WP1- PM/MF Phase III Clinical Trial

DNDi
Drugs for Neglected Diseases *initiative*

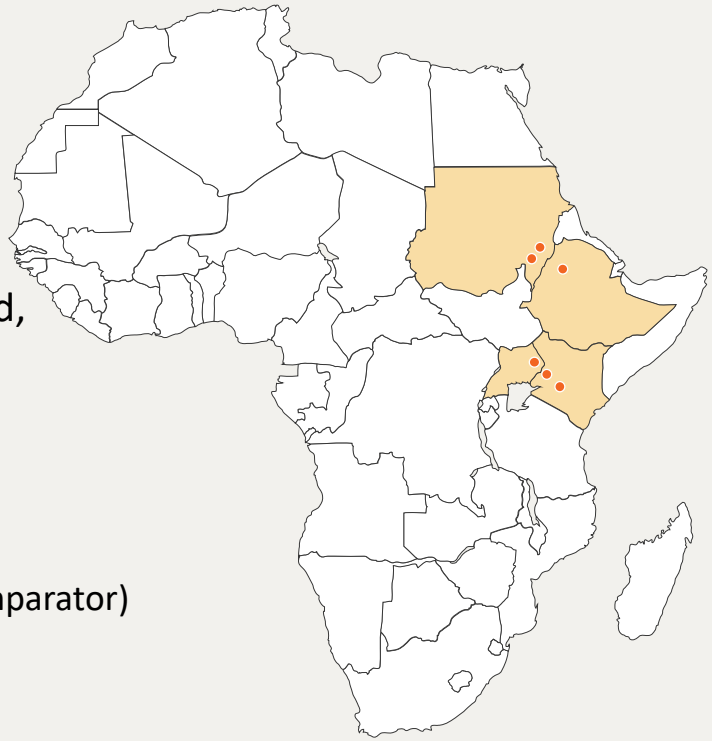
PM/MF phase III Clinical Trial

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

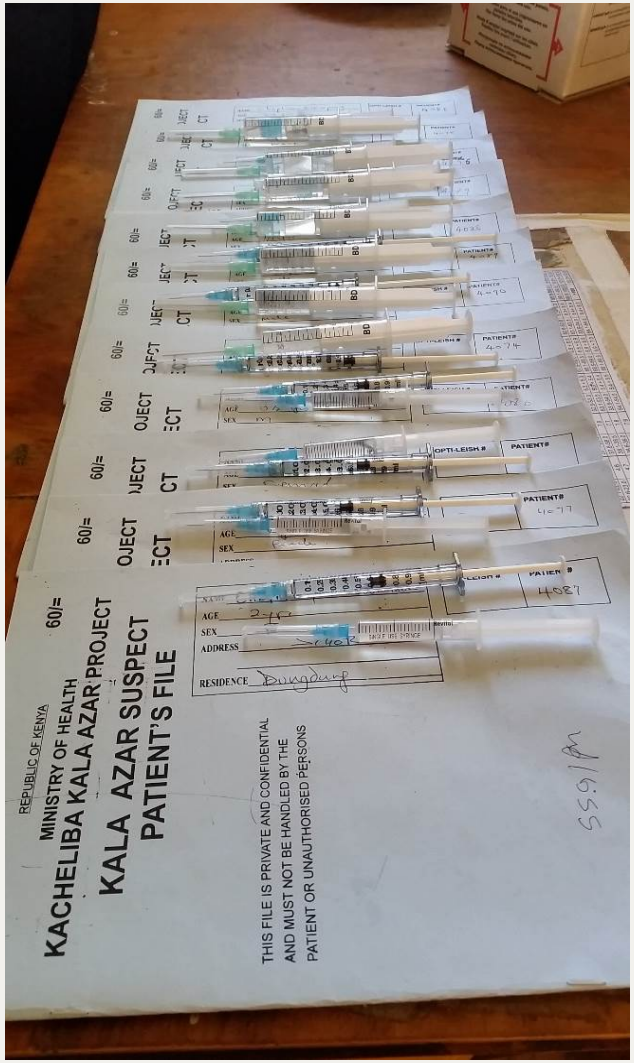
- Study Arms:
  - Arm 1. PM (20mg/Kg/d) 14 days + MF allom for 14 days
  - Arm 2. PM (20mg/Kg/d) 14 days + MF allom for 28 days **vs**
  - Arm 3. SSG (30mg/Kg/d) 17 days + PM (15mg/Kg/d) 17 days (comparator)

- Sample size: 192/arm, total of 576 VL patients

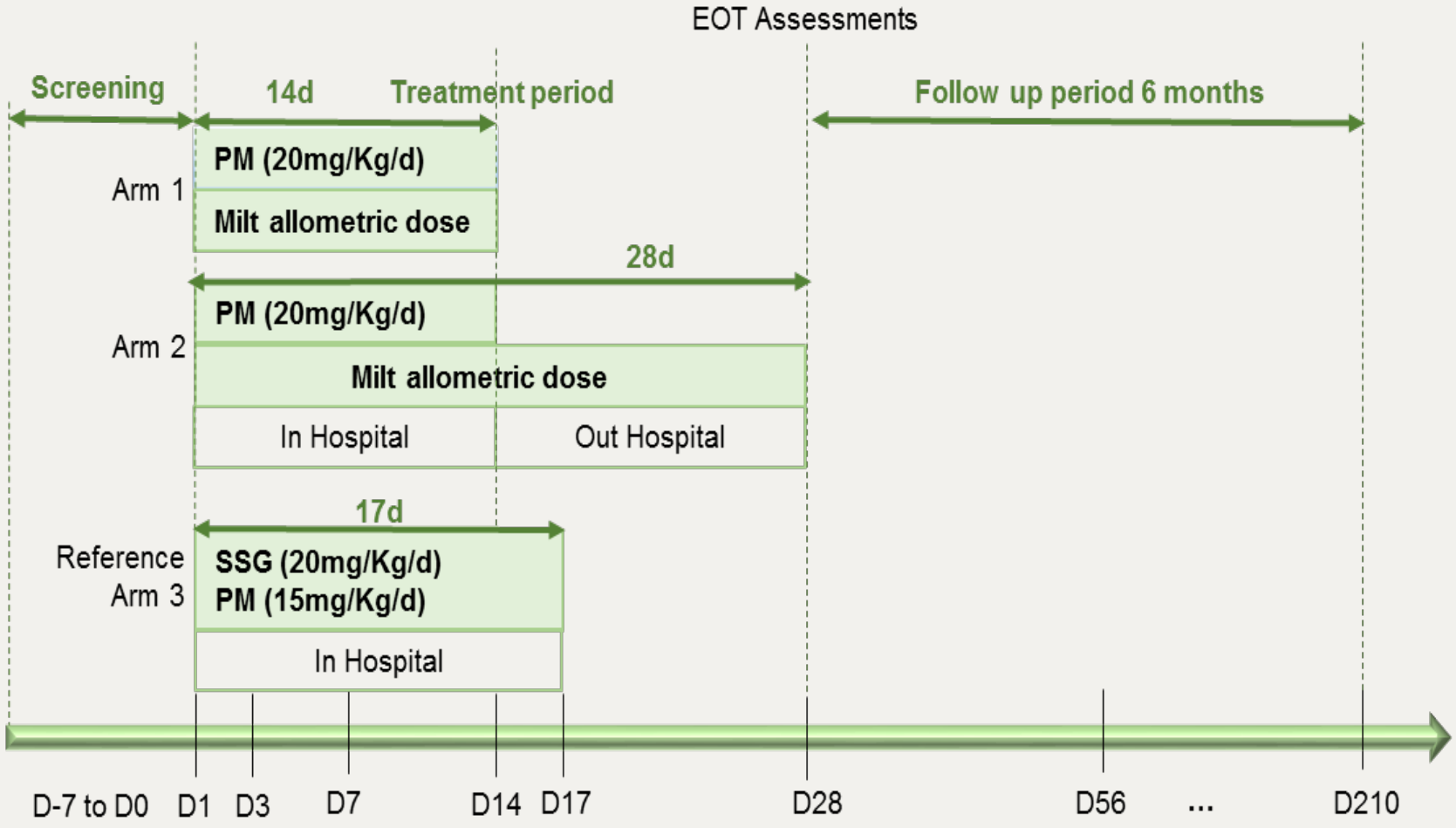
Background – SSG/PM: an improvement, but with limitations

- 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

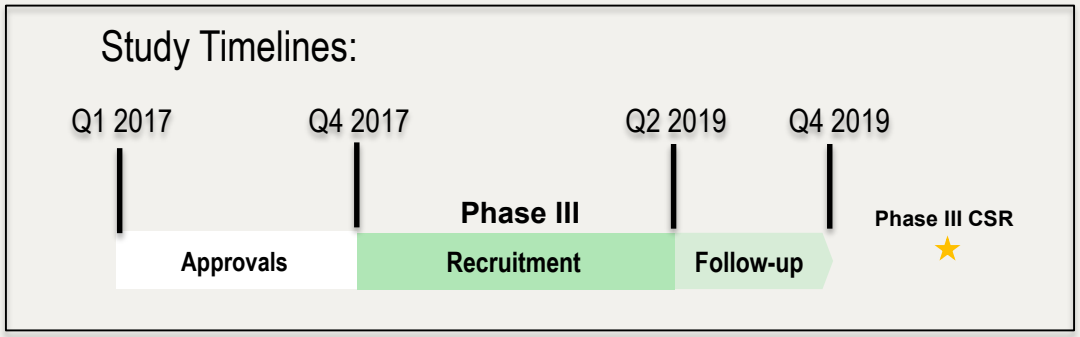


WP1- To develop a safe, efficacious and field-adapted combination therapy for VL in Eastern Africa by 2020



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



PM/MF Phase Clinical III trial - Recruitment

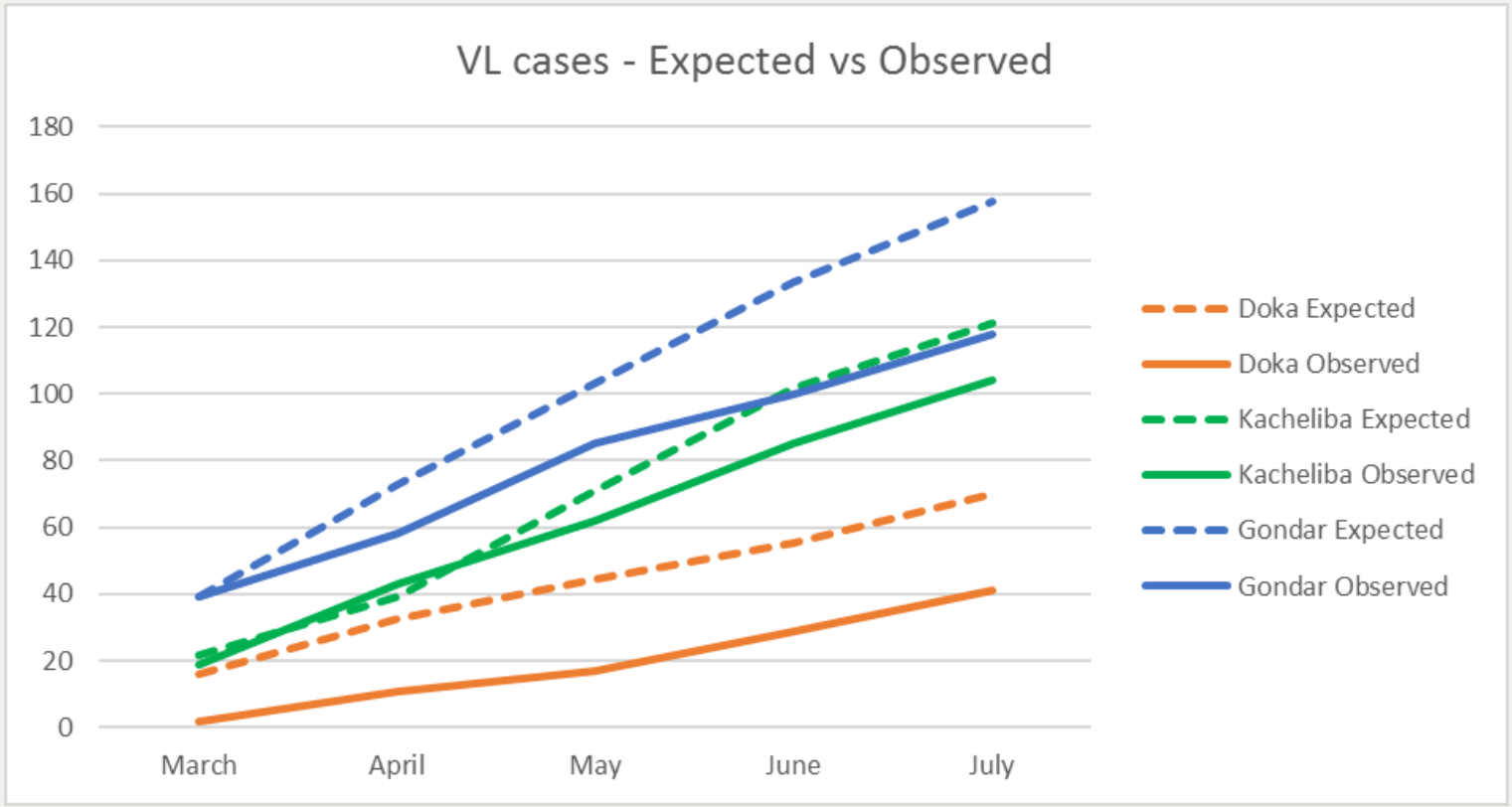
Sites	Kacheliba	Gondar	Doka	Total
# Screened	189	121	166	476
# VL positive	178	75	59	312
# enrolled	48	10	19	77
% enrolment	27%	13%	32%	25%

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

Building the assumptions of estimated recruitment for the PM/MF Phase III Clinical trial

- 4years 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

Expected vs observed number of VL cases in the 3 active sites



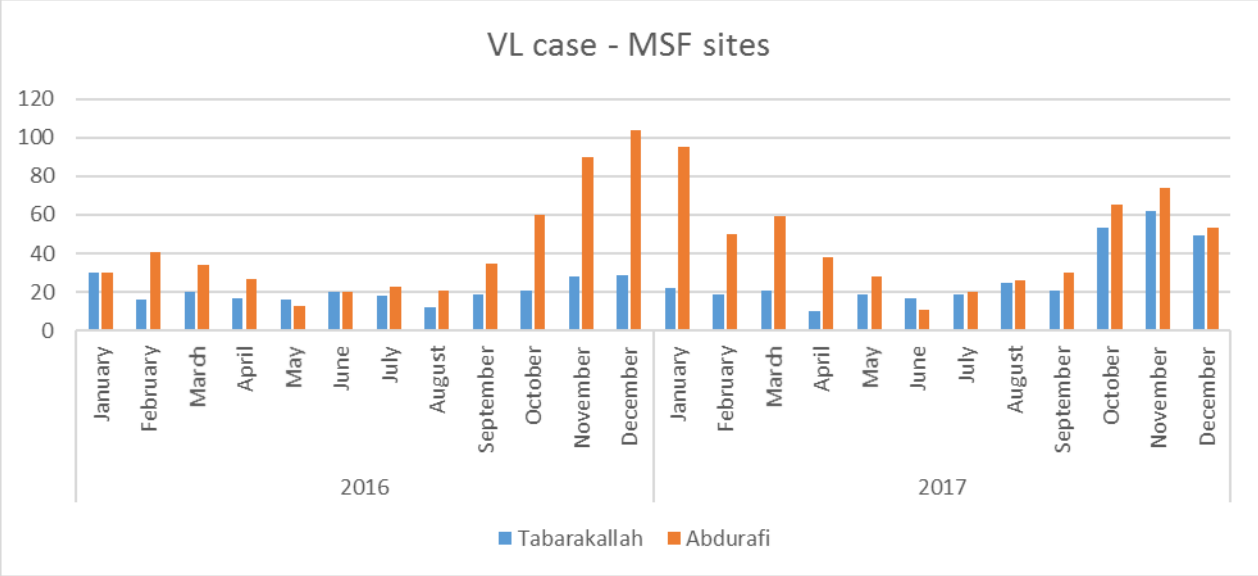
Observed number of VL cases (especially in Dooka and Gondar) are considerably below the expected based in the 4y historical data.

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