WP1- PM/MF Phase III Clinical Trial
**PM/MF phase III Clinical Trial**

**Trial design:**
An Open Label, Phase III, Randomized Controlled, Multicentre Non-Inferiority Trial to Compare Efficacy and Safety of Miltefosine and Paromomycin with SSG and PM Combination for Treatment of Primary Visceral Leishmaniasis (VL) Patients in Eastern Africa

**1ary objective:** To compare the efficacy of two combination regimens of PM (14 days) and MF (14 or 28 days) with the standard 17-day course of SSG-PM for the treatment of primary VL patients in eastern Africa

**2ary objectives:** safety, PK, PD, compliance to oral treatment

- Countries: Ethiopia, Kenya, Sudan and Uganda
- 6 study sites → 8 study sites
- Patient population: confirmed primary VL patients 4-50y old, HIV neg, signed ICF

- Study Arms:
  - Arm 1. PM (20mg/Kg/d) 14 days + MF allom for 14 days
  - Arm 2. PM (20mg/Kg/d) 14 days + MF allom for 28 days vs
  - Arm 3. SSG (30mg/Kg/d) 17 days + PM (15mg/Kg/d) 17 days (comparator)

- Sample size: 192/arm, total of 576 VL patients
Background – SSG/PM: an improvement, but with limitations

- Efficacy of 91% at 6 months
- 17 days of 2 painful injections
- Toxicity related to SSG
- Lower efficacy (81% EOT) and higher mortality (9%) in > 50y
- Not recommended for HIV-VL

Replacement of SSG by miltefosine has the potential of a safer treatment with shorter hospitalization, suitable for children and more field adapted
WP1- To develop a safe, efficacious and field-adapted combination therapy for VL in Eastern Africa by 2020
WP1 – PM/MF Phase III Clinical trial update

- All EC and regulatory approvals obtained in the 4 countries
- **4 out of 8 SIVs completed**: Dooka and Tabarakallah in Sudan, Kacheliba in Kenya and Gondar in Ethiopia
- As of end of September, a total of **77 patients** have been recruited. 19 in Dooka, 48 patients in Kacheliba and 10 patients recruited in Gondar
- Kimalel, Amudat and Abdurafi to be initiated; Um el Kher site, Sudan to be operational by November 2018
- Recruitment plan – highest peak expected in Q4 2018/Q1 2019
- Integration of the WP2 ‘sub-study’ – to be implemented in Ethiopia and Sudan

<table>
<thead>
<tr>
<th>Study Timelines:</th>
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<tbody>
<tr>
<td>Q1 2017</td>
</tr>
<tr>
<td></td>
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<tr>
<td><strong>Approvals</strong></td>
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</table>
### PM/MF Phase Clinical III trial - Recruitment

<table>
<thead>
<tr>
<th>Sites</th>
<th>Kacheliba</th>
<th>Gondar</th>
<th>Doka</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td># Screened</td>
<td>189</td>
<td>121</td>
<td>166</td>
<td>476</td>
</tr>
<tr>
<td># VL positive</td>
<td>178</td>
<td>75</td>
<td>59</td>
<td>312</td>
</tr>
<tr>
<td># enrolled</td>
<td>48</td>
<td>10</td>
<td>19</td>
<td>77</td>
</tr>
<tr>
<td>% enrolment</td>
<td>27%</td>
<td>13%</td>
<td>32%</td>
<td>25%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reason for screening failure</th>
<th>Kacheliba</th>
<th>Gondar</th>
<th>Doka</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 - Age less than 4 years or more than 50 years</td>
<td>25%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>4 - Declined consent</td>
<td>1%</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>5 - Female is pregnant, lactating, or refused contraception</td>
<td>14%</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>6 - Severely malnourished</td>
<td>3%</td>
<td>38%</td>
<td>18%</td>
</tr>
<tr>
<td>7 - Patient cannot comply with scheduled visits and procedures</td>
<td>1%</td>
<td>0%</td>
<td>6%</td>
</tr>
<tr>
<td>8 - VL relapse case</td>
<td>2%</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>9 - HIV positive</td>
<td>0%</td>
<td>10%</td>
<td>2%</td>
</tr>
<tr>
<td>10 - Lab abnormalities</td>
<td>15%</td>
<td>18%</td>
<td>24%</td>
</tr>
<tr>
<td>11 - Patient with clinical signs of severe VL disease</td>
<td>1%</td>
<td>0%</td>
<td>10%</td>
</tr>
<tr>
<td>12 - Patient with para kalazar dermal Leishmaniasis</td>
<td>2%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>13 - Patient with history of treatment for Kalazar in last 6 months</td>
<td>2%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>14 - Concomittant severe infection or chronic underlying disease</td>
<td>1%</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>15 - Abnormal ECG</td>
<td>4%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>16 - Pre-existing hearing loss based on Audiometry</td>
<td>1%</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>17 - Others</td>
<td>4%</td>
<td>1%</td>
<td>0%</td>
</tr>
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</table>
Building the assumptions of estimated recruitment for the PM/MF Phase III Clinical trial

- 4 years historical data from LEAP sites, 2014-2017 number of VL cases per month/site.
- Demographic data from VL patients in East Africa, exclusion based on experience from previous trials. Applied adjustment of 30% enrolment rate:
  - Exclusion: 15% age criteria (<4y, >50y), 25% lab test or severe malnutrition, 15% female patient who cannot use contraception, +15% additional buffer
- No competing trials at the LEAP sites for primary VL
- Estimated time for SIV at each site based on approval process
Observed number of VL cases (especially in Dooka and Gondar) are considerably below the expected based in the 4y historical data.
Delay in initiating 3/6 study sites

• 3 sites not initiated
  • Amudat - > 18mo approval process.
  • Kimalel – delayed renovation by KEMRI.
  • Um el Kher – delayed construction by IEND.
Actions taken to mitigate the delayed recruitment

- Including 2 MSF sites, in Sudan and Ethiopia
  - Amendment approved in the 2 countries
  - SIV Tabarakallah, Sudan, week of 10th Sept 2018
  - SIV Abdurafi, Ethiopia, in Oct 2018

Approx number of VL cases/year:
- Abdurafi: 300
- Tabarakallah: 380
Actions taken to mitigate the delayed recruitment, cont..

- Exclusion criteria – BMI in Ethiopia
  - Analysis of MSF cohort data, BMI cut-off to predict poor outcome – under discussion if justifies an amendment to have a more representative population in Ethiopia (increase by ~ 15% enrolment rate)
- Referral network (Gondar, Doka?)
- Construction of Um el Kher to be finalized by Nov 2018
- Boost recruitment in Kacheliba (active case search plan)
- Abdurafi and Amudat: SIV in Oct 2018
- Investigate potential to open new sites
**Short and medium-term strategies**

- VL cases are decreasing in some LEAP sites, which makes them no longer cost-effective – need a flexible platform that adapts to the disease dynamics
- **Short-term – take actions to mitigate the risks of 3-7mo delay in recruitment for the Phase III MF/PM trial**
  - Initiate new sites with sense of urgency (MSF sites, Um el Kher, Amudat)
  - Boost active case search and/or network of referrals (upon context)
  - Assess feasibility/cost to open new sites ‘where the patients are’
- **Medium-term – prepare for the future studies with NCEs:**
  - LEAP sites policy on use of the sites
  - Identify/invest in sites with infra-structure to implement PoC trials with NCEs (open new sites Ethiopia, assess Gedaref hospital as referral in Sudan, KEMRI CCR?)
  - Access/PV sites: plan for reducing support in access/PV sites during periods where no clinical trials are planned (e.g. Kacheliba model)
Thank You