



## R&D Model & Portfolio

# Paving the Way to Improve R&D Outcomes for Neglected Diseases

**D**rug discovery and development is inherently challenging, and failure (or attrition) – while often providing a key source of knowledge for next steps – is inevitable. Given the high attrition rates in the R&D process, keeping a steady flow of backups to feed into the pipeline is of paramount importance. The early phase of research therefore requires not only access to large libraries of compounds to screen from, but also the knowledge, data, and expertise that go with them.

### Experimenting new R&D pathways

In 2012, at the launch of the London Declaration, DNDi called for a move beyond the silos of bilateral agreements with pharmaceutical partners and

sought more 'out-of-the-box' mechanisms of working in new, multilateral ways. In order to accelerate the early phases of research, and to multiply effectiveness while potentially reducing cost, DNDi began to engineer a Drug Discovery Booster that would allow for cross-company screening. Unthinkable years ago, the partnership model of drug discovery is ripe for experimentation in innovation when the benefits for all can outweigh the risks.

In just over a decade, DNDi has developed partnerships with many major pharmaceutical and biotechnology companies that range from bilateral screening of selections of libraries, to the beginnings of multi-lateral screening projects. In addition, agreements can be targeted to a specific drug that has already

shown great promise for a particular disease, such as the agreement concluded last year with Bayer HealthCare for the development of emodepside as a potential oral macrofilaricide for onchocerciasis. Further down the pipeline, solid manufacturing and distribution partners are key to ensuring that when a drug passes through the threshold of attrition, and proves safe and effective in patients, access to the treatment is guaranteed.

**R&D for policy change and access**

The year 2014 saw some important results that show the extent to which evidence from clinical research can feed directly into policy decisions of ministries of health, and can help to ensure that regulatory approval is not hindered by lack of evidence. For example, SSG&PM pharmacovigilance study results in Africa were key for inclusion of the leishmaniasis treatment in **Ethiopia's** essential drug list, which is part of the regulatory requirements to ensure procurement and treatment access in this high-burden country. India awaited results of a pilot study for visceral leishmaniasis treatments in order to adapt its national guidelines, thus aligning with the WHO-

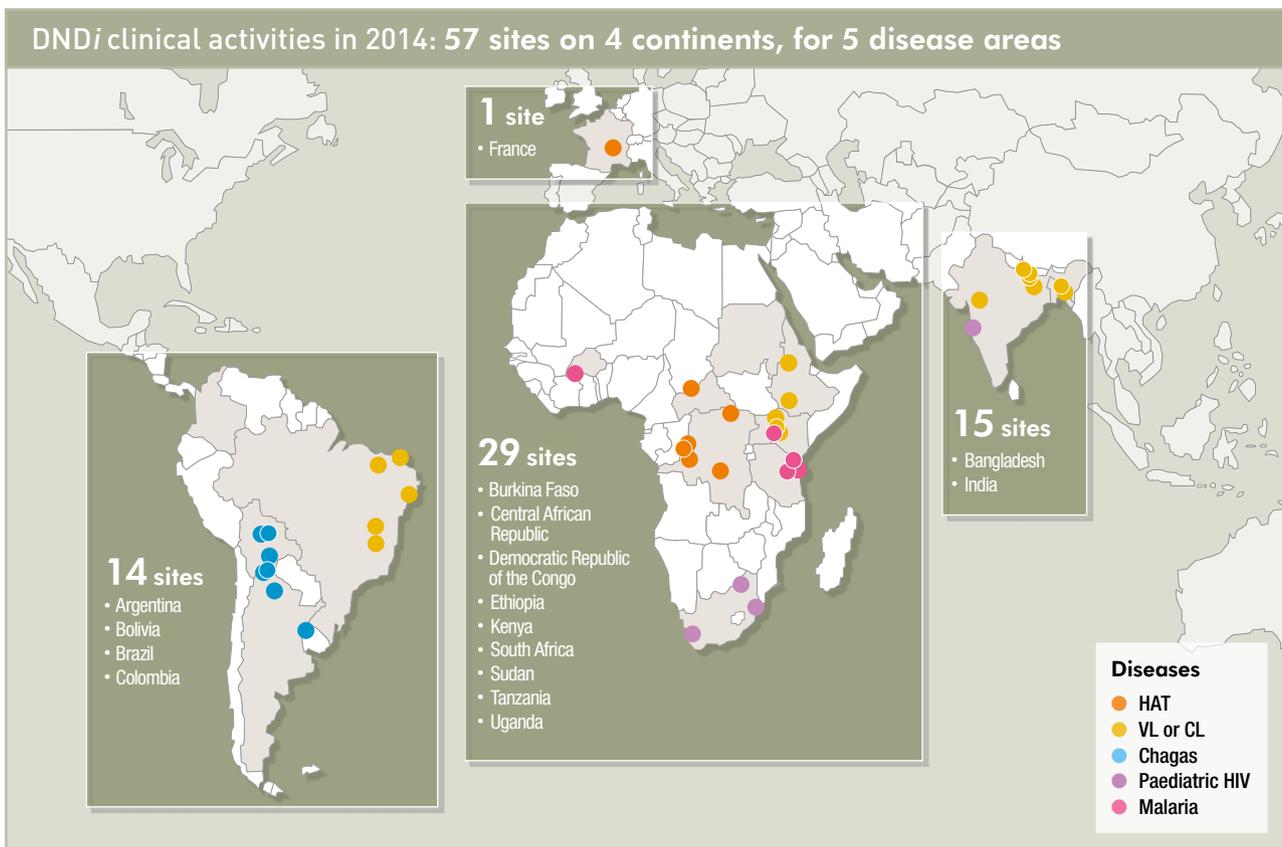
recommended treatments being tested in the trial. In addition, a comparable drug trial was completed in **Bangladesh**, with a view to similar policy changes, as was also the case in **Nepal**. These trials in Asia share the important outcome of replacing the use of miltefosine as a monotherapy. These examples show the extent to which national guidelines require in-country clinical testing of treatments, which then allow governments to take important policy decisions that affect their populations.

In the field of Chagas disease, support was given to prepare a deployment strategy in **Argentina, Brazil, Bolivia, Mexico, Colombia**, and the **USA**, in collaboration with the Pan-American Health Organization/WHO and national control programmes, through the work of the Global Chagas Disease Coalition, aimed at analysing and acquiring accurate numbers of cases to improve demand forecasting for treatments. Projects such as these can pave the way to greater access to existing treatments when appropriate, but also ensure that when new essential medicines reach fruition through clinical trials, they respond as quickly as possible to urgent public health needs.

*DNDi Africa*

*DNDi India*

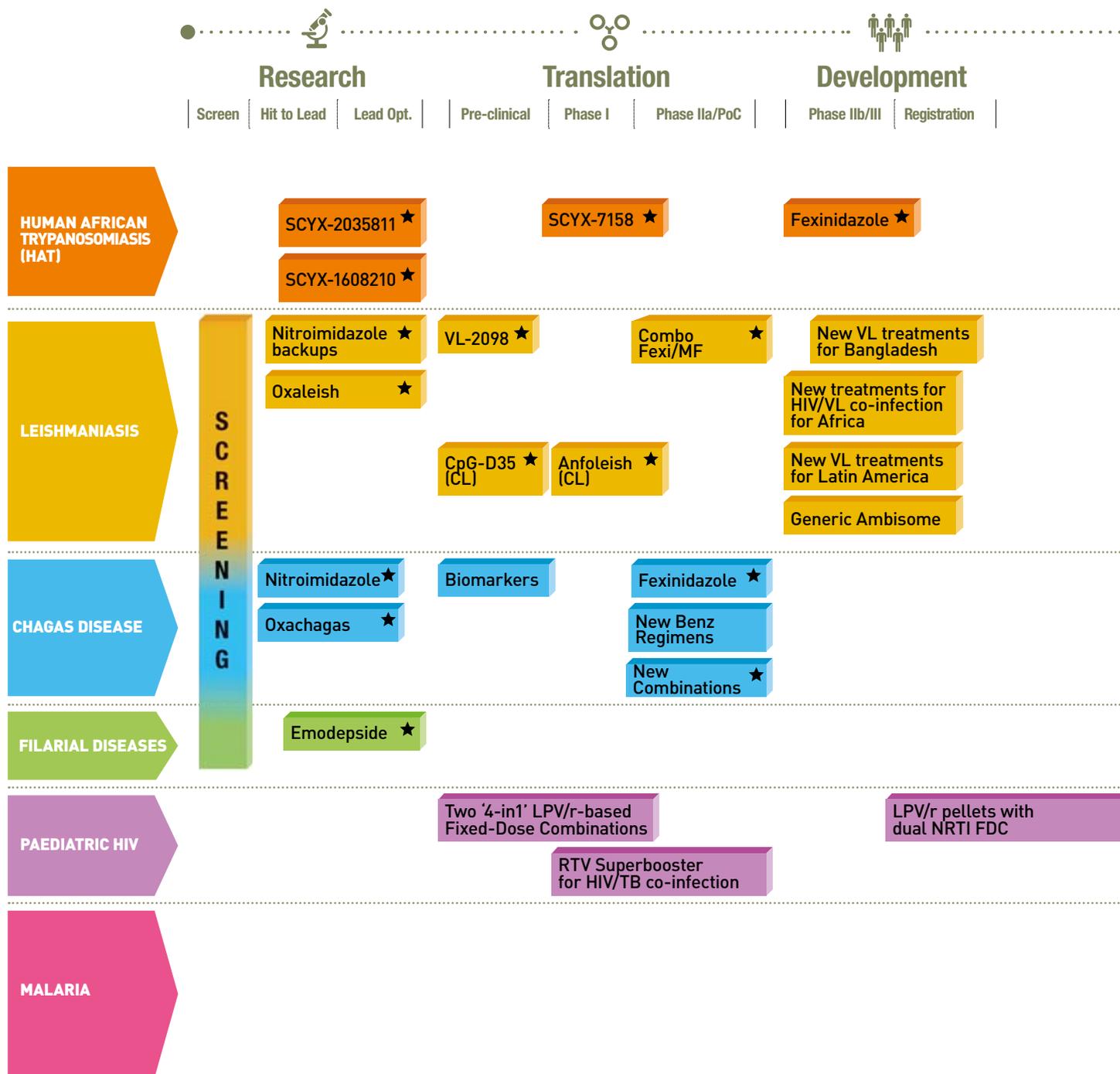
*DNDi Latin America*



# Building a robust portfolio

Projects are divided into five categories:

- **New treatments (involving NCEs) developed from novel compounds identified through screening, lead optimization, or licensing.** These drugs must meet target product profiles (TPPs) and may be used in monotherapy or as part of combination therapies when appropriate.



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

- **New treatments developed from compounds with known antimicrobial/antiparasitic activities** aiming to maintain or improve efficacy and tolerability.
- **Compound repurposing for new indications of existing treatments in other diseases** (therapeutic switching).
- **Combinations or new formulations of existing drugs that are better adapted to field conditions and patient needs** (paediatric dosage forms, long-acting forms, new route of administration, fixed-dose combinations, co-packaging, or co-administration).
- **Geographical extension of existing treatments**, including completion of regulatory dossiers in new countries.



## Implementation

Access

### NECT

Nifurtimox-Eflornithine Combination Therapy

### SSG&PM

Sodium Stibogluconate & Paromomycin Combination Therapy for VL in Africa

**New VL treatments for India**

**Benznidazole**  
Paediatric dosage form

### ASAQ FDC

Artesunate Amodiaquine Fixed-Dose Combination

### ASMQ FDC

Artesunate-Mefloquine Fixed-Dose Combination

## Key R&D milestones in 2014

### HUMAN AFRICAN TRYPANOSOMIASIS (HAT)

- Oxaborole SCYX-7158 phase I trial nearing completion
- Fexinidazole: 359 patients recruited into a pivotal trial by end of year and two complimentary studies initiated: one for early second stage/first stage HAT in adults, and another for children aged 6 to 14 years

### LEISHMANIASIS

- Pharmacovigilance results confirmed safety and high efficacy of SSG&PM to treat VL in East Africa
- Trials with combination treatments and AmBisome monotherapy confirmed safety and efficacy for kala-azar in Bangladesh (Phase III), with interim results from the pilot implementation study used by the Indian government to revise VL treatment policy
- Two nitroimidazole pre-clinical candidate drugs identified for VL
- VL-2098 safety studies completed
- CpG-D35 nominated as a pre-clinical candidate for CL

### CHAGAS DISEASE

- Fexinidazole proof-of-concept trial initiated
- E1224/benznidazole interaction study undertaken
- A nitroimidazole series identified for optimization in Chagas disease

### FILARIAL DISEASES

- Agreement signed with Bayer to develop emodepside as new oral treatment for onchocerciasis

### PAEDIATRIC HIV

- Over 20 solid formulations of taste-masked LPV/r were tested in animal models
- Recruitment into RTV superbooster pharmacokinetics trial nearing completion

### MALARIA

- Multicentre study in African children found ASMQ FDC to be as safe and efficacious as artemether-lumefantrine FDC
- Large scale field-monitoring trial with ASAQ FDC almost complete in partnership with MMV and Sanofi (results expected in 2015) and DNDi malaria projects formally handed over to MMV (in 2015)

# Discovery

**D**NDi has a pragmatic approach to early stage drug discovery in order to maximize success from screening campaigns and minimize the attrition rate in subsequent hit-to-lead and lead optimization programmes, whilst working within the confines of limited resources.

## Optimizing the number of 'hit' compounds

Screening against *Leishmania* parasites is particularly challenging and gives rise to very low hit rates, no doubt due in some part to the intracellular nature of the parasite. Core diversity libraries offer the best opportunities for maximizing the number of hits obtained. Screening for Chagas and visceral leishmaniasis (VL)

against these and other pharmaceutical or commercial libraries – including natural products, collections made up of particular classes, or of compounds with specific properties – generates 'hit' compounds for further evaluation and optimization. The Swiss Tropical and Public Health Institute (Swiss TPH) and the University of Antwerp (LMPH) serve as reference screening centres to ensure that screening methodologies are comparable, and that assays performed at different sites and with different groups meet the same standards.

Compound mining of well-annotated chemical compound libraries aims to identify new active starting points for VL, Chagas, and filariasis, for which data on chemistry, early pre-clinical profiling, druggability, and possibly even targets

## Transmission



Chagas disease is caused by the kinetoplastid protozoan parasite *Trypanosoma cruzi*. It is primarily transmitted by large, blood-sucking reduviid insects widely known as 'kissing bugs'.



HAT is caused by two sub-species of kinetoplastid protozoan parasites: *Trypanosoma brucei gambiense* (West and Central Africa), and *T. b. rhodesiense* (East Africa). Parasites are transmitted to humans by tsetse flies.



Leishmaniasis is a diverse and complex disease caused by more than 20 species of the kinetoplastid protozoan parasite. *Leishmania* parasites can be transmitted to humans by some 30 species of phlebotomine sandflies.



Malaria is caused by the *Plasmodium* parasite. Five species are involved: *P. falciparum*, *P. malariae*, *P. vivax*, *P. ovale* & *P. falciparum*. They are transmitted from person to person by the bite of infected anopheline mosquitoes.



Onchocerciasis (River blindness), Lymphatic filariasis (Elephantiasis) and Loiasis (*Loa loa* infection) are all caused by parasitic filarial nematode worms. They are transmitted between humans by blood-sucking insects.



The human immunodeficiency virus is a lentivirus that causes HIV infection and acquired immunodeficiency syndrome. About 90% of the infected infants acquire the HIV virus from their HIV-positive mothers during pregnancy, delivery, or through breast-feeding (known as mother-to-child transmission).

and modes of action are already available. Promising compound classes are identified by sampling a subset of representative compounds and testing for antiprotozoal activity. Classes successfully identified, and which form part of the DNDi's lead optimization programme, include oxaboroles (Anacor Pharmaceuticals), nitroimidazoles (TB Alliance and other compound sources), and aminopyrazoles (Pfizer), with numerous series from different companies in hit-to-lead research. Re-purposing of pre-clinical and clinical candidates – active compounds which have been previously developed for different therapeutic indications, and for which there may be a significant amount of pre-clinical or even clinical data available – has resulted in the successful development of fexinidazole, a nitroimidazole currently undergoing clinical development.

DNDi  
Latin  
America

Working with lead optimization consortia, and most recently within the DNDi Lead Optimization Latin America (LOLA) programme, DNDi aims is to advance new chemical classes identified through its screening programmes, and to develop backups in case of failure of more advanced compounds. Optimization efforts focus on, amongst others, improving antiparasitic activity, increasing tolerability and safety, and enhancing compound absorption and distribution in the body whilst mitigating breakdown and excretion.

### Adopting a multilateral approach

With a view to rapidly expanding promising hits/hit series against *L. donovani* (leishmaniasis parasite) and *T. cruzi* (Chagas disease parasite), DNDi is moving from a bilateral to a multilateral approach with drug companies, and was in negotiation with a number of companies throughout 2014 with the aim of building a global consortium for its Neglected Tropical Disease (NTD) Drug Discovery Booster experiment. This will provide series with well-developed structure activity relationships (SAR) ready for immediate *in vivo* proof-of-concept studies or, where necessary, focused medicinal chemistry optimization to provide improved tools ready for *in vivo* studies.

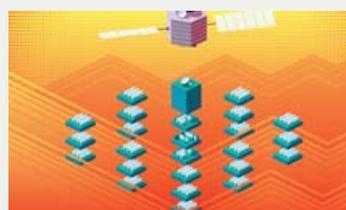
## Snap shots of the NTD drug discovery booster experiment\*



Today DNDi is identifying promising new compounds to develop effective drugs, by searching through segments of their partners' vast compound libraries, and testing them against infected cells.



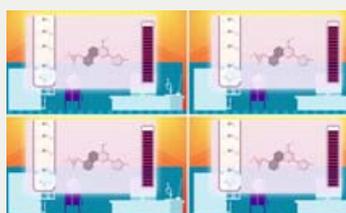
But working in this bilateral way, with limited capabilities and limited access means only a small amount of compounds are screened. Imagine this process being multilateral rather than bilateral.



The Drug Discovery Booster is an experiment in innovation and collaboration, between several pharmaceutical companies working together through DNDi, as a consortium, to achieve faster, cheaper, more efficient process.



As before, the same 'hit' is sent to each consortium member as the seed for growing into a collection of related molecules: a chemical series. But now there are several libraries, with each member looking simultaneously for similar yet potentially better structures than that of the seed.



Not only is the consortium cutting the time, but the quality of the hit and the series to which it belongs, is greater, due to the increased amount of information that went into its creation.



If it works, we hope it reveals another avenue to creating the drugs of tomorrow, today, by reducing the time and cost of development, and accelerating patient access to new life-saving drugs.

\* To see the full animated film about the NTD drug discovery booster experiment please visit [www.dndi.org/drugdiscoverybooster](http://www.dndi.org/drugdiscoverybooster)

# Screening

## Screening for kinetoplastids (leishmaniasis, Chagas disease, human African trypanosomiasis)

**OVERALL AIM:** Establish a robust portfolio of drug discovery quality hits for the three kinetoplastid diseases, with a focus primarily on visceral leishmaniasis (VL) and Chagas disease

**2014 OBJECTIVES:** Access and screen compound collections from pharmaceutical and commercial sources for kinetoplastids; secure a high-quality screening capacity; focus high throughput screening on identification of novel hit series for VL and Chagas

High-throughput screening (HTS) of core diversity libraries from several pharmaceutical companies (Sanofi, Takeda, Eisai, Merck, AbbVie) was completed against *Leishmania donovani* and *Trypanosoma cruzi* in 2014, in collaboration with screening partners (University of Dundee and Institut Pasteur Korea). Several new starting points are currently being followed up in hit profiling, annotation, and hit-to-lead programmes. A high-throughput screening assay which uses cidal axenic *L. donovani* was previously developed by the University of Dundee and is now part of DNDi's routine VL screening cascade there, enabling the screening of very large collections (more than 50,000 compounds).

Over 170,000 compounds screened in assays against leishmaniasis and Chagas disease in 2014

Several VL active series were identified from GlaxoSmithKline's global compound library screen and progressed through a hit-to-lead programme by DNDi during 2014 in collaboration with the University of Dundee. Furthermore, a screening collaboration agreement with the university signed in December 2014 aims to screen approximately 500,000 compounds against VL.

**PARTNERS:** AbbVie, USA; Anacor, USA; Astellas, Japan; AstraZeneca, Sweden; Bayer, Germany; Bioascent, UK; Bristol-Myers Squibb, USA; Celgene, USA; Centro Nacional de Pesquisa em Energia e Materiais (CNPq) LN Bio, Brazil; Drug Discovery Unit (DDU) at the University of Dundee, UK; E.I. du Pont de Nemours, USA; Eisai Co. Ltd, Japan; GlaxoSmithKline, Tres Cantos, Spain; Institut Pasteur Korea (IPK), South Korea; Johnson & Johnson, USA; Laboratory of Microbiology, Parasitology, and Hygiene (LMPH), University of Antwerp, Belgium; London School of Hygiene & Tropical Medicine (LSHTM), UK; Medicines for Malaria Venture (MMV), Switzerland; Merck (MSD), USA; Microbial Chemistry Research Foundation, Japan; Northwick Park Institute for Medical Research, UK; Pfizer, USA; Pfizer Animal Health, USA; Sanofi, France; Sanofi Merial, USA; Special Programme for Research and Training in Tropical Diseases (WHO-TDR); Takeda, Japan; TB Alliance, USA; Swiss Tropical and Public Health Institute (Swiss TPH), Switzerland

## Screening of repurposing libraries for filarial diseases

**OVERALL AIM:** Identify new drug candidates using targeted compounds, primarily from repurposing libraries or focused sets with known antihelminthic activity from animal health companies

**2014 OBJECTIVE:** Identify one or two pre-clinical candidates

With the limited throughput of phenotypic screening against filarial nematodes, screening large chemical libraries is not possible and DNDi has negotiated access to smaller focused chemical series that are more likely to give rise to drug candidates. These include indications sets (compounds that have progressed to pre-clinical or clinical research but failed to reach the market), well-annotated sets of compounds (e.g. bioavailable sets or compounds which have been through lead optimization), chemical series from veterinary anti-infective research programs, or orthologous sets (compounds directed against human targets with similar gene sequences to the parasites). Over 7,000 compounds were screened *in vitro* (*Onchocerca*) and *in vivo* (*Litmosoides* model) in 2014, including from bioavailability sets (such as AbbVie, GlaxoSmithKline, Sanofi), and other libraries with specific properties or indications (for example NIH, MMV): approximately 100 compounds have shown activity. Those with appropriate pharmacokinetic profiles are being screened in rodent models of onchocerciasis and lymphatic filariasis. Drug repurposing is high risk, but with the potential to be highly rewarding if successful; and although most compounds will probably not be suitable as macrofilaricidal drugs, they will be a rich resource for developing new clinical candidates.

In addition to compounds that kill the adult worm, DNDi is also investigating compounds that target the endosymbiotic *Wolbachia* bacterium. A number of promising drug candidates for both targets are under review.

**PARTNERS:** Northwick Park Institute for Medical Research, UK; University Hospital of Bonn, Germany; AbbVie, USA; Sanofi Merial, USA; GlaxoSmithKline, UK; Novartis AH, Switzerland; Johnson & Johnson, USA; National Museum of Natural History Paris (MNHN), France; Medicines for Malaria Venture, Switzerland; National Institute of Health, USA; Merck Sharp & Dohme, USA

Over 7,000 compounds screened in 2014



## Lead Optimization

**OVERALL AIM:** Establish a robust portfolio of drug discovery quality lead series for the three kinetoplastid diseases

**2014 OBJECTIVES:**

- Leishmaniasis – progress two new chemical classes into lead optimization
- Chagas disease – develop new tools (*in vitro/in vivo*) to improve translation to humans

With new chemical entities currently undergoing clinical development for human African trypanosomiasis (HAT), since 2012 the focus of screening and lead optimization efforts has been on identifying compounds to develop for VL and Chagas disease.

Many advances have been made during 2014. The first *in vivo* proof of concept for a new chemical class (VL series 12 – aminopyrazoles) from Pfizer was achieved in the early curative model of VL. A full lead optimization programme is now underway. Several compounds demonstrated excellent activity *in vivo*. Two advanced lead oxaboroles, DNDi-2166148 and DNDi-2310789, were identified and will be scaled up to enable exploratory toxicology studies, which could enable selection of one as an optimized lead for VL.

A programme is ongoing to identify nitroimidazole backups in case VL-2098 (see p.27) does not successfully complete pre-clinical testing. Over 200 analogues have been pre-

pared so far, and two backup compounds originating from different core structures have been selected and are being further profiled for *in vivo* efficacy and safety. Multiple hits from screening with several pharmaceutical partners or from other sources were progressed into hit confirmation and expansion studies. Several series have moved into the hit-to-lead stage for both Chagas disease and VL.

A number of pharmacokinetic and pharmacodynamic studies have been conducted in animal models of VL using existing and experimental drugs to build improved PK/PD models and ameliorate the translation of new drugs from discovery into clinical studies. In addition, a new screening cascade for Chagas disease has been implemented: the insight gained into the PK/PD relationship of compounds from additional *in vitro* assays coupled with a new *in vivo* model will enable compounds to be moved forward with more confidence.

**PARTNERS:** Centre for Drug Candidate Optimisation (CDCO)/ Monash University, Australia; Epichem, Australia; Griffith University (Eskitis), Australia; iThemba, South Africa; LMPH, University of Antwerp, Belgium; LSHTM, UK; Novartis Institute for Tropical Diseases (NITD), Singapore; Pfizer, USA; Sandexis, UK; WuXi AppTech, China; Pace University, USA; LNBio, Campinas, Brazil; University of Campinas, Brazil; TCG Life Sciences, Kolkata, India; AbbVie, USA



**HAT in Democratic Republic of the Congo (DRC)**

DNDi mobile teams arrive by boat and car, to a remote village in the region of Bandundu in DRC. Firstly the mobile teams explain the screening procedure to the local population. Then blood tests are carried out by a member of the mobile team. The blood samples are examined to determine the presence of trypanosomes which is responsible for HAT. From these results patients are identified who need follow up treatment.

# DEVELOPING ORAL TREATMENTS FOR USE AT VILLAGE LEVEL

Sleeping sickness, or HAT, was on the verge of elimination in the 1960s, but relaxed surveillance, civil unrest, lack of investment and competing health priorities, combined with population displacement and poverty, led to a rise in the number of cases. The number of detected cases peaked in 1998, but efforts since then by the WHO, National Control Programmes, NGOs and other partners have improved detection, treatment, and control of the disease, resulting in significant decreases. HAT elimination as a public health problem (less than 1 case per 10,000 inhabitants in at least 90% of endemic foci) is targeted by the WHO for 2020. Part of this success is due to the introduction of nifurtimox-eflornithine combination therapy (NECT) in 2009, developed by DNDi, MSF, and partners, which is now the first-line treatment for the advanced stage of HAT in all endemic countries and is included in the WHO Essential Medicines List for adults and children. But there is no room for complacency.

**Advancing towards oral treatments**

While extremely successful, NECT is only effective against gambiense HAT, and still requires a lumbar puncture test to confirm the disease stage, and intravenous drug administration in hospital by skilled medical practitioners. There is also a desperate need for a less toxic treatment for rhodesiense HAT than the current melarsoprol. Furthermore, determination of the stage of the disease, necessary to decide which treatment should be used, is currently ascertained by microscopic examination of cerebrospinal fluid obtained by a painful lumbar puncture. Fexinidazole, in Phase III clinical development, is intended to be the first

fully oral treatment for HAT covering both stages of the disease and without the requirement of a risky lumbar puncture: as such it would represent a fundamental change in the management of the disease. It is expected that SCYX-7158 be administered as a one-dose-only treatment and may become part of a less specialized programme, integrated into other health activities, to be used as a village-focused treatment. The combination of a safe and effective oral treatment for both parasite sub-species and disease stages, together with a simplified diagnostic tool, would transform the health system approach to the disease, taking diagnosis and treatment out of the hospital and into the village.

**Recruiting patients in neglected areas**

In the meantime, the clinical trials conducted by DNDi and partners are, in themselves, contributing to improved patient care and access to treatment, by supporting the mobile teams who go out into the remote villages where patients live in order to screen, determine the stage, and ensure patients are referred for treatment. In 2014, DNDi treated in its trials 8.5% of all patients worldwide, and supported almost 25% of all populations screened by the mobile teams in the Democratic Republic of the Congo. While taking place in very remote areas, patient recruitment for the fexinidazole pivotal Phase II/III study was completed on time and at the highest international standards of drug trials, which is no small feat. It is vitally important that financing of mobile healthcare is sustained until the tools and expertise required to carry out these activities at the primary healthcare level become available.

**21 million people** living in areas at medium to high risk (above one case per 10,000 population)

**36 countries** in sub-Saharan Africa are endemic to the Tse-tse fly, but DRC reported 89% of all cases in 2013 Chad and South Sudan detected over 100 cases in 2013 each

**3,796 cases** reported in 2014

Disease is caused by *Trypanosoma brucei gambiense* (98%) and *T. b. rhodesiense* (2%) and occurs in two stages: the early stage 1 has non-specific symptoms and is often undiagnosed without active HAT surveillance, and the advanced stage 2, where the parasite crosses the blood-brain barrier, causing serious sleep cycle disruptions, paralysis, progressive mental deterioration and, without effective treatment, may lead to death. A lumbar puncture is needed to differentiate between stages to choose the appropriate treatment.

Current treatments are difficult to administer, and stage-specific:

#### TREATMENT OF STAGE 1 HAT

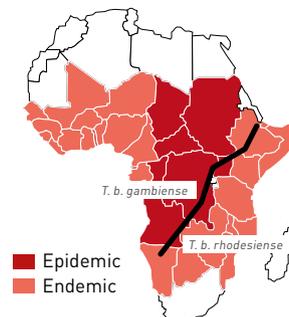
**Pentamidine** (1940) and **suramin** (1920s), require injections and are ineffective for stage 2.

#### TREATMENT OF STAGE 2 HAT

**NECT** – nifurtimox-eflornithine combination therapy (2009): a simplified therapy option for stage 2 *T. b. gambiense* HAT, requires 14 injections of eflornithine over 7 days together with 10 days of oral treatment with nifurtimox. Requires hospital administration.

**Melarsoprol** (1949): the only drug available for stage 2 *T. b. rhodesiense*, a toxic arsenic derivative that causes pain and fatal encephalopathy in up to 5% of patients who receive it.

**Eflornithine** (1981): today rarely used alone, requires an extended stay in hospital during administration (56 intravenous infusions taking two hours each to administer, over 14 days, four times per day).



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

At its inception, DNDi's **short-term strategy** was to make better use of existing treatments by combining drugs already in use. In September 2009, DNDi and partners **launched the first new treatment for sleeping sickness** in 25 years: nifurtimox and eflornithine combination therapy (NECT). NECT is included on the WHO Essential Medicines Lists (EML) for adults (since 2009) and children (since 2013), and all countries with endemic *T. b. gambiense* are now using NECT as first-line treatment for stage 2 HAT.

**As a medium-term strategy**, DNDi initiated a compound mining effort to identify existing chemical compounds with potential against kinetoplastid diseases, resulting in the rediscovery of fexinidazole, currently undergoing evaluation in a **pivotal Phase II/III study** in stage 2 HAT, with two complementary studies examining efficacy and safety in adults with stage

1 and early stage 2 HAT, and in children aged 6-14 years. Sanofi is the industrial partner.

In order to build a strong pipeline for long-term drug discovery, DNDi established a HAT Lead Optimization Consortium resulting in identification of the oxaborole **SCYX-7158**, which successfully progressed through pre-clinical development. **Phase I clinical** development is due for completion in 2015. Other backup compounds were evaluated by the consortium and remain available for further development if necessary.

In addition, DNDi supports the **HAT Platform** (see p. 52) 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 in endemic countries and those involved in HAT from the

international research arena.

**Ideally a new treatment for adults and children** would be effective against **both stages** of the disease and **both parasite sub-species**, **non-toxic**, at least **95% efficacy** at 18 months follow-up, **safe** for pregnant and breastfeeding women, **easy to use** (short-course or once a day), **oral**, requiring no monitoring, **affordable** and **adapted to tropical climates**.

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

- **An oral, safe, effective treatment to be used for both stage two and stage one HAT**



## SCYX-2035811

**OVERALL OBJECTIVE:** Progress a backup nitroimidazole into pre-clinical development

**2014 OBJECTIVE:** Project on hold

**PROJECT START:** June 2011

The nitroimidazole backup programme for HAT identified SCYX-2035811 as a suitable candidate for further exploration, and although initial results in animal models had shown excellent activity, further studies showed the doses tested to give insufficient cure. Given the progress of fexinidazole (Phase II/III) and SCYX-7158 (Phase I), further development was put on hold in 2013, and the project has now been stopped.

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



## SCYX-1608210

**OVERALL OBJECTIVE:** Progress a backup oxaborole into pre-clinical development

**2014 OBJECTIVE:** Project on hold

**PROJECT START:** April 2007

Extensive pharmacokinetic profiling of possible oxaborole compounds led to the selection of SCYX-1608210, which demonstrated cure in the stage 2 mouse model of HAT, as a backup for SCYX-7158 in case of need. Given the current success of other projects for HAT, further development was put on hold in 2013 and will only recommence should problems be encountered with SCYX-7158 in clinical development.

**PARTNERS:** Anacor Pharmaceuticals Inc., USA; Pace University, USA; LMPH, Belgium; SCYNEXIS Inc., USA



## SCYX-7158

**OVERALL OBJECTIVE:** Develop and register SCYX-7158 as a new drug for the treatment of stage 2 HAT caused by *T. b. gambiense*, ideally also for stage 1 HAT

**2014 OBJECTIVES:**

- Complete reprotoxicology and plan additional pre-clinical studies
- Complete SCYX-7158 Phase I programme

The oxaborole SCYX-7158, originally provided by Anacor Pharmaceuticals, was found to be active against *T. brucei* at the University of California San Francisco; was further investigated by a consortium consisting of DNDi, Anacor, SCYNEXIS, Pace University, and Swiss TPH; and was selected as a promising pre-clinical candidate for HAT in late 2009. In pre-clinical studies, SCYX-7158 was shown to be safe and efficacious in treating stage 2 of the disease, as it is able to cross the blood-brain barrier. A tablet formulation demonstrated comparable pharmacokinetics to capsules used in a Phase I study and is therefore suitable for further clinical studies.

A reproductive toxicity package was completed in 2014, showing that the drug did not induce any abnormalities. In March 2012, SCYX-7158 became DNDi's first new chemical entity resulting from lead optimization efforts to enter clinical development. Due to the longer than expected half-life in humans, additional animal studies were performed, which supported continued testing with single ascending doses of treatments in healthy volunteers. Safety profiling above the expected therapeutic dose was ongoing at the end of 2014 with no identified cause for concern. Recruitment for a patient trial will begin in the DRC in 2016.

**PARTNERS:** Anacor Pharmaceuticals Inc., USA; SCYNEXIS Inc., USA; Penn Pharma, UK; BaseCon, Denmark; Optimed, France; PhinC Development, France; Cardiabase, France; SGS Cephac, France; Patheon, UK; Accelera S.r.l., Italy



## DEVELOPMENT



## Fexinidazole

**OVERALL OBJECTIVE:** Develop and register fexinidazole as a new drug for the treatment of stage 2 HAT caused by *T. b. gambiense*, ideally also for stage 1 HAT and *T. b. rhodesiense*

**2014 OBJECTIVES:**

- Complete recruitment in pivotal study
- Initiate recruitment for study in adults with early stage two / stage one HAT
- Initiate recruitment for study in children between 6 and 14 years of age

**PROJECT START:** 2007

**359** patients enrolled thus completing recruitment at **10** sites

The result of successful compound-mining efforts pursued by DNDi in 2005, fexinidazole entered clinical development in September 2009 and is now being co-developed with Sanofi: DNDi is undertaking clinical and pharmaceutical development whilst Sanofi is responsible for the industrial development and production. Preparations for product registration are underway.

A pivotal Phase II/III study, initiated in October 2012, aims to evaluate the safety and efficacy of fexinidazole compared to NECT, initially at eight sites in Democratic Republic of the Congo (DRC) and Central African Republic (CAR). Patient inclusion was halted in December 2013 in CAR due to conflict and security concerns in the country, and at one site in DRC due to a lack of new cases, although these sites remained open. A replacement site was opened in 2014 in DRC and, by the end of the year, the full cohort of 359 patients had been recruited. All trial safety data are regularly reviewed by the Data Safety and Management Board: serious adverse events for other indications were reviewed and no new risks identified. A strategy to accelerate the availability of fexinidazole was submitted to the regulators. Two complementary studies were initiated in May 2014 one for early stage 2 and stage 1 adult HAT patients, and another for children with HAT aged 6 to 14 years.

**PARTNERS:** BaseCon, Denmark; Bertin Pharma, France; Venn Life Sciences (previously Cardinal Systems), France; Cardiabase, France; Médecins Sans Frontières, and other HAT Platform members; Phinc Development, France; National Control Programmes of the Democratic Republic of Congo and the Central African Republic; RCTs, France; Sanofi, France; Swiss Tropical and Public Health Institute (Swiss TPH); SGS, France; Theradis Pharma, France

## IMPLEMENTATION



## NECT – Nifurtimox-Eflornithine Combination Therapy

**OVERALL OBJECTIVE:** Develop and make available a safe, effective, easier to administer and more cost-effective combination therapy which requires shorter hospitalization

**2014 OBJECTIVE:** Finalize NECT field study report and complete the project

**PROJECT START:** May 2004

**630** patients enrolled thus completing recruitment

NECT, a co-administration of intravenous eflornithine and oral nifurtimox, was developed by Epicentre, MSF, DNDi, Swiss TPH, and the national HAT control programmes of the Republic of the Congo and DRC. It quickly became the first-line treatment for the neurological, or late, stage of the *T. b. gambiense* form of sleeping sickness, as it is simpler to administer and less expensive than eflornithine alone, making it more adapted to field conditions. DNDi and partners conducted the 'NECT-Field' study between 2009 and 2012, to document the safety, effectiveness, and ease-of-use of NECT in real-life conditions. Included in the 630 patients enrolled were children and pregnant or breast-feeding women. The final study report has now been received, the results will be submitted for publication in 2015 and the project has reached completion.

NECT was included on the WHO Essential Medicines List in 2009, and extended to the Essential Medicines List for children in April 2013. With the recommendation of NECT as first-line treatment in Nigeria in 2014, it is now available in all endemic countries, all of which receive free supplies from WHO via drug donations by Sanofi and Bayer.

**PARTNERS:** Médecins Sans Frontières (MSF); Swiss TPH; PNLTHA, DRC; HAT Platform members





#### Cutaneous Leishmaniasis, Colombia

About a year ago, Serafin believed he was about to die, 'I counted 98 ulcers in total at a certain point, the worst was the one on my forehead, very deep, I could no longer hide it and could not find work anymore' he recounts. In his village, the waiting period for the medicine was about two months, so Mr Moreno decided to spend the little money he had, leave his wife and children, and sought out treatment in Medellin, 180 kilometres away. Although the treatment was harsh with very difficult side effects, Serafin persevered.

## TAILORED APPROACHES TO REGIONAL DIFFERENCES

Leishmaniasis is one of the most neglected diseases and is strongly associated with poverty and malnutrition. It is a truly global problem, endemic in over 100 countries and prone to outbreaks, with multiple *Leishmania* species spread by over 30 species of the sandfly and responsible for causing the disease. The number of people affected by the cutaneous form varies from 700,000 to 1,300,000 people annually. Visceral leishmaniasis (VL) is deadly if untreated, and there are an estimated 200,000 to 400,000 cases per year, mostly in children. Despite drawbacks in terms of their ease of administration and in some cases their sustainable supply, the current treatments are working well in Asia, but these same treatments are not as effective in patients in East Africa or Latin America. Even within Africa, there are regional differences in treatment response. The role as disease reservoirs of asymptomatic carriers and those affected by post-kala azar dermal leishmaniasis (PKDL) also needs to be better documented. Of increasing concern is that VL co-infection with HIV is causing the disease to spread into previously unaffected areas of southern Europe, Ethiopia, and India.

To address these complex disease scenarios, DNDi has put in place a three-fold strategy for R&D:

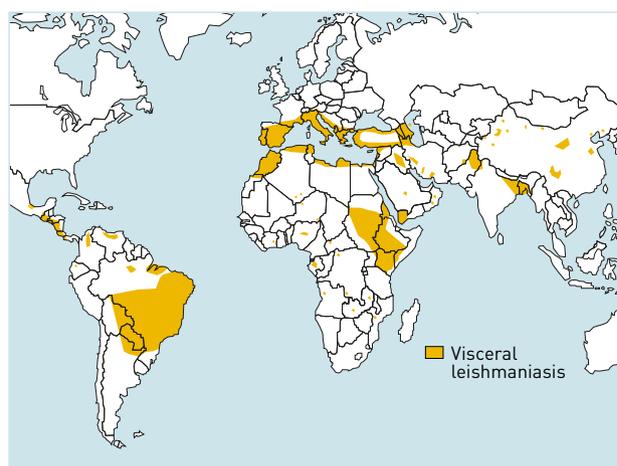
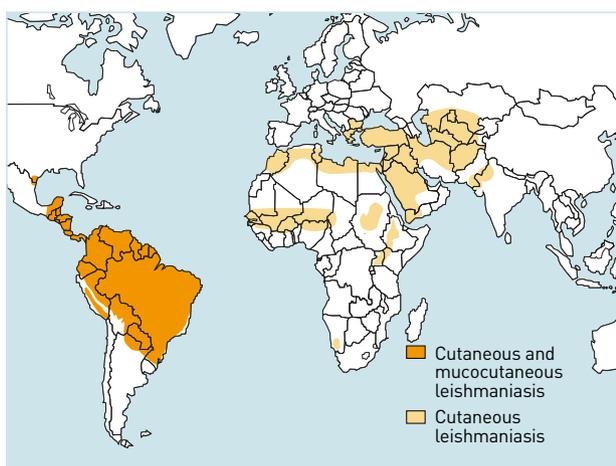
- The first part of the strategy comprises the improvement of patient access to existing treatments in each affected region. For example, the SSG&PM combination as a 17-day regimen is recommended by the WHO as first-line treatment for VL in Eastern Africa. The combination was assessed in real-life conditions in 3,000 patients, over half of whom were children. Results in 2014 confirmed the high safety and efficacy of the combination treatment.
- The second part of the strategy targets the improvement of treatment for specific disease scenarios, including HIV-VL co-infection notably in Africa, PKDL, and VL in Brazil.
- The third part of the strategy is to address the challenge of accelerating the translation of new chemical entities to clinical trials. In order to support sustained elimination of the disease new drugs that are oral-only combinations will be needed, which is why DNDi will continue to invest heavily in drug discovery activities.

In Bangladesh and India, where elimination is targeted by 2020, the WHO-recommended treatments were evaluated in both hospitals and primary healthcare centres to provide evidence to support national policy changes, notably to move away from miltefosine monotherapy to avoid developing resistance. Based on available interim data, the Indian government revised the VL treatment policy in September 2014, so that liposomal Amphotericin B (AmBisome®) alone is the first treatment option, with miltefosine/paromomycin in combination as the second option, a policy also reflected in Bangladesh and Nepal. Policy change and elimination efforts were supported politically at the regional level through a Memorandum of Understanding signed by Asian countries in 2005 and renewed in 2014. Patient access to treatment is part of a larger DFID-supported consortium for the Control and Elimination of Visceral Leishmaniasis, called the KalaCORE, launched in early 2015.

**350 million people**  
at risk in  
**98 countries**

**0.7 - 1.3 million**  
cases of **CL** annually

**0.2 - 0.4 million cases of VL**  
annually, although with a marked reduction  
in the number of cases observed in the Indian  
subcontinent



## CURRENT TREATMENTS AND THEIR LIMITATIONS

**Existing drugs** have serious drawbacks in terms of safety, resistance, stability, and cost. They have low tolerability, long treatment duration, and are difficult to administer.

- Pentavalent antimonials:** (sodium stibogluconate – SSG – and meglumine antimoniate): 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. In monotherapy, they require a 30-day parenteral treatment for VL. Registered in South East Asia, Latin America, and some Mediterranean and African countries.
- Amphotericin B deoxycholate:** only an alternative treatment for VL in areas with high rates of unresponsiveness to antimonials where no other options are available. Need for hospitalization, constant renal monitoring of patients, 28-day duration of treatment, and infusion-related adverse events are notable drawbacks. Amphotericin B displays dose-limiting toxicity. Registered in South Asian countries and some countries in Africa and Latin America.
- AmBisome®:** a liposomal formulation of amphotericin B, which is much safer and highly efficacious. A single infusion of 10mg/kg has shown a 96.4% cure rate in Asia. However, high cost and the need for a cold chain limit widespread use. Registered for VL in India, USA, and Europe and used as a second-line drug for the treatment of PKDL in East Africa at higher doses than in India and for VL in Brazil. It is also used to treat PKDL cases in Sudan. A donation to WHO facilitates free distribution of AmBisome® to the three countries involved in the elimination strategy in South Asia for primary VL patients, and as a rescue treatment for African VL. It is not properly evaluated for cutaneous leishmaniasis (CL).
- Miltefosine:** oral drug registered for use in India for VL, but is expensive and requires 28-day treatment. Major limitations include low compliance, 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, probably associated with drug underexposure in children. For CL, currently approved for lesions caused by three *Leishmania* species. Miltefosine is not registered in many endemic countries and consequently not available.
- Paromomycin (PM):** a low-cost parenteral formulation for VL that requires three weeks of painful intramuscular administration is also highly efficacious in Asia but is associated with some degree of renal and ototoxicity with limited efficacy as monotherapy in East Africa.



# WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?

## ■ VISCERAL LEISHMANIASIS

DNDi's **short-term approach** for VL 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 is the geographical extension of existing drugs in other countries and regions. In 2010, DNDi and LEAP partners **delivered the SSG&PM combination therapy for East Africa**, now recommended as first-line treatment for VL in the region. SSG&PM has been included in the national guidelines of Sudan, South Sudan, Ethiopia, and Kenya. PM is registered in Uganda (2011) and Kenya (2013), and is in the process of registration in Sudan and Ethiopia. In India, a Phase III trial demonstrated the efficacy of combination therapies of already-registered drugs (see p. 30). In 2014, the government of **India** recommended use of single-dose AmBisome® as a first option and paromomycin/miltefosine combination as the second option for treatment instead of using miltefosine as monotherapy. DNDi has collaborated 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 effectiveness and safety of these new treatments at the primary healthcare level and facilitate their introduction. In **Latin America**, DNDi is

## ■ CUTANEOUS LEISHMANIASIS

For CL, DNDi's objective is to develop short, safe, efficacious, affordable, and field-adapted treatments, at least for lesions caused by *L. tropica* and *L. braziliensis*. As a **short-term** strategy, DNDi is developing a topical treatment based on amphotericin B, and aims to improve treatment strategies using currently available treatment modalities in combination. In the **medium to long term**, DNDi aims to develop an oral drug and an immune-modulator for use in combination with chemotherapy. This novel approach aims to initially eliminate parasites with

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. The national control programme has extended the use of AmBisome® as second-line treatment based on the interim safety data from this trial.

**Leishmania and HIV co-infection** is a growing problem, difficult to manage clinically due to poor response to treatment with frequent relapses of disease, and is eventually fatal. DNDi is working with partners towards better treatment for HIV/VL co-infected patients in **Africa** using existing drugs at different dose/regimen and in combination, and is collaborating with ITM-Antwerp in a secondary prophylaxis study.

In the **medium term**, DNDi is assessing the combination of fexinidazole and miltefosine for the treatment of VL patients in terms of efficacy and safety. This could be the first oral-only combination therapy for VL.

DNDi's **long-term** strategy for VL is to bring new oral drug candidates into clinical development through its lead optimization programme with the ultimate goal of improving the safety profile and efficacy of the existing tools with a second oral-only combination treatment.

chemotherapy, followed by enhancement of the patient's immune response with an immune-stimulating agent.

A new topical or oral treatment for CL would ideally be **efficacious against all species**, show at least **95% efficacy**, be **easy to use, short course** (14-28 days), compatible for **combination therapy**, produce **minimal scarring**, be **safe** in pregnant and breastfeeding women, **affordable** and **adapted to tropical climates**.

In addition, DNDi supports the **Leishmaniasis East Africa Platform** (LEAP) (see p. 51). A new VL treatment for adults and children based on a new chemical entity would ideally be **efficacious against all species of Leishmania in all regions** as well as **against resistant strains**, have at least **95% efficacy**, be **short course** (once a day for 10 days oral; or 3 shots over 10 days), **easy to use**, compatible for **combination therapy, safe** in pregnant and breastfeeding women and for immunocompetent/immunosuppressed patients, **affordable**, and **adapted to tropical climates**.



**By 2020, DNDi aims to deliver from its VL-specific portfolio:**

- Potentially a safe, effective, low-cost, and short-course oral combination treatment
- A new treatment for PKDL that is shorter course and better tolerated than current options
- Treatment options for HIV/VL co-infected patients
- A new first-line treatment regimen for VL in Latin America

**By 2020, DNDi aims to deliver from its CL-specific portfolio:**

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

## RESEARCH



## Nitroimidazole series

**OVERALL OBJECTIVE:** Select a backup candidate to move forward in case VL-2098 fails in preclinical toxicology studies or clinical trials

**2014 OBJECTIVE:** Complete profiling of nitroimidazole back-ups to VL-2098 and then put on hold

**PROJECT START:** July 2010

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, with the TB Alliance granting rights to DNDi to develop a class of potential anti-TB compounds showing promise for 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 opposite), and a focused programme is ongoing to identify a backup pre-clinical candidate in case VL-2098 does not successfully complete pre-clinical or clinical testing.

Two potential backups belonging to two sub-series of nitroimidazooxazines (DNDi-0690 from the 7-substituted sub-series; DNDi-8219 from the PA-824 subseries) have been selected for further profiling, as they showed good efficacy *in vivo*, better solubility, and lower hERG potential. Pre-CMC activities to support comparative exploratory toxicity study with VL-2098 were initiated and are on track.

**PARTNERS:** TB Alliance, USA; Auckland University, New Zealand; Laboratory of Microbiology, Parasitology and Hygiene (LMPH), University of Antwerp, Belgium; WuXi AppTech, China



## Oxaleish series

**OVERALL AND 2014 OBJECTIVE:** Select an oxaborole for pre-clinical evaluation

**PROJECT START:** 2009

DNDi and Anacor have been working together over the last few years to identify oxaborole compounds, initially for the HAT programme, and this has expanded to include both leishmaniasis and Chagas disease. DNDi-2035804

had shown excellent reductions in parasitemia in an animal model of VL using *L. infantum*. However, the compound failed in exploratory toxicology testing and has now been replaced with other lead compounds.

**PARTNERS:** Anacor Pharmaceuticals, USA; LMPH, University of Antwerp, Belgium; WuXi AppTech, China; Sandexis, UK; LSHTM, UK

## TRANSLATION



## VL-2098

**OVERALL OBJECTIVE:** Fully investigate the profile of VL-2098 as an NCE for VL

**2014 OBJECTIVE:** Complete reproductive toxicology pre-clinical safety and toxicology studies and manufacture GMP (Good Manufacturing Practice) API (Active Pharmaceutical Ingredient)

**PROJECT START:** July 2010

From the initially selected 70 nitroimidazoles belonging to four chemical sub-classes, VL-2098 was identified as a very potent and safe molecule and was selected for in-depth evaluation of its efficacy, pharmacokinetic, and early safety profile on the basis of these preliminary results. This compound is potent against *L. donovani in vitro* and shows efficacy in acute and chronic VL animal models after oral dosing. Toxicology and pharmacokinetic studies were completed in 2014 and a batch of high purity active pharmaceutical ingredient (API) successfully manufactured.

Results performed in three animal species indicated a link between dose, length of treatment, and testicular toxicity. Further studies of longer duration will be undertaken in the animal model most sensitive to the therapeutic window in order to determine the safety margin, and a decision on whether to move the candidate forward will be taken in 2015.

**PARTNERS:** TB Alliance, USA; Advinus Therapeutics, India; Endolytics, USA; Accelera, Italy; Aptuit, Italy; London School of Hygiene & Tropical Medicine (LSHTM), UK; Laboratory for Microbiology, Parasitology and Hygiene (LMPH), Belgium

## CpG-D35 (CL)

**OVERALL OBJECTIVE:** Characterize and produce GMP-grade D35 to evaluate its protective cellular immunity and its effectiveness to treat PKDL and CL in chemotherapy combinations

**2014 OBJECTIVE:** Advance the development of CpG-D35

**PROJECT START:** June 2014

DNDi initially undertook a survey to identify potential treatments for CL, evaluating available evidence for potential efficacy and drug availability. The U.S. Food and Drug Administration (FDA) had previously undertaken the development and optimization of CpG-D35 and found it to be efficacious in an animal model, and was willing for DNDi to continue its development. The project aims to combine the use of antimicrobials with a novel innate immune modulator that activates the immune cells embedded in the skin and so boosts parasite clearance.

The development of CpG-D35 as an adjunct to chemotherapy for cutaneous leishmaniasis and post kala-azar dermal leishmaniasis (PKDL) has been selected as one of the WHO's CEWG Health R&D Demonstration projects (see p.56), undertaken with the US FDA and the University of Osaka.

The project has four phases: 1) production and characterization of GMP-grade CpG-D35; 2) pre-clinical studies in two species to assess potential toxicities; 3) proof-of-concept clinical trials for CpG-D35 and the combination of CpG-D35 with antimonials establishing safety profile and optimal dose; and 4) establishing efficacy across *L. major* species. The project will demonstrate 'delinkage' of R&D costs and product price through equitable or humanitarian licensing in an agreement to be signed with the FDA which, as part of its mission, has no interest in recovering the agency's investments in R&D.

CpG-D35 is easy to produce at a reasonably low price and was nominated as a pre-clinical candidate in 2014.

**PARTNERS:** University of Osaka, Japan; US FDA, USA



## Anfoleish (CL)

**OVERALL OBJECTIVE:** Develop at least one modality of treatment for CL

**2014 OBJECTIVE:** Continue exploratory trial to evaluate safety, PK, and efficacy of Anfoleish for the treatment of uncomplicated CL in the New World.

**PROJECT START:** September 2011

**22 patients recruited at 2 sites**

The rationale for development of a topical formulation of amphotericin B was to provide a treatment to be applied locally at the CL lesion, showing high anti-parasitic effect, but without the systemic toxicity associated with amphotericin B. Anfoleish, a cream containing 3% amphotericin B, was selected by DNDi for clinical development after completion of pre-clinical assessments. A Phase Ib/II open-label, randomized, non-comparative, two-arm exploratory study is being conducted in Colombia. The first subject was enrolled on 1 February 2014 and it is expected that the initial step (30 patients) will be completed in April 2015. If no safety concerns are identified, 50 additional patients will be included. Initial efficacy will be determined on all 80 patients by measuring the percentage of subjects with initial clinical cure at day 90.

If Anfoleish is shown to be efficacious against *L. braziliensis* and *L. panamensis*, a multi-country Phase III study will be planned in Latin America.

**PARTNERS:** PECET (Program for the Study and Control of Tropical Diseases), Universidad de Antioquia Medellin, Colombia; Humax Pharma, Colombia

## Combo Fexi/MF

**OVERALL OBJECTIVE:** Develop an oral-only therapy for VL by 2022

**2014 OBJECTIVE:** Continue Phase II proof-of-concept fexinidazole study in Sudan

**PROJECT START:** September 2012

**14 patients recruited at 1 site**

Fexinidazole has shown potent activity against *L. donovani* *in vitro* and *in vivo* in a VL mouse model, assessed in studies in healthy volunteers and shown to be safe when given as a single dose or as repeated dosing after 14 days. The Phase II proof-of-concept study with fexinidazole for the treatment of primary VL patients in Sudan aimed to estimate the efficacy of fexinidazole in adult primary VL patients, and to establish safety and the pharmacokinetic/pharmacodynamic (PK/PD) profile. The doses selected for the study were identical to those of the Phase II/III HAT trial. Enrolment began in November 2013 and ended in May 2014, with a total of 164 patients screened and 14 enrolled in the study. Efficacy was not conclusive for the majority of patients although an initial parasite clearance was observed. The study was interrupted and new regimens including fexinidazole are under investigation

An expert safety review of the Phase I data concluded that it would be safe to increase the dose. Safety results from trials in HAT and Chagas disease, expected in 2015, will be taken into account before undertaking any further trials.

Miltefosine is the only other oral drug currently available and will be evaluated in combination with fexinidazole in East Africa. A previous study carried out in Africa indicated miltefosine underdosing in children compared to adults, and that dose adjustment is required. A pharmacokinetic and safety study of miltefosine in children was submitted to ethics committees in Uganda and Kenya. Results should be available at the same time as the PoC fexinidazole trial results.

**PARTNERS:** Kenya Medical Research Institute (KEMRI), Kenya; Institute of Endemic Diseases (IEND), University of Khartoum, Sudan; MSF; Leishmaniasis East Africa Platform (LEAP); BaseCon, Denmark; Utrecht University, The Netherlands; Koninklijk Instituut voor de Tropen, The Netherlands



## DEVELOPMENT



## New VL treatments – Bangladesh

**OVERALL OBJECTIVE:** Provide evidence for adoption of combination treatment as second line option in national policy

**2014 OBJECTIVES:** Provide evidence for policy change to include combinations and complete six-month patient follow-up of Phase III study

**PROJECT START:** July 2010

The Phase III trial conducted by DNDi and its partners in India demonstrated the efficacy of combination therapies based on AmBisome®, miltefosine, and paromomycin. In Bangladesh, this two-step Phase III study (first in hospital settings, then in primary healthcare centres) in 602 patients uses the same combination therapies. Six-month follow-up was completed in April 2014 and sites closed in June. Results, presented in Dhaka in October 2014, showed all tested treatments demonstrated excellent cure rates and were well tolerated by patients, in support of policy change in the country. The Clinical Study Report was finalized by the end of the year.

**PARTNERS:** Ministry of Health and Family Welfare, Bangladesh; GVK Biosciences, Bangladesh; Pvt Ltd, India and Bangladesh

## HIV/VL for Africa

**OVERALL OBJECTIVE:** Develop a new treatment regimen for patients co-infected with HIV/VL

**2014 OBJECTIVE:** Initiate HIV/VL co-infection study in Ethiopia and conduct three interim analyses

**PROJECT START:** September 2011

**20 patients recruited at 2 sites**

This study aims to 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 one year after initial cure (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.

Importation problems encountered with AmBisome®, after a drug recall issued by Gilead, caused a temporary halt to the trial in 2013. These studies are taking place at Gondar and Abdurafi in Ethiopia. Enrolment was initiated in August

2014 and 20 patients had been enrolled by the end of the year, 10 of whom were included in the sub-studies. The arm with AmBisome® alone has been dropped due to lack of efficacy, leaving AmBisome®/miltefosine as the only choice in the study.

**PARTNERS (AFRICOLEISH):** LSHTM, UK; Institute of Tropical Medicine-Antwerp, Belgium; MSF, The Netherlands; Addis Ababa University, Ethiopia; Gondar University, Ethiopia; LEAP; Slotervaart Hospital, The Netherlands Cancer Institute, The Netherlands; Utrecht University, The Netherlands



## New VL treatments – Latin America

**OVERALL OBJECTIVE:** 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

**2014 OBJECTIVE:** Finalize patient recruitment in Phase IV trial

**PROJECT START:** February 2011

**378 patients recruited at 5 sites**

Approximately 90% of VL cases in Latin America occur in Brazil, and most of them are children. In 2013, Brazil reported 3,253 new cases with a fatality rate of 6.7%. DNDi is supporting the implementation of a Phase IV clinical trial, sponsored by the Brazilian Ministry of Health, to assess treatments for VL. In 2014, patient recruitment was stopped following DSMB recommendations based on the interim analysis of 50% of the recruited patients. The five trial sites concluded six months follow-up of the 378 patients enrolled in the study and final study analysis will be available in 2015. Evidence provided by this project will guide policies on the treatment of VL caused by *L. infantum* in Brazil. The Ministry of Health already changed treatment recommendations in 2013, expanding the use of AmBisome® as a second-line treatment, based on interim safety data provided by the trial.

**PARTNERS:** Rene 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; Hospital Sao José de Doencas Infecciosas, Brazil



## Generic AmBisome

**OVERALL OBJECTIVE:** Have pre-qualified generic AmBisome® by 2017

**2014 OBJECTIVE:** Project on hold

**PROJECT START:** November 2013

AmBisome®, an effective but expensive treatment for VL, is still under patent protection in the US until 2016 but no longer in Europe. Several producers in India and elsewhere are in the process of developing generic versions of AmBisome®; however, a thorough analysis on the composition of new products, their physico-chemical characteristics, quality-assurance, and GMP production is needed to assess whether these products have the qualifications to characterize a potential generic version of AmBisome®. At present, WHO has not set any standards for the regulatory evaluation of liposomal drugs and there is a lack of regulatory guidance in stringently regulated countries. A second producer of quality-assured, liposomal amphotericin B would ensure treatment availability for the next decade, particularly given Gilead's past problems (batch recall in 2013), and hopefully competition would lead to lower prices.

With the prospect of an alternative FDA-approved generic AmBisome® being available shortly, together with falling numbers of patients in Asia whose needs are adequately covered by a Gilead donation programme through the WHO, this project has been put on indefinite hold.

**PARTNER:** MSF



## SSG&PM

**OVERALL OBJECTIVE:** Development of short-course (combination) treatments from current drugs, registration of products, and facilitation of access through policy change

**2014 OBJECTIVE:** Complete SSG&PM pharmacovigilance study and complete registration for SSG&PM in East Africa

**PROJECT START:** November 2004

In 2010, DNDi and LEAP successfully showed that the combination of SSG and PM (17 days) was as efficacious as SSG monotherapy (30 days); this shorter course lessens the burden on patients and health systems, and is 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 Eastern Africa by WHO. SSG&PM implementation has begun in the region, and the treatment is included in the national VL guidelines of Sudan, Kenya, and Ethiopia. SSG&PM treatment is part of the national programme in South Sudan and was rolled out in public health structures and MSF centres during the recent massive outbreak.

A large pharmacovigilance study with MSF and Ministry of Health sites in Ethiopia, Sudan, Kenya, and Uganda to monitor safety and efficacy of SSG&PM was undertaken between 2011 and 2013, recruiting 3,000 patients. Study results obtained in 2014 showed a 95% cure rate. The results were presented in September at the LEAP conference in Ethiopia and disseminated to stakeholders.

**PARTNERS:** Kenya Medical Research Institute (KEMRI); IEND, University of Khartoum, Sudan; University of Makerere, Uganda; Addis Ababa University, Ethiopia; Gondar University, Ethiopia; LSHTM, UK; Ministries of Health of Ethiopia, Sudan, Kenya, and Uganda; MSF; i+ solutions, The Netherlands; LEAP

## New VL treatments for India

**OVERALL OBJECTIVE:** To develop one to two new (combination) treatments and support recommendations from the authorities in the main endemic countries

**2014 OBJECTIVE:** Progress significantly in the implementation study and completion of patient follow up from the pilot phase

**PROJECT START:** December 2006

**1761** patients  
recruited  
at **12** sites

The Phase III trial conducted by DNDi and its partners in 2010 demonstrated the efficacy of combination therapies based on AmBisome<sup>®</sup>, miltefosine, and paromomycin, and an additional study showed the efficacy of single-dose AmBisome<sup>®</sup> given as an intravenous infusion. To facilitate the introduction of these new treatments for VL in South Asia, DNDi is carrying out effectiveness studies, including a pilot project in the Bihar State of India implementing combination therapies at the primary healthcare level, and single-dose AmBisome<sup>®</sup> at the hospital level. The project is monitoring pharmacovigilance as well as treatment effectiveness of the different treatment options when used outside a clinical trial by the public sector. The study began in 2012 in two districts in India. A total of 919 patients were enrolled during the pilot phase. In 2014, the study entered into the implementation phase, which aims to treat 6,000 more patients. The trial was expected to end in 2015 and results made available.

In August 2014, the Indian National Roadmap for Kala-Azar Elimination recommended use of single dose AmBisome<sup>®</sup> (shown to be 96.7% efficacious in the implementation study) as a first option treatment for the treatment of VL patients in high endemicity areas, with paromomycin and miltefosine as a second option in areas of lower endemicity. This represents an important policy change in removing the use of miltefosine monotherapy. Following a Technical Advisory Committee meeting, it was agreed that the implementation study would stop recruiting. However, DNDi will continue the 12-month follow up of patients who were included in the study.

**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; MSF





## Chagas, Bolivia

A young mother, Maria, was diagnosed with Chagas disease three years ago. Her baby was born with Chagas and both started treatment. Exams from the baby showed that treatment with benznidazole was a success. He is now free of Chagas disease. Treatment in children has an efficacy rate above 90% and children have a much better tolerability than adults. In 2010, DNDi and partners delivered a paediatric formulation of benznidazole, making treatment easier for children.

## INCREASING ACCESS TO ADAPTED TREATMENTS

Chagas disease is transmitted predominantly through contact with the faeces of infected triatomine bugs, deposited on the skin during a blood meal. These insects typically hide in crevices of poorly-constructed homes in rural or suburban areas. Blood, organ transplant, and congenital transmission also occurs, and cases of oral transmission through ingestion of food infected by bugs have recently been documented.

The distribution and impact of the disease varies from country to country. In Bolivia, it is likely that the majority of the population is affected by Chagas disease: prevalence estimates vary between 40-70% of the adult population, and are difficult to assess more accurately without sero-epidemiological surveys, given the frequently asymptomatic nature of the chronic form of the disease. In Brazil, only 2% of the population is infected, although given that the population exceeds 200 million people, the actual numbers affected are huge.

### Maximizing the impact of diagnosis and treatment

Until recently Chagas disease was confined to the Americas, principally Latin America, but over the years it has spread to North America and Europe due to population flows. Today, one of the most important areas of work in Chagas disease is access to medicines and diagnosis. The majority of patients with Chagas disease are asymptomatic and just a very small fraction of those affected are being detected and treated. The numbers are staggering, with estimates of less than 1% of Chagas disease patients receiving treatment with either

benznidazole or nifurtimox. A number of factors are involved, but there is a clear need for concerted multi-disciplinary action to change the current situation. Despite growing evidence of drug efficacy and the different operational approaches employed, no medical or operational consensus has been reached in many endemic countries. It is necessary and imperative to ensure registration of existing drugs against Chagas disease in all endemic countries. In order to evaluate which deployment models have the greatest local impact, DNDi and partners will initiate a series of pilot projects in strategic countries which aim to assess the impact of scaling up diagnosis and treatment, with integration into local health systems. Different delivery models will be evaluated and defined with local stakeholders, from governments to academia and civil society, and are expected to be sustainable and replicable in similar contexts.

DNDi, as part of the Global Chagas Coalition and with other partners, advocates strongly for increased diagnosis and access to treatment across all age groups, but notably infants, young children and non-pregnant women of child-bearing age. Recent data indicate that treating the latter prevents transmission of Chagas disease during pregnancy, and is therefore an important disease control strategy.

There is also a need for international registries to support surveillance of diagnosis and treatment of chronic cases, pharmacovigilance, and long-term follow-up for a better understanding of Chagas epidemiology and distribution, as well as to identify major gaps in existing data.

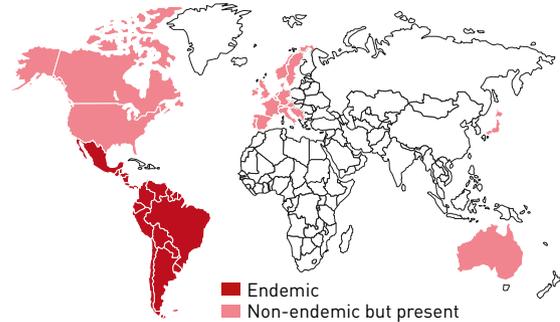
**70 million people**  
at risk in the region

Endemic in  
**21 countries**  
in Latin America

**5.7 million people infected,**  
leading to approximately 7,000 deaths  
every year in the region

The disease has two clinical phases, the **acute phase** (fatal for 2-8% of children), which is often asymptomatic or unrecognized, and the **chronic phase**, which can be divided into two stages:

- The **chronic, asymptomatic (or indeterminate)** stage, during which patients can transmit the parasite to others (mostly through blood, congenital transmission or occasionally organ transplant) and which may last decades after infection.
- The **chronic, symptomatic** stage, developing later in up to 30% of infected patients. Chagas disease causes abnormal dilation of the large intestine (megacolon), and is the leading cause of infectious heart disease (cardiomyopathy) in the world and the leading cause of death from a parasitic disease 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 has been limited due to lack of guidelines and policies supporting implementation. 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 the chronic form of the disease with target organ involvement.

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

DNDi's **short-term** goal was to make better use of existing treatments, for example through the development of a paediatric dosage form of benznidazole – a goal which was achieved in 2011. The treatment is registered in Brazil (2011), and was included on the WHO Essential Medicines List for children in 2013. An agreement signed in 2013 with the Mundo Sano Foundation will ensure a second source of the treatment previously solely manufactured by LAFEPE. Collaborative activities will continue to support country registration and adoption, and greater treatment availability to patients.

As a **medium-term** strategy, DNDi has been assessing known families of compounds such as the new azole antifungal drug, E1224, for activity against *T. cruzi* in adult chronic patients. Results from a proof-of-concept trial showed E1224 monotherapy to have some short-term effect on parasite clearance but with insufficient long-term efficacy, and the current regimen of benznidazole to

be efficacious in the long term, but with side effects. Alternative benznidazole regimens, including reduced dosing and duration of treatment in monotherapy and combination treatment with E1224 are being explored. Fexinidazole, also in development for HAT and VL, is also being evaluated. Additionally, DNDi continues to search for potential biomarkers of treatment response to enhance clinical trial capabilities for evaluation of new compounds.

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 and access through the Chagas Clinical Research Platform (see p. 53), which was launched in 2009.

Ideally, a new treatment would be for **both acute and chronic** phases of the

disease, useful against most parasite species in all regions, with a better **safety** profile than existing drugs, non-inferior **efficacy** to benznidazole, **easy-to-use** (oral, once-a-day for less than 30 days, requiring no hospitalization and little or no monitoring), **affordable, and adapted** to tropical climates.

**By 2020, DNDi aims to deliver from its Chagas-specific portfolio:**

- **An effective and safe new oral treatment regimen of chronic indeterminate Chagas disease, ideally also effective against the acute form of the disease**
- **Biomarkers to gain understanding of disease progression and ease the development of tools for evaluation of treatment response to support drug development**



## Nitroimidazole

**OVERALL OBJECTIVE:** Generate new drug candidates for the treatment of Chagas to be assessed in clinical trials

**2014 OBJECTIVE:** Select at least one back-up compound from VL programme to test *in vivo*

**PROJECT START:** April 2012

An opportunistic approach has been undertaken to assess compounds issuing from the VL-2098 back-up programme (nitroimidazooxazine series) showing activity against *T. cruzi in vitro*, evaluating the most promising candidates in *in vivo* models of Chagas disease. Two VL lead back-ups belonging to different sub-series (7-substituted nitroimidazooxazines and PA-824 analogues) are active and have been selected for further assessment against Chagas disease in the new bioluminescence *in vivo* model at LSHTM.

**PARTNERS:** TB Alliance, USA; Auckland University, New Zealand; Laboratory of Microbiology, Parasitology and Hygiene (LMPH), University of Antwerp, Belgium; WuXi AppTech, China; LSTMH, UK

## Oxachagas

**OVERALL OBJECTIVE:** Generate new drug candidates for the treatment of Chagas disease to be assessed in clinical trials

**2014 OBJECTIVE:** Profile and assess the oxaborole class

**PROJECT START:** May 2011



DNDi is pursuing several oxaborole series optimization projects for kinetoplastid diseases, including Chagas disease. Following significant (between five and ten times) improvement in *in vitro* potency against *T. cruzi*, three oxaborole

candidates were tested in a mouse model of Chagas disease at Murdoch University in 2013. These compounds produced similar reductions in parasitemia and increases in mouse survival to that observed with benznidazole, but did not produce a complete, or sterile, cure. Further profiling of oxaborole candidates is planned in new mouse models once validated, which are under development to include clinical insights into compound profiling resulting from the analysis of data from the E1224 proof-of-concept trial (see page 35). Lead optimization of the oxaborole series for Chagas disease is now being managed by a new partnership between Anacor and the University of Georgia, which will work closely with the DNDi lead optimization project for leishmaniasis for this class in order to maximize cross-fertilization of ideas and leads.

**PARTNERS:** Anacor Pharmaceuticals, USA; WuXi AppTech, China; Sandexis, UK; LMPH, Belgium; LSHTM, UK



## Biomarkers

**OVERALL OBJECTIVE:** To identify and evaluate new biological markers of therapeutic efficacy in chronic Chagas disease and to promote research

**2014 OBJECTIVES:** Progress Non-Human Primate Study through dosing period and 12 month assessments; conclude PCR work and data review; follow-up validation studies on selected markers

**PROJECT START:** 2010

The lack of clear and early biological markers that can indicate parasitological outcome following treatment and, ultimately, definitive cure is a major problem in drug development for Chagas disease. To date, the only measurable outcomes are clinical benefit and seroconversion, but the latter can take several decades.

The initial focus has been on optimizing blood sampling procedures and validation of DNA quantification through polymerase chain reaction (PCR). The TRAENA and BENEFIT projects, two placebo-controlled clinical studies of benznidazole in adult patients with chronic Chagas disease, offer the opportunity to correlate serological response and PCR outcomes with long follow-up after treatment. In the longer-term, DNDi is working towards identifying new biological markers including those identified through proteomic platforms, lytic antibodies, T-cell assays, multiplex serodiagnostic assays and gene expression profiling. Continued follow-up evaluation of lytic antibodies and PCR is underway, together with an analysis of the landscape of known biological markers.

A project with the University Hospitals of Geneva and McGill University to assess the use of proteomic signatures in serum samples of nifurtimox-treated Chagas patients identified biological markers of potential for early assessment of therapeutic response, and preliminary results from children treated with benznidazole have now been obtained.

DNDi is collaborating with the University of Georgia and the Texas Biomedical Research Institute in a Wellcome Trust funded, non-human primate study in naturally infected animals with chronic Chagas disease, to further determine PCR and other markers as sensitive tools to consistently differentiate parasitological cure from treatment failure. The dosing period of this study has now been concluded and a 12-month follow-up assessment is to be completed in August 2015. DNDi is a member 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 (GRESIB), Spain; Dr Mario Fatala 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; University Hospitals of Geneva, Switzerland; NHEPACHA network; Universidad San Martin, Buenos Aires

## Fexinidazole

**OVERALL OBJECTIVE:** Evaluate fexinidazole for treatment of chronic Chagas disease

**2014 OBJECTIVE:** Initiate proof-of-concept evaluation of fexinidazole

**PROJECT START:** December 2013

**47 patients  
in 2 sites**

Nifurtimox and benznidazole are currently the only treatments available for Chagas disease, but concerns about their safety and tolerability mean that alternative treatments, or treatment regimens, are necessary, especially for adult patients. Pre-clinical results with fexinidazole showed that the safety profile and activity in acute and chronic animal models of disease support its clinical evaluation in patients. In July 2014, the Phase II PoC trial started in Bolivia, to determine whether at least one of six dosing regimens of fexinidazole administered orally at either 1200mg/day or 1800mg/day over two, four, or eight weeks (longer period of administration than that of HAT Phase II/III study) are efficacious and safe compared to placebo in clearing *T. cruzi* parasitemia in adult patients with chronic Chagas disease. After recruiting 47 participants by October 2014, some safety and tolerability issues were noticed. DNDi, the investigator teams and the data safety committee reviewed all data and agreed to conclude the trial without inclusion of additional participants. The safety review did not identify the same frequency or severity of adverse events for other fexinidazole indications.

**PARTNERS:** Platform of Integral Care for Patients with Chagas Disease, Tarija and Cochabamba (Bolivia); Molecular Biology Laboratory (BioMol) - Universidad Mayor de San Simón, Cochabamba, Bolivia; Universidad Mayor de San Simón, Bolivia; Universidad Autónoma Juan Misael Saracho, Bolivia; Collective of Applied Studies and Social Development (CEADES), Bolivia; Centre de Recerca en Salut Internacional de Barcelona (CRESIB), Spain; National Council of Scientific and Technological Research (INGEBI/CONICET), Argentina; PhinC, France; JSS Medical Research, Canada; Cardiabase, France; CREAPHARMA, France

## New benznidazole regimens

**OVERALL OBJECTIVE:** Develop a new benznidazole monotherapy regimen for chronic Chagas disease

**2014 OBJECTIVE:** Initiate proof-of-concept evaluation of alternative treatment regimens of benznidazole (short course)

**PROJECT START:** December 2013

The E1224 proof-of-concept trial carried out in 2013 showed that E1224 had good safety and was effective at clearing the parasite, but efficacy was not sustained. Benznidazole, the standard treatment for Chagas, had sustained efficacy until 12 months post-therapy, but was associated with side effects that resulted in treatment discontinuation. An expert meeting in 2014 reviewed the available data in support of the evaluation of benznidazole-sparing (shorter duration courses and lower dosing) regimens for Chagas disease. Proof-of-concept evaluation of new treatment regimens of benznidazole in monotherapy or in combination with E1224, for the treatment of adult patients with chronic Chagas disease, will be initiated in 2015, to determine if the safety and tolerability issues of benznidazole can be managed by reduced doses and treatment duration.

**PARTNERS:** Eisai Co. Ltd, Japan; Platform of Integral Care for Patients with Chagas Disease, Spain/Bolivia; Universidad Mayor de San Simón, 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; Instituto Nacional de Epidemiología Dr Fatala Cháben, Argentina

## New combinations

**OVERALL OBJECTIVE:** Development of a new benznidazole and E1224 combination treatment regimen for chronic Chagas disease

**2014 OBJECTIVES:** Evaluate drug-drug interaction of E1224 and benznidazole in combination

**PROJECT START:** December 2013

Within the context of the partnership between DNDi and Eisai Co. Ltd for the development of E1224, a Phase I drug-drug interaction study was performed in 2014, to assess the safety and pharmacokinetics interaction of E1224 and benznidazole administered first separately and then in combination in healthy human volunteers. The study was undertaken in a Phase I clinical unit in Buenos Aires, Argentina. Twenty-eight healthy human volunteers were recruited and the trial concluded with no major clinically relevant safety or tolerability issues identified.

**PARTNERS:** Eisai Co. Ltd, Japan; Platform of Integral Care for Patients with Chagas Disease, Spain/Bolivia; Universidad Mayor de San Simón, Bolivia; Universidad Autónoma Juan Misael Saracho, Bolivia; Collective of Applied Studies and Social Development (CEADES), Bolivia; Nucleus of Pharmaceutical and Cosmetics Development (NUDFAC), Brazil; Centre de Recerca en Salut Internacional de Barcelona (CRESIB), Spain; National Council of Scientific and Technological Research (INGEBI/CONICET), Argentina; LAT Research, Argentina; FP Clinical Pharma - Ethel Feleder, Argentina; Fundación Mundo Sano and ELEA, Argentina; PhinC, France





## Paediatric dosage form of benznidazole

**OVERALL OBJECTIVE:** Develop and make available an easily dispersible, simpler to administer, safer, age-adapted dosage for children under two years old

**2014 OBJECTIVES:** Ensure paediatric benznidazole availability in Latin American Chagas-endemic countries and secure a second source of treatment

**PROJECT START:** May 2011

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. A population pharmacokinetic study involving 81 children aged 0 to 12 years with Chagas disease was conducted and showed complete parasitic clearance in all children after treatment and that those assessed 12 months later were still clear of *T. cruzi* parasites. The study also showed that children have lower blood levels of benznidazole than previously documented in adults, suggesting a reduction of adult dosing regimens may be possible. The paediatric formulation, adapted for babies and children up to two years of age, was registered in Brazil (2011). In July 2013, the treatment was included on the WHO Essential Medicines

List for children. In November 2013, the Mundo Sano Foundation and DNDi signed a collaboration agreement to deliver a second source of the treatment in partnership with ELEA (producers of Abarax®). ELEA produced pilot and scale-up batches in 2014, and stability testing is underway. Submission for regulatory approval is planned initially in Argentina in 2015, and will proceed in all countries where Abarax® is currently registered.

Through this project, DNDi has also stepped up efforts to support the scale up of treatment with benznidazole for adult patients with Chagas disease.

**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; Mundo Sano Foundation, Argentina; Laboratorio ELEA, Argentina





#### Paediatric HIV, Nairobi

Simon is 21 months old, and HIV positive. His mother Gloria struggles every day to administer the treatment in a syrup form while he cries and tries to get away because of its terrible taste. Gloria lost her regular job when she was diagnosed with HIV, and as a consequence has no money for a refrigerator or electricity with which to keep Simon's medicine cool. She therefore resorts to storing the syrup in a bucket containing water and sand, but, as it cannot be kept at room temperature for more than six weeks, she must leave her family every month to go refill his medicine and take him for a check-up at the health clinic. DNDi is working to develop a four-in-one formulation suitable for babies and small infants that will be easier to administer.

## REMOVING THE BARRIERS TO TREATMENT ACCESS

It is a harsh reality that over 3.2 million children under the age of 15 are currently infected with HIV, mostly in sub-Saharan Africa. The virus is transmitted during pregnancy, childbirth, or breast-feeding. The WHO recommends that the HIV status of pregnant women be known as soon as possible in order to start antiretroviral therapy and so prevent transmission. However many mothers do not know their HIV status and therefore do not receive the treatments that would preserve their own health and avoid transmission to their child. In 2013, 190,000 children died from the disease.

Most of these children were under the age of two – deaths which could have been avoided if diagnosis had been made in the first weeks of infection and treatment started immediately. Unfortunately, only 15% of infants exposed to HIV are tested in the first two months of life. Thanks to international efforts in preventing mother to child transmission, the number of infants newly infected with HIV is now declining, but the need for paediatric treatment will continue to increase until at least 2020.

Furthermore, the vast majority of infants and young children lack access to treatment, without which half of them die before their second birthday and 80% before reaching the age of five. Only a very limited number of drugs have been approved for use in infants and young children, and antiretroviral therapies are not well adapted to tropical environments or easy for caregivers to administer.

In May 2014, UNITAID, DNDi, and the Medicines Patent Pool (MPP) launched a partnership, now also including the Clinton Healthcare Access Initiative (CHAI), to expedite the development and delivery of new antiretroviral formulations, with a focus on overcoming the barriers to developing and delivering specific formulations and combinations appropriate for children (see p.58). In December of the same year, in agreement with AbbVie, lopinavir and ritonavir were placed into the MPP, thus removing any intellectual property barriers to the development of treatments containing these drugs, including those which are currently under development by DNDi and Cipla Ltd.

**3.2 million children**  
under the age of 15 living with HIV/AIDS,  
more than 91% in sub-Saharan Africa

**190,000 children**  
under 15 years of age died of AIDS-related illness  
in 2013 globally

## WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

The 2013 WHO guidelines recommend early diagnosis, and immediate treatment of HIV-positive infants and children under the age of five, regardless of CD4 count; infants under the age of three should be treated with an antiretroviral treatment (ART) combination that includes protease inhibitors regardless of whether they have been exposed to ARVs for the prevention of mother-to-child transmission (PMTCT). The combination of a **boosted protease inhibitor (PI) with two nucleoside reverse transcriptase inhibitors (NRTIs)** is considered by the WHO as the most effective first-line therapy for infants and children.

However, this combination therapy is not being widely used. According to a WHO survey performed in 45 countries, in 2010 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 difficult to store and transport.

In some places, the levels of co-infection of TB and HIV in infants and children are high. 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 antiretroviral (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 imposed by its short shelf-life.

## 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.

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 two 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 heat stable stand-alone ritonavir booster formulation that is well taste-masked and 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.

Before these formulations are made available however, as a **short-term strategy**, DNDi will start testing the use of PI-based treatment with existing LPV/r-based solid formulations before the availability of the 4-in-1 FDC, in order to provide better treatment for infants today and promote in-country adoption. The heat-stable pellets are already a great improvement, however the bitter taste remains and is a barrier to use in treating this chronic disease. DNDi participated in the CHAPAS-2 trial that compared LPV/r sprinkles (hereafter referred to as pellets) to the LPV/r liquid formulation. These pellets will be used in combination with NRTI dispersible tablets in implementation studies (LIVING Study).

In the **longer-term**, DNDi is working with its industrial partner, Cipla Ltd., on combining taste-masked 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. As a short-term strategy, DNDi is conducting a study to establish the pharmacokinetics, efficacy and safety of superboosted LPV/r in children in South Africa with the existing ritonavir solution.

The ideal first-line treatment for paediatric HIV would be a protease inhibitor-based **all-in-one** antiretroviral regimen for HIV-infected children which is a **safe and efficacious, is an adapted formulation** suitable for infants and children, is an **easy-to-use** fixed-dose combination, **is palatable, addresses drug-drug interaction** with medicines for tuberculosis, and is **adapted to tropical climates** (no refrigeration needed).

**By 2019, DNDi aims to deliver from its paediatric HIV portfolio:**

- **Two new four-in-one paediatric formulations containing a PI (LPV/r) and two NRTIs (ABC or AZT and 3TC)**
- **One stand-alone paediatric booster RTV for HIV-TB co-infected children**

## TRANSLATION



## Two 4-in-1 LPV/r based fixed-dose combinations

**OVERALL OBJECTIVE:** Develop and register two solid taste-masked first-line LPV/r-based fixed-dose formulations with two NRTIs, 3TC plus ABC or AZT

**2014 OBJECTIVE:** Develop a taste-masked and bioavailable paediatric formulation

**PROJECT START:** 2012

**27 formulations tested in 2014** Pharmacokinetic modelling was carried out and results, for LPV/r, ABC, 3TC, and AZT, shared with WHO paediatric experts. The proposed dosing for the two 4-in-1 LPV/r based FDCs and RTV booster were incorporated into Annex 7 of the 2013 WHO's new *Consolidated Guidelines on The Use of Antiretroviral Drugs for Treating and Preventing HIV Infection*, under 'urgently needed ARV drugs for children recommended by the Paediatric ARV Working Group', and published in 2014.

The first test formulation of LPV/r 40/10 mg taste-friendly granules to be mixed with the NRTI components of the FDCs was found not to be bio-equivalent to originator liquid formulations. Reformulation of LPV/r and RTV granules is challenging and these formulations require further optimization; the Chapas-2 extension study in children has been put on hold. Since the start of the project 39 formulations of LPV/r and nine formulations of Ritonavir have been tested in animal models, 27 of which in 2014, taking into account the data already generated. The most promising formulations will be evaluated in healthy human volunteers in 2015.

**PARTNERS:** Cipla Ltd., India; UNITAID; National Department of Health, South Africa; Centre for Disease Control and Prevention (CDC)/President's Emergency Plan for AIDS Relief (PEPFAR), USA; Médecins Sans Frontières; Medical Research Council, UK; Necker Institute, Paris; various academic partners in South Africa and Kenya; AbbVie, USA; WuXi, China

## 'Superboosting' – TB/HIV

**OVERALL OBJECTIVE:** To develop a stand-alone pharmacokinetic enhancer/booster formulation to be added to any PI-based paediatric ARV regimen

**2014 OBJECTIVE:** Ongoing recruitment for the RTV superboosting (PK) study in South Africa

**PROJECT START:** 2012

**82 patients recruited at 5 sites** Rifampicin is commonly used to treat tuberculosis (TB) in children. However, rifampicin reduces the bioavailability of protease inhibitors (PIs) in treatments used to combat HIV infection. A stand-alone ritonavir booster formulation is being developed that can be added to any PI-based paediatric ARV regimen, in order to counteract the

negative drug interactions between PIs and rifampicin-containing TB treatment.

A pharmacokinetic (PK) study is being carried out in infants and young children co-infected with TB and HIV at five sites in South Africa to supplement existing information and evaluate the effect of the 'super-boosting' strategy. The study will evaluate the effect of lopinavir/ritonavir in a 1:1 ratio on the PK of lopinavir in children concomitantly receiving rifampicin as treatment for TB. Recruitment began in January 2013 and is expected to end in 2015. By the end of 2014, 82 patients had been included.

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

## DEVELOPMENT



## LPV/r pellets with dual NRTI FDC

**OVERALL OBJECTIVE:** Start penetrating the market with LPV/r based products immediately, before the availability of the final, better-adapted 4-in-1 products

**2014 OBJECTIVE:** Initiate implementation studies

**PROJECT START:** 2014

Cipla Ltd., India, has developed LPV/r pellets (mini-'melt' tablet formulation), stored in 40/10 mg capsules, which can be opened and administered orally to small children, allowing the drug to be mixed with food and offering the advantage, over the current liquid formulation of these drugs, of being alcohol-free. These pellets do not require a cold chain and are less costly in terms of weight of product for transport; however, their poor taste is still a barrier.

This project comprises large-scale implementation studies to provide supportive clinical data on the feasibility, efficacy, safety, and PK of LPV-based therapies in routine treatment settings in order to facilitate registration in the countries concerned. Originally scheduled to begin in 2014, the study was delayed pending regulatory approval but this was obtained by the end of 2014 and the LIVING study will start in Kenya and Uganda in 2015 using the first generation of LPV/r pellets, expanding to additional countries soon after.

**PARTNERS:** Cipla Ltd., India; UNITAID; National Department of Health, South Africa; Kenya Partners: University of Nairobi; KEMRI Walter Reed Project; St Lumumba Health Centre, Kisumu; Mbagathi District Hospital; KEMRI Wellcome Trust; Gertrudes Children's Hospital; Moi Teaching and Referral Hospital; Kenyan Ministry of Health; Joint Clinical Research Centre (JCRC) in Uganda, Baylor International Pediatric AIDS Initiative; Epicentre, Uganda; Elizabeth Glaser Paediatric AIDS Foundation (EGPAF) in Tanzania



Filarial disease, Ghana

A medical team visits a village in Kumasi, Ghana, to assess the needs of patients with lymphatic filariasis (elephantiasis).

## DEVELOPING NEW TREATMENTS FOR DEBILITATING INFECTIONS

**D**NDi aims to develop improved treatments for the millions of people worldwide that suffer from filarial diseases: **lymphatic filariasis** (elephantiasis) and **onchocerciasis** (river blindness). Although current treatments for these debilitating and stigmatizing illnesses help to prevent infection, health tools that rapidly cure patients are lacking.

### What are filarial diseases?

Filarial diseases are caused by parasitic worms of the helminth family. While rarely fatal, these diseases affect millions of people and inflict immense hardship. Onchocerciasis is the world's second leading infectious cause of blindness and has a host of other symptoms, including skin discoloration and intense itching. The disease is contracted through the bite of an infected female blackfly. *Lymphatic filariasis* is the second cause of chronic disability worldwide and is transmitted to humans by mosquitoes. It may lead to lymphoedema (massive swelling, principally of the legs and genitals), elephantiasis (the late disfiguring stage), and hydrocele (fluid accumulation in the testes). Together, these two diseases are responsible for considerable financial and social burden on people already living in deep poverty.

### Addressing R&D gaps in existing treatments

Large-scale programmes for the control of filarial diseases have been in place for over twenty years, based on the mass drug administration (MDA) of medicines donated by the pharmaceutical industry. These programmes have been successful in reducing transmission but significant R&D gaps remain. MDA programmes use microfilaricidal drugs that kill juvenile worms (microfilariae) but leave adult worms (macrofilariae) alive in the body for up to 15 years. Therefore, MDA needs to

be repeated for a number of years until the adult worms naturally die out. Evidence also shows that current treatments for filarial diseases can cause neurological damage or even death for those also infected with *Loa loa* by causing sudden, massive death of juvenile *Loa loa* worms.

A safe, short-course drug that can kill adult filarial worms is therefore needed. This macrofilaricidal drug could be an essential tool for health workers in rural areas and also greatly shorten the length of MDA programmes, thus contributing to the WHO goals of eliminating lymphatic filariasis (defined as 70% of countries free of disease and 30% engaged in post-surveillance activities) and controlling onchocerciasis by 2020. New treatments are also essential for areas where *Loa loa* and other filarial diseases are co-endemic, to enable the safe treatment of co-infected patients.

DNDi aims to register a new drug as a short course, oral macrofilaricide with potential application to treat both onchocerciasis and lymphatic filariasis, and has a two-fold strategy in place. As part of its medium term strategy DNDi will focus on repurposing candidates used for other indications in the pharmaceutical and the animal health industries, such as emodepside, a potent drug used in veterinary medicine, which will be developed for patient use with Bayer HealthCare. The second strategy is based on partnering with other discovery initiatives on developing compounds identified from DNDi's screening campaign. In 2014, DNDi began putting in place a clinical research platform for filarial diseases by expanding its existing network of partners and other platforms (see p.50).

Without R&D for better treatments, filarial diseases will continue to exact a terrible burden on the most neglected patients.

## 37 million people infected with onchocerciasis

worldwide, with 99% cases in 31 African countries, and 169 million at risk

## Over 120 million people infected with lymphatic filariasis globally,

with about 40 million disfigured or incapacitated; more than 1.4 billion people in 73 countries at risk of infection

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

Current treatments for onchocerciasis and lymphatic filariasis are based on repeated mass drug administration (MDA) of antiparasitic drugs through programmes directed by the WHO. WHO recommends MDA for onchocerciasis at least once yearly for 10-15 years, and for lymphatic filariasis once yearly for at least five years. The drugs used in MDA programmes are **ivermectin** for onchocerciasis; and for lymphatic filariasis, **albendazole** plus either **ivermectin** in areas where onchocerciasis is also endemic (*i.e.* African countries), or **diethylcarbamazine** (DEC) in areas where onchocerciasis is not co-endemic (*i.e.* non-African countries).

By killing microfilariae, and inducing a temporary sterilization of adult worms, MDA drugs can prevent vector-borne transmission for several months, until the adult worms produce more microfilariae larvae. However, because adult worms continue to live in the body, they eventually produce new microfilariae, often before the next MDA, thus requiring repeated MDAs for several years to decades until the adult worms die naturally.

Ivermectin is safe and has been used widely as a monotherapy in MDA programmes for onchocerciasis, killing the microfilarial stage of the parasite. However, in lymphatic filariasis and onchocerciasis patients co-infected with *Loa loa*, the sudden death of large numbers of *Loa loa* microfilariae following treatment can lead to serious adverse events, such as encephalopathy, possibly resulting in permanent brain damage and death. Furthermore, reports of a suboptimal response to ivermectin by *O. volvulus* may be a sign of developing resistance.



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

**DNDi's strategy** is to develop a new compound with macrofilaricide activity for use as a safe and field-adapted macrofilaricidal drug for patient case management and possibly later MDA if needed. As a **medium-term strategy**, DNDi is assessing emodepside, a potent antihelminthic drug used in combination with praziquantel to treat parasitic worms in cats and dogs, as a clinical candidate to treat humans.

As a **long-term strategy**, DNDi is assessing additional opportunities through an active screening programme of drug compounds emanating from animal health/pharmaceutical companies and academic institutions, with the goal of selecting one or two candidates to move into clinical development.

**Ideally a new treatment for adults and children will be a macrofilaricide (efficacious against the adult form of worms), oral, short-course treatment, well tolerated, affordable, and adapted to tropical climates.**

## Emodepside

**OVERALL OBJECTIVE:** Develop emodepside as a new macrofilaricidal treatment for patients suffering from onchocerciasis

**2014 OBJECTIVE:** Sign agreement with Bayer HealthCare

**PROJECT START:** March 2013

Emodepside is a semi-synthetic product (originated by Astellas and out-licensed to Bayer Animal Health for animal use); its precursor is synthesized by a fungus living in the leaves of *Camellia japonica*. It is a potent antihelminthic drug used in combination with praziquantel (Profender®) and in combination with toltrazuril (Procox®) for the treatment of parasitic worms in cats and dogs. Originating from the Japanese pharmaceutical company Astellas, the compound has been developed by Bayer Animal Health for animal health uses and commercialized as an anthelmintic veterinary drug for cats and dogs in combination with praziquantel (Profender™) and in combination with toltrazuril (Procox™). Following its successful animal use, the compound has been found in relevant animal models of the human diseases to be effective in killing the adult worm in pre-clinical studies, a unique feature permitting to envisage a shorter therapeutic intervention to treat infected patients. Emodepside shows outstanding activity against filarial parasites. In 2014, DNDi signed an agreement with Bayer HealthCare to develop emodepside for treatment of patients with onchocerciasis. DNDi will be responsible for the pre-clinical and clinical development of emodepside and Bayer for the pharmaceutical development, manufacturing, registration, and supply of the drug. The agreement ensures that emodepside, if successful in subsequent phases of drug development, would be available at the lowest sustainable price to ensure affordability and access in 31 African disease-endemic countries. The rights to use technology or data generated within the collaboration allow each party to pursue the project with third partners in case of withdrawal of the other party, thus securing the development and accessibility of emodepside for the benefit of patients. DNDi is also exploring other potential drug candidates.

**PARTNER:** Bayer HealthCare, Germany





# MALARIA

## ASAQ AND ASMQ, TWO INNOVATIVE APPROACHES

**A**mong the very first projects undertaken by DNDi was the development of two artemisinin-combination therapies (ACTs) to treat malaria, based on recommendations made by the WHO in 2001.

The FACT (Fixed-Dose Combination Therapy) consortium was formed in 2002 to develop combinations of artesunate (AS) with amodiaquine (AQ) or mefloquine (MQ). Having fixed dose combinations (FDCs) of drugs would lead to simplified administration and increased compliance, the aim being to develop field-adapted formulations that would be easy to administer to all age/weight categories of patients, particularly to infants and young children, whilst also able to withstand the heat and humidity of tropical climates.

In 2007, ASAQ FDC became the first treatment to be launched by DNDi, having been developed by a number of partners across almost the full development range, from formulation work through to post-registration studies. The development of ASAQ FDC required innovation in four ways: through the establishment of an innovative partnership with a major pharmaceutical company, Sanofi, including agreement to develop ASAQ FDC as a non-patented product at the price of one US dollar per treatment; an innovative approach to developing this product with public and private partners; an innovative implementation strategy, which began with manufacturing the product at Sanofi's facility in Morocco and its registration in African countries; and an innovative Risk

Management Plan with Sanofi and MMV, the first of its kind to be submitted to the WHO, and the first to be entirely undertaken in Africa.

The ASMQ FDC, launched in 2008, was developed in collaboration with Farmanguinhos/Fiocruz, a Brazilian public pharmaceutical company, and for which DNDi received the Funding Authority for Studies and Projects (FINEP) award for Innovation in Social Technology in November 2014. A South-South technology transfer agreement to Cipla Ltd in India ensures a second supplier of the treatment, principally for the Asian market but also for Africa. Recent results from the multi-centre trial carried out in Africa showed ASMQ FDC is as safe and efficacious as artemether-lumefantrine – Africa's most widely adopted treatment – in children under five years of age.

### **Malaria projects handed over to MMV**

The successful development of these two antimalarials, although not always easy, provided good lessons learned and experience to DNDi's team and partners in building an alternative model for R&D.

In May 2015 the malaria projects were formally handed over to the Medicines for Malaria Venture (MMV), long term partners of DNDi, who have successfully built the largest portfolio of antimalarials ever seen in the history of the disease, ensuring the future implementation of these two treatments.



## ASAQ Winthrop

**OVERALL OBJECTIVES:** Develop and make available an affordable, field-adapted FDC of AS and AQ, which is easy to administer to all age/weight categories, particularly to infants and children

**2014 OBJECTIVES:** Contribute to disseminate ASAQ broadly and participate in large-scale data assessments (see WWARN); support the technology transfer of ASAQ manufacture to Zenufa in Tanzania

**PROJECT START:** January 2002

**400 million ASAQ treatments distributed by Sanofi and generic companies in 35 countries by end of 2014**

ASAQ Winthrop, the fixed-dose combination (FDC) of artesunate (AS) and amodiaquine (AQ), was the first treatment made available by DNDi in 2007 through an innovative partnership with Sanofi.

ASAQ Winthrop was pre-qualified by WHO in October 2008 and included on the WHO Essential Medicines List (EML) in 2011. First registered in Morocco, where it is manufactured, ASAQ is now registered in 31 African countries, as well as in India, Bangladesh, Colombia, and Ecuador.



There were significant challenges to overcome: the development of a stable bilayer formulation of the two drugs, together with the dual-aluminium blister packaging designed to withstand the rigors of a tropical environment; as a result it is the only ACT FDC with a three-year shelf-life currently available. ASAQ Winthrop obtained WHO authorization in 2010, for a three-year shelf life, giving the product the longest shelf life of any pre-qualified FDC artemisinin-based treatment available for malaria. Registration, manufacture and distribution of this stable formulation was undertaken with Sanofi, the industrial partner, who were already providing co-blistered Coarsucam™ to Africa at the time, and who committed to making the generic ASAQ Winthrop® available at less than one US dollar per adult treatment for the public market. Its low price and prequalified status, allowing purchases by procurement agencies, led to price decreases not only of ASAQ but also other ACTs, and having an affordable

drug on the market led to increased patient access to high quality treatments.

In partnership with Sanofi, MMV and National Malaria Control Programmes, high-quality data on ASAQ effectiveness and safety in 'real-life' conditions is being collected, as part of a Risk Management Plan (RMP). The largest study, undertaken by Sanofi and MMV with support from DNDi, has been ongoing in 15,000 patients in Côte d'Ivoire, and results are expected in 2015.

DNDi and partners are also working on the transfer of technology to a second manufacturer in Africa, Zenufa, based in Tanzania (see p. 49).

By the end of 2014, 400 million treatments had been distributed, by Sanofi and generic companies.

**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 de Bordeaux Faculté de Pharmacie, France; Mahidol University, Thailand; Bertin Pharma, France; Médecins Sans Frontières; Epicentre, France; WHO-TDR; Kenya Medical Research Institute (KEMRI), Kenya; Indian Council of Medical Research (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

## ASMQ FDC

*DNDi  
Latin  
America*

**OVERALL OBJECTIVE:** Develop and make available worldwide an affordable fixed-dose combination of AS and MQ which would be easy to administer, particularly to infants and children, targeted initially for use in Asia and Latin America

**2014 OBJECTIVES:** Increase the number of countries where ASMQ FDC is approved; conclude the study performed in children in Africa

**PROJECT START:** January 2002

**over 830,000 treatments distributed by end of 2014**

The ASMQ fixed-dose combination treatment (ASMQ FDC) was developed by the FACT consortium created by DNDi and TDR in 2002.

Within FACT, the Brazilian government-owned pharmaceutical company, Farmanguinhos/Fiocruz, was the first manufacturer of ASMQ FDC. Through a South-South technology transfer, ASMQ FDC production was transferred to the Indian pharmaceutical company Cipla in 2010 to ensure availability in India and Asia at affordable, pre-agreed prices. Both Farmanguinhos and principally Cipla supplied treatments in response to a large request from Venezuela in 2013 (over 382,000 treatments). ASMQ FDC is now registered in Brazil (2008), India (2011), Malaysia and Myanmar (2012), Tanzania (2013), Vietnam, Niger and Burkina Faso (2014), Thailand and Cambodia (2015). The Cipla ASMQ FDC product was prequalified by the WHO in 2012 and was included in the WHO Essential Medicines Lists for adults and children in April 2013,

*DNDi  
Malaysia*



in line with current treatment guidelines. Farmanguinhos/Fiocruz was admitted into the PAHO Strategic Fund in April 2013, allowing procurement by South American national control programmes. In 2014 Farmanguinhos was requested to obtain WHO prequalification in order to remain in the Fund. The pre-qualification file is being generated and submission is planned for 2015.

Additional clinical studies are ongoing that will provide information of ASMQ FDC use in children, adults, and pregnant women in Africa. According to WHO recommendations, AS+MQ could be considered for use in some countries in Africa. DNDi sponsored a key multicentre Phase IIIB study in Tanzania, Burkina Faso, and Kenya to assess the efficacy, safety, and pharmacokinetics

of ASMQ FDC compared to artemether-lumefantrine in children below the age of five with uncomplicated *P. falciparum* malaria. The study found ASMQ FDC to be as safe and efficacious as Artemether-Lumefantrine (AL) FDC – Africa’s most widely adopted treatment - results which were presented at ASTMH in November 2014. The pharmacokinetic data collected confirmed there was no need to change the dosing in children. The report is being finalized and publications are planned for 2015.

By the end of 2014, 832,000 ASMQ treatments were distributed.

**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 (CHUV), Switzerland; National Institute of Medical Research (NIMR), Tanzania; Kenya Medical Research Institute (KEMRI), Kenya; Centre National de Recherche et de Formation sur le Paludisme (CNRFP), Burkina Faso; Medicines for Malaria Venture (MMV), Switzerland; Ifakara Health Institute, Tanzania; Worldwide Antimalarial Resistance Network (WWARN)

## After more than a decade, DNDi hands over its malaria programme to MMV

In May 2015, DNDi and MMV signed a landmark project transfer agreement and convened a high-level event exploring 15 years of progress in the fight against malaria. The event was hosted to mark the handover of DNDi’s malaria activities to MMV, according to DNDi’s 2011-2018 Business Plan objectives.

The two fixed-dose artemisinin combination therapies (ACTs) developed by DNDi and partners, artesunate-amodiaquine (ASAQ) and artesunate-mefloquine (ASMQ), will be henceforth managed by MMV.

The event was chaired by Prof. Marcel Tanner, Chairman of the DNDi Board and Director of the Swiss Tropical and Public Health Institute, and opened with a keynote speech from Dr Pedro Alonso, Director of the WHO Global Malaria Programme. A panel discussion included the Minister of Health of Côte d’Ivoire, as well as high-level representatives from Ethiopia, Roll Back Malaria, Asia Pacific Leaders Malaria Alliance, UNITAID, Cipla, Sanofi, and Novartis.

Before passing over a commemorative rugby ball to Dr David Reddy, CEO of MMV, to symbolize the handover, Dr Bernard Pécoul, Executive Director of DNDi, applauded his team for their work in launching the two ACTs, stating that ‘these projects have proved how essential a nimble partnership model is to success, and how crucial the engagement and dedication of numerous public and private partners, and individuals, is to reaching a common goal’. Dr Reddy replied declaring that ‘the goal is to ensure these medicines reach as many vulnerable people as possible and save lives’.



From left to right: Representative of Health Ministry, Ethiopia – Dr Ben Rolfe, Executive Secretary, APLMA – Dr James Banda, Senior Advisor RBM – Brigadier General (Dr) G Gwinji, Permanent Secretary for Health and Child Welfare, Republic of Zimbabwe – H. E. Dr Raymonde Goudou Coffie, Minister of Health and HIV/AIDS Programme, Côte d’Ivoire.



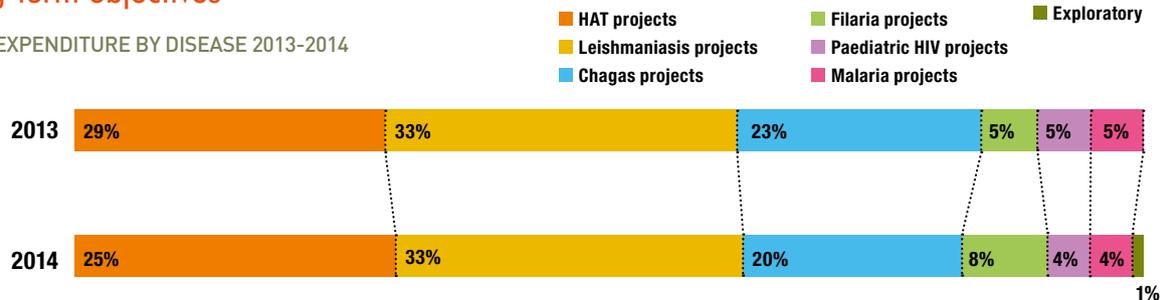
Dr David Reddy, CEO, MMV and Dr Bernard Pécoul, Executive Director, DNDi at the malaria handover event.



## 2014 KEY FINANCIAL PERFORMANCE INDICATORS

EUR 27.6 million to achieve key milestones while maintaining a robust pipeline to support long-term objectives

R&D EXPENDITURE BY DISEASE 2013-2014



Overall R&D expenditures (EUR 27.6 M) increased by 19% (EUR 4.4 M) compared to 2013.

Percentage breakdown highlights of 2014 R&D expenditures per disease (screening and lead optimization expenditures are split and allocated toward disease expenditures):

- HAT:** With a total of EUR 7.1 M, HAT investments increased (+EUR 1.3 M) due to the growth in clinical activities for fexinidazole in 2014 (+EUR 2.6 M), with the opening of one new clinical trial site (reaching a total of 10 operating sites) in DRC that helped to recruit 359 patients for our fexinidazole phase II/III clinical study. Two new complementary cohort trials, one for stage 1 and early stage 2 in adults included 110 patients, and another with children between 6 and 14 years of age included 56, for a total of 525 patients included in the three trials. The SCYX-7158 project continued the phase I study (total 128 patients enrolled by end of 2014) incurring a decrease of EUR 0.7 M in expenditures. Work on publication for the NECT study was ongoing in 2014 (- EUR 0.1 M). Screening and lead optimization efforts were entirely redirected towards leishmaniasis and Chagas disease (- EUR 0.5 M).

- Leishmaniasis:** This disease represents the most substantial R&D expenditure (33%) in 2014. The overall expenditures increased by EUR 1.3 M in 2014 (EUR 8 M in 2014 compared to EUR 6.7 M in 2013). New activities such as PKDL for VL with an infectivity study and CpG-D35 with manufacture non-GMP API for CL (+EUR 0.2 M) started in 2014: The HIV co-infection for VL study (+EUR 0.4M) progressed with a total of 18 patients recruited. The toxicology package for VL-2098 was completed (+EUR 0.5 M). Screening and lead optimization work focused more intently on VL, leading to an increase from 43% in 2012 to 50% in 2013 and 63% in 2014 (+ EUR 0.2 M).

- Chagas disease:** Projects remained stable in 2014 (+EUR 0.2 M), with EUR 5 M (20%) of R&D expenditures. The preparation of a new combination study for benznidazole new regimen, including a drug-drug interaction study started at the end of 2014 (+ EUR 0.3 M). The phase II fexinidazole for Chagas study was completed in 2014, incurring an increase of EUR 1.1 M. The E1224 phase II study was completed in Q1 2014 (-EUR 1.2 M).

- Portfolio expansion:** The three disease areas represent 12% compared to 10.5% in 2013. This increase (+EUR 0.7 M, +34%) is the most significant of the DNDi portfolio.

- Paediatric HIV:** Project expenditure remains stable in 2014. One new activity started in 2014: preparation of the implementation study for a 4-in-1 product (+EUR 0.1 M). The clinical 'super boosting' study (ritonavir for super boosting LPV/r) in South Africa (-EUR 0.3 M), and the formulation development of the 4-in-1 with Cipla Ltd as an industrial partner (+EUR 0.2 M) are ongoing.

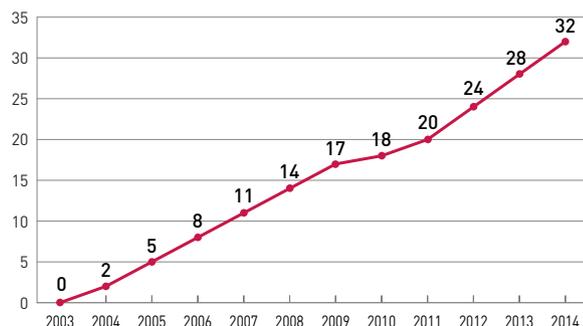
- Filaria:** Project expenditures increased by 70% (+EUR 0.7M). Three activities are ongoing: The preclinical activities increased with a new preclinical candidate (+EUR 0.1 M) and the flubendazole project that has been terminated (+EUR 0.4 M). The screening work is ongoing and maintained at the same level as in 2013. Preparation of clinical activities was set up in 2014 (+EUR 0.2 M)

- Malaria:** Despite the nearly completed handover to MMV, two activities are still on going in 2014 with the same level of expenditures as in 2013.

## Regular increase of partnerships with research companies

CUMULATIVE NUMBER OF NEW PARTNERSHIPS ESTABLISHED WITH RESEARCH COMPANIES

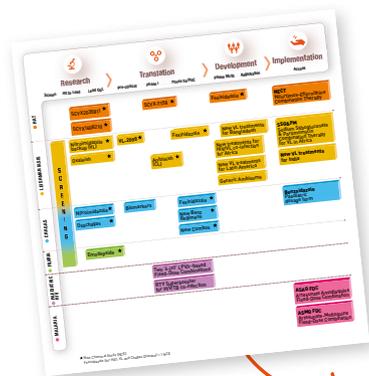
Number of partnership agreements signed per year



By the end of 2014, 32 partnership agreements had been signed between DNDi and research companies (pharmaceutical and biotech companies), including access to compound libraries, pre-clinical activities, and industrial development (+14%).



## 2014 KEY FINANCIAL PERFORMANCE INDICATORS



Development and translation increase with several new projects entering into pre-clinical stage or clinical development

R&D EXPENDITURE PER R&D STAGE



Overall R&D expenditure increased by 19% between 2013 and 2014 to reach a total of EUR 27.6 Mio.

The most important fluctuation relates to growth of development projects (+39%), and the progress of translational projects (pre-clinical; phase I; phase IIa/proof of concept: + 21%). The R&D coordination & supervision costs (EUR 3.1 M) are included proportionally in the R&D expenditure per stage of new exploratory (+EUR 0.2 M).

• **Implementation:** Projects costs decreased by 13% (-EUR 0.3 M) in 2014 compared to 2013.

With six projects in implementation (the first one entered in 2007), two projects were terminated:

NECT finalized the final report for the field study (- EUR 0.1 M) and SSG & paramomycin combination therapy for VL in Africa ended (- EUR 0.2 M).

• **Development:** The progression of fexinidazole for HAT phase IIb/III clinical study (+EUR 2.6 M) with 10 operational sites in DRC and the respect of ambitious timelines is the major achievement for 2014.

The VL co-infection HIV (+EUR 0.4 M) study started the recruitment of patients in 2014.

The new VL treatment in Africa was stopped in 2014 and replaced by a combination fexinidazole /miltefosine study that is in preparation and allocated against the translation phase (- EUR 1 M).

• **Translation:** Expenditures increased between 2013 and 2014 (+EUR 1.7 M) because new projects entered this stage in 2014:

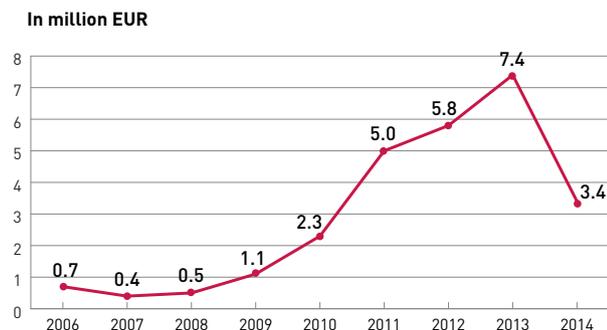
- Progress of two new fexinidazole projects: one for VL and one for Chagas disease (+EUR 2 M).
- Start of a new CpG-D35 project for CL (+EUR 0.2 M).
- Preparation of a combination study for a new benznidazole regimen for Chagas disease (combination of E1224 and benznidazole: +EUR 0.3 M).
- Pre-clinical package for VL2098 almost completed (+EUR 0.4 M)
- Completion of flubendazole project and a new candidate for filarial project entering into pre-clinical stage (+EUR 0.7 M).
- The E1224 phase II study for Chagas disease terminated in 2014 (- EUR 1.2 M).
- The SCYX-7158 expenditure decreased in 2014 compared to 2013 (- EUR 0.7 M).

• **Research:** Screening and lead optimization activities increased (+EUR 0.7 M) due to the purchase of compounds libraries (+EUR 0.3 M) and an increase of four FTE with partners involved with the lead optimization consortium (+ EUR 0.4 M).

• **Exploratory:** In relation to the new business plan that will be presented in 2015, exploratory activities were implemented for HCV, mycetoma, and anti-infective (+ EUR 0.2 M).

### Leveraging partners' resources

IN-KIND CONTRIBUTIONS 2006-2014



NUMBER OF COMPOUNDS SCREENED



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

The cumulated in-kind contribution over nine years amounts to EUR 26.4 M, reflecting DNDi's investment in building strong partnerships. The 49% decrease in 2014 compared to 2013 (- EUR 4 M) is largely due to the fact that the flubendazole macrofilaricide project is phasing out and the in-kind contribution from the partner decreased by EUR 3.1 M (from EUR 4.1 M in 2013 to 1 M in 2014). More than 50% of the contribution relates to pharmaceutical and formulation development (reformulation for humans and new chemical entities (NCEs)). The Sanofi contribution towards the Fexinidazole projects is an important and strategic contribution, but it is not recognized financially due to the DNDi In-Kind Donation policy.

DNDi has access to pharmaceutical libraries that will allow the development of innovative medicines with NCEs. The pharmaceutical companies provide compound libraries for screening and lead optimization at no cost. It is complicated for companies to value such contributions given the number of internal and external collaborators involved in this important effort and the existence of many indirect and intangible contributions. To illustrate this contribution, the total number of compounds screened in 2012, 2013 and 2014 was consolidated and compared; it showed a 22% decrease (-47,263 compounds) that was compensated with the access to 1.8M data/hits resulting from the screening of the global GSK compound collection.