KALA-AZAR

Visceral Leishmaniasis (VL)

New combination treatment soon available

PRIORITY TARGET PRODUCT PROFILE FOR VL

- **A new treatment for adults and children**
  - Efficacious against all species in all regions
- **Comparable or better safety profile than existing drugs**
  - Ideally requiring no monitoring
- **Equal or better efficacy profile than existing drugs**
  - ≥95% clinical efficacy at 6 months after treatment
- **Easy-to-use treatment**
  - Short course (ideally ≤7 days, up to 11 days is acceptable)
  - Preferably oral; if injectable, intramuscular depot
  - Preferably once-a-day treatment, ideally outpatient
- **Affordable**
  - Stable in tropical climate
  - Preferably 3-year shelf life

Kala-Azar or Visceral Leishmaniasis (VL) is caused by the parasite *Leishmania* transmitted by the sand fly. It principally occurs in South Asia, East Africa and South America, but is also endemic in parts of Southern Europe. Left untreated, the disease is fatal. Kala Azar is characterised by prolonged fever, enlarged spleen and liver, substantial weight loss, and progressive anemia. Existing treatments are difficult to administer, toxic, and costly. Drug resistance is an increasing problem.

Based on the current R&D landscape, the realities in Visceral Leishmaniasis (VL)-endemic regions and the limited treatment options, DND*i* and its partners have determined that the **ideal treatment** should be **oral, safe, effective, low cost, and short course (≤10-day)**. Ideally, this treatment will be effective against all forms of the disease and adequate for use in rural health settings.

As it can take five to ten years to bring a compound through the preclinical and clinical phases of development, DND*i* is currently building on previous research by extending the registration and availability of current drugs, while maximising their potential and minimising their drawbacks. **Combination therapies** of these new treatments represent **a critical path forward** because they could offer the following important advantages: shorter course of treatment, better tolerability, reduction in the work load on the health systems in resource-limited areas, better affordability, and potential to prevent or retard resistance development and prolong the life span of these drugs. DND*i* has two active clinical projects: one examining combination treatment (AmBisome®, paromomycin, miltefosine) in India and one developing

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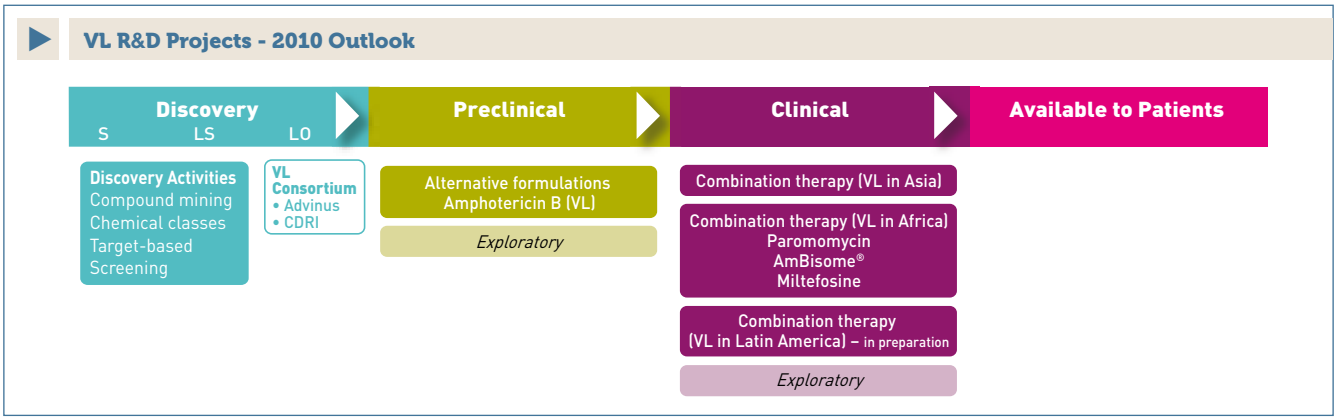


combination treatment in East Africa. In addition to completing these projects, DND*i* will conduct further work to geographically extend other existing drugs. For Latin America, a similar strategy of combination of current drugs will be undertaken.

As the existing drugs are few and are mostly parenteral, there is a need to increase the number of therapeutic options focusing on new drugs that can be administered orally and that can be new components of improved combination treatments. Several compounds at late preclinical phase are under careful evalutation. In addition, DND*i* has a lead optimisation programme which will bring new candidates into clinical development over the next few years. All of these new drugs will also be considered for combination therapy. **Using a multi-disciplinary approach, DND*i* will bring practical, safe and effective treatments to VL patients** that will be a significant step in helping to control the disease in South Asia, East Africa, and Latin America.

DISCOVERY

LEAD OPTIMISATION CONSORTIUM

- **Partners:** Advinus, India; CDRI, India
- **DND*i* project manager and coordinator:** Denis Martin, Delphine Launay
- **Project start:** November 2007

With a full team in place including 12 team members at the two primary partner sites, assessment of three series of synthetic compounds has been conducted and chemistry-biology activities have begun to bear fruit with the series of 2-quinolines. Partners at the "Institut de Recherche et Development" (IRD) originally isolated the 2-quinolines from Bolivian plants, which are used in traditional medicine to treat cutaneous leishmaniasis and malaria. After some promising early results, the DND*i*-managed Lead Optimisation consortium has synthesised more than 250 diverse analogues of 2-quinolines. These modified quinolines were significantly more effective than the parent compounds and a few compounds have shown >90% parasite killing at <1.0µM. Metabolic stability, which is a known liability of this series, has been improved through the introduction of halogen substituents in more than ten compounds. Further studies of the most promising compounds are underway to confirm the *in vivo* efficacy and safety profiles. More hits from the other chemical series, including oxaboroles and nitroimidazoles, provided by partners of DND*i* will be further evaluated by Advinus and CDRI. This strategy as well as promising early results were presented during the World-Leish4 meeting in February 2009. They are available at www.dndi.org.

PRECLINICAL

ALTERNATIVE FORMULATIONS OF AMPHOTERICIN B POLYMER

- **Partners:** Polytherics, UK; London School of Pharmacy, UK; Imperial College, UK; LSHTM, UK; BioDelivery Sciences International (BDSI), United States
- **DND*i* project manager and coordinator:** Denis Martin, Delphine Launay
- **Project start:** September 2006

The goal of this project is to identify an amphotericin B-based formulation, which shows the most promise in terms of *in vivo* efficacy, safety, heat stability, as well as in cost. Amphotericin B, under various formulations, has become one of the most efficient treatments for VL. The standard formulations (oily suspension) have limitations related to side effects. AmBisome®, a liposomal formulation has overcome these limitations, but its cost and stability add serious limits to a widespread use. Because of its high cost there has been only limited use in VL-endemic regions of Africa and Asia, where the disease burden is the highest. Recently, new formulations have emerged and are approved or under clinical development in India. However, their intravenous route of administration is still a barrier for appropriate use in the field. Studies, aimed at replacing the lipid-based component with a narrow molecular weight polymer, are ongoing with the goal of developing a soluble complex, that is cheaper, and exhibiting increased thermal stability. Polymers can also prevent the systemic toxicity of amphotericin B to which they are conjugated, still allowing the drug intracellular delivery. The team in the UK has been investigating a less expensive, modified metacrylic polymer; initial efforts to establish adequate *in vivo* efficacy in a disease model while optimising key characteristics of the polymer did not yield promising results; so this part of project was concluded in early 2009 and alternate paths are currently explored with the UK team. Recently, two new formulations of amphotericin B - phospholipid-based cochleates and a lipid-based form with enhanced gastrointestinal tract absorption - have been reported to show activity as antifungals when administered orally in animal models. Early reports suggest that they also exhibit activity in murine models of visceral leishmaniasis. BDSI has developed an oral formulation that is currently in Phase I, targeting fungal infections. DND*i* is conducting an exploratory preclinical evaluation of this oral formulation for VL and, if successful, will proceed to clinical development.

CLINICAL

COMBINATION THERAPY FOR VL IN SOUTH ASIA (INDIA, BANGLADESH, AND NEPAL)

- **Partners:** INDIA: Indian Medical Research Council (ICMR), Delhi; Kala-azar Medical Research Centre (KAMRC), Muzaffarpur; Rajendra Memorial Research Institute of Medical Sciences (RMRIMS), Patna; WHO/TDR.

BANGLADESH: International Centre for Diarrhoeal Disease Research (ICDDR), Dhaka; Shaheed Suhrawardy Medical College and Hospital, Dhaka; Community Medical College (CMC), Mymensingh; NEPAL: BP Koirala Institute of Health Sciences, Dharan; USA: Institute for One World Health, San Francisco.

• **DND*i* project manager and coordinator:** Farrokh Modabber, Sally Ellis

• **Project start:** December 2006; revised protocol approved October 2007

With the objective to identify a safe and effective short-course combination therapy using existing drugs, which could be easily deployed in control programmes, this four armed, definitive phase III combination therapy study is using drugs already registered in India: AmBisome®, miltefosine, and paromomycin. Three arms with a combination of two drugs for treatment of a maximum of 11-days will be compared with the standard 30 day therapy (15 infusions every other day using amphotericin B). In June 2008, the first patient was enrolled into the study. Enrolment of 634 patients was completed in June 2009, and results are expected by early 2010. A phase III/IV trial is planned to start in Bangladesh in the first quarter of 2010 and discussions are ongoing to initiate a trial in Nepal to evaluate the safety of one or more combinations with the same drugs. The study has been designed to provide data for authorities in India, Bangladesh, and Nepal to make informed recommendations for combination treatment, which can be used in the programme of VL elimination of these countries. In addition, an implementation-feasibility-demonstration study consisting of larger trials for further evaluation of safety and efficacy and cost effectiveness in different healthcare settings is being planned to start in early 2010 in India as the results of the present trial become available. It is anticipated that these combination treatments will be shorter, safer and cheaper than the current standard treatments in the region.

COMBINATION THERAPY FOR VL IN AFRICA

• **Partners:** Kenya Medical Research Institute, Kenya; Institute of Endemic Diseases (IED), University of Khartoum, Sudan; Addis Ababa University, Ethiopia; Gondar University, Ethiopia; University of Makarere, Uganda; LSHTM, UK; ASK (AMC, Sloterdvaart Hospital, KIT), the Netherlands; Ministries of Health of Ethiopia, Sudan, Kenya and Uganda; Médecins Sans Frontières (MSF); i+ solutions, the Netherlands; Institute for OneWorld Health, USA; LEAP (Leishmaniasis East Africa Platform) group.

The Kala Azar Medical Research Centre is one of the clinical research partners for the VL combination studies in Asia.

• **DND*i* project manager and coordinator:** Manica Balasegaram, Sally Ellis.

• **Project start:** November 2004

In Africa, VL is difficult to treat with existing drugs due to various issues such as toxicity, emerging resistance, difficulty of use, and cost. SSG (sodium stibogluconate), a relatively toxic drug requiring 30 days of injections, remains the mainstay of treatment in the region. Other drugs such as paromomycin and miltefosine are not registered or available in the region. Since 2004, DND*i* and the Leishmaniasis East Africa Platform (LEAP) have embarked on a clinical research programme with two specific objectives: to geographically extend all currently available VL drugs in the region and to develop one to two new combination treatments. Currently DND*i* is conducting three clinical trials in the programme. The first trial, LEAP 0104, is studying paromomycin as well as evaluating the shorter course combination of paromomycin plus SSG as an alternative treatment for VL. Paromomycin is an aminoglycoside antibiotic identified as an antileishmanial in the 1960s. This drug has the potential to be an improved treatment at a lower cost when combined with the standard treatment of SSG.

Paramomycin is currently being made available throughout the Indian subcontinent by fellow PDP, the Institute for One World Health (IOWH). In Africa, DND*i* and LEAP have recently completed the LEAP 0104 study, including over 1100 patients in Ethiopia, Kenya, Sudan, and Uganda.

Registration of paromomycin and adoption of the combination treatment is therefore anticipated for 2010/11. Over 1000 patients have been recruited so far into the various arms of the study.

DND*i* and LEAP are also conducting two other clinical trials. The first is the 0106 AmBisome® study. The goal of this project is to identify the minimum dose for monotherapy of AmBisome® that is efficacious, safe, and cost effective. AmBisome®, a liposomal formulation of amphotericin B manufactured by Gilead is used to treat VL especially in Europe and has recently been more accessible because of a preferential price offered by the manufacturer to patients in the public sector. It is possible that AmBisome® could become affordable for treatment even in resource-poor countries. Facilitating registration and adoption of AmBisome® in the region will be an important step in developing further combinations for Africa and in preventing the development of drug resistance. The study has received ethics approval and has started in Ethiopia and Sudan. The second study LEAP 0208 is a safety and efficacy study on miltefosine and AmBisome® combination treatment. Miltefosine is the only orally effective drug against VL. The trial will therefore collect safety, efficacy and pharmacokinetic data on miltefosine. The goal is to geographically extend the use of the drug in the region. In addition, combination treatments with AmBisome and either miltefosine or SSG are evaluated, and if the results are promising it will be taken into phase III development. The study is due to start beginning 2010.

COMBINATION THERAPY FOR VL IN LATIN AMERICA

• **Partners:** Brazilian Ministry of Health and a network of hospitals and universities

• **DND*i* project manager and coordinator:** Isabela Ribeiro, Fabiana Piovesan Alves

• **Project start:** in preparation

DND*i*'s objective is to evaluate the safety and efficacy of different drug combinations to treat VL patients in Brazil. For this, a feasibility assessment and VL site selection have been performed, with potential study sites identified in different regions of Brazil.

KALA-AZAR – **Visceral Leishmaniasis (VL)**

350 million people[1] at risk worldwide

WHAT IS THE ANNUAL IMPACT OF LEISHMANIASIS?

500,000 cases of VL; 1.5 million cases of CL (per year)[2]
51,000 deaths (per year)[3]
1,757,000 DALYs[3]
It is difficult to estimate the accurate incidence and case-fatality rate of VL due to frequent misdiagnosis and a lack of surveillance systems.

WHAT IS LEISHMANIASIS?

Leishmaniasis occurs in several forms of which the two most common are:

1. Visceral Leishmaniasis (VL). This form is characterised by prolonged fever, enlarged spleen and liver, substantial weight loss, and progressive anemia. The symptoms occur progressively over a period of weeks or even months. Almost all clinically symptomatic patients die within months if left untreated. Coinfection with other infectious diseases is an increasing concern: HIV-VL coinfection has been reported in 35 countries worldwide.

2. Cutaneous Leishmaniasis (CL) is characterised by lesions on the skin, which can be either self-healing or become chronic.

CL is generally not life-threatening, DND*i* therefore focuses on VL as a target disease.

HOW IS LEISHMANIASIS TRANSMITTED?

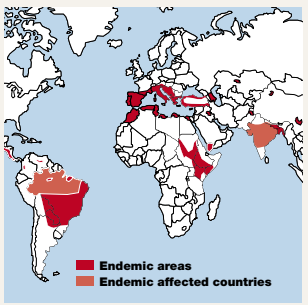
More than 20 species of the kinetoplastid protozoan parasite *Leishmania* can be transmitted to humans via around 30 species of phlebotomines sandflies.

WHERE DOES LEISHMANIASIS OCCUR?

Leishmaniasis affects approximately 12 million people in 88 countries. VL affects poor populations living in remote areas of around 70 countries across Asia, East Africa, South America and the Mediterranean region (see map). The seven most affected countries, which represent over 90% of new cases, are Bangladesh, Brazil, Ethiopia, India, Kenya, Nepal, and Sudan.

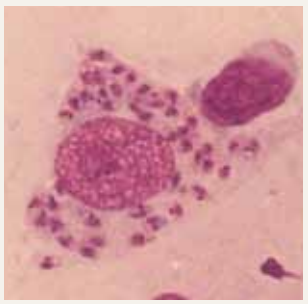
WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

The number of treatment options has increased in the past decade, but each treatment still has numerous drawbacks. Mostly they are difficult and lengthy to administer, toxic, expensive, and in addition resistance is an increasing problem:
– **Pentavalent antimonials:** toxic and increasingly ineffective due to resistance, takes 30 day, hospital-based parenteral treatment.
– **Amphotericin B:** dose-limiting toxicity; 15-20 day, hospital-based intravenous treatment.
– **Liposomal amphotericin B (AmBisome®)**: Effective, but expensive[4].
– **Paromomycin:** registered in India only, requires 3 weeks of intramuscular administration.
– **Miltefosine:** first orally available drug registered in India but expensive[4] and teratogenic.



WHAT ARE THE PATIENTS' TREATMENT NEEDS?

Patients need a treatment which is easy to administer (orally), safe, effective, low cost, and of short course, possibly less than 10 days.



WHAT IS DND*i* DOING TO ADDRESS UNMET TREATMENT NEEDS?

Short term: better use of existing treatments through geographical extension and new combinations
– **Combination in Africa:** Registration of paromomycin in 2010, recommendation of combination including paromomycin and sodium, stibogluconate (SSG). Registration of AmBisome® in 2011, registration of miltefosine, development of combination with short-course AmBisome®
– **Combination in India:** Recommendation in India, Bangladesh and Nepal by 2011
– **Combination in Latin America:** Recommendation in 2013

Medium to Long term: registration of one new drug through new formulations of existing treatments and therapeutic switching
– Potential compounds in-sourced at late preclinical phase – DND*i* is actively pursuing potential candidates ready for clinical development in the short term
– New drugs developed from compounds identified through VL lead optimisation consortium
– Multi-country, multi-partner LEAP to strengthen regional research capacity

By 2014, DND*i* aims to deliver from its VL-specific portfolio:
– 1 new drug at late stage of clinical development
– 1-3 geographical extensions in endemic regions outside India by 2014
– 1-3 coadministrations recommended by WHO
– A robust pipeline

(1) WHO, India, may 07 (2) WHO, 2010 http://www.who.int/leishmaniasis/burden/magnitude/burden_magnitude/en/index.html (3) VL+CL: 2006 IBRD/The World Bank http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=dcp2&part=A3155&rendertype=table&id=A3155 (4) Through the WHO, significant cost reduction of both AmBisome® and miltefosine is available for the public sector of developing countries as of 2007.