New treatments for visceral leishmaniasis in Africa – The story so far

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LEAP0104 Study Group

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The story begins…

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LEAP 0104 clinical trial design

- A randomised, open-label, multicentre, comparative Phase III trial of efficacy and safety of:
  - sodium stibogluconate (SSG)
  - paromomycin (PM)
  - combination of SSG and PM
- Sample size 705, 90% power, between treatment difference of no more than 10%
- Countries:
  - recruiting: Ethiopia, Kenya, Sudan

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Treatment regimens

- SSG 20mg/kg/day for 30 days iv/im
- PM 15mg/kg/day for 21 days im
- Combination
  - SSG 20mg/kg/day for 17 days iv/im
  - PM 15mg/kg/day for 17 days im

PM dose was selected based on the dose used in the Indian trial

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Primary endpoints

- Safety:
- Efficacy: Parasitological clearance at 6 months post-treatment by splenic, lymph node, or bone marrow smear

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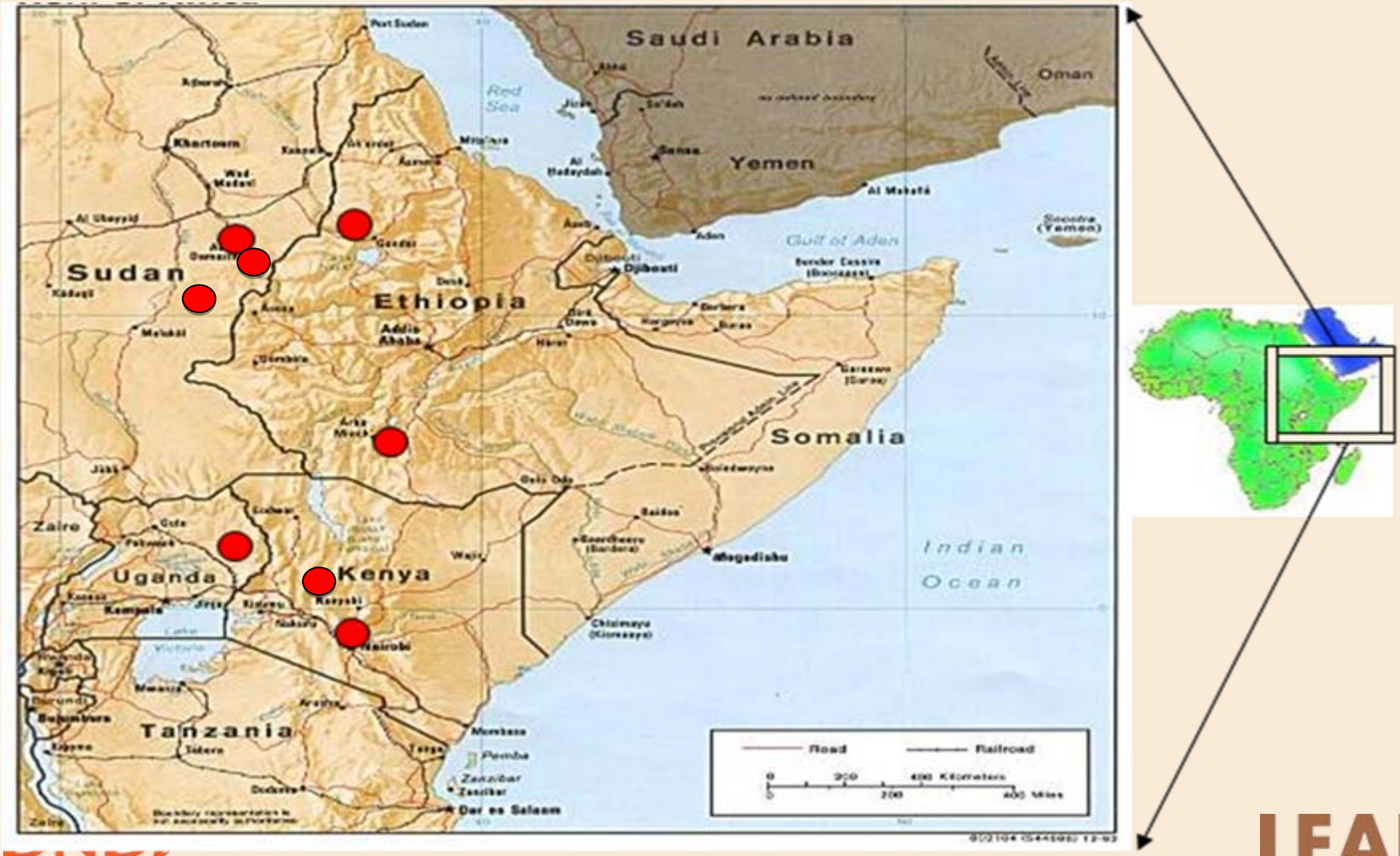
LEAP 0104 Study Sites



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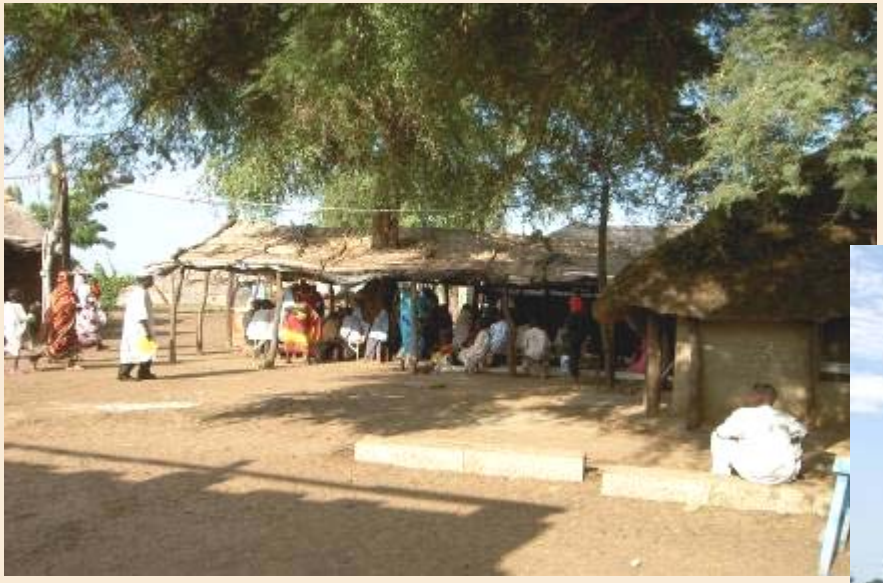
MSF – Um el Kher, Sudan



(Photo courtesy of Dr M Balasegaram)

(Photo courtesy of Dr C Royce)

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Kassab Hospital, Sudan

(Photo courtesy of Dr Musa)

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Laboratory – Kassab Hospital

(Photo courtesy of Dr C Royce)

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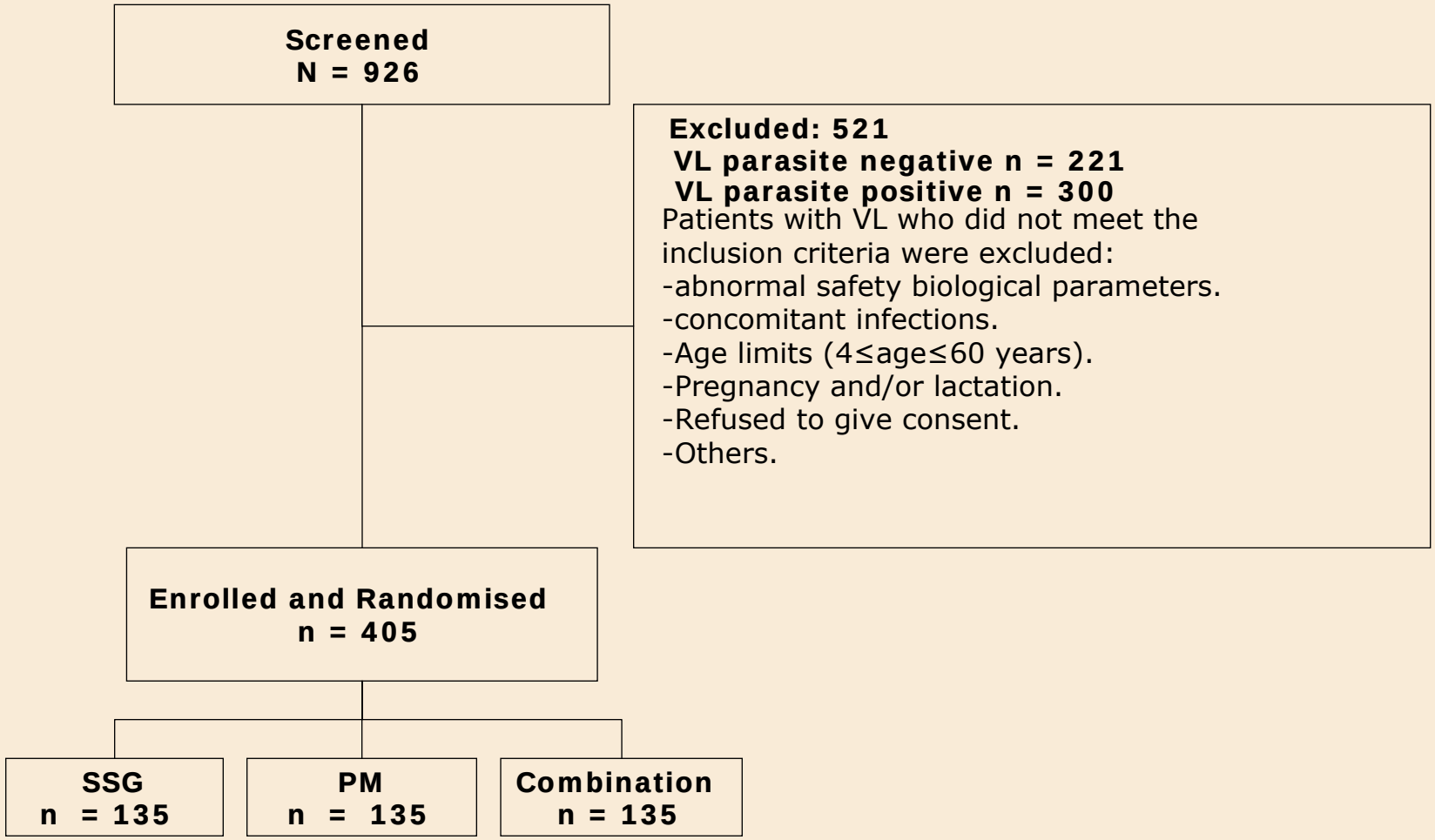
LEAP0104A Patient Disposition



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Patient Demographics - Baseline

Demographics, n (%)		SSG N = 135	PM N = 135	SSG + PM N =135
Age (years)	mean (SD)	16.7 (10.4)	17.8 (11.1)	16.1 (9.4)
	4 – 14	69 (51.1)	67 (49.6)	68 (50.4)
	≥ 15	66 (48.9)	68 (50.4)	67 (49.6)
Sex	Female	34 (25.2)	31 (23.0)	34 (25.2)
	Male	101 (74.8)	104 (77.0)	101 (74.8)
Randomised at Centre	Kenya	15 (11.1)	15 (11.1)	15 (11.1)
	Um El Kher	30 (22.2)	30 (22.2)	30 (22.2)
	Kassab	15 (11.1)	15 (11.1)	15 (11.1)
	Gondar	45 (33.3)	45 (33.3)	45 (33.3)
	Arba Minch	30 (22.2)	30 (22.2)	30 (22.2)

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Safety: SAEs and AEs

- Patients with SAEs: 16
  - 13 treatment-related (7 SSG, 3 PM, 3 Combo)
- Patients with AEs: 269
  - Spread among treatment arms
  - Total number of AEs: 566
    - SSG: 217 (38.3%)
    - PM: 168 (29.7%)
    - Combo: 181 (32.0%)

Efficacy at 6 Months: Definite Cure Complete Case Analysis

Estimation	SSG N = 115	PM N = 127	Comb N = 123
Treatment Efficacy at 6 months, n (%)	107 (93.0)	81 (63.8)	110 (89.4)
Difference between SSG & PM (95% CI)	29.3% (19.7 to 38.8)		
Difference between SSG & Combination (95% CI)	3.6% (-3.5 to 10.8)		
Test of difference across arms: p-value*	< 0.001		
Test of difference across centres, after adjustment for treatment : p-value*	0.003		

No patients failed on rescue medication – AmBisome®

*p-value from likelihood ratio test, comparing models with and without variable being tested.

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Efficacy at 6 Months: Definite Cure Complete Case Analysis: By Centre

Site	SSG	PM	Comb
Um el Kher	14 / 16 (87.5%)	4 / 28 (14.3%)	18 / 20 (90.0%)
Kassab	14 / 15 (93.3%)	7 / 15 (46.7%)	14 / 15 (93.3%)
Kenya	15 / 15 (100.0)	12 / 15 (80.0%)	11 / 15 (73.3%)
Gondar	37 / 40 (92.5%)	30 / 40 (75.0%)	39 / 43 (90.7%)
Arba Minch	27 / 29 (93.1%)	28 / 29 (96.6%)	28 / 30 (93.3%)

Summary

- Trial feasible in a rural setting
- Comparatively few safety concerns
- Efficacy of PM (15 mg/kg/d at 21 d) inadequate in Eastern Sudan

Dose-ranging study

- Two-armed sub-study in Sudan
- Increased the PM dosage by 33%:
  - 15 mg/kg/d for 28 days (n=21).
  - 20 mg/kg/d for 21 days (n=21).
- Pharmacokinetics (PK) was performed on a subset of patients.
- Other LEAP sites continued recruitment.

Actions:

- 0104B: 20 mg/kg/d for 21 days into the original trial.

What's Next?

- Paromomycin
  - Complete ongoing study in 2009
    - recruiting: Ethiopia, Kenya, Sudan, Uganda
  - What's the proper use?

- Continue research for new treatment combinations across region
  - AmBisome® dose-finding
  - Phase II combo: AmBisome®, SSG, miltefosine

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Acknowledgements

- Patients and communities
- Research teams
- LEAP members
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