Phase II Randomized Clinical Trial of the Efficacy and Safety of AmBisome® in Combination with SSG or Miltefosine versus Miltefosine Monotherapy for African VL

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DNDi Africa Regional office

WorldLeish6 Congress, Toledo Spain
Background

Visceral leishmaniasis, (or kala-azar), is a parasitic disease which is fatal without treatment.

The disease burden is high in Eastern Africa with an estimated 29,400 - 56,600 cases annually.

In eastern Africa VL is caused by *L. donovani*, and affects the poorest of the poor.

A 17-day combination treatment of SSG&PM is the recommended first line treatment by WHO in eastern Africa.

AmBisome® and Miltefosine are safe and effective in India but no published data from Africa.
Trial Objectives

Primary:

• To assess the efficacy of the treatments for primary VL at day 28

Secondary

• To assess the efficacy of the treatments for primary VL at day 210
• To assess the safety up to day 60 of the treatments for primary VL
• To assess the pharmacodynamics of the treatments for primary VL
• To study the pharmacokinetics of miltefosine alone and in combination with AmBisome® in adult and paediatric patients
Endpoints

Primary Endpoint

- **Initial cure:** proportion cured at Day 28

Secondary Endpoint(s)

- **Final cure:** proportion cured at day 210 (6 months follow up)
- **Adverse events** and serious adverse events occurring in the three study arms up to day 60
- Description of the **pharmacodynamic** properties of all 3 arms
- Description of the **pharmacokinetic** properties of miltefosine
Inclusion Criteria

- Patients with clinical signs & symptoms of VL. **Confirmed diagnosis** by visualization of parasites in tissue samples (lymph node, bone marrow, or spleen where relevant).
- Patients aged between 7 and 60 years who are able to **comply with the protocol**.
- Patients for whom **written informed consent** has been signed by the patients themselves (if 18 years and over) or by parent(s) or legal guardian (if under 18 years of age).
- HIV negative status
Exclusion Criteria

- Anti-leishmanial drugs in the last 6 months/ relapse cases
- **Severe protein and or caloric malnutrition** (kwashiorkor or marasmus ; Adults: BMI ≤15, Children W/H<70, presence of oedema)
- **Severe concomitant infection** eg. TB or other serious disease which precludes evaluation of patient’s response to study medication
- **Female of child bearing age** (females who achieved menarche) /pregnant or lactating
- Haemoglobin < 5gm/dl , WBC < 1 x 10³/mm³ , Platelets < 40,000/mm³
- Abnormal liver function (ALT and AST) tests 3 x ULN
- Serum creatinine outside the normal range for age and gender
Sample size

- Max. sample size per arm = 63 patients (189 patients in total)
- Max. number of sequential analyses = 5 (15, 30, 45, 60, & 63 patients per arm)
The Treatment Arms

- **Group1:**
  - AmBisome® one dose of 10mg/kg bw (iv) on day 1
  - 10 days of SSG at 20mg/kg bw (im/iv) from days 2-11
- **Group2:**
  - AmBisome® one dose of 10mg/kg bw (iv) on day 1
  - 10 days miltefosine at 2.5mg/kg bw (oral) from days 2-11
- **Group3:**
  - Monotherapy course of miltefosine at 2.5mg/kg bw for 28 days

<table>
<thead>
<tr>
<th>Weight Range (kg)</th>
<th>Total Approximate Dose (2.5mg/kg)</th>
<th>Morning</th>
<th>Evening</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.0-13.9</td>
<td>30</td>
<td>10mg x 2</td>
<td>10mg x 1</td>
</tr>
<tr>
<td>14.0-17.9</td>
<td>40</td>
<td>10mg x 2</td>
<td>10mg x 2</td>
</tr>
<tr>
<td>18.0-21.9</td>
<td>50</td>
<td>50mg x 1</td>
<td>-</td>
</tr>
<tr>
<td>22.0-25.9</td>
<td>60</td>
<td>50mg x 1</td>
<td>10mg x 1</td>
</tr>
<tr>
<td>26.0-29.9</td>
<td>70</td>
<td>50mg x 1</td>
<td>10mg x 2</td>
</tr>
<tr>
<td>30.0-49.9</td>
<td>100</td>
<td>50mg x 1</td>
<td>50mg x 1</td>
</tr>
<tr>
<td>≥50.0</td>
<td>150</td>
<td>50mg x 2</td>
<td>50mg x 1</td>
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</tbody>
</table>

*Dosing of miltefosine capsules according to weight ranges*
## Results: Demographics

<table>
<thead>
<tr>
<th></th>
<th>AmBisome® + SSG (Arm 1)</th>
<th>AmBisome® + miltefosine (Arm 2)</th>
<th>Miltefosine (Arm 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( N = 51 )</td>
<td>( N = 49 )</td>
<td>( N = 51 )</td>
</tr>
<tr>
<td>Age (years) - n (%)</td>
<td>15 (8)</td>
<td>14 (6)</td>
<td>15 (8)</td>
</tr>
<tr>
<td>Site - n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dooka</td>
<td>19 (37)</td>
<td>18 (37)</td>
<td>20 (39)</td>
</tr>
<tr>
<td>Kassab</td>
<td>5 (10)</td>
<td>6 (12)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Kimalel</td>
<td>27 (53)</td>
<td>25 (51)</td>
<td>24 (47)</td>
</tr>
<tr>
<td>Sex - n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>14 (27)</td>
<td>9 (18)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Male</td>
<td>37 (73)</td>
<td>40 (82)</td>
<td>46 (90)</td>
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## Results

### Efficacy analysis at D28 and D210, ITT

<table>
<thead>
<tr>
<th></th>
<th>AmBisome® + SSG</th>
<th>AmBisome® + miltefosine</th>
<th>miltefosine</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>51</td>
<td>49</td>
<td>51</td>
</tr>
<tr>
<td>Proportion cured (p\textsubscript{28}, Day 28)</td>
<td>47/51 (85%)</td>
<td>46/49 (85%)</td>
<td>45/51(85%)</td>
</tr>
<tr>
<td>95% confidence interval for p\textsubscript{28}</td>
<td>0.73 – 0.92</td>
<td>0.73 – 0.92</td>
<td>0.73 – 0.92</td>
</tr>
<tr>
<td>Proportion cured at day 210, (p\textsubscript{210})</td>
<td>47/51 (87%)</td>
<td>40/49 (77%)</td>
<td>38/51 (72%)</td>
</tr>
<tr>
<td>95% confidence interval for p\textsubscript{210}</td>
<td>0.77-0.97</td>
<td>0.64-0.90</td>
<td>0.60-0.85</td>
</tr>
</tbody>
</table>

None of the combinations had >90% efficacy to move for Phase III development.

<table>
<thead>
<tr>
<th>Efficacy at D210, ITT by age group</th>
<th>AmB+Milt</th>
<th>Miltefosine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 12y</td>
<td>20/27 (74%)</td>
<td>13/22 (59%)</td>
</tr>
<tr>
<td>12 years and above</td>
<td>20/22 (90%)</td>
<td>25/29 (86%)</td>
</tr>
<tr>
<td>Fisher exact test p-value (2-sided)</td>
<td>0.159</td>
<td>0.050</td>
</tr>
</tbody>
</table>

Children had poorer clinical response as compared to adults, which could be explained by underexposure to the drug.

### Number of Patients Reporting SAE / AE

<table>
<thead>
<tr>
<th></th>
<th>AmBisome® + SSG (Arm 1)</th>
<th>AmBisome® + miltefosine (Arm 2)</th>
<th>Miltefosine (Arm 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number randomized</td>
<td>51</td>
<td>49</td>
<td>51</td>
</tr>
<tr>
<td>Number of patients with at least one SAE: n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse drug reaction*</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Unrelated to study drug¶</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Patients with at least one AE (whether serious or not): n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse drug reaction*</td>
<td>38 (75)</td>
<td>39 (80)</td>
<td>45 (88)</td>
</tr>
<tr>
<td>Unrelated to study drug¶</td>
<td>17 (33)</td>
<td>20 (41)</td>
<td>13 (25)</td>
</tr>
</tbody>
</table>

*AE recorded as unlikely, possible or probable relation to study drug
¶AE recorded as not related to study drug. Note that since patients may have a combination of drug-related and -unrelated adverse events, the numbers of people with each may sum to more than the number of people with at least one event.

There were no major safety concerns in all the arms.
Parasite Clearance from the Blood in the First Week of Treatment

All parasite blood loads are relative to the individual parasite load at baseline. The lines indicate the mean and the error bars its 95% confidence interval, stratified per treatment arm.
Comparison of End of Treatment Miltefosine Plasma Concentrations Between Bodyweight Categories

The left plot shows the AmBisome®+ miltefosine arm (10 days of miltefosine), the right plot the miltefosine alone arm (28 days of miltefosine).
Conclusion

- None of the treatment regimens tested achieved target efficacy of 90%.
- **Children are less exposed** to miltefosine than adults, in Eastern Africa.
- Patients weighing <30 kg (most children) were less exposed to miltefosine.
- No unexpected safety event.
- Data showed faster parasite clearance with both AmBisome® combinations than with miltefosine monotherapy.
- Miltefosine is an oral drug, and a further study to test the allometric dose is recommended.
- Allometric dosing of miltefosine has been tried in eastern Africa in another Phase II POC study.
Acknowledgements

- **Co authors:** Simon Njenga, Manica Balasegaram, Neal Alexander, Raymond Omollo, Tansy Edwards, Thomas P.C. Dorlo, Brima Musa, Mohammed Hassan Sharaf Ali, Mohamed Yassein, George Kirigi, Rashid Juma, Anke E. Kip, Gerard J. Schoone, Asrat Hailu, Joseph Olobo, Sally Ellis, Robert Kimutai, Susan Wells, Eltahir Awad Gasim Khalil, Nathalie Strub-Wourgaft, Fabiana Alves, and Ahmed Musa

- **Study participants and the communities**

- **Trial Sites and the field team** (Nurses and lab technicians, clinical monitors, DSMB)
  - MoH Kenya and Gederaf State, Sudan
  - DNDi Geneva and DNDi Africa Regional Office team
LEAP Partners

1. Institute of Endemic Diseases
2. Addis Ababa University
3. Kenya Medical Research Institute
4. University of Gondar
5. Médecins Sans Frontières
6. World Health Organization
THANK YOU TO ALL OUR DONORS

BBVA

Agencia Española de Cooperación Internacional para el Desarrollo

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from the British people

Federal Ministry of Education and Research by KfW

Schweizerische Eidgenossenschaft

Confédération suisse

Confederazione Svizzera

Confederazione svizzera

Ministry of Foreign Affairs of the Netherlands

medicor foundation

MEDECINS SANS FRONTIERES
Thank you!
BACKUP SLIDES
Study Design

A phase II randomized, parallel arm, open-labeled clinical trial to assess the safety and efficacy of three treatment regimens for the treatment of primary visceral leishmaniasis in eastern Africa.

Sequential analysis performed on every 15 patients per arm on the day 28 primary endpoint; maximum of 5 performed. Maximum sample size is 189.

0= Assessment and informed consent  
1= Commencement of treatment  
2= End of combination treatment regimens (day 11)  
3= Primary efficacy endpoint at day 28 (miltefosine arm ends day 28)  
4= Further safety and follow up assessment at day 60  
5= Final assessment at 6 months after day 28 primary endpoint (day 210)
Exclusion Criteria

- Anti-leishmanial drugs in the last 6 months/ relapse cases
- Negative lymph node/bone marrow (or spleen) smears
- Severe protein and or caloric malnutrition (kwashiorkor or marasmus; adults: BMI ≤15, children W/H<70, presence of oedema)
- Previous history of hypersensitivity reaction to SSG or Amphotericin B
- Concomitant severe infection eg. TB or other serious disease which precludes evaluation of patient’s response to study medication
- Patients with conditions associated with splenomegaly e.g. schistosomiasis
- Previous history of cardiac arrhythmia /abnormal ECG
- Female of child bearing age (females who achieved menarche) / pregnant or lactating
- Haemoglobin < 5gm/dl, WBC < 1 x 10³/mm³, Platelets < 40,000/mm³
- Abnormal liver function (ALT and AST) tests 3 x ULN
- Serum creatinine outside the normal range for age and gender
- Major surgical intervention within 2 weeks prior to enrolment
Schedule of Assessment

• **Clinical assessments include:**
  – pulse, blood pressure, temperature, weight, height, spleen size, liver size

• **Clinical Laboratory assessments**
  – **Haematology:** haemoglobin, WBC, platelets
  – **Biochemistry:** urea, creatinine, serum electrolytes (Na⁺, K⁺, Mg²⁺), and liver function (AST, ALT, ALP, bilirubin) tests
  – Urinalysis

• **Return for an assessment:**
  – between day 60 and 210 in the event of any medical problems
  – Blood count, biochemistry, liver function tests, parasitology and PK analysis will be done in the event of such a visit
  – At the day 210 visit, flexibility (of +/- 21 days) will be allowed due to practical difficulties patients may face in meeting the exact timing of visits.
  – Parasitology will only be done in the follow up period after day 28 if clinically indicated (i.e. reappearance of symptoms and signs of VL)
PK / PD Samples

Blood volumes
- 2.5 ml of EDTA blood for complete blood count;
- only 0.2 ml EDTA blood used for PCR
- 7.5 ml blood for urea, creatinine, liver function test

PK study
- Was done on the specified days with 2.5 ml of EDTA blood taken before/after 0.5 ml during Day 1 of Miltefosine treatment, 2.5 ml blood samples will be taken:
  - prior to first dose,
  - 4 hours post first-dose
  - 8 hours post first-dose
  - Other PK samples will be taken prior to the morning dose.
Rescue Medication

• Rescue medication was given if there was:
  – failure to respond to treatment during the first 28 days
  – failure to tolerate trial medication / occurrence of AEs during receipt of test drugs that requires (treatment) withdrawal
  – recurrence of symptoms, signs and presence of parasites after day 28 (treatment failure)
  – development of severe PKDL

• Any patient who receives rescue medication at any point will be considered a treatment failure

• Rescue treatment given includes:
  – AmBisome®: 30mg/kg IV split into multiple doses (according to country protocol: Sudan - 3mg/kg/day for 10 days)
  – SSG 20mg/kg IM for 30-60+ days: for patients not responding to initial rescue treatment or patients requiring treatment for severe PKDL
Adverse Events

AE reporting period
Begin - Upon receipt of first dose of trial medication for AEs and SAEs
Ends - at day 60 when a further safety evaluation occurs

Adverse Event definition
• Any untoward medical occurrence (unfavourable & unintended sign, symptom or disease, inc. abnormal laboratory finding) in temporal association with the study treatment which may or may not be causally related to it.
• Abnormal laboratory (haematology and biochemistry) results will be reported as AEs if the abnormality occurs or worsens after start of study treatment, and if they require clinical intervention or further investigation.
AE Grading

AE Grading
- Adapted CTC AE grading was used.
- If AE not in adapted CTC AE, the following was used
  - **Mild** - does not interfere with subject's usual functions
  - **Moderate** - interferes to some extent with subject's usual functions
  - **Severe** - interferes significantly with subject's usual functions
Randomised n = 151

AmBisome + SSG n = 51
- Died, no rescue n = 1
- End of Treatment n = 50
  - Rescued n = 3
- End of Trial: n = 47
  - ITT Complete-case n = 51 (3 rescued, 1 VL death)
  - BMI = 15 n = 1
  - PP Complete-case n = 50

AmBisome + Miltefosine n = 49
- Treatment stopped due to AE & rescue given n = 1
- End of Treatment n = 48
  - Death (VL) n = 1
  - Rescued n = 6
  - BMI = 15 n = 1
  - PP Complete-case n = 48

Miltefosine n = 51
- Treatment stopped & rescue given:
  - Due to AE n = 1
  - Concomitant condition n = 1
- End of Treatment n = 49
  - Rescued n = 9
  - BMI ≤ 15 n = 1
  - Concomitant condition n = 1
  - PP Complete-case n = 49

Died, no rescue n = 1
- End of Treatment n = 48
  - ITT Complete-case n = 49 (7 rescued, 1 VL death)
  - BMI = 15 n = 1
  - PP Complete-case n = 48

Screened n = 970
- VL parasite negative n = 439
  - Refused consent n = 40
  - Age < 7 years n = 109
  - VL treatment within 6 months n = 13
  - Concomitant condition n = 32
  - Female of child bearing age = 47
  - Abnormal biological safety parameter n = 102
  - Severe malnutrition n = 8
  - HIV positive n = 10
  - Unable to follow-up n = 2
  - History of cardiac arrest or abnormal ECG n = 3
  - Referred to alternative treatment centre n = 1
  - PKDL n = 2
  - No guardian to provide consent n = 2
  - Not documented n = 9

Rescued n = 6
- Death (VL) n = 1
- ITT Complete-case n = 51
  - (11 rescued)
Discussion

- **Parasite clearance in the first week of treatment:**
  - Lower clearance in miltefosine alone compared to combos
  - Higher clearance in multiple vs single AmBisome®
  - Same between combos
  - Lower in relapsing patients compared to patients who are cured

- **Children are less exposed to miltefosine than adults, also in E-Africa**
  - Implementation of daily/optimal miltefosine dosing algorithm instead of mg/kg dosing: tolerability?
  - Pending final analysis of clinical vs PK/PD data

- **The 1st phase II randomized trial of short course combo of AmBisome® in Africa**
  - AmB+SSG or AmB+miltefosine or miltefosine monotherapy achieved <90% cure
  - No unexpected safety event.
  - VL data showed faster parasite clearance with both AmBisome® combinations than with miltefosine monotherapy.
  - Patients with weighing <30 kg (most children) less exposed to miltefosine