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

DNDi
Drugs for Neglected Diseases *initiative*

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

DNDi Drugs for Neglected Diseases *initiative*

DNDi was created in 2003

DNDi
Drugs for Neglected Diseases *initiative*

Current Treatments

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

DNDi Drugs for Neglected Diseases *initiative*

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

DNDi Drugs for Neglected Diseases *initiative*

VL Combination Therapy Africa

Paromomycin

Objectives:

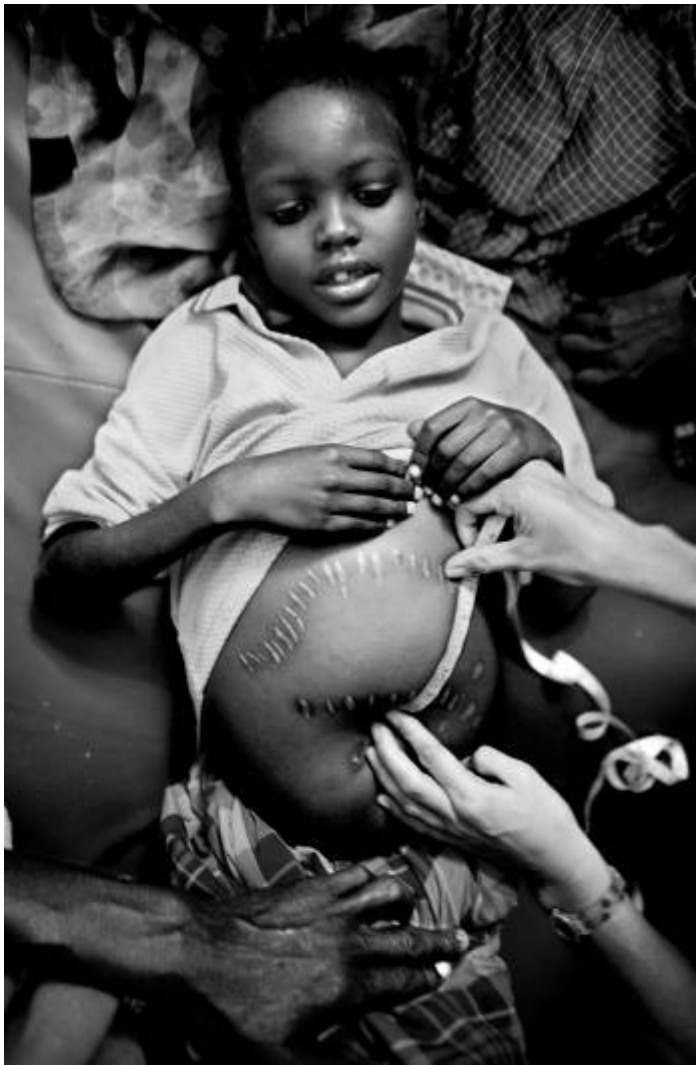
- Registration of Paromomycin (PM) as new alternative treatment for VL in East Africa (Sudan, Ethiopia, Kenya and Uganda)
- Evaluation of shorter course PM+SSG co-administration as alternative treatment for VL

Status:

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

Partners:

- LEAP Group



DNDi Drugs for Neglected Diseases *initiative*

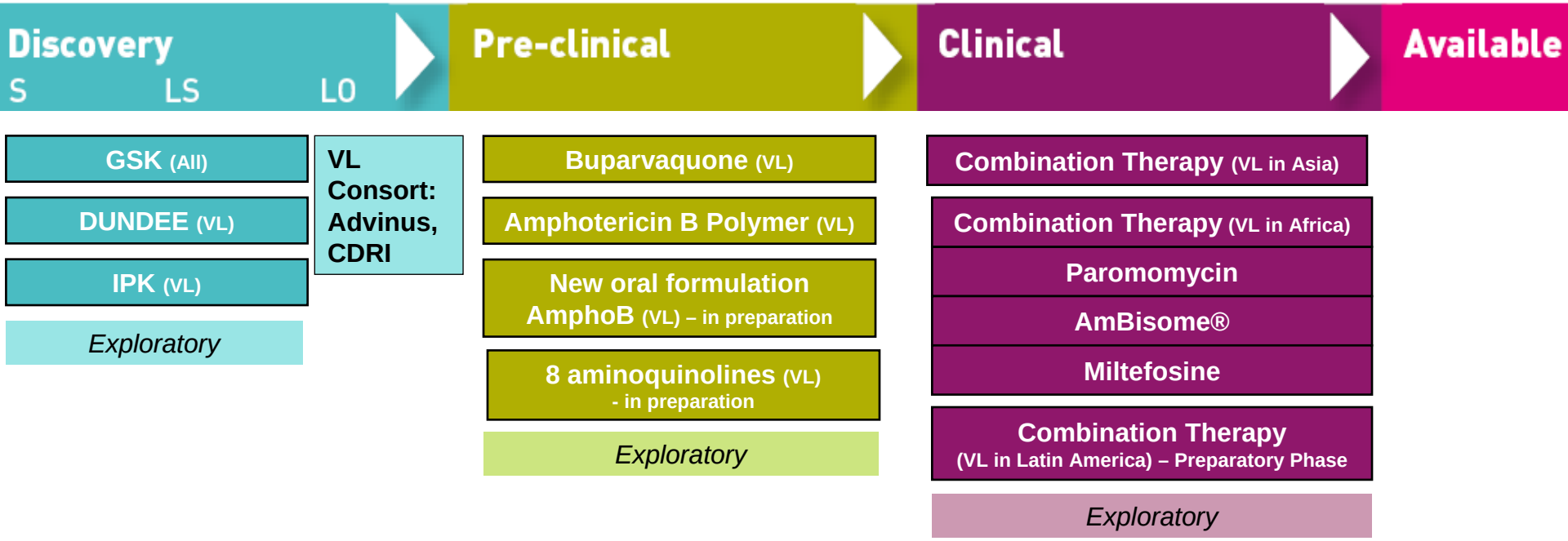
Planned DNDi/ LEAP studies in Africa

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"**

DNDi Drugs for Neglected Diseases *initiative*

DNDi R&D VL Projects – 2009 Outlook



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