DNDi’s objective is to deliver 11 to 13 new treatments by 2018 and to maintain a robust pipeline to support long-term objectives.
At the end of 2011, DNDi had delivered six new treatments and built a robust pipeline with 11 new chemical entities at pre-clinical and clinical stages, a major achievement in the field of R&D for neglected diseases. DNDi also added two diseases to its portfolio in 2011, specific helminth infections and paediatric HIV.

The year 2011 has been one of transitions for DNDi, with a maturing portfolio of molecules progressing through the development pipeline, including 11 new chemical entities (NCEs) at various stages of development for the kinetoplastid diseases (human African trypanosomiasis (HAT), visceral leishmaniasis (VL), and Chagas) and helminth infections, one new treatment registered, and five at the implementation phase.

At its inception in 2003, DNDi’s Business Plan aimed to deliver between six and eight new treatments for patients in need by 2014. By the end of 2011, this objective was achieved, as six new treatments have been registered or made available to patients – the paediatric dosage form of benznidazole for the treatment of Chagas disease was registered by the Brazilian regulatory authorities in December 2011.

DNDi’s R&D strategy relies on the combination of long-term goals, through the development of NCEs to support sustainable control or elimination of neglected diseases, with short-term goals based on the optimization of existing drugs, to address immediate and urgent patient needs. Building the future of novel and effective treatments for neglected diseases includes progressing promising compounds through the development pipeline, establishing collaborations with the pharmaceutical industry, biotechs, academia, and increasingly with other PDPs to access new chemical libraries or compounds, using cutting-edge technologies, such as high-throughput screening (an imaging technology-based high-content screening assay against intracellular Leishmania and T. cruzi), as well as developing strong lead optimization consortia. DNDi also builds capacity for clinical research in the field by supporting regional platforms for each kinetoplastid disease.

Each year, DNDi updates its target disease strategies, defining the need and desired outcome, and taking into account the current research landscape. Target product profiles (TPPs) define the key features of the new drugs/treatments and are developed with input from disease experts. By keeping the focus on patients and their needs, DNDi’s project portfolios balance long-term and short/medium-term projects.

**BY KEEPING THE FOCUS ON PATIENTS AND THEIR NEEDS, DNDi’S PROJECT PORTFOLIOS BALANCE LONG-TERM AND SHORT/MEDIUM-TERM PROJECTS**

- **Long-term projects** – to develop innovative medicines with new chemical entities.
- **Medium-term projects** – to identify existing pre-clinical or clinical stage compounds suitable for therapeutic switching, or for further improvements via improved formulations.
- **Short-term projects** – to make existing drugs available in broader geographic areas and to develop better treatments, including combinations, from existing drugs.
experts, representatives of Ministries of Health and National Control Programmes in endemic countries, WHO representatives, leading clinicians and researchers, as well as health workers who deal with the realities of the diseases in the field. DNDi’s TPPs are publicly available on the website.

So far, DNDi has delivered six new treatments for malaria, sleeping sickness, visceral leishmaniasis, and Chagas disease.

The latest is a paediatric dosage form of benznidazole, developed in partnership with LAFEPE and registered in Brazil in December 2011 (see page 37), a real progress in that it enables accurate, easier-to-administer, and safer treatment of Chagas disease in infants and children under the age of two.

DNDi is working with its partners to ensure that these new treatments are effectively available to patients.

The past year was marked by projects progressing through the pipeline. Successful advancement of new leads and optimized leads in the discovery and pre-clinical phases is the key to building a robust pipeline for the coming years. Taking into account the realities of the field is an essential element when progressing candidates from the pre-clinical to the clinical phase. And finally, successfully completing the transition from the clinical phase to the implementation phase is the guarantee that patients will benefit from new, optimal treatments.

DNDi’s R&D PROJECTS – FILLING THE GAPS

<table>
<thead>
<tr>
<th>DISCOVERY</th>
<th>PRE-Clinical</th>
<th>CLINICAL</th>
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<tr>
<td>Gap 1: Lack of basic research and pre-clinical research due to lack of funding</td>
<td>Gap 2: Validated drug candidates do not enter clinical development</td>
<td>Gap 3: Patient cannot access drugs because they are expensive, unavailable, or not adapted</td>
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TARGET PRODUCT PROFILE (TPP)

- **Indications:** Which diseases?
- **Population:** Which type of patients and where?
- **Clinical Efficacy:** Does it treat the parasitic infection effectively?
- **Safety and Tolerability:** What level of acceptability for adverse events?
- **Stability:** How long is the shelf life of the drug(s), and necessary storage conditions?
- **Route of Administration:** How is it administered to patients?
- **Dosing Frequency and Treatment Duration:** How often and how long must it be given?
- **Cost:** Will it be affordable to target population?
- **Time to Availability:** How long will it take to develop?
In 2011, DNDi’s portfolio was extended to integrate two new diseases, specific helminth infections [see page 42] and paediatric HIV [see page 45]. Both programmes are at the pre-clinical phase.

**Key accomplishments 2011:**

**HAT:** NECT is now on the national essential medicines lists of 12 countries across Africa and increasingly replacing treatment with melarsoprol and eflornithine monotherapy; Phase I studies for fexinidazole were completed in 2011; SCYX-7158, an oxaborole, is ready for Phase I studies. Promising backups are in lead optimization and pre-clinical phases.

**VL:** SSG&PM is available and implemented in Sudan and Uganda. New drug combination therapies are available for Asia. Three backup compounds are at the pre-clinical stage and promising leads are in the lead optimization phase.

**Chagas disease:** The paediatric dosage form of benznidazole was registered in Brazil at the end of 2011. DNDi has one project in the clinical phase and two in the pre-clinical phase, as well as promising perspectives in lead optimization.

**Malaria:** Both treatments are in the implementation phase. ASAQ Winthrop: by the end of 2011, 120 million ASAQ treatments had been distributed in 30 African countries. In addition, more than 20 million treatments were ordered for the private sector in 7 countries in Africa within the Affordable Medicines Facility – malaria [AMFm]. ASMQ was registered in India after completion of the technology transfer between Brazilian and Indian partners. WHO pre-qualification, registration, and launch of the product in member countries of the Association of Southeast Asia Nations (ASEAN) are planned for 2012.
In 2011, DNDi decided to evolve its discovery strategy and lead optimization platforms toward a more efficient mode to better integrate knowledge, data, and resources from its partners.

The earliest stages of drug discovery consist of three phases, sourcing and screening compounds, hit-to-lead expansion up to lead selection, and lead optimization (LO). In its early days, DNDi relied on opportunities arising from academic and biotechnology collaborations to fill its discovery pipeline. Even though this model successfully delivered several leads, its intrinsic challenges (low throughput for drug screening, limited capacity for compound evaluation, and insufficient resources) led DNDi to restructure its drug discovery model and adopt a more pragmatic and structured discovery strategy that relies on partnerships with public (e.g. universities and academia) and private partners (pharmaceutical and biotechnology companies).

In addition, in 2011, DNDi restructured its LO activities to enable more flexibility and increase cost effectiveness, and moved from three disease-specific LO consortia to two, which work across all three kinetoplastid diseases. This reorganization enables greater cross-talk between diseases for each compound series being investigated.

In recent years, DNDi has also taken steps to address two main concerns: the low throughput in screening against intracellular protozoa (such as Leishmania and Trypanosoma cruzi) and the sourcing of quality compounds. DNDi now relies mainly on phenotypic screening to generate hits, and has successfully supported the development and validation of medium- to high-throughput in vitro assays using whole-cell assays against Trypanosoma brucei at Griffith University in Australia.

In addition, the Institut Pasteur Korea has developed, in partnership with DNDi, imaging technology-based high-content screening assays against intracellular Leishmania and T. cruzi. These newly developed assays have significantly increased DNDi’s capacity to screen compound collections against its target pathogens.

Main partners: Anacor Pharmaceuticals, USA; Drug Discovery Unit (DDU) at the University of Dundee, UK; Eskitis Institute (Griffith University), Australia; Genomics Institute of the Novartis Research Foundation (GNF), USA; GlaxoSmithKline, Tres Cantos, Spain; Institut Pasteur Korea (IPK), South Korea; London School of Hygiene & Tropical Medicine (LSHTM), UK; Merck, USA; Pfizer, USA; Sanofi, France; SCYNEXIS Inc., USA; Swiss Tropical and Public Health Institute (Swiss TPH); TB Alliance, USA; TI Pharma, The Netherlands; University of Antwerp, Belgium; Special Programme for Research and Training in Tropical Diseases (WHO-TDR).

Management: Discovery and Pre-Clinical Director: Robert Don; Discovery Manager: Jean-Robert Ioset.

\textbf{\textit{\textarrow{Compound-mining}}}  
This approach is based on proactive acquisition and investigation of compounds from selected series associated with a significant level of available information (biological activities, pre-clinical dossier, published data, safety profile, among others) in order to identify candidates with a potential for further development – ideally ready to enter into pre-clinical or later stage without further optimization – for the target diseases. Following the successful example of fexinidazole, DND\textit{i} has extended this approach in collaboration with its pharmaceutical partners, including Sanofi (repositioning collection of 300 marketed drugs and clinical candidates, an initiative of Sanofi for Neglected Diseases) and GSK (collections of marketed drug sets, as well as terminated leads and candidates).

\textbf{\textit{Chemical diversity}}  
This approach aims to mine new chemical territories to identify additional classes of molecules of potential interest in terms of drug development for DND\textit{i}'s target diseases. Illustrating this approach is the recent research collaboration with Pfizer to screen the Pfizer GDRS II set (representative of the entire Pfizer library in terms of chemical diversity, i.e. 150,000 compounds) against all three kinetoplastid diseases at the Eskitis Institute (HAT) and IPK (VL and Chagas disease). More recently, DND\textit{i} has started evaluating various libraries based on chemical diversity with its pharmaceutical partners, including, among others, Sanofi and GSK.

\textbf{\textit{Mining for chemical classes}}  
Discovery activities are typically associated with high attrition rates, especially in the case of candidates not associated with any pre-clinical data other than in vitro efficacy. In order to lower this attrition rate, mining for chemical classes relies on the identification of promising chemical classes of which a member has been successfully advanced in drug development for other disease indications. From libraries of collaborating pharmaceutical and biotech companies, promising compound classes can be identified by sampling a subset of representative compounds and testing them for antiparasitological activities. Examples of interesting classes include oxaboroles (Anacor Pharmaceuticals), pyridones (GSK), and nitroimidazoles (TB Alliance).

\textbf{\textit{Target-based}}  
This early discovery approach is based on screening compounds and assessing their activity against a specific target essential for parasite growth. In collaboration with the Drug Discovery Unit (DDU) at the University of Dundee, DND\textit{i} aims to discover and, through hit-to-lead efforts, deliver one to three leads active against \textit{Leishmania donovani}. This collaboration takes advantage of the unique existing capabilities of the partner in lead generation and their active engagement in high-throughput molecular target screening.

Additional capabilities at DDU have also been applied to the drug discovery efforts, such as cell and organism-based phenotypic screening (including high-content platforms), structure-based drug design, computational and medicinal chemistry, drug metabolism and pharmacokinetics, and \textit{in vivo} animal models of infection.

\textbf{\textarrow{High-throughput screening}}  
High-throughput screening of large libraries for \textit{Leishmania}, \textit{T. cruzi} (IPK) and \textit{T. brucei} (Eskitis) have been developed and are used to identify novel hit compounds. Adequate screening capacity is a key element of DND\textit{i}'s discovery strategy, as it enables the screening of large libraries/series of compounds and therefore a quicker identification of hits/leads.

\textbf{\textarrow{Reference screening centres}}  
The Swiss TPH, the University of Antwerp, and the LSHTM serve as reference screening centres to ensure that screening methodologies are comparable, and that in vitro and \textit{in vivo} assays at different sites and with different groups meet the same standards. The centres also provide expert parasitology advice that ensures the quality of DND\textit{i}'s data and work.
Of the three kinetoplastid diseases, HAT is the only one slated for global elimination by the year 2020 in the WHO roadmap for implementation published in early 2012.(1) Thanks to the efforts and successes of National Control Programmes (NCPs), together with WHO, MSF, Sanofi, Bayer, DNDi, and others, there is indeed reason to hope: the number of reported cases has substantially decreased within the past years, dropping below 10,000 for the first time in 50 years in 2009. A new combination therapy, NECT, that simplifies treatment, was introduced in 2009 for patients with stage 2 HAT.

However, additional efforts and new treatments are still needed to make elimination possible and sustainable: surveillance and control programmes need to be maintained and expanded to all endemic areas and field-adapted tools need to be developed to detect and treat, in primary healthcare settings, those patients who are not reached by current strategies.

Treatments for HAT are toxic or complex to administer. Treatment is stage-specific, and requires in-hospital infusions for stage 2 of the disease, which is the life-threatening, neurologic phase. Together with complicated and invasive diagnostic methods, such as the lumbar puncture, the reality of HAT management remains challenging, even more so in the most remote, low-resource settings. In addition, the possibility of disease resurgence, together with that of emerging resistance to existing treatments, call for the development of new drugs, compatible with the realities of the disease in the field.

The ideal treatment is a safe, effective, and orally administered drug active against both stages of the disease.

WHAT IS THE IMPACT OF HAT?
The number of reported cases in 2010 was just over 7,000, but the estimated number of actual cases is currently approximately 30,000.[2]

Fatal if untreated, the disease affects mainly those living in remote areas with limited access to adequate health services. Almost eliminated in 1960, transmission increased again as a result of war, population displacement, poverty, and the collapse of health systems.

Recent successes and an impressive drop in the number of reported cases call for renewed hope, but there is still work to be done, as some areas are not covered by surveillance and control efforts.

HOW IS HAT TRANSMITTED?
HAT is transmitted to humans by two subspecies of the parasite Trypanosoma brucei (T. b.) through the bite of the tsetse fly: T. b. gambiense (West and Central Africa, responsible for the vast majority of cases) and T. b. rhodesiense (East Africa). The disease affects 36 countries in sub-Saharan Africa, but 8 countries report 97% of all cases (see map), and over two-thirds of those are reported in the Democratic Republic of the Congo (DRC).[3]

WHAT ARE THE SYMPTOMS?
HAT occurs in two stages:

-> Stage 1: the hemolymphatic stage – includes non-specific symptoms like headaches and bouts of fever (and generally goes undiagnosed without active HAT surveillance).
-> Stage 2: the later, neurologic stage – occurs when the parasite crosses the blood-brain barrier and can lead to serious sleep cycle disruptions, paralysis, progressive mental deterioration, and ultimately, without effective treatment, death.

A lumbar puncture is needed to differentiate between the two stages for the administration of proper treatment.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?
Available treatments are limited, difficult to administer, often toxic, and stage-specific.

-> Stage 1: pentamidine and suramin are fairly well-tolerated treatments, but require injections and are ineffective for stage 2.

-> Stage 2: melarsoprol is a toxic arsenic derivative that causes pain and fatal encephalopathies in up to 5% of those who receive it,[4] and is increasingly ineffective, with reports of drug resistance and treatment failure in some foci; eflornithine is difficult to administer: treatment requires trained health staff and an extended hospital stay (56 intravenous infusions taking two hours each to administer, over 14 days and four times each day); NECT (nifurtimox–eflornithine combination therapy) is a simplified therapy option for stage 2 T. b. gambiense sleeping sickness, with only 14 injections of eflornithine over 7 days and 10 days of oral treatment with nifurtimox. While not the most appropriate treatment to support elimination efforts, it provides an incremental improvement in case management at the field level.

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?
At its inception, DNDi’s short-term strategy was to make better use of existing treatments by combining drugs already in use. In September 2009, DNDi and partners launched the first new treatment for sleeping sickness in 25 years: nifurtimox and eflornithine combination therapy (NECT). NECT was included on the WHO Essential Medicines List in 2009 and is now recommended as first-line treatment for HAT in 12 endemic countries.

As a medium-term strategy, DNDi initiated a proactive compound mining effort to identify existing chemical compounds with potential against kinetoplastid diseases. This resulted in the rediscovery of fexinidazole, which completed Phase I clinical development in 2011. Fexinidazole is now ready to be assessed in a pivotal Phase II/III study in 2012. An agreement was signed in 2009 with Sanofi as the industrial partner for this project.

In order to build a strong pipeline for long-term drug discovery, DNDi established the HAT Lead Optimization Consortium. The identification of the Oxaborole SCYX-7158 represents the first success of this consortium. SCYX-7158 successfully progressed through pre-clinical development and at the end of 2011, all necessary documentation was submitted to relevant authorities for the start of Phase I clinical development in early 2012. Other backup compounds continue to be evaluated by the consortium.

Finally, DNDi supports the HAT Platform (see page 50) that was launched in Kinshasa (DRC) in 2005. The HAT Platform is a clinical research and access-supporting network that brings together key players in the fight against sleeping sickness from Angola, the Central African Republic, Chad, DRC, Republic of the Congo, Sudan, South Sudan, and Uganda.

By 2018, DNDi aims to deliver from its HAT-specific portfolio:

-> An oral, safe, effective treatment for stage 2 HAT, ideally to be used with the same regimen for stage 1 HAT

HAT Lead Optimization Consortium – Nitroimidazoles backup – Oxaboroles backup

2011 OBJECTIVES:
→ To develop backups from the oxaborole and nitroimidazole series
→ To facilitate transition of discovery research to the new consolidated lead optimization programme during the second semester

DNDi’s strategy for the lead optimization consortia is to develop a backup compound in each of the oxaborole and nitroimidazole series, whilst also advancing new chemical classes from the screening programmes. In case of failure of one of the current developed compounds, the backup should be able to replace it rapidly. These consortia bring together expertise in chemistry, biology, drug metabolism, and pharmacokinetics (DMPK), in vivo screening, drug safety assessment and pre-formulation development. Optimization efforts are focused on improving the molecule’s characteristics to be absorbed into the bloodstream, to be distributed effectively to the infection sites, to survive in the body, to kill the parasite, and not to harm the patient.

In 2011, potential backup oxaboroles for HAT were identified and profiled in vivo for efficacy. The most advanced compounds were selected for exploratory toxicity studies. Potential backup nitroimidazoles for HAT were selected for further in vitro and in vivo DMPK studies. Promising leads were progressed towards in vivo efficacy studies. All selected compounds have the attributes described in discovery manuals and could match the aims of the TPP for HAT.

They are being assessed to ensure that they offer quality backups to SCYX-7158 and fexinidazole, should these two compounds not succeed through clinical development. Work will continue in 2012, with the aim to complete exploratory toxicity studies and further PK studies with the leading oxaborole backups for HAT, such that an optimized lead could be presented by end 2012. Nitroimidazoles will continue to be triaged and profiled to provide an optimized lead backup to fexinidazole by the end of 2012. In addition, DNDi and its partners aim to bring at least one new hit series through hit-to-lead studies into lead optimization.

Nota Bene: the lead optimization (LO) consortia were re-organized in 2011, from three separate HAT, VL, and Chagas disease-specific consortia, into two consolidated consortia, LO USA and LO Australia, for all three diseases.

Oxaborole SCYX-7158

2011 OBJECTIVES:
→ Complete a GLP pre-clinical package, develop a process for drug formulation, manufacture the Active Pharmaceutical Ingredient (API)
→ Submit regulatory files for Phase I clinical trials

SCYX-7158 belongs to a unique boron-based chemical class, the oxaboroles, which was originally provided by Anacor Pharmaceuticals and screened for activity against T. brucei at the University of California San Francisco. A unique collaboration between DNDi, Anacor Pharmaceuticals (a biopharmaceutical company in Palo Alto, California, USA) and SCYNEXIS (a drug discovery and development company based in Research Triangle Park, North Carolina, USA), within a consortium that also included Pace University (USA) and the Swiss TPH, enabled the identification of SCYX-7158, selected as a promising pre-clinical candidate in late 2009. In pre-clinical studies, SCYX-7158 was shown to be safe and efficacious to treat stage 2 of the disease, as it is able to cross the blood-brain barrier.

Pre-clinical development progressed successfully through 2010, and all pre-clinical data were published in PLoS NTD in June 2011.10 In 2011, regulatory toxicology studies were performed to assess the compound’s safety. Batches of drug substance and drug product were produced according to current good manufacturing practices (cGMP).

Finally, the Investigational Medicinal Product Dossier (IMPD) and the study protocol were submitted to the ethics committee and to the French regulatory authority, AFSSAPS. Following their clearance, SCYX-7158 is set to enter First-in-Human studies in early 2012 and become DNDi’s first entity resulting from lead optimization efforts to enter Phase I clinical studies. These studies will assess its safety, tolerability, pharmacokinetics, and pharmacodynamics in healthy volunteers of sub-Saharan origin.

**Fexinidazole**

**2011 OBJECTIVES:**
- Complete Phase I clinical studies
- Determine the therapeutic dose to use in the subsequent pivotal Phase II/III study
- Develop an analytical method to measure pharmacokinetics (PK) in field conditions (dry blood spots)
- Finalize the protocol for the pivotal Phase II/III study

Fexinidazole is the first success of the extensive compound mining efforts pursued by DNDi within the nitroimidazole project initiated in 2005 to explore new and old nitroimidazole drug leads. This rediscovered drug entered Phase I First-in-Human studies in September 2009 and is now ready to enter Phase II/III. In addition to the single ascending dose, food effect, and multiple ascending dose studies carried out in 2010, studies to determine the optimal treatment dose and duration were performed in 2011. An analytical method to measure the PK of fexinidazole was completed during the year. In early 2011, DNDi and Sanofi requested joint scientific advice from the FDA and the EMA (through Article 58), on the clinical development plan for fexinidazole, which led to the development of a protocol for a single pivotal Phase II/III study to prove the safety and efficacy of fexinidazole, with NECT as the active comparator. Preparatory activities to conduct trials in the Democratic Republic of the Congo, the Central African Republic, and possibly South Sudan have taken place, such as selection of trial sites and training in good clinical practices (GCP). The protocol was submitted for review to an international ethics working group meeting convened by the Société Française et Francophone d’Ethique Médicale (SFFEM) with WHO support in early 2012, and the trial is expected to start in the second quarter of 2012.

**NECT**

**Nifurtimox-Eflornithine Combination Therapy**

**2011 OBJECTIVES:**
- Support the inclusion of Nifurtimox-Eflornithine Combination Therapy (NECT) in the Essential Medicines List of all HAT Platform countries
- Continue follow-up of patients included in the NECT-Field trial initiated in 2009 (Q2 2012)

NECT was developed by DNDi, MSF, Epicentre, Swiss TPH, and the National Trypanosomiasis Control Programmes of the Republic of Congo and DRC as a combination of eflornithine and nifurtimox. Available since late 2009, it reduces the number of eflornithine infusions needed, has a higher cure rate than eflornithine alone and fewer severe adverse events. By reducing the quantity of eflornithine needed to treat each patient, it also significantly lessens the cost of treatment. NECT also reduces the burden on health systems, as it is much simpler to administer, making it much more adapted to the field conditions where it is used.

NECT was included on the WHO Essential Medicines List in 2009. Since then, melarsoprol and eflornithine monotherapy are increasingly being replaced by NECT – in 2010, only 12% of cases were treated with melarsoprol; as of December 2011, 12 countries had added NECT to their national essential medicines list: Angola, Cameroon, Central African Republic, Chad, DRC, the Republic of the Congo, Equatorial Guinea, Guinea Conakry, Gabon, Ivory Coast, South Sudan, and Uganda. All of them have received supplies from WHO – over 4,000 treatments in 2011. The HAT Platform continues to advocate for the use of NECT, a more field-adapted, simpler and safer treatment for stage 2 sleeping sickness. DNDi and its partners continue follow-up of patients included in the “NECT-Field” study launched in 2009. This Phase IIb study will further document the safety and ease of use in real-life conditions, in specific populations such as children, and pregnant and breastfeeding women. A total of 630 patients were enrolled in the study, including 100 children, 13 pregnant women, and 34 breastfeeding women. The two-year follow-up period will end in mid-2012.
Implementing new VL treatment options is crucial to disease management, notably in Africa and in Asia.

Main clinical manifestations of leishmaniasis include visceral leishmaniasis (VL) (also known as kala-azar), cutaneous leishmaniasis (CL), and post-kala-azar dermal leishmaniasis (PKDL). VL is characterized by prolonged fever, enlarged spleen and liver, substantial weight loss, and progressive anemia, and is generally fatal if left untreated. CL is characterized by lesions of the skin that can become chronic and/or disfiguring. PKDL is a disseminated skin infection; a common sequel of VL, it serves as a parasite reservoir, thus contributing to the transmission of the disease.

While the last decade has seen improvements in the treatment, diagnosis, and prevention of leishmaniasis mostly in South Asia, much more remains to be done to reach the WHO aim of eliminating visceral leishmaniasis from the Indian sub-continent by 2020.[1] The disease still remains one of the world’s most neglected, affecting the poorest of the poor. More work is needed to consolidate the progress achieved in South Asia and extend it to other parts of the world, in particular East Africa and Latin America. Chemotherapy remains one of the most important tools in the control of visceral leishmaniasis, but existing treatments have serious drawbacks: potential of resistance development, low tolerability, long treatment duration and difficulty in administration, as well as high cost. New treatments that address these issues and cater for geographical variations and local realities are essential. Effective treatments for cutaneous leishmaniasis have yet to be discovered.

The ideal treatment for VL is a safe, effective, oral, short-course (10 days maximum) drug that would also be efficacious against PKDL. The ideal treatment for CL is a safe, short course, affordable, field-friendly topical or oral agent that cures lesions fast, with minimal scarring.

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IDEAL TARGET PRODUCT PROFILE FOR VL

A new treatment for adults and children
- Efficacious against all species of parasite in all regions
- At least 95% efficacy after two months
- Easy-to-use: Short course, oral or topical, requiring no monitoring
- Safe in pregnant and lactating women
- Affordable
- Adapted to tropical climates (minimum three-year shelf life)

IDEAL TARGET PRODUCT PROFILE FOR CL

A new topical or oral treatment
- Efficacious against L. tropica and L. braziliensis
- At least 95% efficacy
- Minimal scarring
- Safe in pregnant and lactating women
- Affordable
- Adapted to tropical climates (minimum three-year shelf life)

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Leishmaniasis

A still neglected disease affecting five continents

WHAT IS THE IMPACT OF LEISHMANIASIS?

Leishmaniasis occurs on five continents with endemic transmission reported in 98 countries and three territories. Among parasitic diseases, morbidity and mortality caused by leishmaniasis are surpassed only by malaria and lymphatic filariasis.

It is estimated that 350 million people are at risk of the disease, most of them children. The annual incidence is estimated at over 1.5 million cases (400,000 for VL and 1.2 million for CL)[1], with 40,000 VL deaths each year.[2] However, due to underreporting and misdiagnosis, estimation of the leishmaniasis disease burden is challenging and actual case loads are expected to be higher.

In addition, co-infection with other infectious diseases is an increasing concern: HIV-VL co-infection has been reported in 35 countries worldwide. The risk of death from VL is nine times higher in those who are co-infected with HIV.

HOW IS LEISHMANIASIS TRANSMITTED?

More than 20 species of the kinetoplastid protozoan parasite Leishmania can be transmitted to humans via some 30 species of phlebotomine sandflies.

CL is most frequently caused by Leishmania major, L. tropica and L. aethiopica in the Old World, and L. braziliensis, L. mexicana, and related species in the New World.

VL is usually caused by L. donovani and L. infantum.

PKDL occurs during, or more often after, recovery from VL. It is caused by L. donovani and is believed to be a reservoir of parasites for human VL.

WHAT ARE THE SYMPTOMS?

CL is a small erythema that develops after a variable period at the site where an infected sandfly has bitten the host. The erythema develops into a papule, then a nodule that progressively ulcerates to become the lesion characteristic of the disease. CL usually heals spontaneously within one to two years, but results in a lifelong scar, which, depending on its size and location, may cause substantial trauma in affected individuals, particularly children.

VL is characterized by progressive fever, weight loss, enlarged spleen and liver, and anemia. Untreated VL is fatal in almost all cases.

PKDL is characterized by a macular, maculopapular and nodular rash; starting from the face, it spreads to other parts of the body.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

Existing therapies have serious drawbacks in terms of safety, drug resistance, stability and cost. [3] They have low tolerability, long treatment duration, and are difficult to administer.

→ Pentavalent antimonials (sodium stibogluconate – SSG – and meglumine antimoniate) have been used in the treatment of VL and CL for more than 60 years. Acquired resistance has developed in areas of high prevalence and high transmission. Cardiotoxicity has been reported as a drug-induced effect and serious cardiotoxicity leading to death is well documented.

In addition, these drugs require a 30-day parenteral treatment. They are registered in Southeast Asia, and some Mediterranean and African countries.

→ Amphotericin B is used as first-line treatment for VL in areas with high rates of unresponsiveness to antimonials and second-line treatment elsewhere. Need for hospitalization, constant monitoring of patients, prolonged duration of treatment and infusion-related adverse events are notable drawbacks. Amphotericin B displays dose-limiting toxicity and requires 15-20 day treatment. It is registered in South Asia and some African countries.

→ Miltefosine is the first orally administered drug registered in India for the treatment of VL but it is expensive[4] and requires a 28-day treatment. The major limitation of miltefosine is its contraindication in pregnancy and mandatory contraception for women of child-bearing age for the duration of therapy and 2-3 months beyond. It is also registered in Colombia for treatment of CL.

→ Paromomycin (PM): a low-cost parenteral formulation registered in India in 2007 by Gland Pharma in collaboration with OneWorld Health (OWH). It requires 3 weeks of intramuscular administration.

Leishmaniasis

A still neglected disease affecting five continents

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?

DNDi’s short-term approach is to develop new treatments by combining existing drugs and/or shortening treatment duration in order to increase tolerability, reduce burden on health systems, and offer greater affordability, whilst also preventing or delaying emergence of resistance. Another short-term objective is to assess efficacy and safety of existing drugs in other countries and regions to extend their registration and availability to more patients.

In 2010, DNDi and partners delivered the SSG&PM combination therapy for East Africa that is now recommended as first-line treatment for VL in the region by the WHO Expert Committee on the Control of Leishmaniasis. In India, together with its partners, DNDi also conducted a Phase III trial to evaluate the combination of already registered drugs: AmBisome®, miltefosine, and paromomycin. The study showed that the three possible 2-drug combinations were all highly efficacious, and they are now, together with single-dose AmBisome®, recommended by the WHO Expert Committee. Together with OWH and TDR, DNDi will collaborate with the National Control Programmes of India and Bangladesh, MSF, the Bihar State Health Society, and the Indian Council for Medical Research to facilitate the introduction of these new treatments for VL in South Asia. In Latin America, DNDi is participating in a study sponsored by the Brazilian Innovation Agency (FINEP) to evaluate the safety and efficacy of Glucantime®, AmBisome®, amphotericin B, and AmBisome® + Glucantime® combination to treat VL patients in Brazil.

As a medium-term approach, DNDi is looking into new formulations of amphotericin B.

In order to develop new drugs for the treatment of leishmaniasis, DNDi’s long-term strategy is to bring new candidates into clinical development through its lead optimization programme.

Finally, DNDi supports the Leishmaniasis East Africa Platform (LEAP, see page 50) that aims to geographically extend all currently available VL drugs to East Africa and to develop new therapies suitable for the region, as well as to build capacity in the region for conducting clinical trials.

By 2018, DNDi aims to deliver from its VL-specific portfolio:

→ An oral, safe, effective, low-cost and short-course treatment
→ A new treatment for PKDL that is shorter course and better tolerated than current options
→ Treatment options for HIV-VL co-infected patients that would limit recurrences

By 2018, DNDi aims to deliver from its CL-specific portfolio:

→ A safe, effective, and shorter-course treatment for CL
**VL Lead Optimization Consortium**

**2011 OBJECTIVES:**

→ To develop new chemical entities (NCEs) with the aim of advancing two candidates into clinical development by 2014

→ To facilitate transition of discovery research to the new consolidated lead optimization programme during the second semester

DNDi’s strategy for the lead optimization consortia is to advance new chemical classes from the screening programmes, as well as to develop backup compounds that can rapidly replace currently developed compounds in case of failure. These consortia bring together expertise in chemistry, biology, drug metabolism, and pharmacokinetics (DMPK), in vivo screening, drug safety assessment, and pre-formulation. Optimization efforts are focussed on improving the molecule’s capacity to be absorbed into the bloodstream, to be distributed effectively to the infection sites, to survive in the body, to kill the parasite, and not to harm the patient.

In 2011, oxaboroles with promising pre-clinical in vivo activity for treating VL were identified. Selected compounds have the attributes described in discovery manuals and could match the TPP for VL. This class of molecules could provide a possible prototype candidate in a new chemical class. A decision will be made on their potential by mid-2012.

Nota Bene: the lead optimization (LO) consortia were re-organized in 2011, from three separate HAT, VL, and Chagas disease-specific consortia, into two consolidated consortia, LO USA and LO Australia, for all three diseases.

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**Nitroimidazole backup**

**2011 OBJECTIVE:**

→ Maintain a limited and focused backup programme to identify a backup compound for VL-2098, improving compound solubility and adjusting PK parameters

In 2010, the Global Alliance for Tuberculosis Drug Development (TB Alliance) and DNDi entered into a first-ever royalty-free license agreement between two not-for-profit drug developers. The TB Alliance granted rights to DNDi to develop a class of potential anti-TB compounds that also show significant promise for treating other neglected diseases, such as VL. Within TB Alliance’s nitroimidazole library, VL-2098 was identified as a candidate with potent efficacy against VL (see below). A focused programme is ongoing to identify a backup pre-clinical candidate in case VL-2098 does not successfully complete pre-clinical testing. Over 150 have been prepared so far.

A few of these were identified as potential leads with an in vitro potency comparable to that of VL-2098, improved solubility, metabolically stable, and with reduced hERG channel binding. Work is ongoing to improve in vivo efficacy.

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**Partners:**

SCYNEXIS Inc., USA; Laboratory of Microbiology, Parasitology and Hygiene, University of Antwerp, Belgium; London School of Hygiene & Tropical Medicine (LSHTM), UK; Wuxi AppTech, China

**Management:**

Discovery and Pre-clinical Director: Robert Don; Head of Drug Discovery: Charles Mowbray; Project Manager: Ivan Scandale; Project Coordinator: Delphine Launay

**Pre-clinical programme:**

TB Alliance, USA; Advinus Therapeutics, India; Central Drug Research Institute, India; London School of Hygiene & Tropical Medicine (LSHTM), UK; Auckland University, New Zealand

**Management:**

Head of Chagas Discovery and Pre-clinical Programme: Eric Chatelain; Project Coordinator: Delphine Launay

**Project start:**

July 2010
**VL-2098**

**2011 OBJECTIVE:**

→ Undertake the pre-clinical assessment of VL-2098

From the initially selected 70 nitroimidazoles belonging to four chemical subclasses, VL-2098 was identified as a very potent and safe molecule and was selected for in-depth evaluation of its efficacy, pharmacokinetic, and early safety profile on the basis of these preliminary results. This compound is potent and selective *in vitro* and shows efficacy in acute and chronic VL animal models. Appropriate exposure is obtained after oral dosing in rodents and the compound does not induce major acute toxicity after multiple administrations at several multiples of the efficacious dose. Ongoing safety studies and pharmaceutical development are planned for 2012.

**Partners:**
TB Alliance, USA; Advinus Therapeutics, India; Central Drug Research Institute, India; London School of Hygiene & Tropical Medicine (LSHTM), UK; Auckland University, New Zealand; Bertin Pharma, France.

**Management:**
Discovery & Pre-clinical Director: Robert Don; Head of Visceral Leishmaniasis Discovery & Pre-clinical Programme: Denis Martin; Project Coordinator: Stéphanie Braillard

**Project start:**
July 2010

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**Alternative formulations of amphotericin B**

**2011 OBJECTIVES:**

→ Recommend a novel amphotericin B formulation for advanced evaluation
→ Develop a polymer-based formulation active through intra-venous or intra-muscular administration

The goal of this project is to identify an improved formulation of amphotericin B that shows the most promise in terms of *in vivo* efficacy, safety, heat stability, and cost. Amphotericin B, under various formulations, is one of the most efficacious treatments for VL. The standard formulations (oily suspension) have side effects. AmBisome®, a liposomal formulation, has overcome these limitations, but its high cost and lack of heat stability limit its utility in disease-endemic countries. Recently, new formulations have emerged and have either been approved or are under clinical development in India. However, they are still not field-adapted and there is no safety and VL efficacy data available yet. DNDi and its UK partners are investigating improved polymer-based formulations to replace the lipid-based component with a narrow molecular weight range polymer. Ideally, the selected polymer can form an amphotericin B conjugate that is soluble, cheaper, better tolerated, and has increased thermal stability. Initial results show that reproducible *in vivo* activity could be achieved without signs of amphotericin-induced toxicity in test animals. A biodegradable polyglutamic acid polymer has been selected and will be assessed for safety, efficacy, and scalability in the first half of 2012.

**Partners:**
Polytherics, UK; London School of Pharmacy, UK; LSHTM, UK

**Management:**
Head of Visceral Leishmaniasis Discovery & Pre-clinical Programme: Denis Martin

**Project start:**
September 2006
Cutaneous leishmaniasis

DNDi’s objective is to develop a new treatment for CL based on three components – anti-parasitic, wound-healing, and immune-modifying. As an ultimate goal to be achieved stepwise, the strategy is to select an already-developed wound-healing agent, to be combined with an anti-parasitic drug, identified by one of two approaches:

→ Development of a topical treatment containing amphotericin B
→ Screening of selected oral drugs used for other indications

In the long term, DNDi will seek to combine these two elements with an immune-modifier, such as an oligo-deoxy-nucleotide (CpG, or CpG-containing agents – with TLR-9 agonist activities). At each step, an incremental benefit may be achieved over what is currently available for treating CL.

New VL treatments – Africa

2011 OBJECTIVES:

→ Finish recruitment of the Phase II/III trial assessing single dose AmBisome®
→ Complete exploratory Phase II trial assessing miltefosine combinations in East Africa
→ Apply for registration of miltefosine in Sudan, Kenya, and Uganda
→ Continue to evaluate and monitor parasite drug sensitivity to current treatments
→ Apply for registration of paromomycin (PM) in Uganda, Sudan, Ethiopia, and Kenya

Due to toxicity, difficulty of use, and high cost of existing drugs, VL is complex to treat in Africa. SSG&PM is now recommended as the first-line treatment for VL in East Africa. Other drugs, such as miltefosine, are neither registered nor available in the region. Since 2004, DNDi and LEAP have embarked on a clinical research programme with two specific objectives: to geographically extend all clinical research programme with two specific objectives: to geographically extend all currently available VL drugs and to develop one to two new treatments.

In order to achieve these objectives, DNDi and LEAP conducted two clinical trials in the region during 2011:

AmBisome® / AMBI 0106 Study
AmBisome®, a liposomal formulation of amphotericin B manufactured by Gilead, is approved to treat VL in India, USA, and Europe. Gilead has worked with the WHO and NGOs to provide AmBisome® at a preferential price for the treatment of leishmaniasis in resource-limited settings. This study aims at determining the minimum dose of AmBisome® that is efficacious, safe, and cost-effective to treat VL in Africa, to reduce duration of hospitalization and to facilitate the registration and adoption of the drug in the region. Recruitment for the study was closed at the end of 2010. Patient follow-up and data collection and analysis were completed in 2011 and publication is planned for 2012.

Miltefosine-AmBisome® / LEAP 0208 Study
This study is conducted to evaluate the safety and efficacy of miltefosine and AmBisome® combination treatment. Recruitment started in Kenya and Sudan in 2010. Miltefosine, a drug originally developed for the treatment of cancer, is the only orally administered drug against VL. It is registered and used in India and in some countries in Latin America. The trial will collect safety, efficacy, and pharmacokinetic data on miltefosine to geographically extend the use of the drug into East Africa. In addition, combination treatments of AmBisome® with either miltefosine or SSG are being evaluated. If the results are promising, one of the combinations will be taken into Phase III development.

New VL treatments – Bangladesh

New VL treatments – Latin America

2011 OBJECTIVE:
→ Support the Brazilian Ministry of Health and its partners to conduct a Phase III trial assessing the efficacy and safety of amphotericin B, AmBisome®, and the combination of AmBisome® + Glucantime®

About 90% of VL cases in Latin America occur in Brazil, and most of them affect children. In 2009, Brazil reported 3,693 new cases with a fatality rate of 5.8%. DNDi is supporting the implementation of a Phase III clinical trial sponsored by the Brazilian Ministry of Health to assess treatments for VL. The primary objective of the study, led by Dr Gustavo Romero of the University of Brasilia, is to assess the efficacy and safety of amphotericin B deoxycholate, AmBisome®, and AmBisome® combined with Glucantime®, as compared to the first-line treatment, Glucantime®, for the treatment of VL patients in Brazil. The project was implemented in 2011 in VL reference centres throughout different regions of the country, and is expected to be completed by 2014. Evidence provided by this project will guide policies on the treatment of VL caused by L. chagasi in Brazil.
New VL treatments – Asia

**2011 OBJECTIVE:**

1. Implement effectiveness studies in the region to demonstrate feasibility in implementing new treatment modalities in primary healthcare settings in both the public and private sectors.

The Phase III trial conducted by DNDi and its partners in 2010 demonstrated the efficacy of combination therapies based on AmBisome®, miltefosine, and paromomycin. An additional study by Sundar et al. (1) showed the efficacy of single-dose AmBisome® given as an intravenous infusion.

To facilitate the introduction of these new treatments for VL in South Asia, DNDi developed a partnership consortium with TDR and OWH (2), in collaboration with health authorities at state, national, and regional levels. DNDi will work to implement single dose AmBisome® in the public sector in India (with TDR) and new combination therapies in the private sector (with OWH).

Effectiveness studies are being implemented in the region to demonstrate that such treatments can be safely implemented through primary healthcare systems in both the public and the private sectors. These studies include:

- A pilot project in the Bihar State of India implementing combination therapies at the primary healthcare level and single-dose AmBisome® at the hospital level. The project has two main components, surveillance and pharmacovigilance to monitor treatment effectiveness and safety in the public sector. In 2011, approvals were obtained from key stakeholders in India, an agreement was signed with the Bihar State, and partnerships were established with local implementing organizations. The study is expected to begin mid-2012.
- A two-step Phase III study (first in hospital settings, then in primary healthcare centres) using the combination therapies in Bangladesh; recruitment started in July 2010 and continued in 2011.

**SSG&PM**

**Sodium stibugluconate & paromomycin**

**2011 OBJECTIVES:**

1. Continue registration of paromomycin (PM) in East Africa
2. Facilitate uptake and implementation in key endemic areas of East Africa with local partners
3. Facilitate pharmacovigilance activities for SSG&PM to monitor safety and effectiveness post-implementation

In 2010, DNDi and LEAP successfully showed that the combination of sodium stibugluconate (SSG) and PM was as efficacious as single-dose SSG, with the advantage of being shorter course, therefore lessening the burden on health systems, and more cost-effective. Since then, DNDi and LEAP have worked with local ministries of health to ensure recommendation and uptake of the new treatment. First registration (of PM) was obtained in Uganda at the end of 2011, and registration is ongoing in Kenya, Sudan, and Ethiopia. Implementation has already begun in the region, as the treatment was recommended as first-line therapy for VL patients in East Africa by the WHO Expert Committee on the Control of Leishmaniases. In addition, it has been added to the national drug lists of Sudan, South Sudan, and Ethiopia. SSG&PM treatment has been rolled out in Sudan and Uganda in public health structures, as well as in important NGO centres. Over 10,000 doses of SSG&PM have been distributed since the end of the Phase III trial – principally in South Sudan.

A pharmacovigilance study to monitor safety and effectiveness of SSG&PM was initiated in 2011 and will be completed in 2013.
A replenished pipeline and a new paediatric dosage form registered in 2011.

Of all the neglected diseases, Chagas disease is among those that receive the least investment for R&D. In 2010, reported funding for R&D for neglected diseases totalled just over USD 3 Billion. Of this amount, only USD 20 Million went to Chagas disease, and only USD 4.5 Million was invested in drug discovery for the disease. The only two drugs approved for treating acute Chagas disease were developed over 40 years ago and are far from ideal. Until recently, the main focus of the fight against Chagas disease was to interrupt transmission through the deployment of vector-control strategies and the screening of blood donors. Whilst sustained vector control has largely contributed to reducing transmission in Latin America, the Pan American Health Organization (PAHO) currently estimates that approximately 8 million people are infected in the region, and that tens of thousands of new cases occur each year. Imported Chagas disease is increasingly recognized as an emerging problem in the USA and Europe, due to immigration from Latin America. The US Center for Disease Control (CDC) estimates that over 300,000 persons with Trypanosoma cruzi infection live in the USA.

The existing drugs, benznidazole and nifurtimox, have been used for decades, but because their efficacy against the chronic phase of the infection is poorly documented, they are of limited use in disease control strategies. In addition, long treatment periods (60-90 days) make patient compliance challenging, with increased risk of drug resistance development. Side-effects range from skin rashes to seizures and other nervous system disorders.

In order to effectively fight the disease, new treatments that are safe, efficacious, and effective against the chronic phase of the disease – which is when most patients are diagnosed – are sorely needed. In addition, to gain understanding of the disease progression and ease the development of test-of-cure diagnosis tools that support drug development, a better understanding of biomarkers is essential.

American Trypanosomiasis – Chagas Disease

A ‘silent killer’ that remains hidden and under-acknowledged

WHAT IS THE IMPACT OF CHAGAS DISEASE?

Chagas disease is endemic to 21 countries in Latin America, where 100 million people are at risk. It is estimated that eight million people are infected, leading to approximately 12,000 deaths every year.11 Hundreds of thousands of people across the world, in Europe, North America, Japan, and Australia also carry the disease,20 often without knowing it.

HOW IS CHAGAS DISEASE TRANSMITTED?

Chagas disease is related to infection by the kinetoplastid protozoan parasite Trypanosoma cruzi, transmitted through the bite of a triatomine vector known as the ‘kissing bug’. Other routes of transmission include blood transfusion, organ transplantation, as well as congenital and, less often, oral routes through ingestion of contaminated food or beverage.

WHAT ARE THE SYMPTOMS?

The disease has two clinical phases:

- The acute phase (fatal for 2-8% of children)10 is often asymptomatic or unrecognized due to non-specific symptoms, such as fever, malaise, and enlarged lymph nodes, spleen, and liver. In less than half the cases, first visible signs can be a skin lesion or a purplish swelling of one eyelid (known as Romaña’s sign). These symptoms spontaneously resolve in 4-6 weeks.
- The chronic phase that can be divided into two stages:
  - The chronic, silent, and asymptomatic ‘indeterminate’ stage, during which patients can transmit the parasite to others, especially through vertical transmission or transfusion, while showing no signs of the disease, and which may last decades after infection.
  - The chronic, symptomatic stage, which develops later in up to 30% of infected patients, and causes cardiopathies, digestive tract pathologies, and nervous system irregularities.14

is the leading cause of infectious heart disease (cardiomyopathy) in Latin America.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

Current treatments, benznidazole and nifurtimox, are effective against the acute phase of infection, but have limited efficacy against the chronic phase. Other drawbacks of these treatments include long treatment periods (60-90 days), dose-dependent toxicity, and a high drop-out rate of patients due to side-effects. There is currently no approved treatment for chronic disease with target organ involvement and until recently, there was no adapted paediatric dosage form for either of the existing drugs.

WHAT IS DNDI DOING TO ADDRESS UNMET TREATMENT NEEDS?

DNDi’s short-term goal was to make better use of existing treatments, notably through the development of a paediatric dosage form of benznidazole – a goal which was achieved: This treatment was granted registration by the Brazilian regulatory authorities in December 2011 and DNDI is working with LAFEP, the manufacturer, to ensure it is widely accessible to all those in need.

As a medium-term strategy, DNDI is assessing known compounds already in development against fungal infections, such as the new azole antifungal drug, E1224, active against T. cruzi in adult chronic patients, as well as biomarkers of treatment response.

As part of its long-term strategy, DNDI continues to identify and engage partners from private and public sectors within the Chagas lead optimization consortium in order to identify, characterize, and advance the development of promising compounds.

In addition, DNDI supports clinical research capabilities through the Chagas Clinical Research Platform (see page 50), which was launched in 2009.

By 2018, DNDI aims to deliver from its Chagas-specific portfolio:

- An effective and safe oral treatment for the treatment of chronic Chagas disease, ideally effective also against the acute form of the disease
- Biomarkers to gain understanding of the disease progression, ease the development of test-of-cure diagnosis tools that support drug development

Chagas Lead Optimization Consortium

**2011 OBJECTIVE:**

→ Further characterize fenarimols and oxaboroles as potential pre-clinical candidates

The Chagas lead optimization consortium was set up by DNDi in 2008, bringing together analytical and medicinal chemists, pharmacologists, and parasitologists, with the objective of developing at least one new optimized series for Chagas disease by the first quarter of 2012 and to identify a new chemical series of interest.

The consortium has been working on the fenarimol series, from which two candidates have been characterized as potential pre-clinical candidates. The team had also been evaluating oxaboroles, taking advantage of the compounds generated within the HAT lead optimization programme. However, work on the oxaborole series has been stopped, as structure-activity relationship work on the oxaborole series has been driven by in vivo models/data, which is not suitable for a lead optimization programme.

The work of the consortium has provided a better understanding of the essential features for a drug to be efficacious for the treatment of Chagas disease. This insight will be used to propose a new pre-clinical candidate from the nitroimidazole class that is more potent and safer than the drugs currently used (nifurtimox and benznidazole).

In parallel, hit series identified through the screening of the NIH library by the Broad Institute (Broad screen), as well as other series emanating from DNDi’s screening efforts, will be profiled and prioritized according to their potential.

Nota Bene: the lead optimization (LO) consortia were re-organized in 2011, from three separate HAT, VL, and Chagas disease-specific consortia, into two consolidated consortia, LO USA and LO Australia, to address the needs for all three kinetoplastid diseases.

Fenarimol

**2011 OBJECTIVE:**

→ Further characterize the leads of the fenarimol series before candidate nomination

As mentioned above, the Chagas lead optimization consortium yielded two interesting candidates from the fenarimol series of compounds. The project is now in its non-regulatory pre-clinical phase, with further profiling of candidates before nominating one candidate for further regulatory pre-clinical development.

K777

**2011 OBJECTIVE:**

→ Progress IND enabling studies for K777

K777 is a vinyl sulfone cysteine protease inhibitor, which inhibits cruzain, a key protease required for the survival of T. cruzi. K777 was originally characterized by the Sandler Center for Research in Tropical Parasitic Disease at UCSF and has since been shown to be safe and efficacious in animal models of acute and chronic Chagas disease.

The main objective of the project is to conduct pre-clinical safety and toxicology studies in order to complete the IND package for clinical evaluation of K777 for the treatment of Chagas disease.
An additional study is ongoing to optimize procedures for the use of the polymerase chain reaction (PCR) blood test as a measure of treatment response in Chagas disease in collaboration with MSF-Spain, with PCR assay support provided by the UMSS in Bolivia and quality assurance from INGEBI-CONICET in Buenos Aires, Argentina. Patient recruitment was finalized in December 2011 and patients will be followed-up for 12 months.

In parallel, DNDi started the assessment of biomarkers for Chagas disease with respect to their potential for application to clinical research. Collaboration with different partners was initiated and a strategy is being defined for 2012 and the following years.

In the context of the E1224 study, markers of treatment response, such as conventional and non-conventional serology, selected pro-thrombotic factors and Apolipoprotein A1, will be assessed.

Additional activities were initiated in 2011 in collaboration with the University Hospitals of Geneva (Switzerland) and McGill University in Montreal (Canada) to evaluate proteomic signatures and identify potential new markers. The clinical samples collected during the TRAENA (Tratamiento en Adultos) trial will be tested by PCR for the presence of T. cruzi DNA.

In addition, funding from the Wellcome Trust was obtained in 2011 for a study on macaques to determine whether blood PCR assays can differentiate between parasitological cure and treatment failure. The study is due to start at the beginning of 2012.

Finally, DNDi is part of a new network of investigators (NHEPACHA) created for the long-term evaluation of potential biomarkers.
Paediatric dosage form of benznidazole

2011 OBJECTIVES:

→ Submit registration dossier for paediatric dosage form of benznidazole
→ Begin a population pharmacokinetic study in Argentina

Treatment of Chagas disease has always focused on paediatric patient populations, but initially, treatment was recommended only for acute and congenital cases (including newborns diagnosed at birth). Based on recent evidence, treatment recommendations were extended to children with the early chronic indeterminate form of Chagas disease up to 12-14 years of age. In 2002, the second report of the WHO Expert Committee on Etiological Treatment in the Chronic Phase recommended that all individuals with positive serology for Chagas disease be treated with specific drugs.

Despite these recommendations, adequate available treatment options for children have been lacking.

Benznidazole, a nitroimidazole introduced by Roche in 1971 and licensed to Brazil’s Pernambuco State pharmaceutical laboratory (Laboratório Farmacêutico do Estado de Pernambuco, LAFEPE), is one of the two products registered for Chagas disease treatment and is included in the WHO Essential Medicines List. Benznidazole was only available as an adult tablet strength of 100 mg. Most treatments for infants and young children were based on the use of tablet fractions, macerated tablets, and other extemporaneous formulations, introducing variation and imprecision in drug dosing.

Policymakers and clinicians long stressed the urgent need for a paediatric drug formulation in Chagas control. Several international meetings (most notably the 2005 Scientific Working Group for Chagas Disease of the Special Programme for Research and Training in Tropical Diseases (WHO-TDR) and the 2007 TDR Working Group on Chagas Disease) highlighted the unmet medical need for new paediatric formulations for Chagas disease.

To respond to this need, in July 2008, DNDi and LAFEPE entered a joint development programme that led to the determination and production of the most appropriate paediatric dosage formulation, strength, and dosing regimen of benznidazole.

The new 12.5 mg tablet is easily dispersible and adapted for babies and children up to two years of age (20 kg body weight). Treatment is designed to use one, two, or three tablets, depending on weight (recommended dose, 5-10 mg/kg bodyweight/day).

The new paediatric dosage form was granted registration from Brazil’s National Health Surveillance Agency (ANVISA) in December 2011.

This new dosage form for children represents real progress for several reasons. Children are at especially high risk of infection, with a majority of them born from infected mothers. It is known that early treatment using benznidazole in the first year of life can eliminate the parasite in more than 90% of infected newborns. Thus, babies infected with Chagas disease will benefit the most from this new paediatric tablet.

Tools to facilitate implementation of and access to the new treatment include a Demand Forecast, a Procurement Guide, and a Tool Box providing training and educational materials for doctors, other health professionals, mothers, and caregivers regarding appropriate use of the treatment. DNDi is also collaborating with LAFEPE to make the drug widely available, notably by working to register the drug in Argentina, Bolivia, Colombia, and Paraguay – priority countries where Chagas disease prevalence is high and treatment is urgently needed.

In addition, a population pharmacokinetic study involving 80 paediatric Chagas disease patients was launched in Argentina to gain more information on pharmacokinetics, treatment safety, and efficacy in paediatric patients. The results of the study will be available by the end of 2012.
Sustained malaria control and elimination requires developing new tools, but also making good use of existing ACTs developed recently.

At the beginning of the new century, malaria was out of control throughout Africa and in many other parts of the world. With endemic countries implementing solid national strategies and increased levels of funding, major changes have occurred. In the past decade, hundreds of thousands of lives have been saved and child mortality rates are estimated to have fallen by 20%.[1] Despite these successes, according to the World Health Organization (WHO), malaria killed an estimated 655,000 people in 2010, 86% of which were children under the age of five.[2] Other estimates are even higher.[3] By all accounts, however, progress is fragile and the path to eliminating malaria is long and strenuous. Malaria remains a leading public health problem in a large number of countries, especially in Africa. Effective strategies that rely on effective tools are essential to continue the fight. The arsenal of strategies currently available for the control of malaria includes vector control, diagnosis, and prompt and effective treatment with effective antimalarials.

In 2001, in response to the increasing failure of Plasmodium falciparum malaria treatment with chloroquine, and to contain and control the spread of drug resistance in malaria-endemic regions, the WHO recommended worldwide abandonment of chloroquine and the use of artemisinin-based combination therapies (ACTs) as first-line treatment for uncomplicated P. falciparum malaria. Artemisinin derivatives available for oral administration include dihydroartemisinin, artesunate, and artemether. Fast-acting artesunate-based compounds are combined with a drug from a different class, such as amodiaquine, lumefantrine, mefloquine, pyronaridine, piperquine, and sulfadoxine/pyrimethamine. The advantages of ACTs are high efficacy, fast onset of action, and very good patient tolerance. They can be taken orally for a shorter duration than artemisinins alone and are safe to be used by pregnant women in their second and third trimester.

Recent evidence of resistance to artemisinin, first reported in 2009 at the Thai-Cambodia border region, today represents one of the major threats to progress achieved so far. In Southeast Asia, ACTs are taking longer and longer to clear the parasite from patients. Expanded, intensified, and better coordinated actions at both the global and local levels are needed in order to prevent the loss of ACTs as effective treatment.[4] These actions include consistent and accurate diagnostic testing, better access to ACTs for confirmed cases, compliance with ACT treatment and removal of artemisinin-based monotherapies as well as of substandard and counterfeit drugs. Expanding access to ACTs has been partially addressed by the AMFm (Affordable Medicines Facility – malaria), but many challenges remain in terms of supply, affordability, and availability of ACTs. Sustained malaria control and elimination requires developing new tools, but also, making good use of existing tools. In particular, making efficacious, easy-to-take ACTs available to the highest number is essential to winning the fight against malaria.

In 2002, the Fixed-dose Artesunate-Based Combination Therapies (FACT) Consortium, created by DNDi, started to develop two fixed-dose artemunate (AS)-based combination therapies (out of the four initially recommended by WHO):

- **ASAQ**, the fixed-dose combination of artesunate and amodiaquine (AQ) developed in partnership with Sanofi, was first registered in 2007 and prequalified by WHO in 2008.
- **ASMQ**, the fixed-dose combination of artesunate and mefloquine (MQ) developed in partnership with Farma-guinhos, was first registered in 2008.

Fixed-dose combinations (FDCs) enable simple treatment regimens, therefore increasing patient compliance.

FDCs enable simple treatment regimens, therefore increasing patient compliance. ASAQ and ASMQ, together with CoArtem®, the FDC of artemether and lumefantrine developed by Novartis, Pyramax®, the FDC of artesunate-pyronaridine and Eurartesim®, the FDC of dihydroartemisinin-piperquine (DHA/PQP), both developed by the Medicines for Malaria Venture (MMV), strengthen the global ACT portfolio of FDCs now available for the treatment of uncomplicated P. falciparum malaria. Together with diagnosis and vector control tools, they represent a key element of the anti-malaria arsenal.

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Malaria

Making available ACTs is essential to fight malaria

**WHAT IS THE IMPACT OF MALARIA?**

The WHO estimates that there were 216 million cases of malaria in 2010, and that 655,000 deaths were attributable to the disease, 86% of which in children under five and 91% in sub-Saharan Africa. A recent study by C. Murray et al., however, estimates that in 2010 malaria was the underlying cause of death for 1.24 million individuals, including 714,000 children younger than five years. [1]

Recent successes and a reduction in the number of cases are reason for optimism, but many people at risk of malaria still lack access to critical treatment and prevention options, including to artemisinin-based combination therapies (ACTs), and malaria control continues to face serious challenges. [1]

**WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?**

Since 2001, the recommended first-line treatment for uncomplicated P. falciparum malaria is ACT. The appearance of resistance to antimalarial drugs has always been a challenge, as illustrated by the widespread resistance to drugs such as chloroquine, which greatly undermined previous efforts in combating malaria. Recent reports of resistance to artemisinin underlines the need for effective combination therapies, as the use of artemisinin oral monotherapies is believed to be an important factor in resistance development. ACTs have been adopted as first-line treatment in 84 countries across the world, but access to these treatments is still limited in many parts of Africa and some parts of Asia, because of accessibility (proximity to health facilities), affordability, availability (presence of the medicine at the service delivery point), acceptability (presence of the medicine at the service delivery point), acceptability, and training of caregivers. Children, the primary victims of malaria worldwide, often do not have access to adequate paediatric formulations of ACTs.

In addition, emerging evidence of artemisinin-resistance development threatens the world with the loss of the most effective treatment for malaria if nothing is done to contain resistance.

**WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?**

Through 2014, DNDi aims at ensuring widespread access to the two ACTs developed within FACT, and to support their proper use to maintain the effectiveness of artemisinin-based therapies as first-line treatment for uncomplicated P. falciparum malaria. This includes facilitating registration in a growing number of countries, supporting policy and practice change, improving quality supply by facilitating technology transfers to second suppliers in Africa (ASAQ) and in Asia (ASMQ), as well as working to decrease drug costs by various mechanisms.

**WHAT ARE THE SYMPTOMS?**

Malaria is an acute febrile illness, the initial symptoms of which can be difficult to recognize. Symptoms of uncomplicated malaria include fever, headache, chills, and vomiting. If treatment is not given within 24 hours, P. falciparum malaria can progress to severe illness, which can lead to death or serious brain damage, especially in children, who are particularly vulnerable due to their lack of immunity to the parasite.

**HOW IS MALARIA TRANSMITTED?**

Malaria is caused by Plasmodium parasites, spread to people through the bite of an infected female anopheline mosquito. Four species of the parasite cause malaria in humans, P. falciparum, P. vivax, P. malariae, and P. ovale. P. vivax and P. falciparum are the most common, with P. falciparum the most deadly.

Approximately half of the world’s population is at risk of malaria. Most malaria cases and deaths occur in sub-Saharan Africa, but Asia, Latin America, and to a lesser extent the Middle East and parts of Europe are also affected. In 2010, 99 countries and territories had ongoing malaria transmission.

**ASMQ:** fixed-dose combination of artemunate and amodiaquine

**ASAQ:** fixed-dose combination of artemunate and amodiaquine

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**ASMQ FDC**

**2011 OBJECTIVES:**

→ Technology transfer and registration:  
- Support activities for pre-qualification by WHO and PAHO  
- Obtain registration authorization for ASMQ FDC in India and Southeast Asia  
- Reduce the cost of MQ to decrease the price of ASMQ FDC

→ Clinical studies  
- Progress the multi-centre comparative study conducted in three African countries

**Partners:**  
Farmanguinhós, Brazil;  
Cipla, India;  
Shoklo Malaria Research Unit, Thailand;  
Universiti Sains Malaysia;  
Oxford University, UK;  
WHO-TDR; Indian Council of Medical Research (ICMR), India;  
Centre National de Recherche Vaudois (CHUV), Switzerland;  
WHO-TDR; Indian Council of Medical Research, Tanzania;  
Kenya Medical Research Institute (KEMRI), Kenya;  
Centre National de Recherche et de Formation sur le Paludisme (CNRFP), Burkina Faso;  
Epicentre, France;  
Institute for Malaria Venture (MMV), Switzerland

**Management:**  
Senior Pharma Advisor & Product Manager: Jean-René Kiechel;  
Clinical Manager: Gwenaëlle Carn;  
Medical Coordinator FACT Project: Graciela Diap

**Project start:** January 2002

**ASMQ FDC**

**Used in the field for many years, the combination of artesunate (AS) and mefloquine (MQ) is one of the five ACTs recommended by WHO for the treatment of uncomplicated P. falciparum malaria, preferably as a fixed-dose combination.**

The ASMQ fixed-dose combination treatment (ASMQ FDC) was developed by the FACT consortium created by DNDi and TDR in 2002. Within FACT, the Brazilian government-owned pharmaceutical company, Farmanguinhós/Fiocruz, was the first manufacturer of ASMQ FDC. ASMQ FDC was registered in Brazil in March 2008 and adopted as treatment policy by the Ministry of Health, following excellent outcomes of a major intervention study with ASMQ in the Amazon Basin, sponsored by the National Malaria Control Programme (NMCP). ASMQ FDC tablets (25/55 mg and 100/220 mg) offer an easy-to-use treatment regimen with one single daily dose of one or two tablets to be taken over three days. Following an agreement signed in 2008, the technology transfer between Farmanguinhós and the Indian generic pharmaceutical company Cipla was successfully completed in 2010 and will facilitate the availability of ASMQ throughout Asia and other parts of the world.

ASMQ was granted registration in India in November 2011, a crucial step towards further registration in Asian countries. A full dossier was submitted by DNDi and partners for WHO pre-qualification in 2010 and is currently under final assessment for approval in 2012. ASMQ FDC is of particular relevance for Asia: mefloquine and artesunate therapy has been evaluated since 1991 in camps for displaced persons located along the Thai-Myanmar border. Since then, clinical data on the use of AS+MQ from almost 8,000 patients in Southeast Asia and more than 2,000 in the Western Pacific have been made available in the medical literature. The strategy of artesinin-based combination therapy with mefloquine was developed and adopted in 1994 in Thailand, where treatment of uncomplicated malaria has been modified several times during the past 30 years to counter the rapid emergence and spread of drug resistance. The deployment of the combination has led to a reduction in incidence of P. falciparum malaria and has been associated with a halt of mefloquine resistance. Since the confirmation of resistance of P. falciparum to artesininins at the Cambodia-Thailand border in 2009, containment activities to limit the spread of artesinin-resistant parasites have been ongoing. One of the most urgent and challenging priorities in the Global Plan for Artemisinin Resistance Containment (GPARC) in Cambodia and Thailand is to replace the use of artesinin monotherapy with an FDC, such as ASMQ.

Additional clinical studies using ASMQ FDC are ongoing and will provide information of ASMQ FDC use in children, adults, and pregnant women in Africa. According to WHO recommendation, AS+MQ could be considered for use in some countries in Africa. To provide key information on the efficacy and tolerability of ASMQ FDC, DNDi is sponsoring a multicentre Phase IV study in Tanzania, Burkina Faso, and Kenya to assess efficacy, safety, and pharmacokinetics of ASMQ FDC compared to artemether-lumefantrine in children below the age of 5 with uncomplicated P. falciparum malaria. Recruitment of patients is ongoing and expected to be completed by the end of 2012. Effectiveness data on ASMQ in field conditions are planned to be collected in India in a large implementation project conducted with partners.

ASQA Winthrop

2011 OBJECTIVES:
→ Diversify ASQA suppliers by transferring technology to a partner in Africa
→ Facilitate implementation of ACT FDCs in general and specifically ASQA, in all countries where it could benefit patients and abide local practices

ASQA Winthrop, the fixed-dose combination (FDC) of artesunate (AS) and amodiaquine (AQ), was the first treatment made available by DNDi in 2007 through an innovative partnership with Sanofi. ASQA Winthrop was pre-qualified by WHO in October 2008 and included on the WHO Essential Medicines List (EML) in 2011. By the end of 2011, over 120 million treatments had been distributed in 30 African countries. In addition, more than 20 million treatments of ASQA FDC have been ordered for the private sector in seven countries in Africa within the Affordable Medicines Facility – malaria (AMFm).

In parallel, DNDi, together with partners, is working on the transfer of technology to a second manufacturer in Africa, Zenufa, based in Tanzania. A project team consisting of members of participant organizations and the industrial partner has been set up for the duration of the transfer up to pre-qualification by WHO.

Following the antimalarial market assessments conducted by DNDi in Burundi and Sierra Leone in 2009, DNDi and its partner Komfo Anokye Teaching Hospital, Kumasi (KATH) performed outlet surveys in Ghana as part of the independent evaluation of the AMFm Phase I. The results, included in the AMFm Phase I Independent Evaluation Multi-Country Baseline Report, are publicly available.

(1) http://www.theglobalfund.org/en/amfm/
Helminths are parasitic worms and the most common infectious agents of humans in developing countries. A sub-group of helminths, nematodes, cause filarial diseases, which are transmitted by insect vectors to humans. These diseases, namely Onchocerciasis (or river blindness), lymphatic filariasis (LF, or elephantiasis) and Loiasis (Loa loa, or African eye-worm) affect millions across the world, particularly in Africa.

Even though they do not kill, filarial diseases cause life-long disabilities, such as blindness (Onchocerciasis) and swelling of the limbs (LF), causing great suffering and social stigmatization of those infected.

Programmes to control and eliminate filarial diseases have been in place for over twenty years, such as the African Programme for Onchocerciasis Control (APOC) and the Global Programme to Eliminate Lymphatic Filariasis (GPELF).

These programmes rely on mass drug administration (MDA) of anti-helminthic drugs that are safe and donated: ivermectin for Onchocerciasis, diethylcarbamazine (DEC), as well as albendazole (ALB) in combination with ivermectin or DEC for LF. These drugs are effective because they kill the juvenile forms of the worms, the microfilariae, which cause most of the symptoms. However, they need to be administered repeatedly at regular intervals until adult forms (macrofilariae) die naturally and there are no more microfilariae in the body.

While these programmes have made enormous progress, they are not adapted to areas of Loiasis co-endemicity. Indeed, even though Loiasis is not life-threatening and is usually not treated, infected patients often have a high burden of microfilariae, and the sudden death of these juvenile forms causes a serious adverse reaction, known as Loa loa encephalopathy, which can be fatal or leave long-term sequelae.1

Inclusion of patients in MDA programmes is therefore not recommended in regions of high Loa loa burden. There is an urgent need to develop a safe and highly efficacious macrofilaricide, with little or no effect on microfilariae, as an effective tool for the treatment of Onchocerciasis and LF in regions of Loiasis co-endemicity.

### Ideal Target Product Profile for Helminth Infections

- **A new treatment for adults and children**
- **Macrofilaricide**: Efficacious against the adult form of worms
- **Oral**, short-course treatment
- **No side-effects** following death of worms
- **Safe** in pregnant and lactating women
- **Affordable**
- **Adapted to tropical climates** (minimum three-year shelf-life)
Developing new tools to fill the gaps in existing treatment regimens

WHAT IS THE IMPACT OF HELMINTH INFECTIONS?

Helmint infections are caused by two sub-groups of helminths, nematodes and flatworms. Nematodes (also known as roundworms) include the major intestinal worms (also known as soil-transmitted helminths) and the filarial worms that cause Onchocerciasis, lymphatic filariasis (LF), and Loiasis.

Onchocerciasis (river blindness): A total of 18 million people are affected worldwide, in 36 countries in Africa, as well as in Guatemala, southern Mexico, some areas of Venezuela, small areas in Brazil, Colombia, and Ecuador, and in the Arabian Peninsula. (1)

Lymphatic filariasis (LF, or elephantiasis): More than 1.3 billion people in 72 countries worldwide are threatened by LF, commonly known as elephantiasis. Over 120 million people are currently infected, with about 40 million disfigured and incapacitated by the disease. (2)

Loiasis (African eye-worm): The mapping of Loiasis endemic areas in affected countries is still ongoing, but it is estimated that in Onchocerciasis-endemic communities, over one-fifth of the population also has Loiasis. (3) The disease burden of Loiasis is not significant enough to merit an elimination programme, but its co-endemicity with Onchocerciasis in certain areas of West and Central Africa and the fact that mass ivermectin treatment of Onchocerciasis can lead to serious adverse events in patients who have high Loa loa microfilarial densities, impedes the implementation of Onchocerciasis elimination programmes (see below).

HOW ARE FILARIAL DISEASES TRANSMITTED?

Filarial diseases are caused by parasitic worms transmitted by insect vectors to humans.

Onchocerciasis is a parasitic disease caused by Onchocerca volvulus, a thin parasitic worm that can live for up to 14 years in the human body. The disease is transmitted from one person to another through the bite of a blackfly. The transmitted worm larvae develop into adult worms and settle into fibrous nodules in the human body close to the surface of the skin or near the joints. Lymphatic filariasis is caused by nematodes of the Filariodidea family, mainly Wuchereria bancrofti, transmitted to humans through mosquitoes. When a mosquito with infective stage larvae bites a person, the parasites are deposited on the person’s skin from where they enter the body. The larvae then migrate to the lymphatic vessels where they develop into adult worms in the human lymphatic system.

Loiasis is caused by the parasitic worm Loa loa. The adult worms migrate throughout the body just under the skin and sometimes cross into the subconjunctival tissue of the eye where they can easily be seen. It is transmitted through the repeated bites of deerflies (also known as mango flies or mangrove flies) of the genus Chrysops.

WHAT ARE THE SYMPTOMS?

Onchocerciasis is the world’s second leading infectious cause of blindness and is often referred to as ‘river blindness’. It also causes intense itching, skin discoloration, rashes, and eye disease. Lymphatic filariasis can become chronic, and when it does, it leads to lymphoedema (tissue swelling) or elephantiasis (skin/tissue thickening) of limbs and hydrocele testes (fluid accumulation). Such body deformities lead to social stigma, as well as financial hardship from loss of income and increased medical expenses. The socio-economic burdens of isolation and poverty are immense.

Loiasis leads to recurrent episodes of itchy swellings and to eye-worm, the visible migration of the adult worm across the surface of the eye, which resolves after a few days.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

Current treatments for Onchocerciasis and LF are based on mass drug administration (MDA) of anti-parasitic drugs through programmes directed by the WHO. Drugs used by MDA programmes include ivermectin for onchocerciasis, DEC and ALB in combination or DEC alone for LF. These drugs remove existing microfilariae from skin, thus preventing vector borne transmission, and provide long-term sterilization of adult worms, preventing re-population of the patient with microfilariae for six months or longer. However, in patients co-infected with Loa loa, the sudden death of large numbers of microfilariae can lead to serious adverse events, such as encephalopathy, which can be fatal or leave patients with severe sequelae. Patients infected only with Loa loa are not usually treated.

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?

DNDi’s short-term strategy is to reformulate flubendazole, an anti-helminthic drug with proven efficacy against gastrointestinal infections of soil-transmitted helminths in animals and humans, into a safe, highly efficacious, and field-adapted macrofilaricidal drug candidate.

As a medium-term strategy, DNDi will assess additional opportunities through an active screening programme, with the goal of selecting one or two candidates emanating from the animal health industry or leads in development in pharmaceutical, biotechnology, and academic laboratories.

By 2015, DNDi aims to deliver from its helminth infections portfolio:

- a new drug candidate available for clinical testing that could be used by mass drug administration programmes for filarial infections and/or case management of Onchocerciasis and lymphatic filariasis, especially in Loa loa co-endemic regions.

(1) http://www.who.int/water_sanitation_health/diseases/oncho/en/  
(2) http://www.who.int/mediacentre/factsheets/fs102/en/  
**Flubendazole**

**2011 OBJECTIVE:**

→ Determine potential of flubendazole as a pre-clinical candidate

This project aims to develop flubendazole as a safe, highly efficacious, and field-usable macrofilaricidal drug candidate for Onchocerciasis-Loa loa co-infections. If flubendazole meets the criteria specified for pre-clinical development, the project will also support the necessary studies required to draft an Investigational Medicinal Product Dossier (IMPD) followed by submission and subsequent approval of the IMPD.

In 2011, activities to extensively characterize the flubendazole API (active pharmaceutical ingredient) were conducted and four different formulation strategies to enhance its bioavailability were tested. The amorphous solid dispersion (ASD) formulation achieved sustained plasma levels of flubendazole and will be used for pre-clinical development. The safety profile of flubendazole is not yet defined, in particular with respect to genotoxicity. However, embryotoxicity has been observed at concentrations above 0.25 µg/mL and such levels are achieved with the ASD formulation in vivo. Therefore, embryotoxicity is likely to be observed with flubendazole, which could be a limiting factor for its development as a mass drug administration programme. It will be essential to confirm these results in in vivo reproductive toxicology studies. In 2012, DNDi will conduct IMPD-enabling safety studies, develop an oral formulation suitable for human clinical use and conduct more extensive PK/PD studies to guide/refine the selection of human therapeutic doses.
Paediatric HIV: A neglected disease?

In the past years, good progress has been made in the rolling out of programmes to prevent new HIV infections in children, greatly reducing the global number of AIDS-related deaths. Despite these successes, in 2010, 390,000 children less than 15 years of age were newly infected with HIV and 250,000 children died from AIDS-related illnesses. Over three-quarters of HIV-infected children still do not have access to treatment.

Most children acquire HIV through perinatal transmission during foetal life, birth, or whilst breastfeeding. Whereas in high-income countries, HIV transmission in young children has largely been eliminated due to effective prevention of mother-to-child transmission (PMTCT) interventions, in lower- to middle-income countries, the majority of pregnant women still do not have access to diagnosis or to timely, efficient drugs.\(^1\)

HIV-infected infants frequently develop illness within the first year of their life; approximately one-third of them die before their first birthday, and about half die before they are two years old.\(^2\) Therefore, while the best way of preventing deaths in young children remains prevention of HIV transmission in the first place, provision of adequate treatment to those who do become infected is vital.

In the past years, access to antiretroviral therapy (ART) has been rapidly scaled-up, resulting in remarkable progress in the global fight against HIV. However, provision of ART to HIV-infected children, especially to the very young, has been less successful, notably because of the lack of appropriate tools to diagnose HIV early in the child’s life, and of easy-to-use, safe and stable paediatric ART formulations: in 2010, only 28% of infants had been tested for HIV in the first two months after birth in low- and middle-income countries, and only 23% of children in need of treatment had access to it, compared to 51% of adults.\(^3\) Many of the drugs that are available for the treatment of adults have not been tested and approved for use in children, limiting the number of therapeutic options for caregivers, especially in cases of treatment failure or adverse reactions. Some of the currently available paediatric HIV formulations have serious limitations for use in resource-poor settings, such as liquid formulations, which are difficult to administer, carry a high risk of dosing errors, have a poorly-tolerated taste, and display significant toxicity, in addition to severe logistical constraints linked to short shelf-life, cold chain requirement, large volumes, and high price. In addition, many children need to be treated for both HIV and tuberculosis (TB) and there are significant negative drug-drug interactions between anti-TB drugs and anti-HIV drugs. HIV-infected children co-infected with TB have particularly poor prognosis.\(^6\) Improved first-line therapies for children are urgently needed.

Available paediatric HIV formulations have serious limitations for use in resource-poor settings.

 IDEAL TARGET PRODUCT PROFILE FOR PAEDIATRIC HIV

A first-line, all-in-one antiretroviral regimen for HIV-infected children:

- Safe and efficacious
- Adapted formulation suitable for infants
- Easy to use: once-daily dosing preferred
- Palatable
- Adapted to tropical climates (heat stable)

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Millions of children, most of them in sub-Saharan Africa, are in need of an adapted treatment

WHAT IS THE IMPACT OF PAEDIATRIC HIV?

At the end of 2010, an estimated 3.4 million children below the age of 15 were living with HIV, more than 90% of which in sub-Saharan Africa. That same year, 2.02 million children were estimated to be in need of antiretroviral therapy.

An estimated 250,000 children less than 15 years died of AIDS-related illness in 2010.

HOW IS PAEDIATRIC HIV TRANSMITTED?

In children, HIV transmission can occur during pregnancy through the placenta, during delivery through exposure to body fluids and cervical secretions, and through breastfeeding. In the absence of antiretroviral preventive treatment, 30 to 40% of children born to an HIV-infected mother acquire infection themselves, but with antiretroviral prophylaxis throughout pregnancy, delivery, and breastfeeding, transmission can be decreased down to a few per cent.

WHAT ARE THE SYMPTOMS?

HIV is often difficult to diagnose in children and infants: indeed, symptoms rarely appear in the first few months, and when they do, they are often un-specific, such as weight loss and stunted growth. By the time children become ill, it is often too late and half die before their second birthday.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

Current WHO guidelines recommend early diagnosis and immediate treatment of HIV-positive infants and children under the age of two. The combination of a boosted protease inhibitor [PI] with two nucleoside reverse transcriptase inhibitors [NRTIs] is considered by many experts as the most effective first-line therapy, particularly in the case of infants and children with high viral loads who were previously exposed to antiretrovirals [ARVs] in the context of prevention of mother to child transmission [PMTCT].

However, this recommended combination therapy is not being widely used. According to a WHO survey performed in 45 countries, only 12.2% of children with HIV were receiving a first-line treatment containing a PI (mostly lopinavir/ritonavir), 97% of whom were in South Africa. The current PI-based regimen requires use of multiple paediatric formulations. The only available PI for young children, lopinavir/ritonavir [LPV/r] does not come in a child-friendly formulation: the oral solution formulation is not palatable, contains 42% alcohol and is not adapted to resource-poor settings as it requires refrigeration, has a short shelf-life when exposed to heat, and poses logistical constraints due to its large volume.

In many areas, HIV-positive infants and children are co-infected with tuberculosis [TB]. Drug-drug interactions between PIs in particular and rifampicin, one of the drugs used to treat TB, greatly diminish the blood levels of PIs and hinder the efficacy of the treatment. In order to counteract this interaction, additional ritonavir needs to be added to the standard proportion of lopinavir and ritonavir [LPV/r]. This is called ‘super-boosting’. In order to do that, an infant-friendly formulation of ritonavir also needs to be developed. Currently available ritonavir formulation suffers the same limitations as LPV/r, with regard to taste, high alcohol content, short shelf-life (six months) and limited availability.

WHAT IS DNDI DOING TO ADDRESS UNMET TREATMENT NEEDS?

In 2010, DNDi was called on by various organizations, including Médecins Sans Frontières and the international drug-purchase organization UNITAID, to apply its expertise to the development of paediatric HIV drugs. DNDi’s position was published as a Perspective in the New England Journal of Medicine in August 2011.

DNDi is pursuing two objectives to address the needs of HIV-infected children:

- Develop a first-line, all-in-one formulation containing a boosted PI (lopinavir/ritonavir) and two NRTIs, suitable for infants and young children
- Develop a stand-alone ritonavir booster formulation that can be added to any PI-based paediatric ARV regimen and can be used to counteract the negative drug-drug interactions between PIs and rifampicin-containing TB treatments.

In order to address these objectives, DNDi has set up exploratory activities to investigate a number of options in terms of formulations of the PIs, ritonavir-boosted lopinavir [LPV/r]. These include sprinkles, pro-drugs, nanoparticles, and nanodispersion. As part of its formulation work, DNDi will explore the feasibility of LPV/r sprinkles, in a sachet in association with NRTIs.

In order to address the needs of HIV-TB co-infected children, DNDi is committed to developing a formulation of ritonavir for super-boosting LPV/r at a 1:1 ratio. This strategy will be further investigated during a clinical study involving sites in South Africa.

Finally, DNDi is setting-up an HIV platform that will facilitate its clinical research programme in the longer term.

By 2015, DNDi aims to deliver from its paediatric HIV portfolio:

- One new all-in-one solid paediatric formulation
- One new treatment for HIV-TB co-infected children based on superboosting

(1) Global HIV/AIDS response - Epidemic update and health sector progress towards Universal Access: Progress report 2011. UNAIDS, Geneva, 2011 – the difference between the number of children living with HIV and those in need of antiretroviral therapy is based on eligibility criteria for this kind of treatment (e.g. CD4 count).

**R&D expenditure by disease**

EUR 20.1 million in 2011 for R&D and a balanced kinetoplastid portfolio

<table>
<thead>
<tr>
<th></th>
<th>2010: EUR 19.8 million</th>
<th>2011: EUR 20.1 million</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leishmaniasis</td>
<td>30%</td>
<td>28%</td>
</tr>
<tr>
<td>Chagas disease</td>
<td>43%</td>
<td>33%</td>
</tr>
<tr>
<td>Malaria</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>Other Neglected Diseases</td>
<td>15%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Overall R&D expenditure remains stable between 2010 and 2011 (EUR 20.1 million). With two new treatments available and at least one product in clinical stage and one pre-clinical candidate for each of the three kinetoplastid diseases (Chagas, HAT, and VL), the breakdown of R&D expenditure by disease shows a balanced portfolio.

**Leishmaniasis:** The level of activities remains high with ten projects as of December 2011. Overall expenditure decreased due to slower patient recruitment in clinical trials and additional time required for preparation of the implementation study in Asia.

**Chagas disease:** Expenditure increased in 2011 by 62% with the registration of the paediatric dosage form of benznidazole (+ EUR 0.2 M), the launch of the Azole E1224 Phase II study (two sites in Bolivia, + EUR 0.6 M), the start of a test of cure project - PCR and biomarkers (+ EUR 0.2 M), and completion of the Chagas Lead Optimization Consortium development (+ EUR 0.7 M).

**Malaria:** In accordance with the Business Plan, expenditure continues to decrease (- EUR 200 K in 2011). The main activities were the Phase IV clinical trial in Burkina Faso, Kenya, and Tanzania (+ EUR 100 K) and technology transfer to Zenufa (Tanzania) for the production of ASAQ (+ EUR 150 K).

**Portfolio expansion:** Pre-clinical and screening activities started for the helminth infections project (flubendazole, macrofilaricide: + EUR 0.2 M) and in-kind contributions brought expenditures down in 2011. The paediatric HIV project (+ EUR 0.3 M) started pre-clinical activities following the TPP definition and the set-up of a network of clinical partners.

**R&D expenditure by R&D stage**

Seeking efficiency in building a robust portfolio

![R&D expenditure by R&D stage](chart)

**Discovery:** Lead optimization programmes moved from 3 consortia (1 per disease) to an integrated model with 2 consortia for the 3 kinetoplastid diseases. Each consortium will implement 2 parallel programmes. A new partner was selected in China to work on chemistry, DMPK, and parasitology. This rationalization saves EUR 0.8 M in 2011 as compared to 2010.

**Pre-clinical:** Expenditure increased between 2010 and 2011 (+ EUR 1.4 M), due to progression of 4 drug candidates: completion of pre-clinical studies of Oxaborole SCYX-7158 (+ EUR 0.4 M) for HAT; start of pre-clinical testing for VL-2098 (+ EUR 0.4 M) for VL; pre-clinical tests for flubendazole (+ EUR 0.2 M) for helminth infections; studies on the fenamitol series (+ EUR 0.1 M) for Chagas. Activities began on new formulations and prodrug development for paediatric HIV (+ EUR 0.3 M).

**Clinical:** Expenditure is stable compared to 2010, with 6 clinical studies implemented in 2011: Patient recruitment started for Azole E1224 for Chagas disease (+ EUR 0.6 M); fexinidazole for HAT in transition phase before entering Phase II (- EUR 0.6 M); recruitment continued for new VL treatments (Africa, Bangladesh) but was slower than expected due to protocol criteria and implementation of new sites (- EUR 0.6 M).

**Implementation:** Expenditure is stable in 2011 as compared to 2010, whereas two new treatments were delivered: the paediatric dosage form of benznidazole was registered in December – therefore no implementation costs in 2011 – and VL Asia treatments, which required additional time for preparing the implementation study (+ EUR 0.3 M). Expenditure for malaria projects is decreasing (- EUR 0.3 M) as well as the NECT field study (- EUR 0.2 M) as both projects are entering the follow-up phase.

**In-kind contributions**

Leveraging EUR 5 million for R&D from partners

In-kind contributions are an integral part of the DNDi business model. To present a comprehensive view of activities, DNDi values the in-kind contribution of its partners (private companies, academic groups, individuals). Monitoring in order to more accurately value such contributions and thus obtain more accurate figures is a continually improving process. In six years, in-kind contributions have increased six-fold, reflecting DNDi’s investment in consolidating partnerships.

The total of in-kind contributions in 2011 reached 20% of total operational expenses.

The major increase in 2011 in-kind contributions from those of 2010 (+100%) is due to pharmaceutical development of Azoles E1224 and fexinidazole with industrial partners.