## Abstract:

Background A recent study has shown that treatment of visceral leishmaniasis (VL) with the standard dose of 15 mg/kg/day of paromomycin sulphate (PM) for 21 days was not efficacious in patients in Sudan. We therefore decided to test the efficacy of paramomycin for a longer treatment duration (15 mg/kg/day for 28 days) and at the higher dose of 20 mg/kg/day for 21 days. Methods This randomized, open-label, dose-finding, phase II study assessed the two above high-dose PM treatment regimens. Patients with clinical features and positive bone-marrow aspirates for VL were enrolled. All patients received their assigned courses of PM intramuscularly and adverse events were monitored. Parasite clearance in bone-marrow aspirates was tested by microscopy at end of treatment (EOT, primary efficacy endpoint), 3 months (in patients who were not clinically well) and 6 months after EOT (secondary efficacy endpoint). Pharmacokinetic data were obtained from a subset of patients weighing over 30 kg. Findings 42 patients (21 per group) aged between 4 and 60 years were enrolled. At EOT, 85% of patients (95% confidence interval [CI]: 63.7% to 97.0%) in the 20 mg/kg/day group and 90% of patients (95% CI: 69.6% to 98.8%) in the 15 mg/kg/day group had parasite clearance. Six months after treatment, efficacy was 80.0% (95% CI: 56.3% to 94.3%) and 81.0% (95% CI: 58.1% to 94.6%) in the 20 mg/kg/day and 15 mg/kg/day groups, respectively. There were no serious adverse events. Pharmacokinetic profiles suggested a difference between the two doses, although numbers of patients recruited were too few to make it significant (n = 3 and n = 6 in the 20 mg/kg/day and 15 mg/kg/day groups, respectively). Conclusion Data suggest that both high dose regimens were more efficacious than the standard 15 mg/kg/day PM for 21 days and could be further evaluated in phase III studies in East Africa.