Welcome !!!
Overview on a VL (Kala-azar) Clinical Trial in Bangladesh

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Background

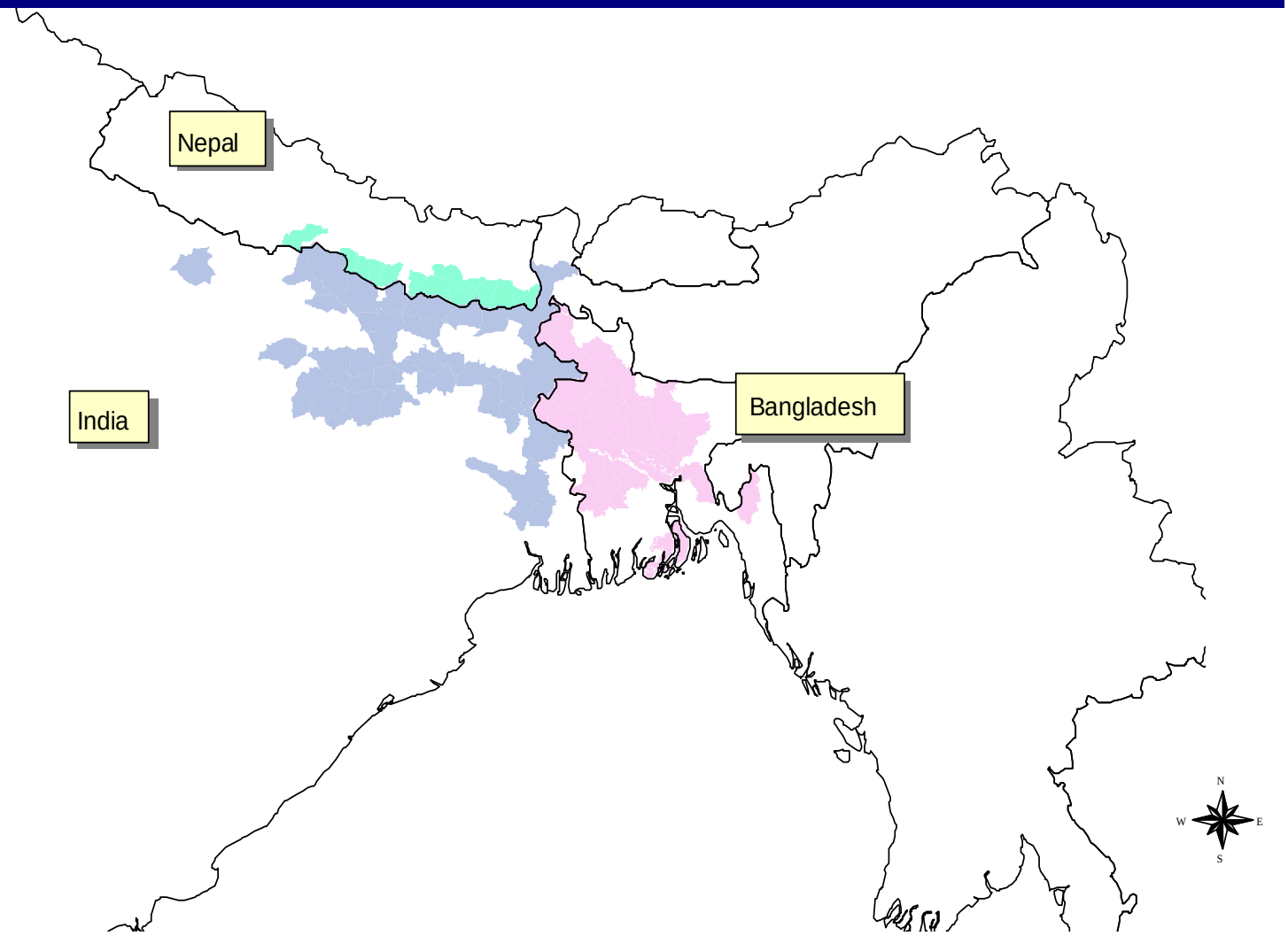
- **Visceral leishmaniasis, (Kala-azar) is one of the most neglected tropical diseases affecting the poorest populations in the three endemic countries of this region, Bangladesh, India and Nepal.**
- **Approximately 200 million people in 109 districts of these countries are “at risk”;**
- **Bangladesh, India and Nepal have committed themselves to collaborate in efforts to eliminate visceral leishmaniasis (kala-azar) from the South-East Asia Region by 2015; MoU signed in May 2005.**

KALA-AZAR IN THREE COUNTRIES

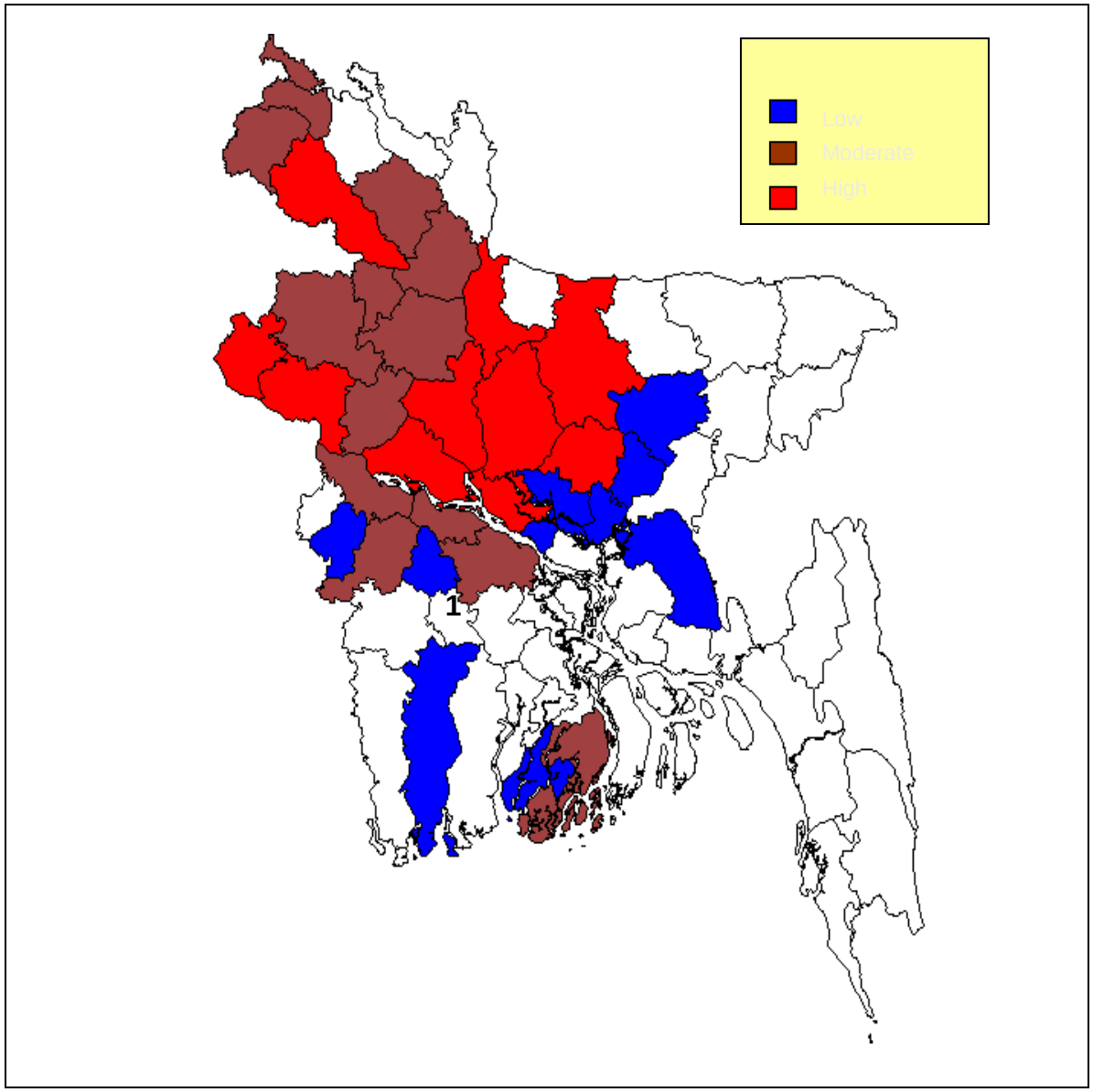
- **Bangladesh**
  - **45 districts**
- **India**
  - **52 Districts**
  - **(State Reporting: Bihar, Jharkhand, West Bengal and Uttar Pradesh)**
- **Nepal**
  - **12 districts of Eastern Nepal Terai**

- **Total 109 affected districts in the 3 endemic countries**

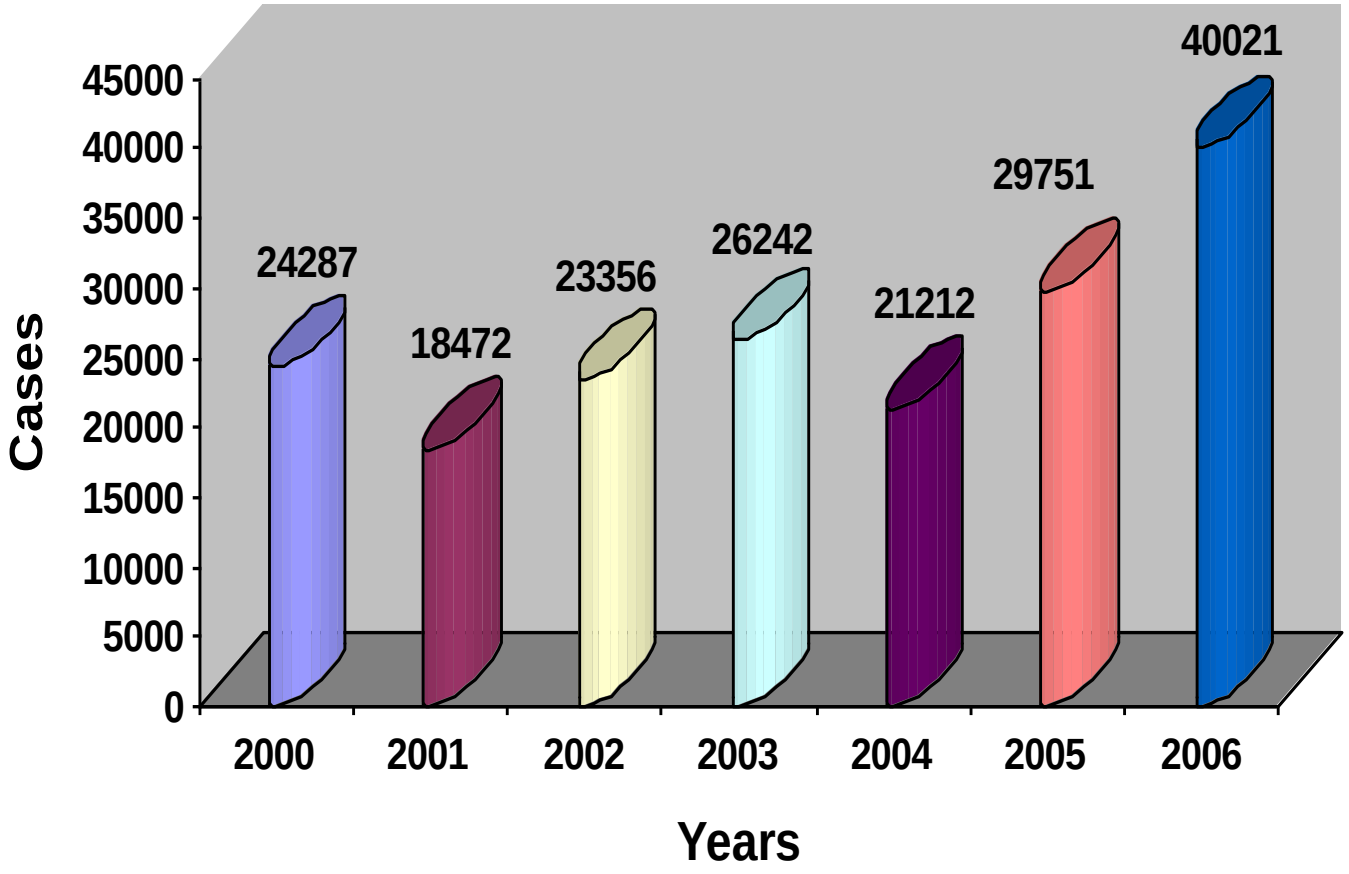
KALA-AZAR ENDEMIC DISTRICTS



Kala-azar Endemic Districts in Bangladesh



Kala-azar in endemic region in South East Asia



FACTORS FAVOURING KALA-AZAR ELIMINATION

- Effective interventions available to interrupt transmission
    - Effective treatment
    - Indoor Residual Spray for vector control
- Diagnostic tools available for field use ‘rK 39’
- No animal reservoir
- In the past, use of DDT almost eliminated Kala azar
- Political commitment expressed by the Health Ministers of 3 affected countries

Miltefosine as a therapeutic tool for ELIMINATION programme (by 2015)

- **Promising (Cures Sb refractory patients also)**
- **Teratogenic,**
- **Long half life (rapid emergence of resistance)**
- **Uninterrupted availability?**
- **Compliance in domiciliary care ? (DOT)**
- **In a recent evaluation 20-33% patients discontinued threrapy**
- **Real danger of loosing this drug in next few years**
  - **Is there a need to revisit the current strategy?**

Multidrug Treatment of VL - Rationale

- Every drug is prone to development of resistance (exception of amphotericin B)
- No new drug in pipeline
- The only way to protect the newly developed drugs is to develop combination chemotherapy
  - Shorten duration; Better compliance
  - Reduce costs; improve cost-effectiveness
  - Less chances of development of drug resistance
  - Reduce drug pressure; protection against resistance → prolong therapeutic life-span of effective use
- Single dose of AmBisome (5 mg/kg) cured 91% patients
- Two weeks of miltefosine cured 89% patients

Suggest - short course multidrug therapy is a feasibility

Study Title

A Phase III, Open label, Randomised, Study of Three Short Course Combination Regimens (AmBisome®, Miltefosine, Paromomycin) compared with AmBisome® alone for the Treatment of Visceral Leishmaniasis (VL) in Bangladesh

Study Objectives - Overall

- **To identify a safe and effective combination, short course treatment for VL which could be easily deployed in a control programme**

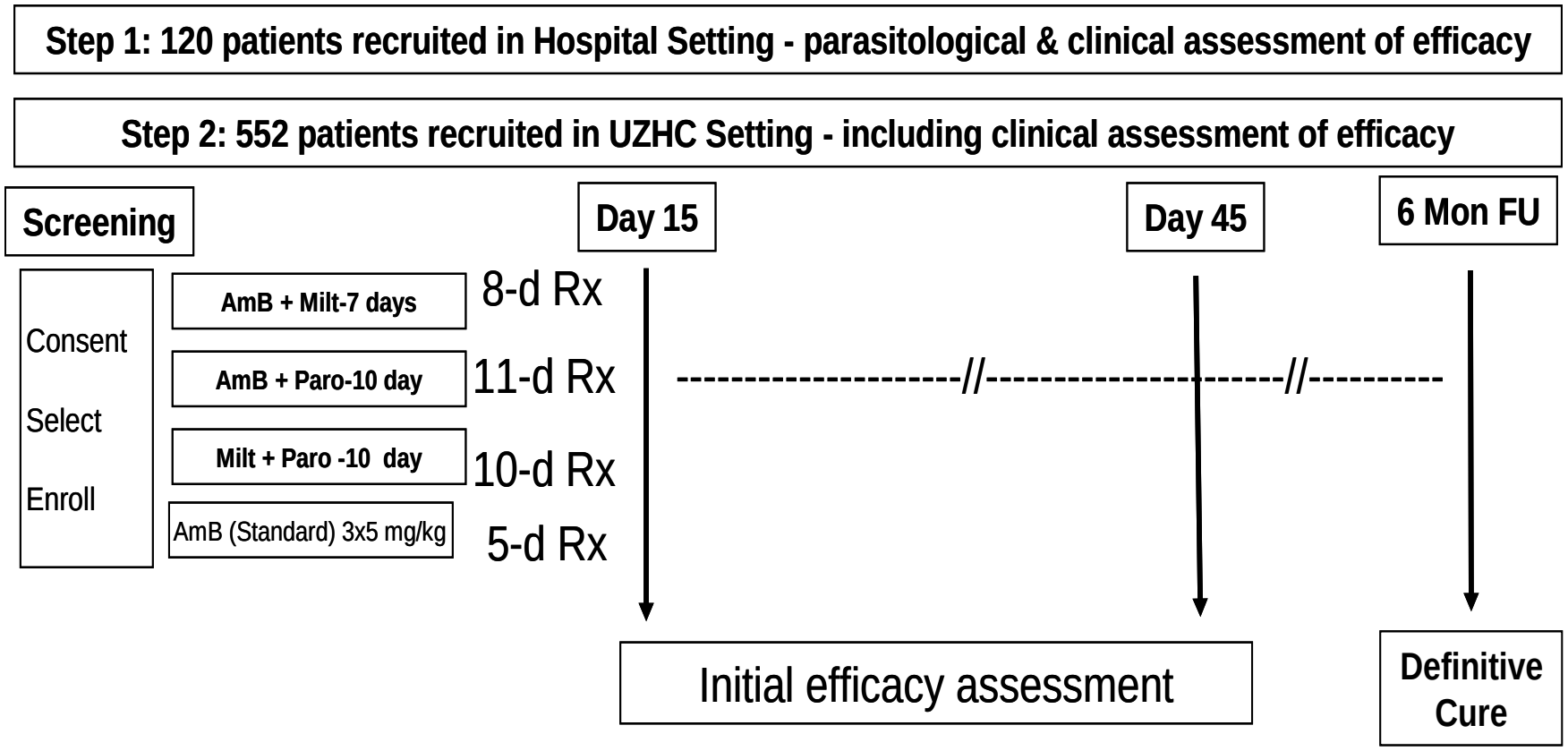
Primary Objective

To evaluate the safety and efficacy during 6 months follow-up of 3 different combination regimens vs. AmBisome monotherapy in Bangladesh VL patients

Secondary Objective

- Evaluate initial cure (D45) of combination regimens vs. AmBisome
- Assess safety & efficacy in different healthcare settings
- To develop a new urine test for diagnosis of VL using urine samples from patients & healthy volunteers

Study Design



Study Design

- **Randomized, Open Label, Parallel Group Study**
- **672 patients to be randomized into 4 treatment arms**
  - **Step 1: 120 patients to be recruited at CBMC,B**
  - **Step 2: 552 Patients to be recruited and treated in UZHCs**

Treatment Design

- **Reference Arm**
  - **AmBisome on D1, D3, D5**

- **Test Arms**

<u>Arm 1</u>

AmBisome on D1

Miltefosine on D2 - D7

<u>Arm 2</u>

AmBisome on D1

Paromomycin on D2 - D11

<u>Arm 3</u>

Miltefosine on D1 - D10

Paromomycin D1 - D10

Primary Endpoint - Definitive Cure

No signs/symptoms of VL at Day 45

- **Lack of fever [axillary temp <99.5°F] & at least one of the following:**
  - **improved Hb, if the patient was anaemic at baseline (Hb <8g/dl)**
  - **spleen regression if the spleen was palpable on admission**
- **Absence of clinical signs and symptoms of VL (fever, weight loss, splenomegaly) at any time during 6 months post treatment period**

Primary Endpoint - Definitive Cure (6 Mths)

- **Absence of parasites in tissue aspirate at Day 15 or +1 parasite at Day 15 with no evidence of parasites in tissue aspirate at 45 days**

If clinical signs and symptoms of VL are present during 6-month follow up, VL will be confirmed by parasitological assessment

Secondary Endpoint - Initial Cure (D45)

- **No signs/symptoms of VL at Day 45**
  - **Lack of fever [axillary temp <99.5°F] & at least one of the following:**
    - **improved Hb, if the patient was anaemic at baseline (Hb <8g/dl)**
    - **spleen regression if the spleen was palpable on admission**
  - **Absence of parasites in spleen/bone marrow aspirate at D15 or +1 parasite at D15 with no evidence of parasite at D45**

Safety Endpoint

During treatment and during 6 months follow-up :

- **Clinical adverse events**
- **Laboratory parameters**

Inclusion Criteria

- VL proven by parasitological examination of splenic or bone marrow aspirate
- History of fever for at least 2 weeks with one or more of the followings clinical signs/symptoms of VL
  - Anaemia (5< Hb <10 g/dl)
  - Loss of weight
  - Splenomegaly

Inclusion Criteria (cont.)

- rK39 positive
- Willing and able to attend follow-up visits
- Male or Female, 5-60 yrs
- Written informed consent
- Married women of child-bearing potential either using an assured method of contraception or willing to use an assured method of contraception for the duration of treatment and 3 months after (IUCD or DepoProvera®)

Exclusion Criteria

- Platelet count <40,000/mm^3
- Prothrombin time 5 seconds or greater than normal range
- Known hepatitis B, C or known HIV positive
- Patients who present with PKDL
- Signs/symptoms indicative of severe VL (Hb < 5gm/dl etc)

Exclusion Criteria (cont.)

- Positive HRP2/pLDH Combo test for malaria
- Pregnant woman or breast-feeding mother
- Known alcohol or other drug abuse
- Concomitant chronic drug treatment eg. TB, HIV etc.
- Known hypersensitivity to AmBisome, Paromomycin and other aminoglycosides and/or Miltefosine

Randomization

- Computer generated randomization codes
- Individual, opaque, sealed and sequentially numbered envelopes
- One envelope per patient – indicating individual patient allocation to the treatment
- Randomization, stratified by centre
- Women of child-bearing potential stratified by marital status

Randomization

- **Men, married women and children to be randomized to receive either of 4 treatment arms in the ratio of 1:1:1:1**

- **Unmarried women of child bearing age shall be randomized to receive AmBisome or AmBi+Para in the ratio of 1:1**

Visit Scheduler

- **Screening**
- **Treatment:**
  - **Reference: AmBisome on Day 1, 3, 5**
  - **Test arm 1: AmBisome on Day 1 & Miltefosine on Day 2-8**
  - **Test arm 2: AmBisome on Day 1 & Paromomycin on Day 2-11**
  - **Test Arm 3: Miltefosine & Paromomycin on Day 1-10**
- **Follow Up Day 45 (± 7 days)**
- **Follow Up 6 Months (-14 + 28 days)**

Schedule of Assessments

Assessment	Follow-up (day)					6 months Follow-up -14/+28d
	-7 - 0	1	7±2	15±2	45±7	
	X					
ICF for Pregnancy test /contraception	X					
rk 39 RDT for VL	X					
Malaria HRP2/pLDH Combo Test	X					
Clinical assessment [5]	X	X	X	X	X	X
VL Clinical assessment	X	X[5]	X	X	X	X
Haemoglobin, Blood glucose	X		X	X	X	X
Haematology[1]	X		X	X	X	X
Biochemistry[1]	X		X	X	X	X
Urinalysis Dipstick[1]	X		X	X	X	X
Urine RDT for VL evaluation[1]	X		X	X	X	
Parasitology[1]	X			X	(X[2])	(X[2])
PKDL Assessment	X				X	X
Pregnancy test[3]	X					
DepoProvera[3]	X					
Randomisation		X				
Start of treatment		X[4]				
Adverse events (and SAEs)		X	X	X	X	X
Concomitant medication		X	X	X	X	

Rescue Medication

- Treatment Failures referred to CBMC,B/ S K Hospital (SKKRC) for parasitological confirmation
- Rescue medication as recommended by the National Treatment Guidelines of Bangladesh
  - AmBisome 5mg/kg daily on Day 1, 3 and 5 (15mg/kg total dose), as per WHO recommendations
- If Ambisome contraindicated
  - SSG - 20mg/kg/ day for 30 days
  - Miltefosine - 2.5mg/kg/day for 28 days

Withdrawal Criteria

All patients to be followed up on Day 45 and 6 months, wherever possible

- **Serious adverse event (drug related or not)**
- **Any condition that significantly impacts the trial**
- **Deviation from protocol**
- **Termination by the sponsor**
- **Withdrawal of consent**

Study Status

- **EC Approval (BMRC)** **17 May 2010**
- **EC ICDDRB** **28 Mar 2010**
- **Site Initiation** **20 Jun 2010**
- **1st Case enrolled (S-1)** **06 Jul 2010**
- **Last case enrolled (S-1)** **08 Mar 2011**
- **DSMB meet** **April 2011**
- **1st Case enrolled (S-2)** **May 2011**
- **Site close outs** **Dec 2012**

SAEs

Total # 3

- **# 1- Deterioration of Acute Hepatitis**
- **# 2- Haematemesis & Malaena due to PUD**
- **# 3- Severe Pneumonia leading to death**

Monitoring & Evaluation

- **Sponsor-**

  Drugs for Neglected Diseases Initiative (DND*i*)

- **Independent Monitoring-**

  GVK Bio

Investigators

Institutes

- ShSMC
- ICDDRB
- CBMC,B
- MMC
- DMC
- BSMMU
- SSMC
- CMC

Subjects

- Clinical Medicine
- Pharmacology
- Microbiology
- Paediatrics
- Neurology
- Public Health

Thank You