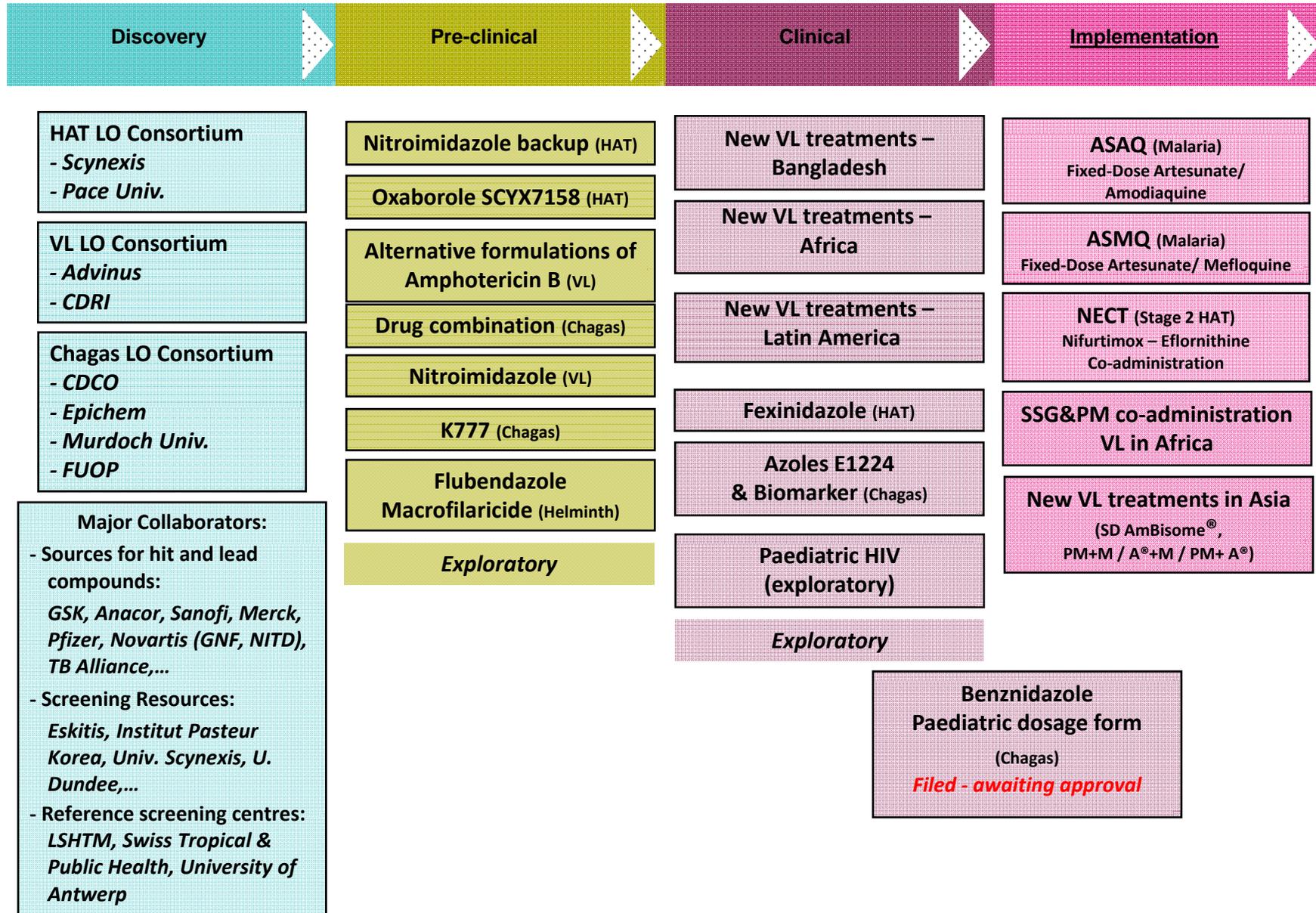
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Portfolio – June 2011

Best Science for the Most Neglected

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Drug for Neglected Diseases Authority





**Sleeping sickness
36 countries at risk
Estimated 30000 cases**

Fatal if untreated

G- 6 years boy with probable relapse of late stage HAT

NECT in 12 countries since 2009

- NECT (nifurtimox-eflornithine combination therapy): a **simplified, shorter**, safe & effective treatment
- WHO Essential Medicines List (May 2009)
- > 6000 Tx (end 2010)
 - **melarsoprol use (36% to 12%)**
- 629 patients in NECT-Field study
- WHO, National Programmes and MSF-logistics ensure availability



epicentre
ÉPIDÉMIOLOGIE • EPIDEMIOLOGY



Bayer

SANOFI

Swiss TPH





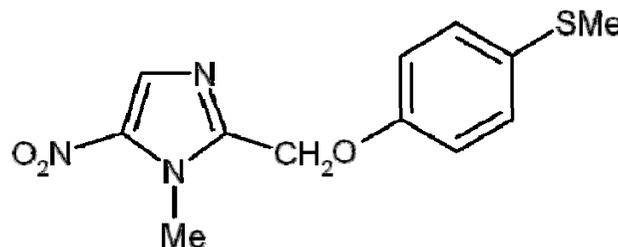
Fexinidazole



TPP: **oral**, short course treatment for both stages caused by either *T.b. gambiense* or *T.b. rhodesiense*



5-nitroimidazole (> 700 compound mining)



Phase I - 2009 to 2011 in Paris
S advice art. 58 EMA & FDA in Q1 2011
Pivotal phase II/III - Q1 2012
DRC, CRA, SS

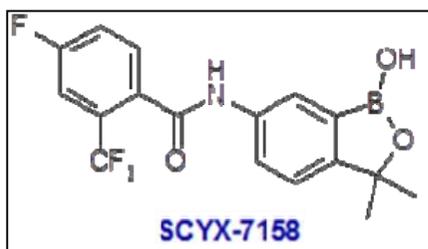
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TPP = Target Product Profile <http://www.dndi.org/diseases/hat/target-product-profile.html>

Oxaborole SCYX-7158

First DNDi Preclinical Candidate Issued from Lead Optimisation Program



- Belongs to new class
- Identified as hits against *T.b. brucei*
- Showed activity in animal models
- Innovative partnership between 2 US biotechs and University and 1 NGO
- Completion of preclinical package
- Results published in PLoS NTD (June 2011)
- FIM study Q4 2011/ Q1 2012

Potential for oral early and late stages

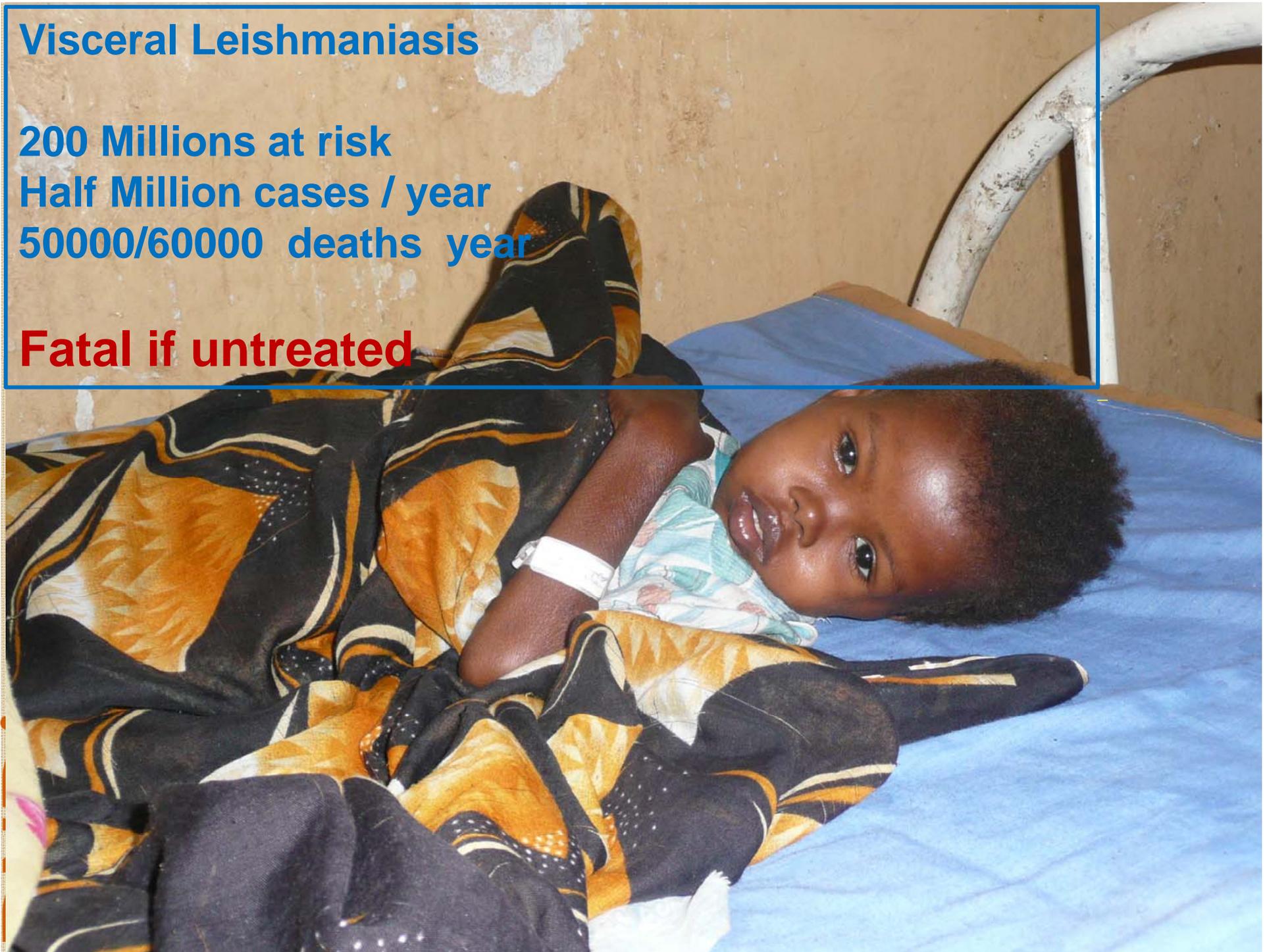
Visceral Leishmaniasis

200 Millions at risk

Half Million cases / year

50000/60000 deaths year

Fatal if untreated



Highly efficacious results in India

N Engl J Med 2010;362:504-12.

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www.thelancet.com Published online January 20, 2011

S Sundar study

VL Combo DNDi study

	AmB SD	Ampho B	Ampho B	AmB+M	AmB+PM	M+PM
ITT	304	108	157	160	158	159
Cure at M6	291	104	146	156	154	157
% 95 CI	95.7% 93.4-97.9	98.1% 95.5-100	93.0% 87.5-96.3	97.5% 93.3-99.2	97.5% 93.2-99.2	98.7% 95.1-99.8
PP	304	106	148	157	155	158
Cure at M6	291	104	146	155	153	156
% 95 CI	95.7% 93.4-97.9	98.1% 95.5-100	98.6% 94.7-99.8	98.7% 95.0-99.8	98.7% 94.9-99.8	98.7% 95.0-99.8

Recommended for region in WHO bluebook (2010)
Large implementation study in India

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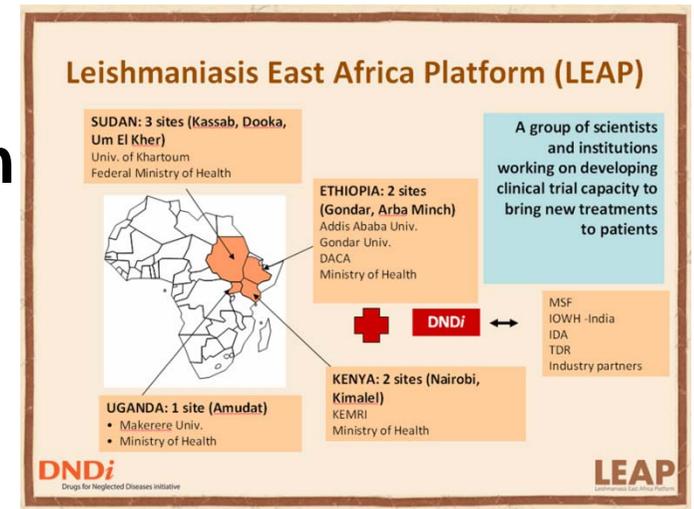
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SSG/PM: effective, safer & cheaper treatment for East Africa

	SSG	PM 20mg/kg	SSG	SSG+PM 15mg/kg
ITT cure rate	30 days IM N = 200	21 days IM N = 198	30 days IM N = 359	<u>17 days IM</u> N = 359
Efficacy at 6 months FU, n (%)	188 (94.0)	167 (84.3)	337 (93.9)	328 (91.4)
Unadjusted difference the 2 arms [95% CI]	9.7% [3.6 – 15.7%] *		2.5 [-1.3 to 6.3%] NS	

*p= 0.002 in favor of SSG, NS = non significant

1st line treatment for the region in WHO bluebook (2010)
Included in National guidelines in Sudan (2010)





Cutaneous Leishmaniasis
82 endemic countries
1-1,5 M new cases/year
Permanently disfiguring

Exploratory work

Chagas Disease
21 countries
108 Million at risk
7.7 Million estimated



Chagas Progress

Pediatric dosage form of benznidazole: Efficacy demonstrated in children with acceptable safety BUT

- Supplied in 100 mg tablets, twice daily for 60 days
- No available formulation for children

➔ An affordable, age-adapted, easy to use, pediatric formulation

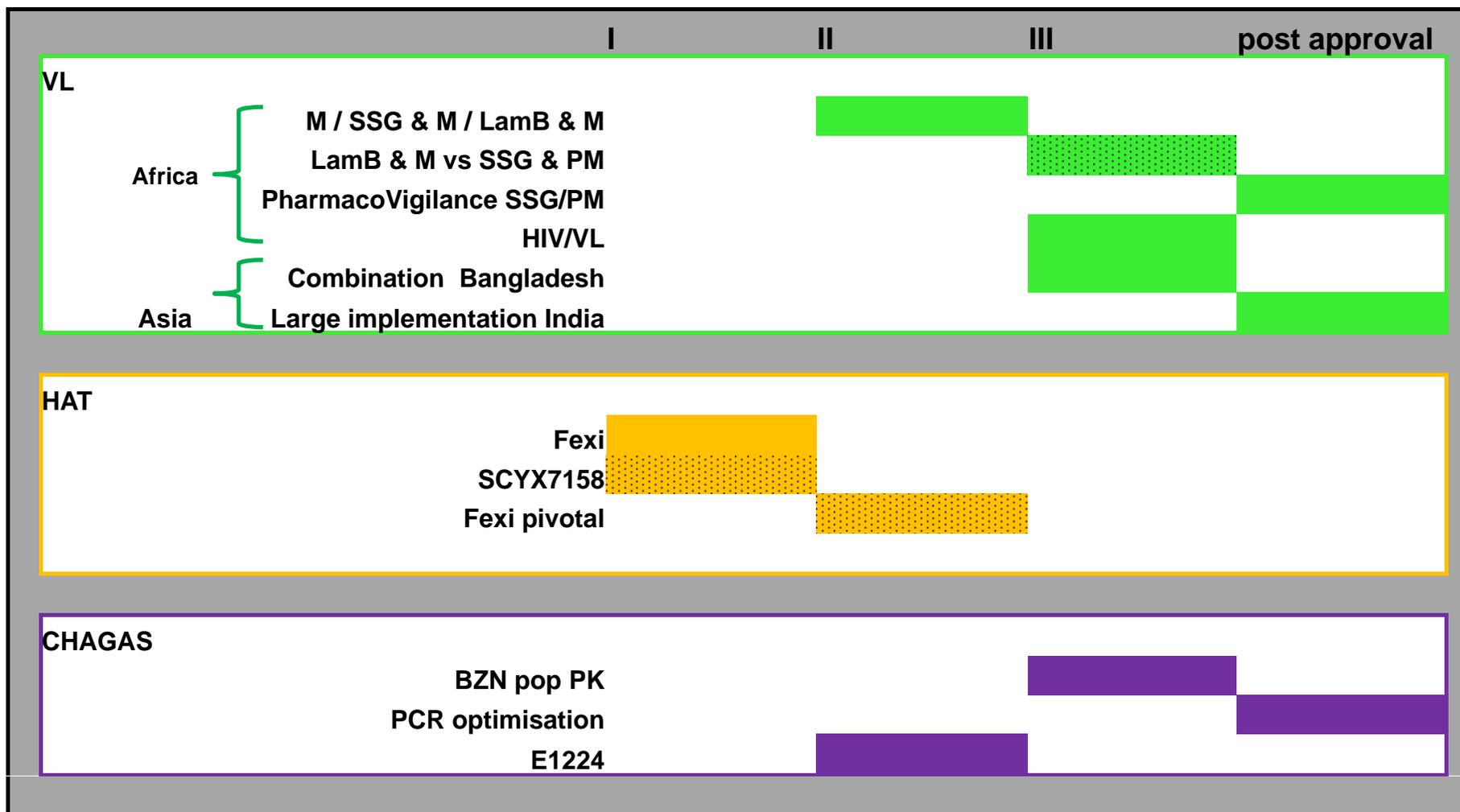


E1224: a new clinical candidate

- Prodrug or ravuconazole (very potent against *T. Cruzi*)
- Favourable PK
- Now in phase II proof of concept in Bolivia



Clinical studies



Challenges ahead

- Implementation
- Registration
- Clinical demonstration of efficacy
- Research & Discovery

2018 Business Plan

Gracias - Thank you



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