**PKDL Sudan Study Synopsis**

<table>
<thead>
<tr>
<th>Protocol Title</th>
<th>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</th>
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<tbody>
<tr>
<td>Phase</td>
<td>Phase II</td>
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<td>Indication</td>
<td>PKDL patients in Sudan</td>
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<tr>
<td>Protocol Number</td>
<td>DNDi-MILT COMB-02-PKDL</td>
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| Trial Objectives| **General Objectives:**  
The overall objective of this study is to assess the safety and efficacy of two treatment modalities for PKDL patients in Sudan.  
**Primary Objective:**  
To assess the safety and efficacy of Paromomycin combined with Miltefosine and AmBisome® combined with Miltefosine for the treatment of PKDL in Sudan.  
**Secondary Objectives:**  
- 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 *Leishmania* 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.  
**Exploratory objectives:**  
- To assess non-invasive tape disc method of skin samples collection for molecular parasitological diagnosis. |
| Trial Endpoints | **Primary Endpoints:**  
- **Efficacy**  
The primary endpoint variable is definitive cure at 12 months after |
treatment onset, defined as clinical cure (100% lesions resolution) and no additional PKDL treatment between end of therapy and 12 months follow-up assessment.

- **Safety**
  - 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

**Secondary Endpoints:**

**Pharmacokinetics**
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.

**Immune Response**
To assess the change in immune response during and after end of treatment by measuring cytokines profiles level in the peripheral blood.

**Parasitology**
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.

** Trial Design**
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.

Evaluation of the response to treatment will be done by clinical assessment which includes the comparison of photographs taken under standardized conditions.

- **Improvement** 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 Cure** at 12 months is defined as complete disappearance of all lesions.
- **Subjects will be hospitalized during the administration of AmBisome® or Paromomycin.**
- **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).**
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.

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.

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

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<th>Study Duration</th>
<th>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.</th>
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| Test Drugs    | 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  
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. |
| Sample size   | 55 subjects will be included in each arm. The overall sample size for the two regimens is 110 subjects. |