# World Leish 4

***DNDi symposia at the 4th congress on Leishmaniasis 2009***
***Tuesday February 3rd 2009***

***Dr Manica Balasegaram, Project manager, DNDi***

## *DNDI's R&D strategy to improve treatment for VL:*

## *A needs-driven approach*

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# DNDi's vision

- Patients' needs-driven agenda
- Collaborative partnerships
- Not-for-profit
- Robust science to develop new treatments for the most neglected diseases

## …and mission

- Deliver 6–8 new treatments by 2014
- Use and strengthen existing capacity in disease endemic countries
- Raise awareness and advocate for increased public responsibility

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# DNDi was created in 2003


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# Current Treatments

| Drugs | Pentavalent Antimonials | Amphotericin B | AmBisome ® Liposomal Amphotericin B | Miltefosine | Paromomycin sulphate |
|---|---|---|---|---|---|
| Regimen | 20 mg/kg daily for 20-30 days<br>(depends on geographic area) | 1 mg/kg e.o.d.<br>for up to 30 Days<br>(15mg/Kg total dose) | 5-20 mg/kg<br>total dose in 4-10 doses<br>over 10-20 days | 1.5-2.5 mg daily<br>over 28 days<br>(India only) | 15mg/kg/ for<br>21 days<br>(India only) |
| Marketing authorisation holder | Albert David (SSG)<br>GSK (Pentostam)<br>Sanofi Aventis (Glucantime) | Bristol Meyers Squibb (Fungizone)<br>Generic companies | Gilead (AmBisome) | Paladin (Impavido) | Gland Pharma / IOWH |
| Administration | iv or im | iv | Iv | Oral | im |
| Clinical efficacy<br>Asia<br>Africa<br>South America | 35-95% (depending on geographic area) | > 97% all regions | > 97%; single dose: 91%<br>Not fully established<br>Not fully established | 94-97% (India);<br>Not established<br>Not established | 94% (India)<br>In evaluation<br>Assumed to be limited |
| Resistance | As high as 60%<br>(Bihar, India) | Not documented | Not documented | Lab isolates | Lab isolates |
| Toxicity | +++<br>Cardiac toxicity, pancreatitis, nephrotoxicity<br>hepatotoxicity | +++<br>Nephrotoxicity<br>(in patient care needed) | +<br>Some nephrotoxicity | +<br>Gastro-intestinal<br>(20-55% of patients, usually mild),<br>nephrotoxicity<br>hepatotoxicity<br>Possible teratogenicity | +<br>Nephrotoxicity<br>ototoxicity<br>hepatotoxicity<br>(all relatively rare) |
| Approximate cost of drugs per course*<br>USD (Euros) | SSG (AD) ~$50 (37€)<br>Glucantime (SA)~ $70 (52 €)<br>(Based on 30 day course) | Generic price:<br>~ $117 (87€) | Preferential price: $280 (207€)<br>(for 20mg/kg total dose)<br>Commercial price:<br>~10x above costs | Preferential price: ~ $74 ( 54 €)<br>(can be obtained at 46€ if buying<br>>75 000 packs)<br>Commercial price: ~ $150 | ~ $10 (7.3 €) |
| Issues | Quality control<br>Availability<br>Length of treatment<br>Painful injection<br>Toxicity<br>Resistance in India | Need for slow iv infusion<br>Dose-limiting nephrotoxicity<br>Heat stability | Price<br>Need for slow iv infusion<br>Heat stability<br>(Stored <25° C) | Price<br>Possible teratogenicity<br>Potential for resistance<br>Patient compliance | Efficacy variable<br>Between and within regions |

# Target Profile for Developing Combinations from Existing Visceral Leishmaniasis Treatments

| | Target | Minimum Acceptable |
|---|---|---|
| **Spp** | All species | *L. donavani* (Covers most endemic areas) |
| **Distribution** | All areas | One region (India or Africa or Latin America) |
| **Target Population** | Immunocompetent and immunosuppressed, Adults and children | Immunocompetent<br>Primary VL<br>Children |
| **Treatment Regimen** | 10 day treatment regimen | 14 day treatment regimen |
| **Feasibility** | Most of treatment given as outpatient (e.g. oral treatment) | Daily ambulatory care possible (e.g. daily im injections) |
| **Clinical Efficacy** | > 95% (phase 3) | > 90% (phase 3) |
| **Resistance** | Active against resistant strains | Active against resistant strains |
| **Safety and Tolerability** | No AEs requiring in patient monitoring | CFR during treatment < 1% (phase 3) |
| **Contraindications** | None | Pregnancy/lactating |
| **Cost per treatment (2008 prices)** | < $75 / course | < $175 / course (only if other cost saving possible through reduction in opportunity costs to patient & hospital care) |

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# Combination Strategy and Geographical Extension

## VL Combo Asia

- Combination trials and recommendation in India, Bangladesh & Nepal

## VL Combo Africa

- Register Paromomycin, AmBisome®, Miltefosine
- Combination trials and recommendation of optimal treatment using PM, AmB, Milt and SSG

## VL Combo Latin America

- Set up in 2009 and execute in early 2010

## VL Combination Therapy Asia

# Phase III Trial in India

**Objective:** To identify a safe and short-course combination therapy using existing drugs already registered in region.

**Status:**

- 4-arm study began enrolment at 2 sites (Patna, Muzaffarpur) in June 2008, with 240 adult patients enrolled as of Dec. 08.
- Enrolment (including children) to continue through June 2009, and results expected by early 2010.
- Nepal, Bangladesh


**Partners:** ICMR, Kala-azar Medical Research Centre, Rajendra Memorial Research Institute of Medical Sciences, GVK BIO, Gilead

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## VL Combination Therapy Africa

# Paromomycin

**Objectives:**

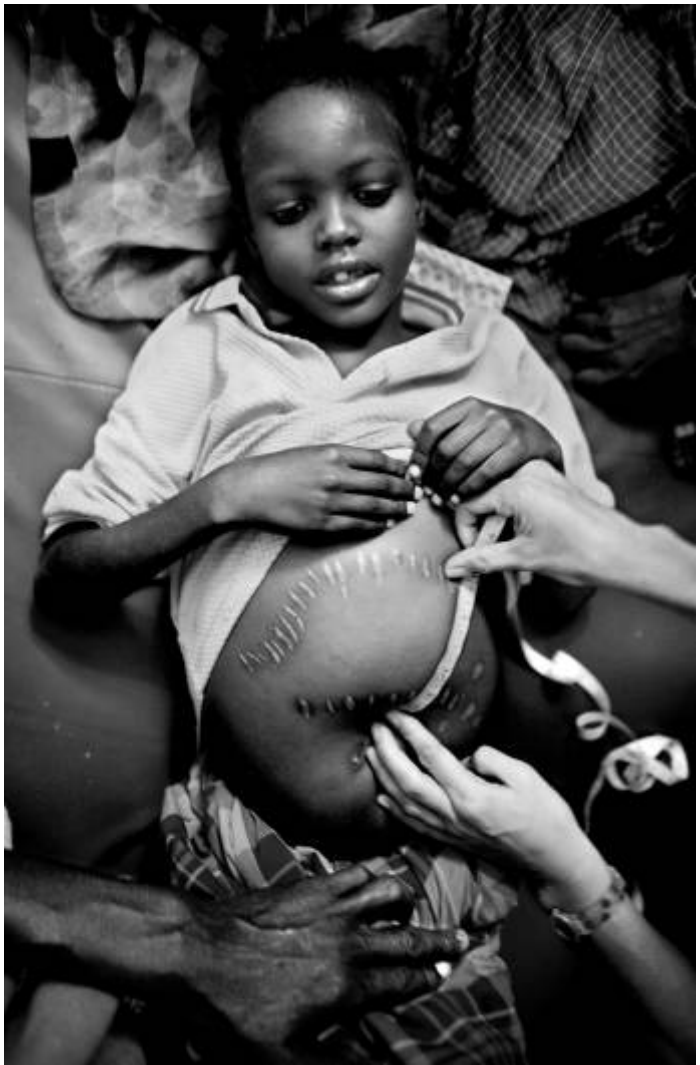
- Registration of Paromomycin (PM) as new alternative treatment for VL in East Africa (Sudan, Ethiopia, Kenya and Uganda)
- Evaluation of shorter course PM+SSG co-administration as alternative treatment for VL

**Status:**

- Over 1000 patients recruited. Study to be completed in 2009

**Partners:**

- LEAP Group



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# Planned DNDi/ LEAP studies in Africa

1. **Open-Label, Sequential Step, Safety and Efficacy Study to Determine the Optimal Single Dose of Ambisome for VL**

- **“A Phase II randomized, 3 arm parallel group, open-labeled clinical trial to assess the safety and efficacy of the combination of SSG plus single dose AmBisome®, Miltefosine plus single dose AmBisome® and Miltefosine alone for the treatment of visceral leishmaniasis in Eastern Africa"**

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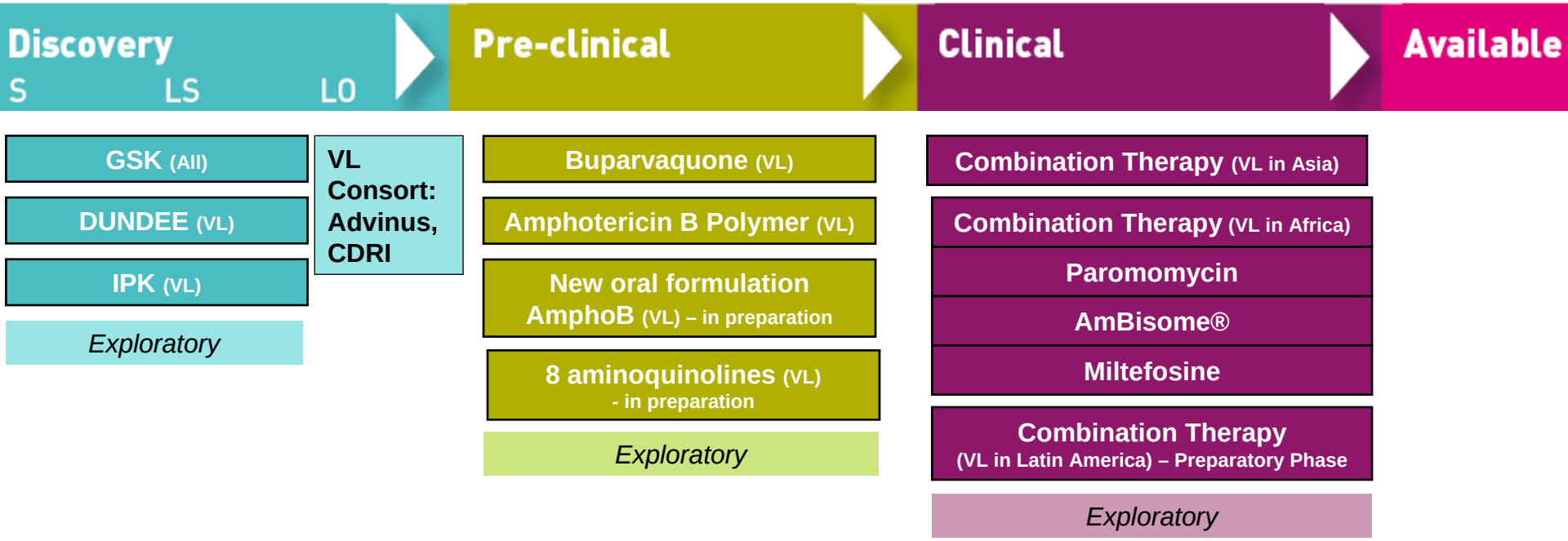
# DNDi R&D VL Projects – 2009 Outlook




Objectives: 1 New Drug + 4 New Treatments (combination and/or geographical extension) by 2014 + A Robust Pipeline