Abstract of Study:

Current WHO-recommended treatment for Visceral Leishmaniasis (VL) in Eastern Africa is a combination of Sodium Stibogluconate (SSG) and paromomycin (PM) administered for 17 days, with an efficacy of 91%. This treatment is far from optimal as it requires 17 days of two separate painful injections, necessitating patients to be hospitalized during the whole treatment period. In addition, the antimonial SSG exhibits life-threatening toxicities such as cardiotoxicity, hepatotoxicity and pancreatitis. Therefore, there is an urgent need to explore alternatives that are efficacious, safe, ideally of short duration, affordable and suitable to be used in remote areas where VL occurs.

Until new chemical entities are developed, opportunities with currently available compounds should be assessed to improve on current treatment options, with the main aim to replace the toxic and patient-unfriendly SSG treatment-component.

Miltefosine (MF) is the only oral drug available for VL treatment. It has been extensively used in Asia for VL treatment as monotherapy for 28 days, with satisfactory cure rates (>90%). However, MF as monotherapy showed lower efficacy in Eastern Africa (72%, 95%CI: 60–85%) than in Asia. PK data indicated under-exposure and higher relapse rates in children compared to adults with the conventional linear 2.5 mg/kg/day MF dose. To overcome this under-dosage in children, an allometrically scaled dosing regimen has been developed. This allometric dosage was assessed for paediatric VL in the LEAP 0714 trial in Kenya and Uganda. The 28 days regimen of MF allometric dose showed a cure rate of 90.0% (95% CI: 73.5-97.9%) at 6 months follow up in a population of 30 patients aged 4 to 12 years. These results showed that the efficacy level could be increased in children treated with the allometric dose, reaching similar efficacy observed in adults (i.e. 86.2%).

PM has been well studied in Eastern Africa during the development of the combination SSG-PM. PM monotherapy of 20mg/kg/d IM for 21 days showed an overall efficacy at 6 months of 84.3%. Intramuscular PM can be administered at primary health care level, requires minimal training of health personnel and the drug can be stored at room temperature.

Replacing the toxic SSG with oral MF can bring better safety and a more field-adapted, patient-friendly treatment.

The current study aims to determine the safety and efficacy of two combination regimens of PM and MF as compared to SSG-PM for the treatment of primary VL patients in Eastern Africa. This will be an open label, Phase III, randomized controlled, parallel arm multicentre non-inferiority clinical trial. The study treatments are:

Arm 1: Paromomycin 20 mg/kg/d IM for 14 days combined with oral miltefosine allometric dosing BID for 14 days
Arm 2: Paromomycin 20 mg/kg/d IM for 14 days combined with oral miltefosine allometric dosing BID for 28 days

The control arm is the current standard treatment for VL in East Africa:

Arm 3: Sodium Stibogluconate 20 mg/kg/day IM/IV combined with Paromomycin 15 mg/kg/day IM for 17 days

MF allometric dosing will be calculated according to patient’s weight, height and sex. For patients weighing < 30 kg, an easy-to-use table with allometric dosing scheme by weight, height and sex will be provided to the investigators. MF will be administered. For patients weighing ≥ 30 kg, the allometric dose will correspond to the conventional dose in mg/kg. Therefore, patients weighing ≥ 30 to 44 kg will receive 100 mg/day and patients ≥ 45 kg will receive 150 mg/day.

Subjects will be hospitalized for 14 days of PM and MF treatment in both arm 1 and arm 2. MF treatment will start at the same time as PM treatment. At discharge (on day 15), patients allocated to arm 2 will be instructed to continue MF treatment on an outpatient basis until completion of the 28 days treatment. Subjects will receive clear instructions as well as a daily diary to guide them in their treatment schedule at home.

SSG-PM combination therapy will be administered for 17 days according to routine VL treatment guidelines and patients will remain hospitalized for the entire duration of the treatment.

The target population will be primary VL patients from 4 to 50 years. It is important to include a paediatric population which is particularly vulnerable and is a major factor in the East African disease burden. The trial will be run in the VL endemic countries at 6 LEAP sites: Kimalel and Kacheliba in Kenya, Amudat in Uganda, Doka and Um El Kher in Sudan and Gondar in Ethiopia.

Enrollment target is 576 patients, 192 in each arm. Each patient’s participation in the study will be for approximately 7 months. This will consist of baseline assessments, treatment period (14, 17 or 28 days) and 6 months follow-up. Recruitment for the entire trial is expected to take 14 to 17 months assuming that 30 to 35% of all VL patients will meet the eligibility criteria. Therefore, study duration (first patient in to last patient, last visit) is
expected to take approximately 24 months. Taking into account the analysis and reporting period, the study shall last at most 31 months.

Primary efficacy endpoint will be the cure at day 210, based on clinical examination only (absence of clinical signs and symptoms of VL and no requirement for rescue treatment during the trial).

Safety assessments will be done through routine monitoring of adverse events. A characterization of the nature and frequency of SAEs, AEs that lead to treatment discontinuation and overall frequency and severity of AEs from start of the treatment until 6 months follow-up will be made.

Pharmacokinetics (PK) profile of PM and MF will be described and parasite clearance in each arm as indicated by direct microscopy and quantitative polymerase chain reaction (qPCR) will be evaluated as pharmacodynamics (PD) markers of cure. The relationship between PK and PD measurements will be further assessed through drug exposure-response modelling.

Finally, compliance to MF treatment in an outpatient setting will also be assessed. If proven non-inferior to SSG-PM, the combination of PM and MF is expected to improve significantly treatment safety and to reduce pain, while ensuring low cost and suitability to be used in remote areas. It will provide the East African region with the first non-antimony-based effective treatment for VL.

Study Title:

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