Efficacy and safety of 14-day treatment with paromomycin and miltefosine for primary visceral leishmaniasis in eastern Africa: non-inferiority trial

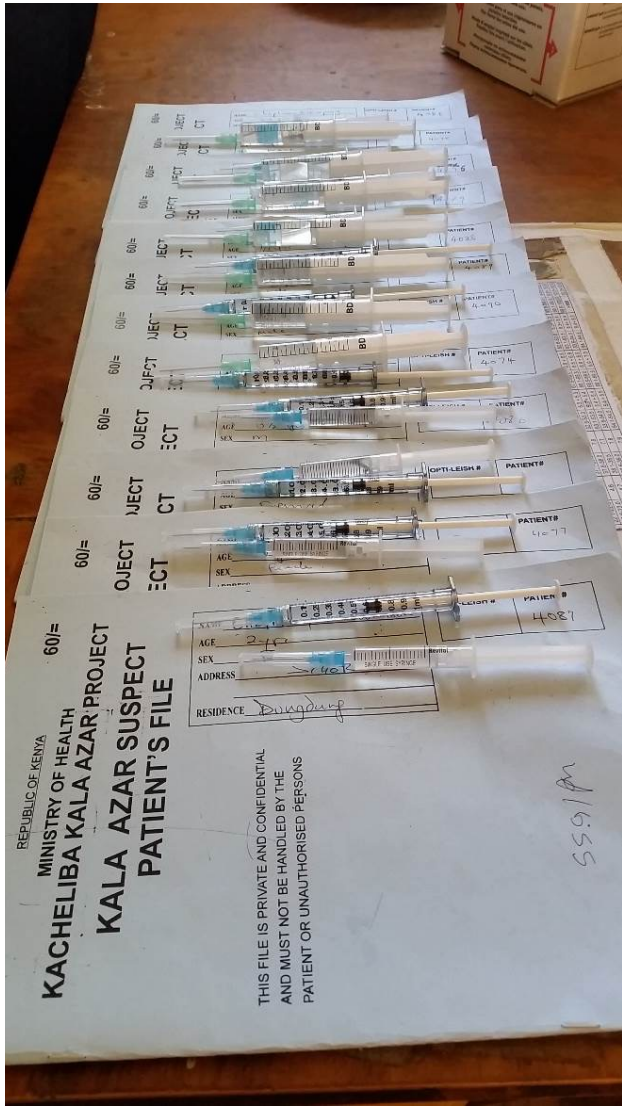
Alexandra Solomos, Ahmed Musa, Jane Mbui, Rezika Mohammed, Joseph Olobo, Koert Ritmeijer, Gabriel Alcoba, Gina Muthoni Ouattara, Thaddaeus Egondi, Prossy Nakanwagi, Truphosa Omollo, Monique Wasunna, Jorge Alvar, Fabiana Alves

Conflict of Interest:
The author has declared no conflict of interest.

SSG-PM for treatment of visceral leishmaniasis: an improvement, but with limitations

- Efficacy of 91% at 6 months
- 2 injections per day for 17 days
- SSG-related toxicity
- Lower efficacy (81% at the end of treatment) and higher mortality (9%) in patients >50 years
- Not recommended for HIV-VL

→ Replacement of SSG by **miltefosine** has the potential to provide a **safer treatment** with **shorter hospitalization** that is **suitable for children** and better adapted to field conditions



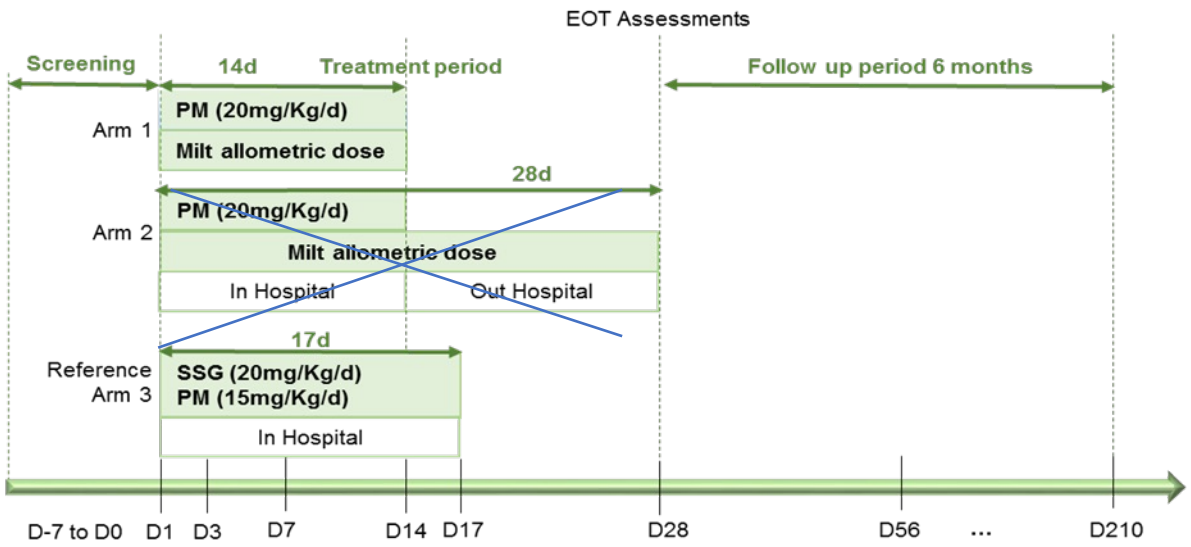
Sources: Musa A et al. 2012 PLoS Negl Trop Dis., Kimutai et al. 2017 Clin Drug Investig.

MF/PM Phase III Clinical Trial

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

Primary objective: To compare the efficacy of a 14-day combination regimen of PM (14 days) and MF with the standard 17-day course of SSG-PM for the treatment of primary VL patients in Eastern Africa

Secondary objectives: Pharmacokinetic (PK) profiles of PM and MF, parasite clearance (direct microscopy and qPCR), PK and PD relationship



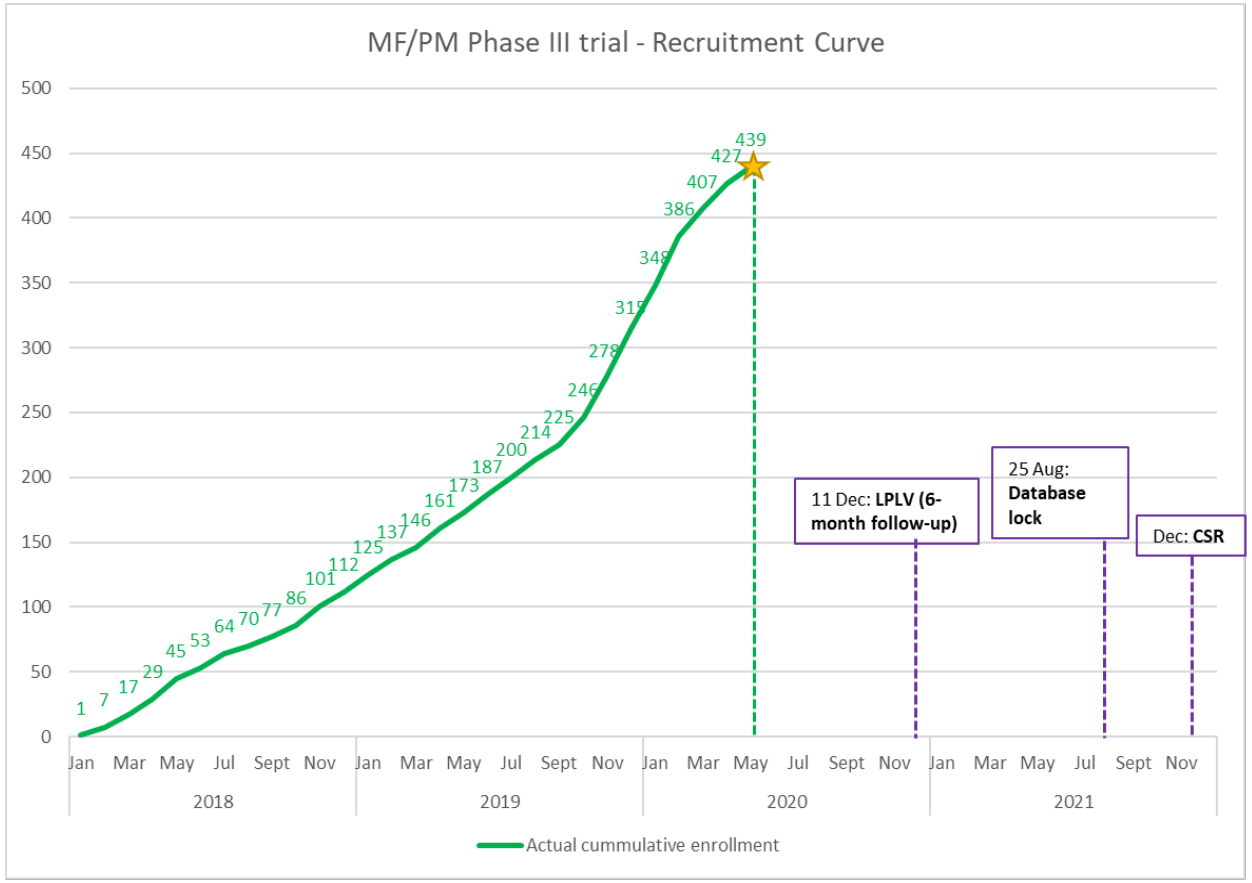
4 countries
Ethiopia
Kenya
Sudan
Uganda

7 sites
Gondar & Abdurafi MSF Center (Ethiopia)
Kacheliba (Kenya)
Doka, Umelkher & Tabarakallah MSF Center (Sudan)
Amudat (Uganda)

MEDECINS SANS FRONTIERES

SCIENTIFIC DAYS

Recruitment



★ Recruitment completed on 17th May 2020

- **Recruitment completed on 17 May 2020** with a total of **439 patients**, despite new challenges of COVID-19
- **Last Patient Last Visit**: 11 Dec 2020
- **Clinical Study Report:** Jan 2022
- **Article Publication**: Sep 2022

	STUDY ARMS			
	MF/PM 14d	**MF/PM 28d**	**SSG/PM**	**TOTAL**
Ethiopia	34	27	34	95 (22%)
Kenya	50	36	56	142 (32%)
Sudan	80	25	76	181 (41%)
Uganda	7	10	4	21 (5%)
TOTAL	171	98	170	439

MEDECINS SANS FRONTIERES

SCIENTIFIC DAYS

Baseline Demographics

Table 5: Baseline demographic characteristics by the treatment group-ITT.

Parameter	Statistic	PM+MF (14D) (n=171)	PM+MF (28D) * (n=98)	SSG+PM (n=170)	Overall (n=439)
Age (years)	N	171	98	170	439
	Mean (SD)	13.5 (7.9)	13.9 (8.0)	13.0 (7.1)	13.4 (7.6)
	Median (Q1-Q3)	10.0 (8.0-19.0)	12.0 (8.0-20.0)	10.0 (8.0-18.0)	11.0 (8.0-19.0)
Age Category	≤ 12 years	103 (60.2)	54 (55.1)	105 (61.8)	262 (59.7)
	> 12 years	68 (39.8)	44 (44.9)	65 (38.2)	177 (40.3)
Sex, n (%)	Female	34 (19.9)	17 (17.3)	38 (22.4)	89 (20.3)
	Male	137 (80.1)	81 (82.7)	132 (77.6)	350 (79.7)

**Discontinued arm*

- Children ≤ 12y represented 60% of trial patients Median age was 11 yrs (IQR 8-19 yrs)
- Predominance of male patients in the trial (80%), comparable with the overall VL population
- A majority of females recruited were ≤ 12 years (due to low acceptability of contraception)

	Gender		
Age	**Male**	**Female**	**Total**
4 to 12yrs	177 (68%)	85 (32%)	262 (60%)
>12 – ≤18yrs	62 (95%)	3 (5%)	65 (15%)
>18 – 50yrs	110 (99%)	1 (1%)	111 (25%)
Total:	349 (80%)	89 (20%)	438

MEDECINS SANS FRONTIERES

SCIENTIFIC DAYS

Primary efficacy outcome by treatment group

Primary efficacy outcome of definite cure with primary imputation by treatment group

	PM+MF (14D) (n=170)		SSG+PM (n=170)
Modified ITT (mITT)	170		170
Number cured	155		156
Efficacy (%)	91.2		91.8
Difference in efficacy⁺		0.6	
97.5% C.I of difference		[-6.2 ; 7.4]	
Per Protocol (PP)	162		169
Number cured	149		155
Efficacy (%)	92.0		91.7
Difference in efficacy⁺		-0.3	
97.5% C.I of difference		[-7.0 ; 6.5]	

⁺*Note 1: Difference in efficacy from SSG+PM i.e. ((SSG+PM) – (PM+MF:14D))*
Note 2: Non-inferiority margin is 7%

Primary efficacy outcome by treatment group and Age group-mITT

	Overall	
	PM+MF (14D) (n=170)	SSG+PM (n=170)
4 to ≤12 years, n	102	105
Number cured	96	100
Efficacy (%): 97.5% CI	94.1: [88.9 - 99.3]	95.2: [90.6 - 99.9]
12+ to 50 years, n	68	65
Number cured	59	56
Efficacy (%): 97.5% CI	86.8: [77.6 - 96.0]	86.2: [76.6 - 95.8]

- Efficacy at Day 210 in the mITT population of **91.2%** in the **MF/PM arm** vs **91.8%** in the **SSG/PM arm** (non-inferiority not demonstrated)
- Efficacy at Day 210 in the PP population: **92.0%** in the **MF/PM arm** vs **91.7%** in the **SSG/PM arm** (non-inferiority demonstrated)
- **No decreased efficacy in children** 4 to ≤12y in both treatment groups
- Initial cure (mITT) at Day 28 was 96.5% in the MF/PM arm vs 95.8% in the SSG/PM arm
- A total of 28 patients presented **PKDL** in Ethiopia and Sudan, representing **4.4%** in the **MF/PM arm** and **20.9%** in the **SSG/PM arm** in both countries

MEDECINS SANS FRONTIERES

SCIENTIFIC DAYS

Safety Update

Adverse Events (AEs):

- Most common ADRs:
  - **Vomiting** related to miltefosine treatment (13.5% of all patients, 20% in arm 1, mild or moderate (majority of single vomiting events)
  - **Injection site pain** related to paromomycin (10% of patients)
  - **Hypoacusis** related to paromomycin (5% of patients)
  - ADRs indicating **cardiotoxicity** related to SSG (6.5% of patients), 3 were grade 3 AEs and one event was fatal.
- Most AEs were **mild** and **moderate**; 6 patients (1.4%) had AEs that led to treatment discontinuation

Serious Adverse Events (SAEs):

13 patients presented 18 SAEs:

- 4 SAEs were considered related to study drugs: 2 cases of acute kidney injury related to MF and MF/PM; cardiotoxicity related to SSG (fatal); bilateral deafness related to PM
- 6 patients had fatal SAEs, 4 happened after IMP administration (0.9%)
- 7 patients with SAEs recovered completely

Conclusion

- Efficacy of **91.2%** at 6 months follow-up in the MF/PM new treatment (mITT), similar to SSG/PM SoC (91.8%)
- New treatment **well tolerated,** ADRs expected based on the safety profile of the study drugs, despite higher frequency of AEs 'vomiting' related to miltefosine
- **More patient-friendly**: no antimonial-related toxicity, hospital stay is reduced by 18% and it removes one painful daily injection of SSG
- **Frequency of PKDL** in patients from Ethiopia and Sudan was **significantly reduced** with the new treatment (4.4 % vs. 20.9% in the SSG/PM arm)

- Results published in *Clinical Infectious Diseases*: https://bit.ly/3BQPAux
- Consultations ongoing with the authorities in the endemic countries and WHO for the adoption and uptake of this new treatment in Eastern Africa

MEDECINS SANS FRONTIERES

SCIENTIFIC DAYS

Acknowledgments

DND*i*:

Fabiana Alves, Jorge Alvar, Gina Muthoni Ouattara, Samuel Tesema, Truphosa Omollo, Thaddaeus Egondi, Josephine Kesusu, Karine Balero, Michael Ochieng, Prossy Nakanwagi, Bonface Kaunyangi Mwarama, Millicent Aketch, Ayub Mpoya, Monique Wasunna

Partners and their staff:

- Prof Ahmed M. Musa, University of Khartoum, Institute of Endemic Diseases (IEND), Sudan
- Dr Brima Younis Musa, IEND, Professor Elhassan Centre for Tropical Diseases, Dooka, Sudan
- Dr Jane Mbui & Dr Simon Njenga, Kenya Medical Research Institute (KEMRI), Kenya
- Dr Rezika Mohammed, Prof Asrat Hailu, Dr Eleni Ayele, University of Gondar, Ethiopia
- Prof Joseph Olobo, Makerere University, Uganda
- Dr Patrick Sagaki, Amudat Hospital, Uganda
- Kacheliba District Hospital
- Dr Koert Ritmeijer, MSF Holland
- Dr Gabriel Alcoba, MSF Switzerland

The Patients and their Communities

AfriKADIA

EDCTP

Ministry of Foreign Affairs of the Netherlands

This project is part of the EDCTP2 Programme supported by the European Union

SPONSORED BY THE

Federal Ministry of Education and Research

through KFW

MEDECINS SANS FRONTIERES

UKaid from the British people

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Swiss Agency for Development and Cooperation SDC

and other private individuals and foundations

THANK YOU

DNDi
Best Science for the Most Neglected
20 Years

facebook.com/dndi.org
youtube.com/dndiconnect
twitter.com/dndi
instagram.com/drugsforneglecteddiseasesinitiative
linkedin.com/company/dndi

MEDECINS SANS FRONTIERES

SCIENTIFIC DAYS