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

Prof Eltahir Khalil on behalf of
Dr Ahmed Mudawi Musa
Institute of Endemic Diseases,
University of Khartoum

LEAP0104 Study Group
The story begins...
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
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
Primary endpoints

- Safety:
- Efficacy: Parasitological clearance at 6 months post-treatment by splenic, lymph node, or bone marrow smear
LEAP 0104 Study Sites
MSF – Um el Kher, Sudan

(Photo courtesy of Dr M Balasegaram)

(Photo courtesy of Dr C Royce)
Kassab Hospital, Sudan

(15/12/2007 1:12 pm)

(Photo courtesy of Dr Musa)
Laboratory – Kassab Hospital

(Photo courtesy of Dr C Royce)
LEAP0104A Patient Disposition

Screened
N = 926

Excluded: 521
VL parasite negative n = 221
VL parasite positive n = 300
Patients with VL who did not meet the inclusion criteria were excluded:
- abnormal safety biological parameters.
- concomitant infections.
- Age limits (4 ≤ age ≤ 60 years).
- Pregnancy and/or lactation.
- Refused to give consent.
- Others.

Enrolled and Randomised
n = 405

SSG
n = 135

PM
n = 135

Combination
n = 135
### Patient Demographics - Baseline

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

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

No patients failed on rescue medication – AmBisome®

*p-value from likelihood ratio test, comparing models with and without variable being tested.
### Efficacy at 6 Months: Definite Cure

#### Complete Case Analysis: By Centre

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

• Patients and communities
• Research teams
• LEAP members
• Ministries of Health, regulatory authorities, cooperating institutes
• Donors