

PKDL Sudan Study Synopsis

Protocol Title	An Open label, Randomized, Parallel arm Clinical Trial of Two Regimens to Assess the Safety and Efficacy for Treatment of Post Kala-azar Dermal Leishmaniasis (PKDL) Patients in Sudan
Phase	Phase II
Indication	PKDL patients in Sudan
Protocol Number	DNDi-MILT COMB-02-PKDL
Trial Objectives	<p><u>General Objectives:</u></p> <p>The overall objective of this study is to assess the safety and efficacy of two treatment modalities for PKDL patients in Sudan.</p> <p><u>Primary Objective:</u></p> <p>To assess the safety and efficacy of Paromomycin combined with Miltefosine and AmBisome® combined with Miltefosine for the treatment of PKDL in Sudan.</p> <p><u>Secondary Objectives:</u></p> <ul style="list-style-type: none"> • To assess skin and plasma concentrations of Paromomycin, amphotericin B and Miltefosine and how drug exposure in skin and plasma relates to the in vitro susceptibility of the causative <i>Leishmania</i> species for each compound. • To evaluate the host immune response in each treatment arm before, during and after treatment. • To evaluate parasite clearance in each arm as indicated by direct microscopy and qPCR • To compare clinical, pharmacological, parasitological and immunological responses to identify a potential biomarker for cure • To assess relationship between pharmacokinetic parameters with clinical outcome and parasite clearance. <p><u>Exploratory objectives:</u></p> <ul style="list-style-type: none"> • To assess non-invasive tape disc method of skin samples collection for molecular parasitological diagnosis.
Trial Endpoints	<p><u>Primary Endpoints:</u></p> <ul style="list-style-type: none"> • Efficacy The primary endpoint variable is definitive cure at 12 months after

	<p>treatment onset, defined as clinical cure (100% lesions resolution) and no additional PKDL treatment between end of therapy and 12 months follow-up assessment.</p> <ul style="list-style-type: none"> • Safety <ul style="list-style-type: none"> ○ Serious adverse events from the start of treatment through 12-month follow period ○ Frequency and severity of adverse events that lead to treatment discontinuation. ○ Frequency and severity of all adverse events from the start of treatment through 12-month follow up period <p><u>Secondary Endpoints:</u></p> <p>Pharmacokinetics</p> <p>To assess the maximal accumulation of Paromomycin, total amphotericin B and Miltefosine in the skin at the end of treatment and correlate these with achieved plasma concentrations.</p> <p>Immune Response</p> <p>To assess the change in immune response during and after end of treatment by measuring cytokines profiles level in the peripheral blood.</p> <p>Parasitology</p> <p>To assess the clearance of parasites by microscopy and qPCR in blood and skin, at various time-points during and after treatment and during follow-up.</p>
<p>Trial Design</p>	<p>This is an open label, randomized non comparative phase II clinical trial conducted on parallel groups, to assess the safety and efficacy of the combination of Paromomycin (20 mg/kg/d) IM for 14 days and Miltefosine (allometric dosing) oral for 42 days, and a combination of AmBisome® (20 mg/kg total dose) IV over 7 days and Miltefosine oral for 28 days (allometric dosing) for the treatment of PKDL patients in Sudan.</p> <p>Evaluation of the response to treatment will be done by clinical assessment which includes the comparison of photographs taken under standardized conditions.</p> <ul style="list-style-type: none"> • <u>Improvement</u> is defined as 1) appearance: darkening of macular lesions and flattening of papular or nodular lesions, and/or 2) extension: reduction in extent of the rash. • Definitive <u>Cure</u> at 12 months is defined as complete disappearance of all lesions. <ul style="list-style-type: none"> • <i>Subjects will be hospitalized during the administration of AmBisome® or Paromomycin.</i> • <i>The Miltefosine treatment will start at the same time as AmBisome® or Paromomycin treatment and will continued on an out-patient basis until completion of 28 days (MF/AmBisome®) or 42 days (MF/PM).</i>

	<p><i>During hospitalization patients will be instructed on Miltefosine treatment, the daily dose (morning and afternoon), and the administration with food to avoid vomiting. Miltefosine treatment as out-patient will be under direct observed treatment (DOT) by the community health worker at the village level, whenever possible.</i></p> <p><i>After a screening period, the study visits will be at D1, D3, D7, D14 and D28. The end of treatment (EOT) assessment will be done at D42, followed by follow-up visits 3, 6 and 12 months after the onset of treatment to assess efficacy and safety.</i></p> <p><i>The patients will be instructed to return to the clinic at any point in time during follow-up if they present any medical condition or if the PKDL lesions</i></p>
Study Duration	6 Months are expected to be needed to obtain all ethical and official clearances. The recruitment period will be 24 months and the follow-up period will be 12 months. Therefore, FPI to LPO will be 36 months.
Test Drugs	<ol style="list-style-type: none"> 1. Paromomycin 20 mg/kg/d IM for 14 days combined with Miltefosine allometric BID PO dosing for 42 days 2. AmBisome® 5mg/kg/d IV infusion at D1, D3, D5 and D7 (20 mg/kg total dose) combined with Miltefosine allometric BID PO dosing for 28 days <p>For Miltefosine allometric dosing an easy-to-use table with dosing scheme by weight and height will be provided to the investigators to define the exact daily dose to be administered.</p>
Sample size	55 subjects will be included in each arm. The overall sample size for the two regimens is 110 subjects.