



**DNDi's objective** is to deliver 11 to 13 new treatments by 2018 and to maintain a robust pipeline to support long-term objectives.



## Beginning with the end in mind

Since its inception, DNDi has delivered six new treatments and built a robust pipeline with 12 new chemical entities in pre-clinical and clinical stages. DNDi's portfolio matured in 2012, with six treatments now registered or available to patients, promising compounds progressing through the clinical pipeline, and new chemical libraries or compounds being screened.

DNDi's R&D strategy is defined by patients' needs and relies on the combination of long-term goals, through the development of new chemical entities (NCEs) to support sustainable control or elimination of neglected diseases, with short-term goals based on the optimization of existing drugs, to address more immediate and urgent 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 product development partnerships (PDPs), to access new chemical libraries or compounds using cutting-edge technologies, such as high-throughput screening (imaging technology-based high-content screening assays against intracellular *Leishmania* and *T. cruzi*), as well as developing strong lead optimization consortia. DNDi also builds and consolidates capacity for clinical research in the field, by supporting regional platforms for each kinetoplastid disease. So far, DNDi has delivered six new treatments for four diseases: malaria, sleeping sickness, visceral leishmaniasis, and Chagas disease.

The key features of the new drugs/treatments DNDi seeks to develop are at the centre of the organization's target disease strategies, which define the patient need and desired outcome of each product, taking into account the current research landscape as well as the health systems in endemic countries. Because drug development can be a long process, it is essential to plan from the outset with the end in sight, i.e. agreeing on what the key features and attributes of the intended

end-product are. These are summarized into Target Product Profiles (TPPs), taking the target population in need as the starting point, then defining the ideal technical attributes of efficacy, safety, and 'user-friendliness' (i.e. duration, mode of administration, storing conditions), as well as cost. TPPs are developed with input from disease experts, representatives of Ministries of Health and National Control Programmes in endemic countries, WHO representatives, leading clinicians and researchers, as well as health workers, all of whom deal with the realities of the diseases in the field. DNDi's target diseases call for clear TPPs that are based on epidemiological data and cater for the needs of specific populations – the poorest of the poor, both adults and children.

### 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

With the right dose, the right formulation, the right taste, no refrigeration required, a well-designed product and adapted packaging, DNDi and partners aim to ensure the best treatment is delivered to those in need in all endemic countries at an affordable price; by engaging and seeking early advice from regulatory authorities and the WHO, regulatory and field adoption can be greatly facilitated. This implies looking for treatments that can be delivered at the village or primary healthcare level to avoid the long distances that many patients must travel, as well as the time and money required for patients and family members to reach and stay at district hospitals (or secondary healthcare level). DNDi's TPPs are publicly available on the web ([www.dndi.org](http://www.dndi.org)).

● **Human African trypanosomiasis (HAT):** In 2012, fexinidazole entered a pivotal Phase II/III study in the Democratic Republic of the Congo and the Central African Republic. If successful, fexinidazole could become the first oral-only treatment for sleeping sickness patients. SCYX-7158, also an oral drug candidate, entered first-in-human studies in healthy volunteers. Promising backups are in lead optimization and pre-clinical phases. NECT is now on the national essential medicines lists of 12 countries across Africa and has almost entirely replaced melarsoprol and eflornithine monotherapy as first-line treatment for second stage *T. b. gambiense* sleeping sickness. It is now included on the WHO Essential Medicines List for children.<sup>(1)</sup>

● **Leishmaniasis:** Recruitment for the LEAP 0208 study in East Africa, which aims to evaluate the safety and efficacy of miltefosine alone as well as combination treatments for VL ended in March 2012 – results will be available at the beginning of 2013 and will inform the decision to evaluate one of the combinations in a Phase III trial. SSG&PM is available and implemented in Sudan and Uganda. In 2012, it was added to Kenya's national VL guidelines. New drug combination therapies are available for Asia. 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, registered in Brazil at the end of 2011, is now included on the WHO Essential Medicines List for children.<sup>(1)</sup> Recruitment for the E1224 Phase II clinical trial concluded in June 2012 and the first results will be available in the second half of 2013. In addition, in 2012, DNDi received funding for the first-ever large-scale study involving treatment of non-human primates (macaques) naturally infected in their outdoor living environment with *Trypanosoma cruzi* with the aim of identifying new biological markers for the evaluation of treatment efficacy in Chagas disease.

● **Malaria:** By the end of 2012, more than 180 million ASAQ treatments had been distributed in 30 African countries. In addition, more than 20 million treatments had been ordered for the private sector in seven countries in Africa within the Affordable Medicines Facility – malaria (AMFm). ASMQ received pre-qualification from the WHO and was registered in Malaysia and Myanmar. It is now included on the WHO Essential Medicines Lists for adults and children.<sup>(1)</sup>

In 2011, DNDi's portfolio was extended to paediatric HIV and filarial diseases:

● **Paediatric HIV:** The added arm to the CHAPAS-2 trial (sponsored by MRC), which aimed to clinically assess the protease inhibitor lopinavir/ritonavir in the existing sprinkle (minitab) formulation in children between 1-4 years of age (additional CHAPAS-2 cohort), was concluded in 2012.

● **Filarial diseases:** Work was undertaken to develop a pre-clinical formulation of flubendazole, a potential macrofilaricide that allows oral absorption, and non-clinical development progressed, notably studies required to file an Investigational New Drug (IND) application.

#### Target Product Profile (TPP)

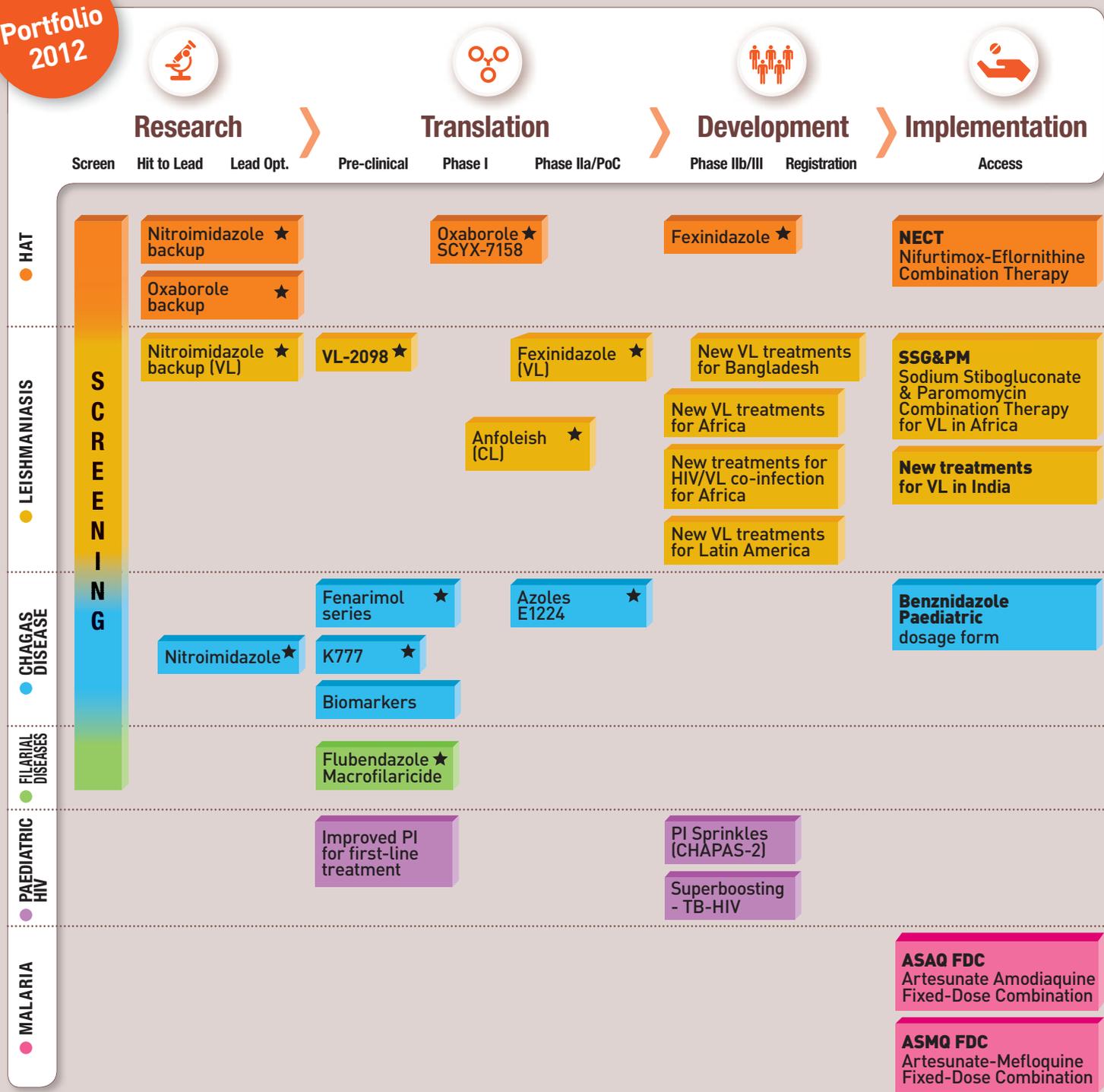
- **Indications:** Which disease(s)?
- **Population:** Which type of patients and where?
- **Clinical Efficacy:** Does it treat the infection effectively?
- **Safety and Tolerability:** What level of acceptability for adverse events?
- **Stability:** How long is the shelf-life of the drug(s), and what are the 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 the target population?

(1) As of July 2013: [www.who.int/medicines/EMP\\_Website\\_notice\\_EML\\_July2013.pdf](http://www.who.int/medicines/EMP_Website_notice_EML_July2013.pdf)



# 6 new treatments and 12 new chemical entities in the pipeline

Portfolio 2012



★ New Chemical Entity (NCE)  
Fexinidazole (for HAT and VL) = 1 NCE

## RESEARCH



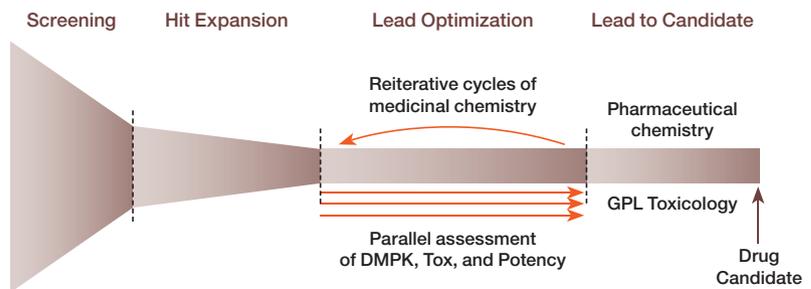
# Increasing efforts to discover new drugs

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 order to ensure an uninterrupted supply of quality active series to its lead optimization programmes, DNDi screens libraries from its pharmaceutical, biotech, academic and PDP partners using defined selection criteria, then reviews/prioritizes series according to the probability of success. At the same time, DNDi secures back-up series to address the attrition rate in optimization programmes.

For 2012, DNDi refocused its early discovery and LO efforts on the discovery and development of novel active lead series for leishmaniasis. This was achieved through a significant increase in the high throughput screening capacity against *Leishmania* parasites in collaboration with the University of Dundee, as well as prioritizing active hit

series to enter the Hit-to-Lead and LO phases in order to bring additional pre-clinical candidates to the DNDi discovery pipeline.

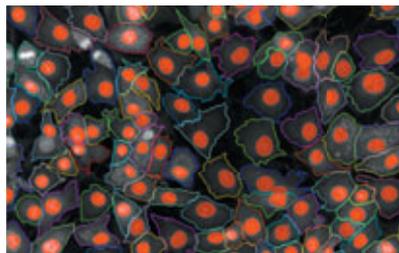
DNDi's discovery strategy relies on partnerships with public (e.g. universities and academia) and private partners (pharmaceutical and biotechnology companies); lead optimization activities are carried out by two consortia that work across all three kinetoplastid diseases, enabling cross-talk between diseases for each compound series being investigated.



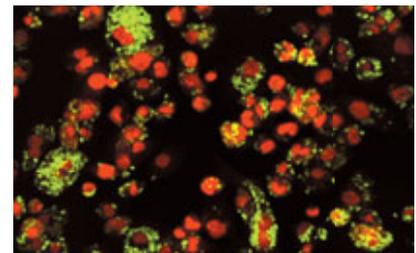
In 2012,  
DNDi screened over  
**150,000**  
compounds in more  
than

**420,000**  
screening assays

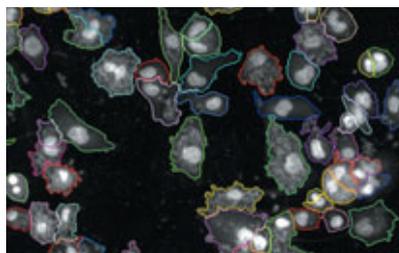
**Over 20**  
active series have been  
advanced to the Hit-to Lead  
and Lead Optimization  
phases for the three  
kinetoplastid diseases with  
priority given to  
visceral leishmaniasis.



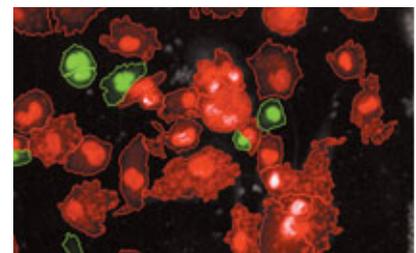
3T3 cells infected with *T. cruzi* (DRAQ5 staining, 20x Objective) Cytoplasm selection



THP1 cells infected with *L. donovani*-eGFP (DAPI staining, 20x Objective)



THP1 cells infected with *L. donovani*-eGFP (DAPI staining, 20x Objective) Cytoplasm selection



THP1 cells infected with *L. donovani*-eGFP (DAPI staining, 20x Objective) Infected cells



## SCREENING

### Main partners:

AbbVie (formerly Abbott), USA; Actelion, Switzerland; Anacor, USA; Astellas, Japan; AstraZeneca, Sweden; Bayer, Germany; Bristol-Myers Squibb, USA; Celgene, USA; E.I. du Pont de Nemours, USA; Eisai Co., Ltd, Japan; Genomics Institute of the Novartis Research Foundation, USA; GlaxoSmithKline, Tres Cantos, Spain; Institute of Medical Microbiology, Immunology, and Parasitology, Hospital University of Bonn, Germany; Medicines for Malaria Venture, Switzerland; Merck (MSD), USA; Northwick Park Institute for Medical Research, UK; Novartis Institute for Tropical Diseases, Singapore; Pfizer, USA; Pfizer Animal Health, USA; Sanofi, France; Sigma-Tau, Italy; WHO-TDR; TB Alliance, USA; Institut Pasteur Korea (IPK), South Korea; Drug Discovery Unit (DDU) at the University of Dundee, UK; Swiss Tropical and Public Health Institute (Swiss TPH), Switzerland; Laboratory of Microbiology, Parasitology, and Hygiene (LMPH), University of Antwerp, Belgium; and London School of Hygiene & Tropical Medicine (LSHTM), UK; TI Pharma, The Netherlands

### Leadership:

Discovery and Pre-Clinical Director: Robert Don;  
Discovery Manager: Jean-Robert loiset

### High-throughput screening

High-throughput screening (HTS) of large libraries for *Leishmania* (IPK and DDU) and *T. cruzi* (IPK) have been developed and used to identify novel hit compounds. Adequate screening capacity is a key element of DNDi's discovery strategy, as it enables the screening of large libraries/series of compounds and therefore a quicker identification of hits/leads for optimization.

### 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 DNDi's target diseases. Illustrating this approach is the 2011 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. In addition, DNDi is evaluating access to various libraries based on chemical diversity with its pharmaceutical partners, including, among others, Sanofi and GSK.

### 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 originating from collaborating pharmaceutical and biotech companies, promising compound classes are identified by sampling a subset of representative compounds and testing for antiprotozoal activity. Examples of interesting classes include oxaboroles (Anacor Pharmaceuticals), pyridones (GSK), and nitroimidazoles

(TB Alliance). Access to specific sets of compounds (inhibitors of a specific target and chemical classes) from DNDi's pharmaceutical partners (e.g. Sanofi, GSK, or MSD) was one of the major focuses of DNDi's discovery strategy in 2012.

### Compound mining

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) enables identification of candidates with potential for further development – ideally ready to enter into pre-clinical or later stage without further optimization – for the target diseases. A successful example of this strategy is fexinidazole. DNDi has extended and applied this strategy in collaboration with its pharmaceutical partners.

### Reference screening centres

The Swiss Tropical and Public Health Institute (Swiss TPH), the University of Antwerp (LMPH), and the London School of Hygiene & Tropical Medicine (LSHTM) serve as reference screening centres to ensure that screening methodologies are comparable, and that *in vitro* and *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 DNDi's data and work.

## LEAD OPTIMIZATION

### Main partners:

Centre for Drug Candidate Optimisation (CDCO)/Monash University, Australia; Epichem, Australia; Murdoch University, Australia; Federal University of Ouro Preto (UFOP), Brazil; Institut Pasteur Korea (IPK), Korea; iThemba, South Africa; LMPH, University of Antwerp, Belgium; LSHTM, UK; Murdoch University, Australia; SCYNEXIS Inc., USA; TB Alliance, USA; University of Auckland, New Zealand; Pace University, USA; Pfizer, USA; WuXi AppTech, China

### Leadership:

Discovery and Pre-Clinical Director: Robert Don; Head of Drug Discovery: Eric Chatelain; Head of Drug Discovery: Charles Mowbray; Project Coordinator: Stéphanie Braillard

DNDi's strategy for its lead optimization consortia is to advance new chemical classes identified through screening programmes, as well as to develop backup compounds that can rapidly replace frontrunner 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 focused on improving the lead compound's properties for absorption into the bloodstream following oral dosing, distribution of the compound to the site of infection(s), modification of residues in the compound that are prone to breakdown or clearance and which increase tolerability and safety for the patient.

## HUMAN AFRICAN TRYPANOSOMIASIS (HAT)

Sleeping  
Sickness



# Working together to develop the right tools for elimination

The WHO, in its recently published NTD Roadmap,<sup>(1)</sup> has slated human African trypanosomiasis for elimination by 2020, measuring elimination by an annual prevalence rate of less than 1 case per 10,000 population in historical foci.<sup>(2)</sup> This objective comes at a time when a steady decline in the numbers of reported cases has been recorded over 15 years, resulting from intensified efforts to detect and promptly treat patients and to control the disease. In 1995, there were 30,000 reported and 300,000 estimated cases of HAT. Today there are approximately 7,000 reported cases and approximately 30,000 estimated cases annually, thanks to the efforts and successes of National Control Programmes (NCPs) of endemic countries, together with WHO, MSF, Sanofi, Bayer, and many other key actors. A new combination therapy, NECT, that is effective and safe, but also simplifies treatment, was introduced by DNDi and partners in 2009 for patients with stage 2 HAT, and two oral drugs are currently in clinical trials. Eliminating the disease,

however, will not happen without concerted efforts to bring simple and safe oral drugs and rapid diagnostics to the field, supported by fine-tuned control strategies according to disease prevalence<sup>(3)</sup> and sustained surveillance programmes.

The reality of HAT management remains challenging, even more so in the most remote settings such as the small villages where the current treatments are not feasible for use, and where the current diagnostics still require specialized mobile teams. The rapid diagnostics, in addition to the two oral treatments in development by DNDi and partners, could dramatically change diagnosis and treatment by making tools available in the rural health centres in sub-Saharan Africa, thus facilitating the decentralization of HAT services and surveillance, and so directly contributing to elimination targets.

In the current context of a declining number of patients that can participate in clinical research projects and with several promising tools still requiring clinical trial testing, the need for stronger collaboration and coordination of the key players is vital. It will later ensure that the right tools reach patients through national programmes.

### Ideal Target Product Profile for HAT

#### A new treatment for adults and children

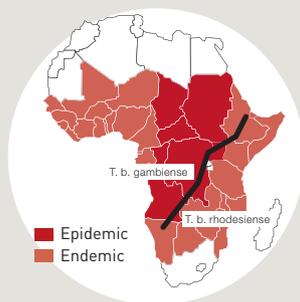
- Effective against **both stages** of the disease
- Active against **both causative parasite sub-species**: *Trypanosoma brucei gambiense* and *T.b. rhodesiense*
- With less than **0.1%** drug-related mortality
- With at least **95%** efficacy at 18 months follow-up
- **Safe** for pregnant and lactating women
- **Easy to use**: short-course (7, maximum 10 days), oral, once a day, requiring no monitoring.
- **Affordable**
- **Adapted to tropical climates** (three-year shelf-life)

(1) Accelerating work to overcome the global impact of neglected tropical diseases: A roadmap for implementation, WHO, January 2012. [www.who.int/neglected\\_diseases/NTD\\_RoadMap\\_2012\\_Fullversion.pdf](http://www.who.int/neglected_diseases/NTD_RoadMap_2012_Fullversion.pdf)

(2) Report of a WHO meeting on elimination of African trypanosomiasis (*Trypanosoma brucei gambiense*), World Health Organization, April 2013.

(3) Simarro PP, et al. (2013) Diversity of human African trypanosomiasis epidemiological settings requires fine-tuning control strategies to facilitate disease elimination. Research and Reports in Tropical Medicine 4:1–6.





# Human African Trypanosomiasis Sleeping Sickness

## WHAT IS THE IMPACT OF HAT?

The number of reported cases is approximately 7,000, but the number of actual cases is estimated to be 30,000.<sup>(1)</sup> Fatal if untreated, the disease affects mainly those living in remote areas with limited access to adequate health services. Almost eliminated in the 1960s, transmission increased again as a result of war, population displacement, poverty, and the collapse of adequate support to the control activities conducted within 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 sub-species 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.<sup>(2)</sup> Man is the essential reservoir for *T. b. gambiense*.

## 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 leads 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, require injections and are ineffective for stage 2.

→ **Stage 2:** melarsoprol, a toxic arsenic derivative that causes pain and fatal encephalopathies in up to 5% of those who receive it,<sup>(3)</sup> and is increasingly ineffective, with reports of drug resistance and treatment failure in some foci; eflornithine, difficult to administer as

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), a simplified therapy option for stage 2 *T. b. gambiense* sleeping sickness, with only 14 infusions of eflornithine over 7 days and 10 days of oral treatment with nifurtimox. While not the most appropriate treatment to support elimination efforts as it requires a hospital setting, NECT does provide a major improvement in case management.

## 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-eflornithine combination therapy (NECT). **NECT** was included on the WHO Essential Medicines List (EML) in 2009 and is now recommended as first-line treatment in 12 endemic countries. In December 2012, it was submitted for inclusion on the WHO EML for children.

As a medium-term strategy, DNDi initiated a 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 entered a pivotal Phase II/III study** in 2012 and is currently recruiting patients in the DRC. 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 a **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 after some additional studies, entered **Phase I clinical** development in early 2012 and should be completed in 2013. Other backup compounds continue to be evaluated by the consortium.

In addition, DNDi supports the **HAT Platform** (see page 49) that was launched in Kinshasa (Democratic Republic of the Congo – 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

(1) [www.who.int/mediacentre/factsheets/fs259/en/](http://www.who.int/mediacentre/factsheets/fs259/en/) (2) Simarro PP, et al. (2008) Eliminating human African trypanosomiasis: where do we stand and what comes next? PLoS Med 5: 55. (3) Blum J, et al. (2001) Clinical description of encephalopathic syndromes and risk factors for their occurrence and outcome during melarsoprol treatment of human African trypanosomiasis. Trop Med Int Health 6: 390-400.



## Research

**Partners:**

TB Alliance, USA; University of Auckland, New Zealand; SCYNEXIS Inc., USA; Pace University, USA; Wuxi AppTech, China

**Leadership:**

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

**Project start:**

April 2007



## Lead Optimization Consortium – Nitroimidazoles backup – Oxaborole backup

**2012 OBJECTIVES:**

- Continue the lead optimization programme with the goal of a backup oxaborole. Assess the front-running compounds SCYX-6086 and SCYX-8210 in rat toxicity studies
- Evaluate the lead nitroimidazole backup RJ164 to determine if suitable to progress further
- Initiate a new Lead Optimization (LO) programme with the LO USA Consortium to select a new chemical series for LO

The prototype oxaborole SCYX-7158 is progressing through Phase I clinical trials. A range of structurally diverse oxaboroles with good activity against *T. brucei* were profiled in an animal pharmacokinetic (PK) study and several promising candidates with shorter half-lives than SCYX-7158 were identified. In depth DMPK and *in vitro* parasitology profiling narrowed the selection to SCYX-8210 and SCYX-0682, which may offer good backups to SCYX-7158 if needed. SCYX-7158 continues to make good progress in Phase I clinical trials, so at present there is no urgent need for a backup compound. Thus, only limited further development of SCYX-8210 and SCYX-0682 will be performed in 2013.

The nitroimidazole backup programme for HAT has been searching for a compound with a lower projected human dose than fexinidazole to simplify dosing and mitigate any potential issues with tolerance. Work at WuXi AppTech and the University of Auckland allowed the preparations of enantiomers of the nitroimidazole SN29971/SCYX-1227; after parasitology and *in vitro* DMPK profiling, the enantiomer SCYX-2035811 was identified as the active isomer and retained the good metabolic stability of the racemate. A synthetic route to SCYX-2035811 has been developed and scaled-up to provide active pharmaceutical ingredient (API) for further characterization. In the mouse acute model of HAT, SCYX-2035811 has shown excellent activity at doses down to 12.5 mg/kg for 7 days. The dose response for this compound will be further explored and a parallel PK assessment, including brain levels, will be carried out before the progression of this compound into the mouse stage 2 CNS model to enable a full comparison with fexinidazole. The nitroimidazole fexinidazole is progressing well in Phase II/III clinical trials. The need for a backup compound is therefore not urgent at this stage and only limited work will be carried out in 2013 on the backup programme.



## Translation

**Partners:**

Anacor Pharmaceuticals Inc., USA; SCYNEXIS Inc., USA; Advinus Therapeutics, India; Penn Pharma, UK; Swiss TPH, Switzerland; Pace University, USA

**Leadership:**

Discovery and Pre-clinical Director: Robert Don; Head of HAT Clinical Programme: Antoine Tarral; Clinical Manager: Séverine Blesson; Head of Pharmaceutical Development: Steve Robinson; Project Coordinator: Delphine Launay

**Project start:** January 2010

## Oxaborole SCYX-7158

**2012 OBJECTIVES:**

- Completion of a GLP (Good Laboratory Practice) safety package (reprotox), process development, manufacture of the API, formulation, and be ready for regulatory submissions for Phase I clinical trials
- Initiate oxaborole SCYX-7158 Phase 1 study

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 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 HAT, as it is able to cross the blood-brain barrier. Pre-clinical



**14 PATIENTS**  
out of  
**120 recruited**  
at 1 site

development progressed successfully through 2010, and all pre-clinical data were published in *PLoS NTDs* in June 2011.<sup>(1)</sup> Batches of drug substance and drug product (capsules) were produced

according to current good manufacturing practices (cGMP) and supplied for the Phase I clinical trial. In 2012, a robust tablet formulation was also developed in order to supply Phase II/III clinical trials, and manufacturing is planned for mid-2013.

Following clearance by the French ethics committee and regulatory authority, SCYX-7158 entered first-in-human studies in March 2012 and became DNDi's first entity resulting from its own lead optimization efforts to enter Phase I clinical studies. These studies are performed in order to assess its safety, tolerability, pharmacokinetics, and pharmacodynamics in healthy volunteers of sub-Saharan origin. Following the first dose of SCYX-7158, pharmacokinetic results showed a longer than expected half-life in human plasma. Additional cohorts in humans assessed the safety profile, and following results from the intermediate dog study, the ascending dose study re-started in early 2013.

(1) Jacobs RT, et al. (2011) SCYX-7158, an orally-active benzoxaborole for the treatment of stage 2 human African trypanosomiasis. *PLoS Negl Trop Dis* 5: e1151.



HUMAN AFRICAN  
TRYPANOSOMIASIS (HAT)

LEISHMANIASIS

CHAGAS DISEASE

FILARIAL DISEASES

PAEDIATRIC HIV

MALARIA

## Fexinidazole

### 2012 OBJECTIVES:

- Start pivotal Phase II/III trial in three African countries
- Launch the trial in Q2 in three sites (DRC) and Q3 in the remaining sites (CAR, DRC, South Sudan)
- Prepare EMA discussion for stage 1 of the disease
- Collaborate with FIND to develop new tools for diagnosis and follow up



17 PATIENTS  
out of 510  
recruited  
at 4 sites

Sanofi: DNDi is responsible for pre-clinical, clinical, and pharmaceutical development, while Sanofi is responsible for the industrial development, registration, and production of the drug at its manufacturing sites. A safe API manufacturing process, able to be commercialized, has been developed in collaboration with Sanofi. The study will recruit patients at six clinical sites in DRC and one in CAR. By the end of 2012, 17 patients had been recruited at four active sites in DRC. Two additional sites will open in 2013: one in CAR, another in DRC ready to start Q2 2013. No site was chosen in South Sudan.

Fexinidazole is the first success of the extensive compound mining efforts pursued by DNDi within the nitroimidazole project initiated in 2005. This drug entered Phase I first-in-human studies in September 2009 and Phase II/III in October 2012. This single pivotal Phase II/III study aims to prove the safety and efficacy of fexinidazole, with NECT as the active comparator. The study was initiated and is conducted by DNDi in collaboration with the Swiss TPH and the human African trypanosomiasis national control programmes of the Democratic Republic of the Congo (DRC) and Central African Republic (CAR), in addition to MSF. DNDi is co-developing the drug with

### Partners:

Sanofi, France; Swiss TPH, Switzerland; Programme National de la Lutte Contre la Trypanosomiase Humaine Africaine (PNLTHA) DRC; Médecins Sans Frontières; and other HAT Platform members

### Leadership:

Head of HAT Clinical Programme: Antoine Tarral; Medical Manager: Olaf Valverde; Clinical Manager: Séverine Blesson; Head of Pharmaceutical Development: Steve Robinson

### Project start:

April 2007



Development



## NECT – Nifurtimox-Eflornithine Combination Therapy

### 2012 OBJECTIVES:

- Support replacement of melarsoprol by NECT as first-line treatment for 2nd stage HAT in remaining sites
- Increase advocacy for continued international support to R&D activities (including diagnostics) for HAT



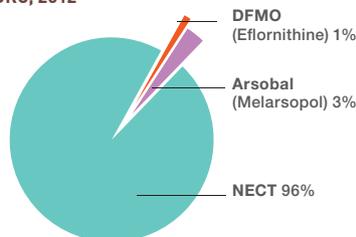
3,000  
TREATMENTS  
in 2012,  
2,618 of which  
in DRC.  
On the EML  
of 12 countries

In September 2012, DNDi and its partners concluded the follow-up of patients included in the 'NECT-Field' study, launched in 2009. The final report is being prepared, and results will be shared through scientific publications. This Phase IIIb study documents the safety, effectiveness, and ease-of-use of NECT 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.

NECT was developed by Epicentre, MSF, DNDi, Swiss TPH, and the national HAT control programmes of the Republic of the Congo and DRC as a combination of eflornithine and nifurtimox. It quickly became first-line treatment for the neurological stage of *T. b. gambiense* sleeping sickness, as it is simpler to administer than eflornithine alone, making it more adapted to field conditions. NECT was included on the WHO Essential Medicines List in 2009. As of December 2012, all countries endemic to *T. b. gambiense* had added NECT to their national essential medicines list. Apart from Angola, all receive free supplies from WHO: 3,000 treatment kits were distributed in 2012.

The HAT Platform continues to advocate for the use of NECT, including supporting its inclusion in the WHO Essential Medicines List for children, for which a decision will be taken in 2013.

Distribution of stage 2 HAT treatments in DRC, 2012



### Partners:

Médecins Sans Frontières (MSF); Swiss TPH; PNLTHA DRC; HAT Platform members

### Leadership:

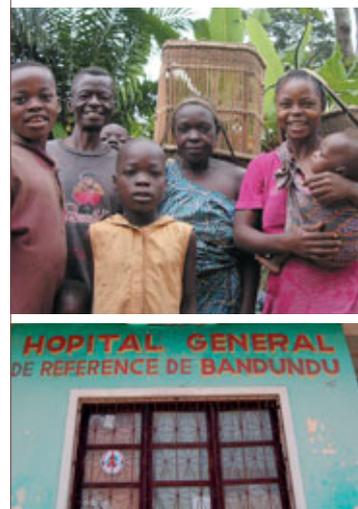
Head of HAT Clinical Programme: Antoine Tarral; Medical Manager: Olaf Valverde

### Project start:

May 2004



Implementation



## LEISHMANIASIS



# Overcoming geographical variations to implement the most effective treatments

Leishmaniasis, caused by more than 20 species of *Leishmania*, is comprised of complex diseases which range from localized skin ulcers to lethal systemic disease. Visceral leishmaniasis (VL) is characterized by prolonged fever, enlarged spleen and liver, substantial weight loss, and progressive anaemia, and is usually fatal within two years if left untreated. Cutaneous leishmaniasis (CL) is characterized by lesions of the skin that can become chronic and/or disfiguring, while post-kala azar dermal leishmaniasis (PKDL) is a disseminated skin infection. A common sequel of VL, PKDL serves as a parasite reservoir, thus contributing to the transmission of the disease.

The natural history of VL is itself complex, its transmission fuelled by poverty and environmental degradation, the latter allowing the interplay of the different elements in the disease cycle (vectors and reservoirs) with humans. The different *Leishmania* species and their adaptation to specific reservoirs determine the cycle, zoonotic (transmission from animals to humans via the vector) or anthroponotic (transmission from humans to humans via the vector), which has implications for disease control.

The last decade has seen improvements in the treatment, diagnosis, and prevention of leishmaniasis in South Asia, notably through the development of liposomal amphotericin B, paromomycin, and miltefosine. Through a combination of active case detection, early treatment, vector control, and social mobilization, the WHO expects to reach its aim

### 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
- Easy to use: short-course, oral or intra-muscular, requiring no monitoring
- Safe in pregnant and lactating women
- Affordable
- Adapted to tropical climates





of eliminating anthroponotic visceral leishmaniasis from the Indian sub-continent by 2020.<sup>(1)</sup> More work, however, is needed to achieve similar results in other parts of the world, particularly East Africa and Latin America. Response to treatment varies between regions, requiring higher doses of the VL drugs, notably in East Africa, than in South Asia. Furthermore, there is evidence of geographical variations within East Africa. While the progress achieved has led to a clearer notion of how to treat patients across different continents, existing treatments are not ideal: potential of resistance development, low tolerability, long treatment duration and difficulty in administration, as well as high cost are still major drawbacks. New treatments that address these issues and address geographical variations and local realities are essential, notably in East Africa.

Although cutaneous leishmaniasis (CL) is not life-threatening, it can have devastating effects on local communities. Indeed, the disfiguring lesions it causes can lead to social stigmatization, with consequences such as ostracism, impaired education, and economic loss – all of this in populations with already limited resources. There is currently no satisfactory treatment for any form of CL, as none bring significant advantages while some have unacceptable safety profiles.

The ideal treatment for VL is a safe, effective, oral, short-course (10 days maximum) drug that would be efficacious in all geographic regions as well as 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.

### Ideal Target Product Profile for CL

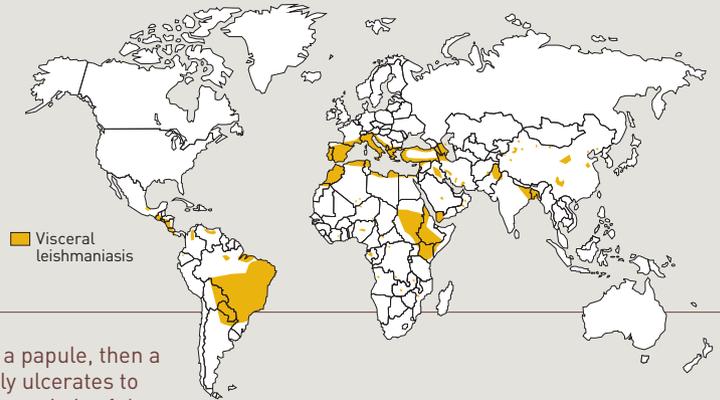
#### A new or oral treatment

- Efficacious against all species of *Leishmania*
- At least 95% efficacy
- Easy to use: short-course, requiring no monitoring
- Leaving minimal scarring
- Safe in pregnant and lactating women
- Affordable
- Adapted to tropical climates (minimum three-year shelf-life)



(1) Sustaining the drive to overcome the global impact of neglected tropical diseases: second WHO report on neglected tropical diseases World Health Organization, 2013.

# Leishmaniasis



## WHAT IS THE IMPACT OF LEISHMANIASIS?

A total of 98 countries and 3 territories on 5 continents reported endemic leishmaniasis transmission. Among parasitic diseases, morbidity and mortality caused by leishmaniasis are surpassed only by malaria and lymphatic filariasis. 350 million people are at risk of the disease, most of them children. The annual incidence is estimated at approximately 0.7 to 1.2 million CL cases and 0.2 to 0.4 million VL cases, with a case-fatality rate of 10% for VL per year (i.e. 20,000 to 40,000 deaths per year).<sup>(1)</sup> However, mortality data are extremely sparse and generally represent hospital-based deaths only, so actual figures are expected to be higher. Co-infection with other infectious diseases is an increasing concern: HIV-VL co-infection has been reported in 25 countries worldwide.

## HOW IS LEISHMANIASIS TRANSMITTED?



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

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

**CL** is most frequently caused by *L. major*, *L. tropica*, and *L. aethiops* in the Old World, and *L. braziliensis*, *L. mexicana*, and related species in the New World. Mucocutaneous leishmaniasis (**MCL**) can develop as a complication of CL.

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

## WHAT ARE THE SYMPTOMS?

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

**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. Depending on the species, CL usually heals spontaneously within one to two years, but results in lifelong scars, which, depending on the size and location, may cause substantial trauma in affected individuals, particularly children.

**MCL** is characterized by partial or total destruction of mucous membranes of the nose, mouth, and throat.

**PKDL** is characterized by a macular, maculopapular, and nodular rash; starting from the face, it spreads to other parts of the body. PKDL is subject to geographical variations and can spontaneously heal, but can also develop into severe or persistent forms, requiring long courses of treatment.

## CURRENT TREATMENTS AND THEIR LIMITATIONS

**Existing therapies for VL have serious drawbacks** in terms of safety, resistance, stability, and cost.<sup>(2)</sup> They have low tolerability, long treatment duration, and are difficult to administer.

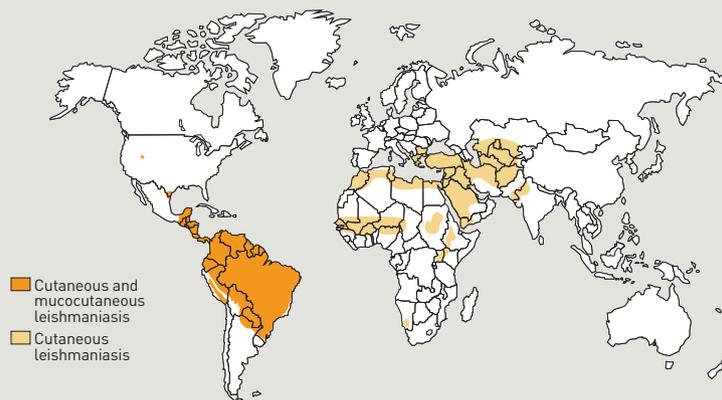
→ **Pentavalent antimonials** (sodium stibogluconate – **SSG** – and meglumine antimoniate, such as Glucantime®): used for VL and CL for over 60 years. Acquired resistance in areas of high prevalence and

high transmission. Serious cardiotoxicity leading to death is well documented. Require a 30-day parenteral treatment for VL. Registered in South-East Asia, Latin America, and some Mediterranean and African countries.

→ **Amphotericin B deoxycholate**: first-line treatment for VL in areas with high rates of unresponsiveness to antimonials and second-line treatment elsewhere. Need for hospitalization, constant renal monitoring of patients, 15-20 day treatment, and infusion-related adverse events are notable drawbacks. Amphotericin B displays dose-limiting toxicity. Registered in South Asia and some countries in Africa and Latin America.

→ **AmBisome®**: a liposomal formulation of amphotericin B, much safer and highly efficacious. A single infusion of 10 mg/kg has shown a 96.4% cure rate in Asia.<sup>(3)</sup> However, high cost and the need for a cold chain limit its widespread use.<sup>(4)</sup> Registered in India, USA, and Europe and used as a second-line drug for PKDL in East Africa and for VL in Brazil.

→ **Miltefosine**: oral drug registered and recommended in India, but expensive<sup>(5)</sup> and requires 28-day treatment. Major



(1) Alvar J. et al. (2012) Leishmaniasis worldwide and global estimates of its incidence. PLoS ONE 7: e35671. (2) Seifert K. (2011) Structures, targets and recent approaches in anti-leishmanial drug discovery and development. Open Med Chem J 5: 31–9. (3) Sundar S. et al. (2011) Comparison of short-course multidrug treatment with standard therapy for visceral leishmaniasis in India: an open-label, non-inferiority, randomised controlled trial. Lancet 377: 477–86. (4) Through the WHO, significant cost reduction of both AmBisome® and miltefosine is available for the public sector of key endemic countries as of 2007. (5) Ibid.



limitations include low compliance, with risk of resistance, and contraindication in pregnancy and mandatory contraception for women of child-bearing age for the duration of therapy and three months beyond. A recent study in Asia indicated an emerging lack of efficacy in monotherapy in the region.<sup>(1)</sup>

→ **Paromomycin (PM)**: a low-cost parenteral formulation that requires three weeks of painful intramuscular administration and is associated with some degree of renal and ototoxicity.

In 2010, DNDi and LEAP 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, DNDi also conducted a Phase III trial to evaluate the combination of already registered drugs: AmBisome®, miltefosine, and paromomycin. They are now recommended by the WHO Expert Committee on the Control of Leishmaniasis (see page 29).

Together with OWH/PATH and TDR, DNDi is collaborating with the National Control Programmes of India and Bangladesh, MSF, the Bihar State Health Society, and the Indian Council for Medical Research to assess the feasibility of these new treatments at the primary health care level and facilitate their introduction for the treatment of 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®, and amphotericin B as monotherapies, and of AmBisome®-Glucantime® combination to treat VL patients.

**Existing treatments for CL are not satisfactory.** Many treatment regimens are associated with significant failure rates and considerable toxicity. Relapses are

common and there are increasing reports of drug resistance emergence.

→ **Pentavalent antimonials**: given as first-line drugs through a series of intramuscular, intravenous, or intralesional injections. Serious side effects, require long treatment, not affordable for most patients and difficult to administer in poor rural areas.

→ Alternative treatments: **Liposomal amphotericin-B**, not fully tested on CL. Even if efficacious, cannot be deployed widely because of cost and delivery requirements. **Miltefosine**, potentially teratogenic and has side effects that make it unsuitable to treat CL. Registered in Colombia. Other treatments, such as

thermotherapy and cryotherapy are used in certain clinics, but are expensive.

→ A promising approach is to combine **chemotherapy with immune-modulation**: initial elimination of parasites with chemotherapy, followed by modification of the patient's immune response by an immune-enhancing agent (either a **therapeutic vaccine** or an appropriate adjuvant) could lead to quick recovery and control of persisting parasites. Therapeutic vaccines have yielded positive results for CL in Brazil and Venezuela. Several chemical immunomodulators have been tested for cancer and other diseases, and could be useful for CL therapy.

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

DNDi's **short-term** approach was 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 objective was to assess efficacy and safety of existing drugs in other countries and regions to extend registration and availability to patients.

*Leishmania*-HIV co-infection is a newly emerging problem. It is very difficult to manage, due to poor response to treatment with frequent relapses of disease, and is eventually fatal. DNDi is working towards a new treatment for HIV/VL co-infected patients in Africa.

DNDi's **long-term** strategy is to bring new drug candidates into clinical development through its lead optimization programme.

For CL, DNDi's objective is to develop short, safe, efficacious, affordable, and field-adapted treatments against *L. tropica* and *L. braziliensis* – because of the severity of the disease and its public health importance. As a **short-term** strategy, DNDi is developing a topical treatment of an existing drug. In the **longer term**, DNDi aims to develop a novel field-adapted modality of treatment that would combine anti-parasite and immune-modifying agents, with a strong emphasis on safety, efficacy, cost, quality of scar and reduced need for follow-up and interaction with health systems.

In addition, DNDi supports the **Leishmaniasis East Africa Platform (LEAP)** (see page 48) that aims to geographically extend all currently available VL drugs in East Africa and to develop new therapies suitable for the region, as well as to build and sustain 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

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

- A safe, effective, and shorter-course treatment for CL

(1) Rijal S. et al. (2013) Increasing failure of miltefosine in the treatment of kala-azar in Nepal and the potential role of parasite drug resistance, reinfection, or noncompliance. Clin Infect Dis 56: 1530-8.



## Research

**Partners:**

TB Alliance, USA; Advinus Therapeutics, India; Central Drug Research Institute, India; LSHTM, UK; Auckland University, New Zealand; Laboratory of Microbiology, Parasitology and Hygiene (LMPH), University of Antwerp, Belgium; WuXi AppTech, China

**Leadership:**

Head of Drug Discovery:  
Eric Chatelain;  
Project Coordinator:  
Delphine Launay

**Project start:**

July 2010

## Nitroimidazole backup

**2012 OBJECTIVE:**

→ **Profile potential backup candidates to VL-2098 for the treatment of VL**

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 200 analogues have been prepared so far.

A number of backup compounds have now been identified as meeting the targets set at the start of the project, including *in vivo* efficacy. Additional studies are in progress to further characterize these and select the compound with the best chance of becoming a successful clinical candidate meeting the criteria for good *in vivo* efficacy and an acceptable safety profile.



## Translation

**Partners:**

TB Alliance, USA; Advinus Therapeutics, India; Central Drug Research Institute, India; LSHTM, UK; Auckland University, New Zealand; Bertin Pharma, France; ChemDepo Inc., USA

**Leadership:**

Discovery & Pre-clinical Director:  
Robert Don; Project Coordinators:  
Stéphanie Brailard, Delphine Launay

**Project start:**

July 2010

## VL-2098

**2012 OBJECTIVE:**

→ **Complete the pre-clinical package (regulatory safety studies and API and drug product manufacturing) in order to start a clinical Phase I study in 2015**

From 70 nitroimidazoles belonging to four chemical sub-classes, VL-2098 was identified as the most potent molecule with a favourable safety profile for in-depth evaluation as a clinical candidate. VL-2098 profiles as selective for *L. donovani* with efficacy in acute and chronic VL animal models following oral dosing. Safety

testing with administrations at several multiples of the efficacious dose is ongoing and we expect to complete these studies and propose VL-2098 as a clinical candidate late in 2013.



## Translation

**Partners:**

PECET (Program for the Study and Control of Tropical Diseases), Universidad de Antioquia Medellin, Colombia; Humax Pharma, Columbia; Imperial College of Science, Technology and Medicine, UK; Centro de Pesquisas René Rachou, Brazil

**Leadership:**

Head of CL Clinical Programme:  
Farrokh Modabber / Byron Arana;  
Clinical Managers: Fabiana Alves,  
Gwenaëlle Carn

**Project start:**

September 2011

## Anfoleish (Cutaneous Leishmaniasis)

**2012 OBJECTIVE:**

→ **Develop a topical anti-parasitic treatment containing amphotericin B for the treatment of CL**



The rationale for development of a topical formulation of amphotericin B was to provide a treatment to be applied locally at the CL lesion, with high anti-parasitic effect, but without the systemic toxicity associated with amphotericin B. Anfoleish was selected by DNDi for clinical development after completion of pre-clinical assessments. The first study will be a Phase Ib/II trial aiming to assess the safety, PK, and efficacy of an amphotericin B cream in patients with CL caused by *L. braziliensis*. If this trial shows that Anfoleish is efficacious against *L. braziliensis*, a multi-country Phase III study will be planned in several endemic countries in Latin America.



## Fexinidazole

### 2012 OBJECTIVE:

- Initiate a Phase II proof-of-concept study to determine the efficacy and safety of using fexinidazole for the treatment of visceral leishmaniasis

Fexinidazole has shown potent activity against *L. donovani* *in vitro* and *in vivo* in a VL mouse model. It was assessed in three Phase I studies in healthy volunteers and was shown to be safe when given as a single dose or as repeated dosing after 14 days. This Phase II proof-of-concept study will evaluate fexinidazole for the treatment of primary VL patients in Sudan. If successful, it will be followed by a Phase II/III programme in South Asia, East Africa, and Brazil.

### Partners:

Kenya Medical Research Institute (KEMRI), Kenya; Institute of Endemic Diseases (IEND), University of Khartoum, Sudan; MSF; LEAP; BaseCon, Denmark; Utrecht University, The Netherlands

### Leadership:

Head of VL Clinical Programme: Manica Balasegaram; Clinical Manager: Sally Ellis; Project Coordinator: Clélia Bardonneau

**Project start:** September 2012



Translation

## New VL treatments – Bangladesh

### 2012 OBJECTIVE:

- Conduct Phase III/IV study to demonstrate feasibility of implementing new treatment modalities recommended by WHO (miltefosine-paromomycin, AmBisome®-miltefosine, AmBisome®-paromomycin, single-dose AmBisome®) in primary healthcare settings in Bangladesh

The Phase III trial conducted by DNDi and its partners in 2010 demonstrated the efficacy of combination therapies based on AmBisome®, miltefosine, and paromomycin. This two-step Phase III study (first in hospital settings, then in primary healthcare centers) is using these combination therapies in Bangladesh. By the

end of 2012, 431 out of 674 patients had been recruited. The trial is expected to end in 2013 and results will be available in 2014.



### Partners:

Ministry of Health and Family Welfare, Bangladesh; International Centre for Diarrhoeal Disease Research (ICDDR,B), Bangladesh; Shaheed Suhrawardy Medical College and Hospital (ShSMC), Bangladesh

### Leadership:

Head of Leishmaniasis Clinical Programme: Manica Balasegaram; DNDi India Director of R&D Operations: Bhawna Sharma; Clinical Managers: Sally Ellis and Vishal Goyal; Project Coordinator: Abhijit Sharma; Assistant Project Coordinator: Pankaj Kumar

**Project start:** July 2010



Development

## New VL treatments – Africa

### 2012 OBJECTIVES:

- Develop new shorter-course treatments for VL in East Africa and geographically extend available anti-leishmanial drugs to all countries of the region
- Support ongoing registration activities for use of SSG&PM
- Assess the efficacy and safety of miltefosine combinations for East Africa

Since 2004, DNDi and the Leishmaniasis East Africa Platform (LEAP) have embarked on a clinical research programme with two specific objectives: to geographically extend all currently available VL drugs and to develop one to two new treatments.

The LEAP 0208 Study, coordinated by DNDi and LEAP, to assess combinations of existing drugs to treat VL in Africa, aimed to evaluate the safety and efficacy of miltefosine monotherapy, AmBisome®-SSG, and AmBisome®-miltefosine combination treatments. Recruitment started in Kenya and Sudan in 2010 and

ended in March 2012. The trial collected 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 were evaluated. Preliminary safety and efficacy results available at the beginning of 2013 will inform the decision to evaluate one of these combinations in a Phase III trial.

The LEAP AMBI 0106 trial which aimed to determine the minimum dose of AmBisome® that is efficacious, safe, and cost-effective to treat VL in Africa was completed in 2011 and results have been submitted for publication.



### Partners:

KEMRI, Kenya; IEND, University of Khartoum, Sudan; Addis Ababa University, Ethiopia; Gondar University, Ethiopia; University of Makerere, Uganda; LSHTM, UK; Slotervaart Hospital, The Netherlands Cancer Institute, The Netherlands; Royal Tropical Institute (KIT), The Netherlands; Ministries of Health of Ethiopia, Sudan, Kenya, and Uganda; MSF; i+solutions, The Netherlands; OneWorld Health (OWH/PATH), USA; LEAP; Institute of Tropical Medicine-Antwerp, Belgium

### Leadership:

Head of DNDi Africa: Monique Wasunna; Head of VL Clinical Programme: Manica Balasegaram; Clinical Manager: Sally Ellis; Project Coordinator: Clélia Bardonneau

**Project start:**

November 2004



Development



Development

**Partners (AfriCoLeish):**

LSHTM, UK; Institute of Tropical Medicine-Antwerp, Belgium; MSF, The Netherlands; Addis Ababa University, Ethiopia; Gondar University, Ethiopia; IEND, University of Khartoum, Sudan; LEAP; Slotervaart Hospital, The Netherlands Cancer Institute, The Netherlands; Utrecht University, The Netherlands

**Leadership:**

Head of Leishmaniasis Clinical Programme: Manica Balasegaram; Clinical Manager: Sally Ellis; Project Coordinator: Clélia Bardonneau

**Project start:**

September 2011

**HIV/VL**

**2012 OBJECTIVE:**

→ **Identify and deliver a safe and highly effective treatment for VL in HIV co-infected patients that will improve long-term survival of these patients**

A first study will evaluate the efficacy of a combination regimen of AmBisome® with miltefosine, and of AmBisome® (at a higher dose) monotherapy in Ethiopian patients co-infected with VL and HIV. A secondary objective is to assess relapse-free survival at day 390 (after initial cure at day 28 or at day 56 after extended treatment). Viral load and CD4 count will be measured in all patients, and the pharmacokinetics of antiretrovirals, AmBisome®, and miltefosine, as well as immune function markers will be examined in a subset of patients.

In anthroponotic transmission areas, the WHO recommends secondary prophylaxis with drugs not given in treating primary VL cases to avoid resistance development. A second, follow-up study, sponsored by the Institute of Tropical Medicine-Antwerp, Belgium, will assess the use of pentamidine as secondary prophylaxis for HIV/VL co-infected patients.



Development

**Partners:**

René Rachou Research Institution – Fiocruz-MG, Brazil; Paediatric Hospital Joao Paulo II – FHEMIG, Brazil; Brasilia University, Brazil; Montes Claros State University, Brazil; Piaui Federal University, Brazil; Sergipe Federal University, Brazil; Leishmaniasis Control Programme/Ministry of Health, Brazil; Universidade Estadual do Rio de Janeiro, Brazil

**DNDi support:**

Clinical Manager: Fabiana Alves

**Project start:**

February 2011



**New VL treatments – Latin America**

**2012 OBJECTIVE:**

→ **Support the Brazilian Ministry of Health and its partners to conduct a Phase III trial assessing the efficacy and safety of amphotericin B deoxycholate, AmBisome®, and AmBisome®-Glucantime® combination for the treatment of VL in Latin America**

About 90% of VL cases in Latin America occur in Brazil, and most of them affect children. In 2011, Brazil reported 3,894 new cases with a fatality rate of 6.7%. 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 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 study progressed well during 2012, with five active sites and a total of 205 patients recruited (out of 426 total), and



**205 PATIENTS**  
recruited  
at 5 sites

is expected to be completed by 2014. Evidence provided by this project will guide policies on the treatment of VL caused by *L. infantum* in Brazil.





## SSG&PM – Sodium stibogluconate & paromomycin

### 2012 OBJECTIVE:

→ Facilitate implementation of and access to SSG&PM in key endemic areas of East Africa by supporting registration of paromomycin (PM) and document safety through a pharmacovigilance study



**2,332 PATIENTS**  
in the pharmaco-  
vigilance study  
treated since 2011  
in 4 countries

In 2010, DNDi and LEAP successfully showed that the combination of SSG and PM (17 days) was as efficacious as SSG monotherapy (30 days), with the advantage of being shorter course, therefore lessening the burden on patients and 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 following its recommendation as first-line therapy for VL patients in East Africa by the WHO Expert Committee on the Control of Leishmaniases. First registration (of PM)

was obtained in Uganda at the end of 2011, and registration was obtained in Kenya in January 2013. The registration process is underway in Sudan and Ethiopia. Nonetheless, implementation has already begun in the region, as the treatment was recommended. In addition, it has been included in the national drugs lists of Sudan, South Sudan, and Ethiopia and in Kenya's national VL guidelines. SSG&PM treatment has been rolled out in Sudan and Uganda in public health structures, as well as in MSF centres. A pharmacovigilance study with MSF to monitor safety and effectiveness of SSG&PM was initiated in 2011 and, by the end of 2012, approximately 2,300 patients had been treated in Ethiopia, Sudan, Kenya, and Uganda. SSG&PM is also being used to treat VL patients in South Sudan as part of its national programme.

### Partners:

KEMRI, Kenya; IEND, University of Khartoum, Sudan; University of Makerere, Uganda; Addis Ababa University, Ethiopia; Gondar University, Ethiopia; LSHTM, UK; Slotervaart Hospital, The Netherlands Cancer Institute, The Netherlands; KIT, The Netherlands; Ministries of Health of Ethiopia, Sudan, Kenya, and Uganda; MSF; i+ solutions, The Netherlands; OWH/PATH, USA; LEAP

### Leadership:

Head of Leishmaniasis Clinical Programme: Manica Balasegaram; Clinical Manager: Sally Ellis; Head of DNDi Africa: Monique Wasunna

### Project start:

November 2004



Implementation

## New VL treatments – Asia

### 2012 OBJECTIVE:

→ Conduct effectiveness studies in South Asia to demonstrate feasibility in implementing the new treatment modalities recommended by WHO (miltefosine-paromomycin, AmBisome®-miltefosine, AmBisome®-paromomycin, single-dose AmBisome® 10 mg/kg) in primary healthcare settings in India with a view to extending their use in the region to support control and elimination strategies in the countries of highest prevalence in South Asia



**213 PATIENTS**  
out of 450  
recruited at  
10 sites in India

**431 PATIENTS**  
out of 674  
recruited  
at 3 sites  
in Bangladesh

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.* 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/PATH, in collaboration with health authorities at state and national 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/PATH). 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. This includes 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 is monitoring pharmacovigilance as well as treatment effectiveness of the different treatment options when used outside of a clinical trial by the public sector. The study began in 2012 in two districts in India. By the end of the year, 213 patients had been recruited, out of 7,000 planned. The trial is expected to end in 2015 and results will be available in 2016.



### Partners:

Indian Medical Research Council (ICMR); Rajendra Memorial Research Institute of Medical Sciences (RMRI), India; Kala Azar Medical Research Centre, India; State Health Society, Bihar (BSHS), India; National Vector Borne Disease Control Programme (NVBDCP), India; Community Based Medical College (CBMC), Mymensingh, Bangladesh; Ministry of Health and Family Welfare, Bangladesh; ICDDR,B, Bangladesh; ShSMC, Bangladesh; University of Tokyo, Japan; OWH/PATH, USA; Institute of Tropical Medicine-Antwerp, Belgium; LSHTM, UK; WHO-TDR; WHO (SEARO, Geneva); MSF

### Leadership:

Head of Leishmaniasis Clinical Programme: Manica Balasegaram; DNDi India Director of R&D Operations: Bhawna Sharma; Clinical Managers: Sally Ellis and Vishal Goyal; Project Coordinator: Abhijit Sharma; Assistant Project Coordinator: Pankaj Kumar

### Project start:

December 2006



Implementation

## CHAGAS DISEASE

American trypanosomiasis



# Treat now and boost innovation for tomorrow – millions are waiting

Over a century after its discovery, Chagas disease is still endemic to 21 countries in Latin America, where PAHO estimates that approximately 8 million people are infected and 100 million are at risk of the disease.<sup>(1)</sup> Imported Chagas disease affecting patients from endemic regions is increasingly recognized as an emerging problem in the USA and Europe, due to migration from Latin America. The Centers for Disease Control and Prevention (CDC) estimates that over 300,000 persons with *Trypanosoma cruzi* infection live in the USA. Most of the true burden of Chagas disease can remain hidden for years – many infected people remain asymptomatic for more than a decade.<sup>(2)</sup> Despite an economic burden equivalent to that of other prominent global diseases, such

as rotavirus,<sup>(3)</sup> Chagas disease is among the neglected diseases that receive the least investment for R&D – less than USD 25 million in 2011, only half of which was invested in drug discovery for the disease<sup>(4)</sup> – of the more than USD 3 billion spent for R&D for neglected diseases.

### Ideal Target Product Profile for Chagas Disease

A new treatment for **both acute and chronic** phases:

- Useful against most parasite species in all regions
- Better **safety** profile than existing drugs
- Non-inferior **efficacy** to benznidazole
- **Easy-to-use** treatment: oral, once-a-day for less than 30 days, requiring no hospitalization and little or no monitoring
- **Affordable**
- **Adapted to tropical climates** (minimum three-year shelf-life)

The only two drugs approved for treating acute Chagas disease were developed over 40 years ago and are far from ideal. Symptom management has generally been the only treatment option for patients with cardiac or digestive involvement at the chronic stage of the disease. There is no vaccine and no appropriate test of cure. 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. Sustaining and consolidating advances made in controlling the disease is a key challenge, as well as expanding availability of diagnosis and treatment of patients.

For the existing drugs, benznidazole and nifurtimox, which have been used for decades, strong clinical trial evidence for the efficacy of either drug for the treatment of adults with chronic disease is lacking,<sup>(5)</sup> though this is likely to change with upcoming results of TRAENA and BENEFIT studies. Safety and tolerability remain important concerns. Side effects range from skin rashes to seizures and other nervous system disorders.<sup>(6)</sup> In addition, long treatment periods (60-90 days) make patient compliance challenging, with increased risk of drug resistance development. Despite these issues, there is consensus that in the lack of better options, drug treatment should be offered to adults (19-50 years of age) without advanced Chagas heart disease and be considered optional for those older than 50.

In order to effectively fight the disease, new treatments that are safe and effective against the chronic phase of the disease – which is when most patients are diagnosed – are sorely needed. Today, approximately 99% of people who require treatment for Chagas disease are not receiving it. In addition, to gain understanding of the disease progression and ease the development of test-of-cure diagnostic tools that support drug development, identification of biomarkers is essential.



(1) [http://new.paho.org/hq/index.php?option=com\\_content&view=article&id=5856&Itemid=4196](http://new.paho.org/hq/index.php?option=com_content&view=article&id=5856&Itemid=4196). (2) Bruce YL. et al. (2013) *Global economic burden of Chagas disease: a computational simulation model*, *Lancet Infect Dis* 13: 342-8. (3) *Ibid.* (4) G-FINDER *Neglected Disease Research and Development: a five year review*, Policy Cures, December 2012: [http://policycures.org/downloads/GF2012\\_Report.pdf](http://policycures.org/downloads/GF2012_Report.pdf). (5) Clayton, J. (2010) *Chagas disease: pushing through the pipeline*. *Nature* 465: S12-5. (6) *Ibid.*



# Chagas Disease

## American Trypanosomiasis

### 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 8 million people are infected, leading to approximately 12,000 deaths every year in the region<sup>(1)</sup> Approximately 55,000 new cases arise each year.<sup>(2)</sup> Increased migration and population movements have changed the epidemiology and geographic distribution of Chagas disease, which is now found outside Latin America, including in the United States, Europe, Australia, and Japan.

### HOW IS CHAGAS DISEASE TRANSMITTED?



Chagas disease is caused 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 especially in Amazonia.

### WHAT ARE THE SYMPTOMS?

The disease has two clinical phases:

→ **The acute phase** (fatal for 2-8% of children),<sup>(3)</sup> 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**, which can be divided into two stages:

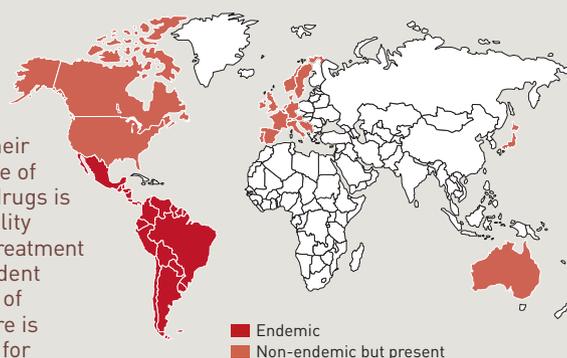
- The chronic, silent, and asymptomatic 'indeterminate' stage, during which patients can transmit the parasite to others, especially through vertical transmission or transfusion, while showing no signs of the disease, and which may last decades after infection.
- The chronic, symptomatic stage, developing later in up to 30% of infected patients, causes cardiopathies, digestive

tract pathologies, and nervous system irregularities.<sup>(4)</sup> Chagas disease 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, and while there is increasing evidence of their efficacy against the chronic phase of the disease, broad use of these drugs is limited due to safety and tolerability issues. Drawbacks 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. In 2011, DNDi and partners produced a paediatric dosage form of benznidazole to fill the treatment gap for this population.



### 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 LAFEPE, 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, for activity against *T. cruzi* in adult chronic patients. Also, we are searching for potential biomarkers of treatment response to enhance clinical trial capabilities of new substances.

As part of its **long-term** strategy, DNDi continues to identify and engage partners from private and public sectors in order to identify, characterize, and advance the development of promising compounds as well as to pursue discovery efforts for innovative therapies.

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 disease progression and ease the development of test-of-cure diagnosis tools that support drug development

(1) [http://new.paho.org/hq/index.php?option=com\\_content&task=view&id=5856&Itemid=4196](http://new.paho.org/hq/index.php?option=com_content&task=view&id=5856&Itemid=4196). (2) Organizacion Panamericana de la Salud. Estimacion cuantitativa de la enfermedad de Chagas en las Americas. Montevideo, Uruguay: Organizacion Panamericana de la Salud, 2006. (3) Parada H. et al. (1997) Cardiac involvement is a constant finding in acute Chagas' disease: a clinical, parasitological and histopathological study. Int J Cardiol 60: 49-54. (4) [www.msfastcess.org/sites/default/files/MSF\\_assets/NegDis/Docs/NEGDIS\\_report\\_Chagas\\_UpdateOnProgress\\_ENG\\_2006.pdf](http://www.msfastcess.org/sites/default/files/MSF_assets/NegDis/Docs/NEGDIS_report_Chagas_UpdateOnProgress_ENG_2006.pdf).



## Research

**Partners:**

University of Auckland, New Zealand; TB Alliance, USA; Centre for Drug Candidate Optimisation (CDCO)/Monash University, Australia; Epichem, Australia; Murdoch University, Australia; Federal University of Ouro Preto (UFOP), Brazil; Institut Pasteur Korea (IPK), South Korea

**Leadership:**

Head of Drug Discovery: Eric Chatelain; Project Coordinator: Delphine Launay

**Project start:**

April 2012



## Nitroimidazole

**2012 OBJECTIVE:**

→ **Assess the nitroimidazole series (developed by TB Alliance) for its potential to identify a candidate for Chagas disease treatment, with the goal of proposing a pre-clinical candidate**

Lead optimization activities have 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 with a better safety profile than the drugs currently used (nifurtimox and benznidazole). Work on the nitroimidazooxazines series has concentrated on compounds from the VL-2098 backup programme (see page 26).

Fexinidazole is a nitroimidazole currently in Phase IIb/III development for HAT. It is very efficacious in a wide variety of rodent Chagas disease models and current work aims to assess fexinidazole suitability for development as a Chagas disease therapy. As safety, pre-clinical and clinical data are available, we aim to rapidly progress fexinidazole to clinical proof-of-concept studies.



## Translation

**Partners:**

University of California San Francisco (UCSF), USA

**Leadership:**

Head of Drug Discovery: Eric Chatelain; Project Coordinator: Stéphanie Braillard

**Project start:**

September 2010

## K777

**2012 OBJECTIVE:**

→ **Review the potential of K777 as a clinical candidate: progress IND-enabling studies**

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 perform the required pre-clinical studies (safety pharmacology and toxicology) in order to complete the Investigational New Drug (IND) application for clinical evaluation of K777 for the treatment of Chagas disease. Safety pharmacology studies were completed, and no effects on electrocardiogram (ECG) or respiratory function were observed, even at the high dose. Dose Range Finding/Maximum Tolerated Dose (DRF/MTD) in non-human primates and 28-day toxicity study will be performed in 2013 in order to finalize writing of IND for submission by early 2014.

## Biomarkers

### 2012 OBJECTIVE:

→ **Identify and evaluate biomarkers to be used in Chagas disease Phase III clinical trials and future registration**

An important hurdle for the development of new drugs for chronic Chagas disease is the lack of clear and early markers that can indicate treatment parasitological outcome and later indicate definite cure. To date, the only definite outcome is seroconversion, which may take up to ten or more years. There is therefore a need to measure treatment effect via an indirect, surrogate marker.

Short-term objectives aim to assess the best sampling strategy to measure parasite clearance via *Trypanosoma cruzi* DNA quantification through polymerase chain reaction (PCR) and validate PCR as a measure of treatment response in Chagas disease, i.e. as a surrogate marker for Phase III clinical trials and regulatory submission:

- A clinical trial conducted 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 aims to evaluate sampling procedures for PCR. Patient recruitment was finalized in December 2011 and patients were followed-up for 12 months. Results are expected by mid-2013.
- In 2012, evaluation of samples from the TRAENA study (a collaboration to support the use of PCR as a method to evaluate treatment response) was concluded. Results are expected in 2013.
- Funding from the Wellcome Trust was obtained in 2011 for a study on naturally infected macaques to evaluate candidate



**PCR STUDY:**  
220 patients

biomarkers, and determine whether blood PCR assays can differentiate between parasitological cure and treatment failure. The study, conducted

in collaboration with the Texas Biomedical Research Institute and the University of Georgia, will be completed at the end of 2014.

- Finally, DNDi is working with FIND and PAHO/TDR to optimize PCR (in particular the extraction step).

In the longer-term, DNDi is working towards identifying new biomarkers of treatment response and to understand the progression of Chagas disease:

- The study on macaques will evaluate lytic antibodies, T-cell assays, multiplex serodiagnostic assay and gene expression profiling.
- In the context of the E1224 study, markers of treatment response, such as conventional and non-conventional serology, multiplex serodiagnostic assays, selected pro-thrombotic factors and apolipoprotein A1, will be assessed.
- A project with Geneva University Hospitals and McGill University will assess the use of proteomic signatures and other biomarkers as potential test of efficacy in sera samples of nifurtimox-treated Chagas patients. A first study was concluded in 2012, for which results will be available in 2013. Results from available proteomic studies will be compiled and additional evaluation may be conducted using adult sera from larger cohorts (e.g. TRAENA and NHEPACHA), and an exploratory study using children sera will be carried out.
- DNDi is part of the NHEPACHA network of investigators created for the long-term cohort evaluation of potential biomarkers.

### Partners:

Médecins Sans Frontières (MSF); Universidad Mayor de San Simon, Bolivia; Universidad Autónoma Juan Misael Saracho, Bolivia; Barcelona Centre for International Health Research (CRESIB), Spain; Dr Mario Fatała Chaben National Institute of Parasitology (INP), Argentina; University of Georgia, USA; Texas Biomedical Research Institute, USA; University of Texas at El Paso, USA; National Council of Scientific and Technological Research (INGEBI-CONICET), Argentina; McGill University, Canada; Geneva University Hospitals, Switzerland; NHEPACHA network

### Leadership:

Head of Drug Discovery: Eric Chatelain; Head of Chagas Clinical Programme: Isabela Ribeiro; Clinical Trial Manager: Jayme Fernandes; Project Coordinator: Bethania Blum

### Project start:

February 2010



Translation

## Fenarimol

### 2012 OBJECTIVE:

→ **Complete studies needed for the nomination of the pre-clinical candidate out of the optimized leads from the fenarimol series**



Two interesting candidates from the fenarimol series of compounds were identified through lead optimization efforts. 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. The objective is to perform Good Laboratory Practice (GLP) safety studies, as well as Chemistry, Manufacturing, and Control (CMC) studies on the selected candidate compound in order to file a formal investigational new drug (IND) application and move the candidate to first-in-man studies.

### Partners:

Centre for Drug Candidate Optimisation (CDCO)/Monash University, Australia; Epichem, Australia; Murdoch University, Australia; Federal University of Ouro Preto (UFOP), Brazil; Institut Pasteur Korea (IPK), Korea

### Leadership:

Head of Drug Discovery: Eric Chatelain; Project Coordinator: Delphine Launay

### Project start:

December 2011



Translation



## Translation

**Partners:**

Eisai Co. Ltd, Japan; Platform of Integral Care for Patients with Chagas Disease, Spain/Bolivia; Universidad Mayor de San Simon, Bolivia; Universidad Autónoma Juan Misael Saracho, Bolivia; Collective of Applied Studies and Social Development (CEADES), Bolivia; NUDFAC – Nucleus of Pharmaceutical and Cosmetics Development, Brazil; Centre de Recerca en Salut Internacional de Barcelona (CRESIB), Spain; National Council of Scientific and Technological Research (INGEBI-CONICET), Argentina

**Leadership:**

Head of Chagas Clinical Programme: Isabela Ribeiro; Clinical Trial Manager: Glaucia Santina; Project Coordinator: Erika Correia, Bethania Blum

**Project start:**

February 2010

## Azole E1224

**2012 OBJECTIVE:**

→ To evaluate the safety and efficacy of E1224 for the treatment of adult patients with chronic indeterminate Chagas disease; conclude recruitment of Phase II study and start planning for Phase III

In 2009, DNDi joined forces with Eisai Co. Ltd – the Japanese pharmaceutical company that discovered E1224 – to develop this new chemical entity for Chagas disease. E1224 is a pro-drug which converts to the active drug ravuconazole in the human body, leading to improved absorption and bioavailability. The Phase II proof-of-concept study started in July 2011 in Cochabamba and Tarija, Bolivia, the country which carries the world's largest Chagas disease burden.

The study evaluates the potential of E1224 as an oral, easy-to-use, safe, and affordable treatment for Chagas disease and will explore promising biomarkers of therapeutic response in Chagas disease (see also 'Biomarkers' project). This randomized, multicentre,



**231 PATIENTS**  
recruited  
at 2 sites

placebo-controlled, safety and efficacy study will evaluate three oral E1224 dosing regimens (high dose for four weeks and eight weeks; low dose for eight weeks) and includes benznidazole (5 mg/kg/day) as a positive control.

The study concluded recruitment of 231 adult patients with chronic indeterminate stage of Chagas disease in June 2012. Twelve month follow-up will be completed mid-2013 and results will be available Q4 2013.



## Implementation

**Partners:**

Laboratório Farmacêutico do Estado de Pernambuco (LAFEPE), Brazil; Hospital de Niños Ricardo Gutierrez, Argentina; Instituto Nacional de Parasitología Dr M Fatała Chabén, Argentina; Hospital de Niños de Jujuy, Argentina; Ministerio de Salud, Provincia de Jujuy, Argentina; Hospital Público Materno Infantil – Salta, Argentina; Centro de Chagas y Patología Regional, Hospital Independencia, Santiago del Estero, Argentina; CONICET/INGEBI, Argentina; Centro Nacional de Diagnóstico e Investigación de Endemo-epidemias (CeNDIE), Ministry of Health, Argentina; University of Liverpool, UK; NUDFAC, Brazil; Administración Nacional de Laboratorios e Institutos de Salud (ANLIS), Argentina

**Leadership:**

Head of Chagas Clinical Programme: Isabela Ribeiro; Clinical Trial Manager: Jayme Fernandes; Project Coordinator: Bethania Blum

**Project start:**

May 2011

## Paediatric dosage form of benznidazole

**2012 OBJECTIVE:**

→ Implement an access plan for broad availability and implementation of paediatric benznidazole in Latin America

Until recently, adequate treatment options for children were lacking: benznidazole was only available as an adult formulation. 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 paediatric formulation, adapted for babies and children up to two years of age, was granted registration by Brazil's National Health Surveillance Agency (ANVISA) in December 2011.



**REGISTERED**  
in Brazil,  
**17,550 TABLETS**  
distributed

DNDi is collaborating with LAFEPE to make the drug widely available, notably in the priority countries where Chagas disease prevalence is high and treatment is urgently needed. The institutions also worked together for the submission for the WHO Essential Medicines List for Children. As an additional component of the paediatric programme, a population pharmacokinetic study involving 80 Chagas disease patients was conducted in Argentina to gain more information on pharmacokinetics, treatment safety, and efficacy in children aged 0-12 years. The results of the study will be available in 2013.





## FILARIAL DISEASES

# Aiming for a faster cure for filarial patients

Filarial diseases are caused by a sub-group of helminths, the nematodes, which are transmitted by insect vectors to humans. 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.

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

### Ideal Target Product Profile for Filarial Diseases

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 breastfeeding women
- **Affordable**
- **Adapted to tropical climates** (minimum three-year shelf-life)

The success of programmes such as the Global Programme to Eliminate Lymphatic Filariasis (GPELF) and the African Programme for Onchocerciasis Control (APOC) has made it possible to consider eliminating LF (defined as 70% of countries verified free of LF and 30% engaged in post-intervention surveillance activities) and controlling onchocerciasis by 2020.<sup>(1)</sup> These programmes have been in place for over twenty years and rely on mass drug administration (MDA) of safe and donated anti-helminthic drugs: community-directed treatment with ivermectin, albendazole, and diethylcarbamazine citrate (DEC).

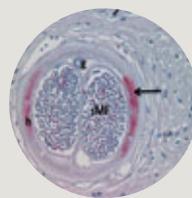
These drugs kill the juvenile form of the worms: the microfilariae cause most of the symptoms and are transmitted to insect vectors.

However, the drugs used in MDA programmes need to be administered repeatedly at regular intervals until adult forms of the worms (macrofilariae) die naturally and there are no more microfilariae in the body. For LF, patients are treated annually or bi-annually for 4-6 years and for onchocerciasis, the treatment duration is 10 years. Importantly, MDA cannot be undertaken in 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 juvenile forms causes a serious adverse reaction, known as *Loa loa* encephalopathy, which can be fatal or leave long-term sequelae.<sup>(2)</sup> The risk of severe adverse reactions is considered to be unacceptable in areas where the microfilarial prevalence exceeds 20%.<sup>(3)</sup>

A macrofilaricide drug, which would kill the adult form of the worm, would enable not only the treatment of patients in regions of loiasis co-endemicity, but could also be used in individual case management at the end of MDA programmes, known as 'mopping up', when the incidence rate is too low to justify initiating a new round of MDA. In addition, if sufficiently safe, the drug could potentially be used for MDA, in which case one or two rounds of treatment would be sufficient to eliminate the diseases from a given community.

(1) *Sustaining the drive to overcome the global impact of neglected tropical diseases: second WHO report on neglected tropical diseases* World Health Organization, 2013. (2) Boussinesq M. (2006) *Loiasis*. Ann Trop Med Parasitol 100: 715-31. (3) Boussinesq M. et al. (2001) *Relationships between the prevalence and intensity of Loa loa infection in the Central province of Cameroon*. Ann Trop Med Parasitol 95: 495-507.





# Filarial diseases

## WHAT IS THE IMPACT OF FILARIAL DISEASES?

### Onchocerciasis (or 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.<sup>(1)</sup>

**Lymphatic filariasis (LF, or elephantiasis):** More than 1.4 billion people in 73 countries worldwide are threatened by LF, commonly known as elephantiasis.

Over 120 million people are currently infected, with about 40 million disabled and incapacitated by the disease.<sup>(2)</sup>

The infection is usually acquired in childhood, but its visible manifestations usually occur later in life, causing temporary or permanent disability.

**Loiasis (African eye-worm):** On the basis of the rapid assessment procedure of *Loa loa* (RAPLOA) results, it is tentatively estimated that some 14.4 million people live in high risk areas where the estimated prevalence of eye worm history is greater than 40%, and 15.2 million in intermediate areas with estimated eye worm prevalence between 20 and 40%.<sup>(3)</sup> The number of people at high risk varies considerably between countries. While the overlap with the geographic distribution of onchocerciasis or lymphatic filariasis is not well documented, where it does exist, there is significant risk of severe adverse events with ivermectin treatment.



## HOW ARE FILARIAL DISEASES TRANSMITTED?

The parasitic worms that cause filarial diseases are 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.

→ LF is caused by nematodes of the *Filarioidea* 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 and from there 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 sub-conjunctival 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.<sup>(4)</sup> The WHO estimates that there are about half a million blind people due to onchocerciasis. It also causes intense itching, skin discoloration, rashes, and eye disease.

LF can become chronic, and when it does, it leads to lymphoedema (tissue swelling) or elephantiasis (skin/tissue thickening) of limbs and fluid accumulation (hydrocele) in the testes. Such body deformities lead to social stigma, as well as financial hardship from loss of income and increased medical expenses.

The socio-economic burden 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, **albendazole** plus either ivermectin in areas where onchocerciasis is also endemic or **diethylcarbamazine citrate (DEC)** in areas where onchocerciasis is not endemic 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 assess flubendazole, an anti-helminthic drug with proven efficacy against gastrointestinal infections of soil-transmitted helminths in animals and man. The aim is to produce a reformulated version of flubendazole with properties for systemic exposure in the patient for use as a safe and field-adapted macrofilaricidal drug candidate in MDA programmes and/or for patient case management.

As a **medium-term strategy**, DNDi is assessing additional opportunities through an active screening programme of drugs emanating from animal health and pharmaceutical companies, with the goal of selecting one or two candidates for proof-of-concept trials in patients.

**By 2015, DNDi aims to deliver from its filarial diseases portfolio a new oral drug candidate, available for proof of concept in patients that could be used for case management of onchocerciasis and lymphatic filariasis, especially in *Loa loa* co-endemic regions.**

(1) [www.who.int/water\\_sanitation\\_health/diseases/oncho/en/](http://www.who.int/water_sanitation_health/diseases/oncho/en/) (2) [www.who.int/mediacentre/factsheets/fs102/en/](http://www.who.int/mediacentre/factsheets/fs102/en/) (3) Zouré HGM, et al. (2011) The geographic distribution of *Loa loa* in Africa: results of large-scale implementation of the rapid assessment procedure for loiasis (RAPLOA). PLoS Negl Trop Dis 5: e1210. (4) [www.who.int/blindness/partnerships/onchocerciasis\\_home/en/index.html](http://www.who.int/blindness/partnerships/onchocerciasis_home/en/index.html)



## Translation

**Partners:**

Johnson & Johnson, USA;  
Michigan State University, USA;  
AbbVie (formerly Abbott  
Laboratories), USA; University of  
Buea, Cameroon; McGill  
University, Canada

**Leadership:**

Discovery and Pre-clinical  
Director: Robert Don; Project  
Manager: Ivan Scandale

**Project start:**

April 2011

## Flubendazole

**2012 OBJECTIVE:**

→ Reformulate flubendazole for the treatment of onchocerciasis and lymphatic filariasis

This project aims to develop flubendazole as a safe, highly efficacious, and field-usable macrofilaricidal drug candidate for the treatment of onchocerciasis and LF. Flubendazole belongs to the benzimidazole class of molecules. Developed by Janssen Pharmaceuticals (a pharmaceutical company of Johnson & Johnson) in the mid-1970s, it is a potent and efficacious anti-helminthic drug for gastrointestinal nematode infections in swine, poultry, companion animals, and humans. In Europe, flubendazole is marketed for human use as Fluvermal. In several animal models<sup>(1)</sup> and in a small human clinical trial for onchocerciasis, in which the drug was administered par-

enterally,<sup>(2)</sup> flubendazole showed very specific potency against the adult stage of the worm. Despite this selective potency, it has not been considered as a treatment for filarial infections, as all of the current formulations have very low bioavailability and these oral forms would not provide sufficient systemic exposure. The first step of this project was to develop, with the help of AbbVie, a new pre-clinical formulation of flubendazole that allows oral absorption.

Non-clinical development of flubendazole is ongoing in collaboration with Janssen Pharmaceuticals: in particular, the necessary studies required to file an Investigational New Drug (IND) application followed by submission of a dossier to the FDA are supported by Janssen Pharmaceuticals, which will also provide DNDi with drug supplies to support clinical development. DNDi will conduct extensive PK/PD studies to guide/refine the selection of human therapeutic doses.

(1) Zahner H., Schares G. (1993) Experimental chemotherapy of filariasis: comparative evaluation of the efficacy of filaricidal compounds in *Mastomys coucha* infected with *Litomosoides carinii*, *Acanthocheilonema viteae*, *Brugia malayi* and *B. pahangi*. *Acta Trop* 52: 221-66. (2) Dominguez-Vazquez A. et al. (1983) Comparison of flubendazole and diethylcarbamazine in treatment of onchocerciasis. *Lancet* 1: 139-43.





## PAEDIATRIC HIV

## Optimizing antiretroviral therapy for infants and young children in resource-poor settings

Despite the successes of programmes rolled out to reduce the number of new HIV infections in children, 330,000 children acquired HIV infection in 2011, more than 90% of whom were in sub-Saharan Africa. An estimated 3.3 million children under the age of fifteen were living with HIV in 2011 and 230,000 died of AIDS-related causes.<sup>[1]</sup> While the absolute number of infants newly infected with HIV is now declining due to progress in prevention of mother-to-child transmission (PMTCT), the need for paediatric treatment will continue to increase until 2020 at least.

The majority of children with HIV are infected through perinatal transmission during foetal development, birth, or whilst being breastfed. Whereas in high-income countries, HIV transmission in young children has largely been eliminated due to effective PMTCT interventions, in low- and middle-income countries many pregnant women do not have access to antenatal care and HIV testing. Therefore they do not benefit from interventions to prevent transmission to their child: in those countries, coverage of effective antiretroviral regimens for PMTCT reached only 57% in 2011.<sup>[2]</sup>

Provision of adequate treatment to those children who do become infected is vital. HIV-infected infants frequently develop illness within their first months of life. In the absence of antiretroviral therapy (ART), almost one-third of them die before their first birthday, and about half die before they are two years old.<sup>[3]</sup> Even though the 2010 WHO guidelines recommend that all children younger than two years start immediately on ART, less than one-third of eligible children under the age of fifteen were receiving the life-saving medicines in 2011.<sup>[4]</sup> ART coverage is even lower in children under the age of five, notably because of the lack of appropriate tools to diagnose HIV early in the child's life and of therapeutic options adapted to their needs. Although more than 25 drugs are approved for adults, many have not yet been tested and approved for use in children, limiting the number of therapeutic options for caregivers and children. The drugs that are approved for children need to be associated to act synergistically in order to suppress HIV replication. These combination antiretroviral therapies (cARTs) of three or four drugs are few, complex to administer, and will have to be taken for life.

With growing evidence of its superiority in infants and young children with very high viral loads, protease inhibitor (PI)-based cART is increasingly preferred as first-line therapy in low- and middle-income countries, as recommended by the 2013 WHO guidelines.<sup>[5]</sup> However, currently available PI-based paediatric formulations have serious limitations. They are in an alcohol-based liquid form with poorly tolerated taste, are difficult to administer, and carry a high risk of dosing errors. In addition, they have a short shelf-life, require a cold chain, and are voluminous and expensive.

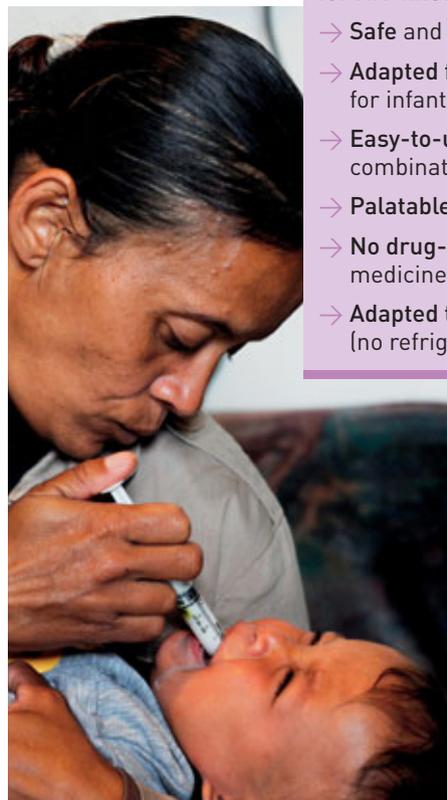
Finally, many children need to be treated for both HIV and tuberculosis (TB) and there are significant negative drug-drug interactions between anti-TB drugs and anti-HIV drugs. HIV-infected children co-infected with TB have a particularly poor prognosis.<sup>[6]</sup> These drug interactions need to be addressed either by new drugs or adapted dosages.

Improved first-line therapies for children are urgently needed.

### Ideal Target Product Profile for Paediatric HIV

A first-line, protease inhibitor-based **all-in-one** antiretroviral regimen for HIV-infected children:

- Safe and efficacious
- Adapted formulation suitable for infants and children
- Easy-to-use fixed dose combination
- Palatable
- No drug-drug interaction with medicines for tuberculosis
- Adapted to tropical climates (no refrigeration needed)



(1) Global report: UNAIDS report on the global AIDS epidemic 2012, Geneva, 2012. (2) Ibid. (3) Newell, M. et al. (2004) Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. *Lancet* 364: 9441. (4) Global report: UNAIDS report on the global AIDS epidemic 2012, Geneva, 2012. (5) Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, WHO, June 2013. (6) Children and AIDS: Fifth Stocktaking Report. New York, UNICEF/UNAIDS/WHO/UNFPA/UNESCO, 2010.

# Paediatric HIV



## WHAT IS THE IMPACT OF PAEDIATRIC HIV?

At the end of 2011, an estimated 3.3 million children below the age of 15 were living with HIV, more than 90% of whom in sub-Saharan Africa. An estimated 230,000 children under 15 years of age died of AIDS-related illness in 2010. In low- and middle-income countries, access to treatment has expanded to reach an estimated 562,000 HIV-infected children under the age of 15. Still, only 28% of HIV-positive children are estimated to be on antiretroviral therapy (ART), compared to 68% of adult women and 47% of adult men.<sup>(1)</sup>

## 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. However, with antiretroviral prophylaxis throughout pregnancy, delivery, and breastfeeding, transmission can be decreased to a few percent.

## WHAT ARE THE SYMPTOMS?

HIV is difficult to diagnose in children and infants: indeed, signs and symptoms are non-specific and are very common in resource-poor settings, such as chronic diarrhea, recurrent infection, and failure to thrive. However, the disease progresses rapidly and can lead to death before HIV has been diagnosed or even suspected. All children born to HIV-infected mothers carry maternal anti-HIV antibodies, and are thus seropositive. A positive serological test therefore does not necessarily indicate HIV infection. Only very expensive diagnostic tests that detect the virus itself can give an accurate diagnosis in the first months of life. New tests are currently under development.

## WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

The 2010 WHO guidelines recommend early diagnosis and immediate treatment of HIV-positive infants and children under the age of two; for those with prior exposure to PMTCT, PI-based first-line therapy is recommended, but results of a superior response to such therapy in children without prior exposure to PMTCT have also been reported.<sup>(2)</sup> The combination of a **boosted protease inhibitor** with **two nucleoside reverse transcriptase inhibitors** (NRTIs) is considered by many experts as the most effective first-line therapy for infants and children, regardless of prior exposure to ARVs.

However, this 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, LPV/r), 97% of whom were in South Africa. The only available PI for young children, LPV/r does not come in a child-friendly formulation: the oral solution formulation is unpalatable, contains 42% alcohol, and is not adapted to resource-poor settings due to major logistical constraints: it requires refrigeration, has a short shelf-life when exposed to heat, is expensive, and is difficult to store and transport.

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 ARV treatment. In order to counteract this interaction, extra ritonavir needs to be added to the standard proportion of LPV/r. This is called 'superboosting', and requires the development of an infant-friendly formulation of ritonavir. The currently available ritonavir formulation suffers the same limitations as the current formulation of LPV/r with regard to taste, high alcohol content, and logistical constraints.

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

In 2010, DNDi was called on by various organizations, including Médecins Sans Frontières, WHO, and UNITAID, to apply its expertise to the development of paediatric HIV treatments. DNDi's position, notably that paediatric HIV is a neglected disease, was published as a 'Perspective' in the *New England Journal of Medicine* in August 2011.<sup>(3)</sup>

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

- Develop and register two solid first-line 4-in-1 LPV/r-based fixed-dose combinations (FDCs) with 2 NRTIs. All components of the combination will be developed in the form of taste-masked granules, stable with no need for refrigeration, presented in a single unit with appropriate strengths to accommodate weight band dosing.
- Develop and register 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.

As a **short-term strategy**, DNDi will start implementing the use of PI-based treatment with existing LPV/r-based products before the availability of the 4-in-1 FDC, in order to provide better treatment for infants today and promote in-country adoption. DNDi participated in the CHAPAS-2 trial that compared LPV/r sprinkles (hereafter referred to as minitables) to the LPV/r liquid formulation. These minitables will be used in association with NRTI dispersible tablets in implementation studies as part of this short-term strategy.

In the mid-term, DNDi is working with its industrial partner, Cipla Ltd., on combining LPV/r granules with two NRTIs into a single unit dose. This modular concept is flexible, so that any of the components can eventually be substituted to provide new fixed-dose combinations.

In addition, in order to address the needs of HIV/TB co-infected children, DNDi is developing a formulation of ritonavir for superboosting LPV/r at a 1:1 ratio. A pharmacokinetic study to establish the efficacy and safety of superboosted LPV/r is ongoing in South Africa with the existing ritonavir solution.

### By 2015-2016, DNDi aims to deliver from its paediatric HIV portfolio:

- Two new all-in-one paediatric formulations containing a PI and two NRTIs
- One stand-alone paediatric booster for HIV-TB co-infected children

(1) Global report: UNAIDS report on the global AIDS epidemic 2012, Geneva, 2012. (2) Violari A. et al. (2012) Nevirapine versus ritonavir-boosted lopinavir for HIV-infected children. *N Engl J Med* 366: 2380-9. (3) Lallemand M. et al. (2011) Paediatric HIV - A Neglected Disease? *N Engl J Med* 365: 581-3.

## Improved PI for first-line treatment

### 2012 OBJECTIVE:

→ **Develop an improved PI that can be incorporated into a fixed-dose combination**

The project aims to improve the formulation of PI-based first-line treatment for young infants and children living with HIV. The development plan includes putting together all four drugs needed for the treatment of HIV in children into a single unit, also known as a fixed-dose combination (FDC), which is heat-stable, well taste-masked, solid, does not contain alcohol or inappropriate solvents and, most importantly, is easy to dose (using WHO-recommended weight band dosing) for the caregiver. The two FDCs in development are AZT/3TC/LPV/r and ABC/3TC/LPV/r. In order to counteract negative drug interactions between PIs and

rifampicin-containing TB treatment, a stand-alone booster ritonavir (RTV) formulation will be developed.

A paediatric pharmacokinetic expert group has been created to determine the optimal weight band dosing of LPV/r and NRTIs in order to deliver all components in an FDC. These doses are modelled using WHO weight band recommendations.

The two 4-in-1 FDCs and the stand-alone RTV booster will be tested in healthy human volunteers in 2013.



### Partners:

Cipla Ltd., India

### Leadership:

Head of Paediatric HIV Programme: Marc Lallemand;  
Project Coordinator: Janice Lee;  
Senior Pharma Advisor & Product Manager: Jean-René Kiechel

### Project start:

December 2011



Translation

## PI Sprinkles (minitabets) (Chapas-2)

### 2012 OBJECTIVE:

→ **Clinically assess the pharmacokinetics and acceptability of LPV/r in the existing sprinkle (minitabets) formulation in children between 1-4 years of age (additional CHAPAS-2 cohort)**

The results of the PK study of LPV/r minitabets versus syrup (CHAPAS 2) in children aged 1 to 4 years were presented at CROI 2013.<sup>(1)</sup> Exposure to LPV/r minitabets was slightly higher than that to the liquid formulation. LPV exposure in this age group was similar to that

observed in infants, older children, and adults. Variability in LPV/r pharmacokinetic parameters was similar in both formulations and neither formulation resulted in sub-therapeutic concentrations. Caretakers preferred the minitabets formulation, particularly for storage/transport reasons. For this group of children, acceptability of both formulations was similar, in particular as regards to taste (these minitabets are not taste-masked).

### Partners:

DNDi joined this trial sponsored by the Medical Research Council (MRC), UK, as an additional partner. Other partners include Cipla Ltd., India; Joint Clinical Research Centre, Uganda; Makerere University/Mulago Hospital, Uganda; Radboud University Nijmegen Medical Centre, The Netherlands

### Leadership:

Head of Paediatric HIV Programme: Marc Lallemand; Project Coordinator: Janice Lee

### Project start:

May 2012



Development

## 'Superboosting' – TB/HIV

### 2012 OBJECTIVE:

→ **Evaluate the safety and pharmacokinetics of increasing LPV/r boosting ratio from 4:1 to 1:1 in HIV/TB co-infected infants and children in order to counteract the negative drug-drug interactions between PIs and rifampicin-containing TB treatments**

This study is essential to support and prepare the development of a stand-alone ritonavir booster formulation that can be added to any PI-based paediatric ARV regimen. It will be performed in infants and young children co-infected with TB and HIV at 5 sites in South Africa. Site initiation visits were conducted in

October 2012, and the first ethics approval was received from Cape Town Tygerberg Hospital at the end of the year.

The study is expected to end in 2014 and results will be available at the beginning of 2015.



### Partners:

SOUTH AFRICA: Stellenbosch University and Tygerberg Children's Hospital; Perinatal HIV Research Unit; Shandukani Research Centre; Empilweni Services and Research Unit, Rahima Moosa Mother and Child Hospital; Enhancing Care Foundation; Department of Health; Department of Science and Technology

### Leadership:

Head of Paediatric HIV Programme: Marc Lallemand; Project Coordinator: Janice Lee

### Project start:

May 2012



Development

(1) Kitaka S. et al. Pharmacokinetics and acceptability of a new generic lopinavir/ritonavir sprinkle formulation in African, HIV+ children 1-4 Years: CHAPAS-2. CROI 2013. Poster 975b.

## MALARIA



# Ensuring access to ACTs to fight malaria

Malaria is a major public health problem that continues to affect millions across the world, mainly children under the age of five. The development of multi-drug resistant *Plasmodium falciparum* parasites and resulting failure of treatment with chloroquine and sulfadoxine-pyrimethamine led the World Health Organization (WHO) to recommend the use of artemisinin-based combination therapies (ACTs) for the treatment of uncomplicated *P. falciparum* malaria in 2001. Recently, delayed parasite clearance indicative of resistance to artemisinin has been reported in some areas of South-East Asia, sparking a global response to contain resistant parasites before they spread around the world. Despite these concerns, ACTs remain the best available anti-malarial medicines and are still highly effective in the majority of malaria endemic areas. Fixed-dose combinations (FDCs) of ACTs are preferred and recommended, as they promote adherence to treatment and reduce the potential of selective use of the medicines as monotherapy. Since 2005, the number of ACT treatment courses procured by the public sector has increased from 11.2 million to 76 million in 2006, and reached 181 million in 2010.

In 2002, the Fixed-Dose Artesunate-Based Combination Therapies (FACT) Consortium, created by the DND Working Group and TDR, started to develop two fixed-dose artesunate (AS)-based combination therapies (out of the four initially recommended by WHO):

- **ASAQ**, the FDC of artesunate and amodiaquine developed in partnership with Sanofi, was first registered in 2007 and pre-qualified by WHO in 2008;
- **ASMQ**, the FDC of artesunate and mefloquine developed in partnership with Farmanguinhos (first registered in Brazil in 2008) and then, after a technology transfer, also produced by Cipla Ltd. (first registered in India in 2011), and pre-qualified by WHO in 2012.

FDCs enable simple treatment regimens, therefore increasing patient compliance. ASAQ and ASMQ, together with CoArtem® (the FDC of artemether and lumefantrine developed by Novartis and the first ACT pre-qualified by the WHO in 2001), Pyramax® (the FDC of artesunate-pyronaridine) and Eurartesim® (the FDC of dihydroartemisinin-piperazine [DHA/PQP]), both developed by the Medicines for Malaria Venture (MMV) and approved in 2011, strengthen the global ACT portfolio of FDCs now available for the treatment of uncomplicated *P. falciparum* malaria. Fixed doses of some of these combinations, developed by other manufacturers,

have recently been developed and pre-qualified by the WHO. Together with diagnosis and vector control tools, they represent a key improvement of the antimalarial arsenal.

### FACT SHEET

## Malaria

#### WHAT IS THE IMPACT OF MALARIA?

The WHO estimates that there were 216 million of cases of malaria in 2010, and that 660,000 deaths were attributable to the disease, 86% of which occurred in children under five and 91% in sub-Saharan Africa. A 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.<sup>(1)</sup>

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 ACTs, and malaria control continues to face serious challenges.<sup>(2)</sup>

#### HOW IS MALARIA TRANSMITTED?

Malaria is caused by *Plasmodium* parasites, spread to people through the bite of an infected female anopheles 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 active malaria transmission.

#### WHAT ARE THE SYMPTOMS?

Malaria is an acute febrile illness with initial symptoms that 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.

(1) Murray, C.J.L. *et al.* (2012) *Global malaria mortality between 1980 and 2010: a systematic analysis*. *Lancet* 379: 413–31.

(2) *A Decade of Partnerships and Results, Progress and Impact Series, number 7, World Health Organization, Geneva, 2011.*

HUMAN AFRICAN  
TRYPANOSOMIASIS (HAT)

LEISHMANIASIS

CHAGAS DISEASE

FILARIAL DISEASES

PAEDIATRIC HIV

MALARIA

## ASMQ FDC

### 2012 OBJECTIVES:

- Technology transfer and registration:
  - Support activities for prequalification by WHO and PAHO
  - Obtain registration authorization in India and South-East Asia
  - Reduce cost of mefloquine to decrease the price of ASMQ FDC
- Clinical studies
  - Progress the multicentre comparative study conducted in three African countries



**PHASE IIIB**  
study in children:  
751/940 patients  
recruited  
by end 2012  
at 4 sites  
in 3 countries

pre-agreed prices. The product was registered in India in 2011, in Malaysia in March 2012, and in Myanmar in October 2012. In September 2012, Cipla Ltd.'s ASMQ FDC received WHO prequalification, an important step in accelerating access in Asia.

Additional clinical studies are ongoing that will provide information on 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 information on the efficacy and tolerability of ASMQ FDC, DNDi is sponsoring a multicentre Phase IIIB study in Tanzania, Burkina Faso, and Kenya to assess its efficacy, safety, and pharmacokinetics compared to artemether-lumefantrine in children below the age of 5. The study is expected to end in October 2013 and the first results will be available at the beginning of 2014.

### Partners:

Farmanguinhos, Brazil; Cipla Ltd., India; Shoklo Malaria Research Unit, Thailand; Universiti Sains Malaysia; Oxford University, UK; WHO-TDR; Indian Council of Medical Research (ICMR), India; Epicentre, France; Centre Hospitalier Universitaire Vaudois, Switzerland; National Institute of Medical Research, Tanzania; Kenya Medical Research Institute (KEMRI), Kenya; Centre National de Recherche et de Formation sur le Paludisme, Burkina Faso; Medicines for Malaria Venture (MMV), Switzerland; Ifakara Health Institute, Tanzania

### Leadership:

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

**Project start:** January 2002



Implementation

The ASMQ fixed-dose combination (FDC) was developed by the FACT consortium created by DNDi and TDR in 2002. Within FACT, the Brazilian government-owned pharmaceutical company, Farmanguinhos/Fiocruz, was the first manufacturer of ASMQ FDC, which was registered in Brazil in March 2008. Through a South-South technology transfer, ASMQ FDC production was transferred to the Indian pharmaceutical company Cipla Ltd. in 2010 to ensure availability in India and Asia at affordable,



### ASMQ FDC WHO Prequalified

At a special DNDi event in Kuala Lumpur, Malaysia, on 3 October 2012, WHO prequalification of the Cipla-manufactured ASMQ FDC is announced at a press conference with Malaysia's Minister of Health, Dato' Sri Liow Tiong Lai. A prequalified status makes ASMQ FDC eligible to tenders that receive funding from international procurement agencies, such as UNICEF and the Global Fund to Fight AIDS, Tuberculosis and Malaria.

## ASAQ Winthrop

### 2012 OBJECTIVE:

- Diversify ASAQ suppliers by transferring technology to a partner in Africa
- Facilitate implementation of ACTs FDC in general and specifically ASAQ, in all countries where it could benefit patients and abides by local practices



**180 MILLION**  
treatments  
distributed  
in 30 African  
countries  
by the end  
of 2012

By the end of 2012, over 180 million treatments had been distributed in 30 African countries. First registered in Morocco, where it is manufactured, ASAQ is now registered in 30 African countries, as well as in India, Bangladesh, and

Colombia. In 2010, ASAQ Winthrop obtained WHO authorization for a three-year shelf life, giving the product the longest shelf-life of any pre-qualified FDC artemisinin-based treatment available for malaria. In partnership with Sanofi, MMV, and National Malaria Control Programmes, high-quality data on ASAQ effectiveness and safety in the field is being collected, as part of a Risk Management Plan (RMP). This was the first RMP submitted to the WHO, and the first to be set up entirely in Africa. It is expected to contribute to building capacity on drug safety and efficacy monitoring in sub-Saharan African countries and could set the precedent for further real-life assessment studies of new ACTs. Together with partners, DNDi is also working on the transfer of technology to a second manufacturer in Africa, Zenufa, in Tanzania.

### Partners:

Sanofi, France; MMV, Switzerland; AEDES, Belgium; Zenufa, Tanzania; National Centre for Research and Training on Malaria, Burkina Faso; Universiti Sains Malaysia; Oxford University, UK; Institute of Research for Development (IRD), Senegal; Université Bordeaux Segalen, Faculté de Pharmacie, France; Mahidol University, Thailand; Bertin Pharma, France; Médecins Sans Frontières; Epicentre, France; WHO-TDR; KEMRI, Kenya; ICMR, India; National Malaria Control Programme, Ministry of Health, Burundi; Ministry of Health, Sierra Leone; Ministry of Health, Ghana; Komfo Anokye Teaching Hospital (KATH), Ghana

### Leadership:

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

**Project start:**  
January 2002



Implementation



# 2012 KEY FINANCIAL PERFORMANCE INDICATORS

## EUR 22.8 million in R&D expenditures to match a flourishing portfolio

R&D EXPENDITURE BY DISEASE 2011-2012



Overall R&D expenditure of EUR 22.8 M increased by 13.5 % (EUR 2.7 M) in 2012. The percentage breakdown of 2012 R&D expenditure by disease highlights:

**HAT:** With a total of EUR 5 M, investments decreased (- EUR 1.3 M) due to redirecting screening and lead optimization to an external partner (- EUR 1.1 M), and clinical activities starting for fexinidazole (+ EUR 0.5 M); the oxaborole SCYX-7158 project expenditure was mainly dedicated to pharmacological studies and PK analysis (- EUR 0.5 M); and NECT two-year follow-up was completed (- EUR 0.2 M).

**Leishmaniasis:** For the first time, leishmaniasis projects became the most substantial part of R&D expenditure (34%) as projected in the Business Plan, with EUR 1.9 M. Expenditure increase illustrates substantial activity: patient recruitment in the Asia implementation study (+ EUR 0.8 M); cutaneous leishmaniasis topical treatment ready to enter clinical phase at end 2012 (+ EUR 0.5 M); preparation of two new clinical trials in Africa for fexinidazole (+ EUR 0.1 M) and HIV/VL co-infection (+ EUR 0.3 M); total investment for the lead optimization (LO) consortium and screening activities was EUR 2.5 M (approx. 43% of the LO and screening costs, + EUR 0.2 M).

**Chagas disease:** Projects remained stable in 2012 with EUR 4.7 M (23% of R&D expenditure).

**Portfolio expansion:** Expansion to include two new diseases areas represents 9% of R&D expenditure. **Paediatric HIV** expenditure doubled, with two activities: preparation of a clinical study for the super-boosting project (ritonavir for superboosting LPV/r) in South Africa (EUR 0.25 M) and DNDi's participation to the PI sprinkles (minitabets) CHAPAS project (EUR 0.25 M) in Ghana. The **filaria** project increased by 270% due to preparing the Investigational Medicinal Product Dossier for flubendazole and to the development of an oral formulation suitable for human clinical use (+ EUR 0.35 M), in addition to screening activities (+ EUR 0.25 M).

## Stark increase in leveraging of partner resources

IN-KIND CONTRIBUTIONS 2006-2012



In order to present a comprehensive picture of its activities, DNDi values the in-kind contribution of its generous partners (private companies, academic groups, and individuals).

In seven years, in-kind contributions have increased eight-fold. This reflects the investment by DNDi in consolidating such partnerships and the increasing engagement of these partners in neglected disease R&D.

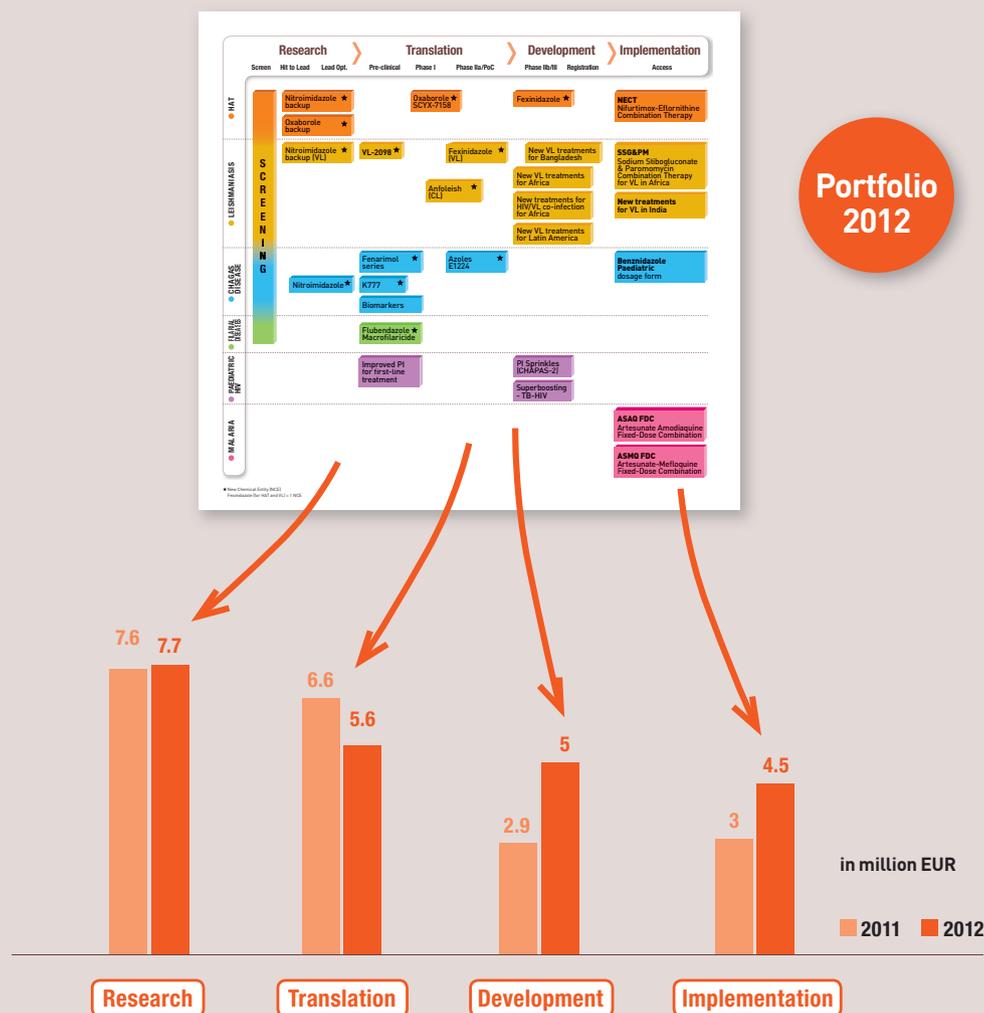
The major contribution reported, 50% of all annual totals from 2009 to present, relates to pharmaceutical development of azole E1224 (Chagas disease) and fexinidazole (HAT) with industrial partners.

As in 2011, the total 2012 in-kind contribution reached approximately 20% of total expenses.

# 2012 KEY FINANCIAL PERFORMANCE INDICATORS

## Development and implementation expenditure increases as treatments approach the end of the pipeline

R&D EXPENDITURE BY R&D STAGE



In 2012, the most important fluctuations relate to growth of clinical development and progress of implementation activities (+ EUR 3.7 M).

**Research:** Screening and lead optimization activities remain stable (+EUR 0.1 M). However, some changes occurred in the set-up of activities, namely in screening for filarial diseases and in the partnerships that have been redesigned in a more suitable way, allowing for greater cost efficiency.

**Translation:** Expenditure decreases between 2011 and 2012 (- EUR 1 M), mainly due to: progression of fexinidazole for HAT to clinical development; four projects in transition phase (VL-2098, oxaborole SCYX-7158, azole E1224 and biomarkers, and K777); increasing activities of the two new disease areas of the portfolio, filarial diseases and paediatric HIV.

**Development:** The progression of two projects to clinical development led to an increase of expenditure (+ EUR 2.1 M): fexinidazole for HAT started Phase II/III study, and the VL and HIV/VL co-infection study started Phase IIb/III.

**Implementation:** With six projects in implementation phase, expenditure increased by 50% (+ EUR 1.5 M) mainly due to the paediatric dosage form of benznidazole implementation after registration in December 2011, and the start of recruitment in India for the VL Asia study, with 300 patients recruited.