

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



IMPROVING CURRENT TREATMENTS AND STRIVING FOR GAME-CHANGING DRUGS

A decade after its launch, DNDi has built a solid portfolio for neglected diseases based on improved formulations, combinations, or dosing regimens of existing drugs, and increasing numbers of new chemical entities (NCEs), now numbering twelve.

Six treatments – two each for leishmaniasis and malaria, one for human African trypanosomiasis (HAT), and one for Chagas disease – are already available. New classes of orally active drugs are currently in development, with candidates emerging from compound mining (e.g. fexinidazole for kinetoplastids) and lead optimization efforts (e.g. SCYX-7158 for HAT).

Drug development for neglected tropical diseases (NTDs) is a challenging process with high attrition rates, and calculations predict only 1 in every 1,000 'hits' will lead to a registered drug.

DNDi aims to evolve its discovery capabilities through accessing new chemical space and innovation, building on endemic country expertise, and improving and enhancing research partnerships.

Rapid identification of new molecules

A growing consortium between DNDi and pharmaceutical partners aims to efficiently screen compound libraries in kinetoplastid parasite assays to rapidly identify hit series for optimization (see page 16, 'NTD Drug Discovery Booster') and increasingly endemic countries, notably emerging economies, play a significant role in drug discovery and optimization (see page 16, LOLA project).

A major difficulty in drug development for NTDs is the lack of animal models capable of predicting how effective a promising drug candidate will be when treating the disease in man. Recent clinical trials with two azoles, the posaconazole study led by the Infectious Disease Department, Vall d'Hebron Hospital in Spain, and the DNDi-Eisai E1224

project, for Chagas disease, were prompted by promising animal data. Unfortunately, both drugs failed to show sustained efficacy as monotherapies in Chagas disease patients. Nevertheless, although this is a disappointing result for the patient, the clinical trial data are informing ways to improve drug discovery paradigms in Chagas disease and expedite translation into new treatments for patients.

Challenges of conducting clinical trials in remote areas

Carrying out clinical trials in disease-endemic countries presents various challenges. Improvements to site infrastructure are frequently necessary, such as equipping a site with electricity, specialized equipment, or internet access to enable the use of electronic case report forms, and local personnel need to be trained in the conduct of clinical trials. Reliable simplified tests would enable diagnosis in field settings, rather than the clinic or hospital, and replace invasive techniques such as the painful lumbar punctures required for HAT diagnosis and follow-up after treatment, or spleen or bone marrow aspirates in visceral leishmaniasis to confirm diagnosis. Furthermore, accepted biological norms (the biochemical and other values used to determine the health status of an individual) can be affected by a number of factors including the genetic constitution of the population. Such norms have not been well developed in Africa for example, and may lead to the exclusion of otherwise suitable trial candidates, or to the erroneous declaration of an adverse event.

Through clinical research platforms and other partners, 25 clinical studies have been carried out since 2003, often in very remote or first-time clinical trial settings. For instance,

the Phase II E1224 trial was the first ever such trial conducted in Bolivia. All DNDi-sponsored trials comply with international quality and ethical standards. At any given time, DNDi and partners have been running up to 10 clinical trials simultaneously, ranging from Phase I trials in healthy volunteers to large-scale post-approval trials.

HUMAN AFRICAN TRYPANOSOMIASIS (HAT)

Two oral drug candidates are in clinical development for sleeping sickness which represents an enormous breakthrough for this disease and can help support the WHO strategy to eliminate the disease by 2020. A pivotal Phase II/III study with fexinidazole started in 2012 and progressed throughout 2013, and a Phase I study of oxaborole SCYX-7158 also advanced throughout the year. Two backup candidates have been identified in case an unforeseen event precludes SCYX-7158 from further clinical development. NECT, on the WHO Essential Medicines List since 2009, was included on the Essential Medicines List for children in April 2013. Since June 2013, all countries endemic to *T. b. gambiense* are using NECT as first-line treatment for second stage HAT, with the exception of Nigeria.

LEISHMANIASIS

After the development of a combination therapy for Africa and a set of treatments in Asia, for which large implementation studies are being conducted, a Phase II proof-of-concept study of fexinidazole for the treatment of primary visceral leishmaniasis (VL) was ready for recruitment in Sudan in late 2013. A backup drug candidate, VL-2098, is in pre-clinical development and if data support, will be proposed as a clinical candidate in 2014. Two other nitroimidazoles were selected and are being further profiled for *in vivo* efficacy. A large implementation study is ongoing in India to document the field effectiveness and safety of the new treatments developed for VL. Approval was obtained for a cutaneous leishmaniasis clinical trial to be conducted in Colombia to test a topical anti-parasitic treatment containing amphotericin B, applied locally at the site of the skin lesion.

CHAGAS DISEASE

Results of the Phase II study for the treatment of chronic Chagas disease showed E1224 monotherapy to be effective at clearing the parasite, but with little to no sustained efficacy one year after treatment. Benznidazole, the standard therapy for the disease, was shown to be effective in the

long term but continues to be associated with side effects. A drug-drug interaction study will be performed in 2014, to assess the safety and pharmacokinetics interaction of E1224 and benznidazole, and a decision taken as to whether to proceed to proof-of-concept evaluation of combination treatment in adult patients with chronic Chagas disease. Clinical data from the E1224 trial has driven a reassessment of the use of benznidazole as a Chagas disease therapy. Alternative regimens of benznidazole, reducing the exposure to treatment, will be considered to assess feasibility of improving the best therapy to date.

The paediatric dosage form of benznidazole, developed by LAPEPE and DNDi, was included on the WHO Essential Medicines List for children, and the provision of a second source of benznidazole ensured.

FILARIAL DISEASES

Johnson & Johnson have undertaken the continued development of flubendazole as a macrofilaricide and transition to Phase I. DNDi is reviewing emodepside as a clinical candidate.

PAEDIATRIC HIV

Consolidated WHO guidelines on the use of antiretroviral drugs, launched in June 2013, recommend a LPV/r-based regimen as first-line treatment for all children under 3 years old infected with HIV.

The pharmacokinetic study to evaluate LPV/r as a 'super-booster' for the treatment of HIV/TB co-infected infants and young children began recruiting in January 2013, with 37 patients out of the total 90 recruited across 4 sites in South Africa by the end of the year.

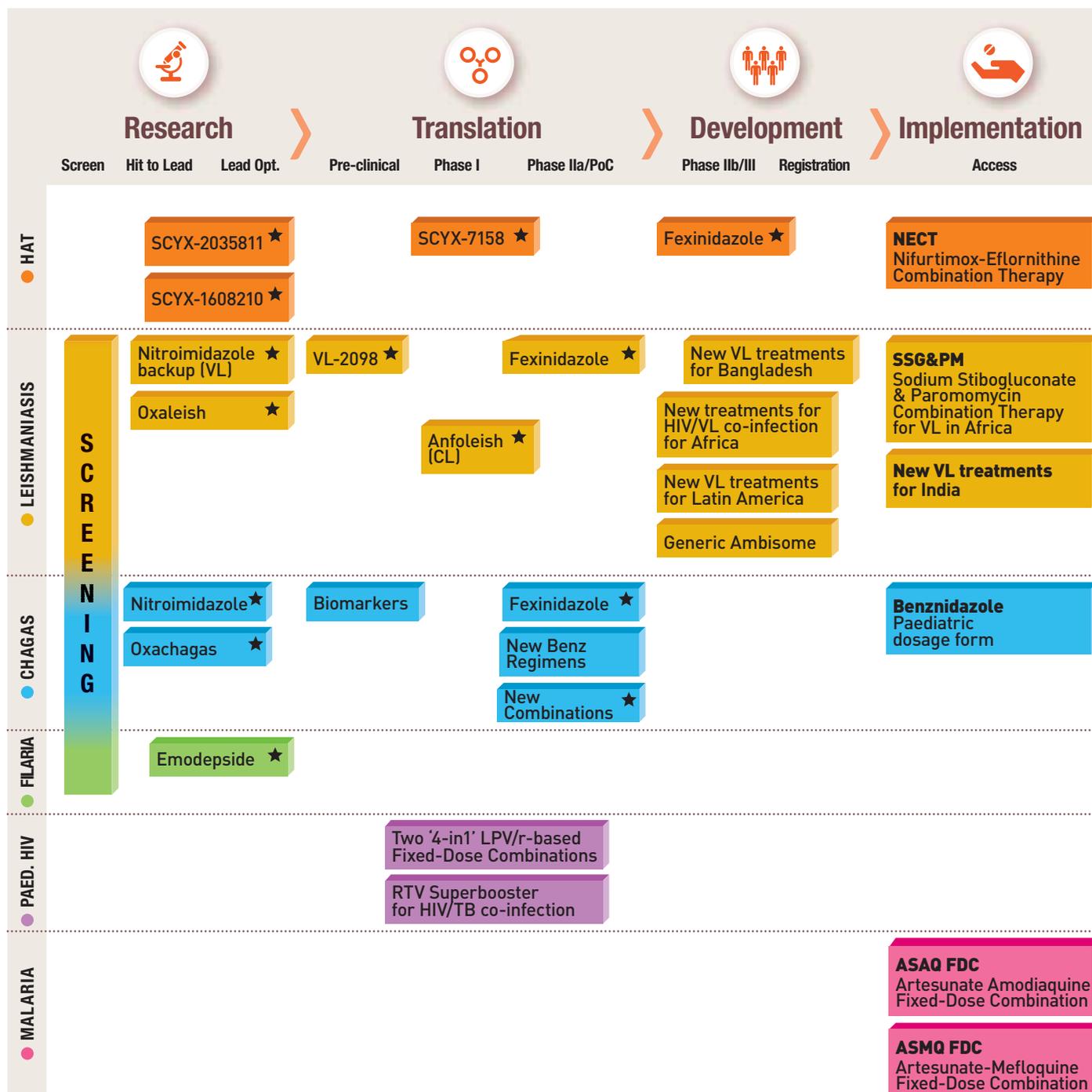
MALARIA

More than 280 million ASAQ FDC treatments had been distributed by the close of the year in 35 countries, of which 31 were in Africa.

ASMQ FDC was registered in Ecuador, Tanzania, Vietnam (low-strength) in 2013 and, in January 2014, in Uganda. In April 2013, ASMQ FDC was included in the WHO Essential Medicines Lists for adults and children. Since 2008, 1,200,000 ASMQ FDC treatments have been distributed. A study conducted in Africa to assess ASMQ in children completed patient recruitment.

6 NEW TREATMENTS AND 12 NEW CHEMICAL ENTITIES IN THE PIPELINE

Portfolio 2013



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

Boosting drug discovery through innovative partnerships



Early stage drug discovery can be an expensive and time-consuming process. The virtual model used by DND*i* through partnerships with pharmaceutical and biotech companies, academic groups, and PDP partners allows compound libraries to be screened *in vitro* and *in vivo* in the search for potential molecules of interest. Identified 'hits' are progressed through hit-to-lead and lead optimization steps, with the best of these moving forward to pre-clinical development.

With the success of the DND*i* clinical programme for new sleeping sickness treatments, the focus in 2013 was on trying to identify compounds that could lead to new treatments for visceral leishmaniasis (VL) and Chagas disease. A new screen, developed in 2013 in collaboration with the University of Dundee, will allow for very large compound libraries (over 1 million compounds) to be efficiently screened against *Leishmania donovani* parasites. In addition, repurposing libraries, containing registered drugs and compounds which have already undergone clinical trials for animal or human health, have been screened against *Onchocerca* parasites with the aim of identifying active compounds for further development to treat filarial diseases.

New mechanisms for more effective discovery

In addition, DND*i* is currently looking at different mechanisms to identify more effective ways of conducting drug discovery. One approach is an 'NTD Drug Discovery Booster', which would entail a consortium of pharmaceutical partners work-

ing with DND*i* in a way that would simultaneously explore high quality libraries to identify, in a speedy and effective way, hit series to optimize.

The goal is to generate a clinical candidate in a fraction of the time generally required through traditional approaches. As compared to existing 'pre-competitive' models of R&D, the innovation of the NTD Booster lies in companies accepting to share with DND*i*, upfront, structural and functional information that is key to rapidly identify promising hit series. Potential partners for this consortium were identified and contractual negotiations had begun by the end of 2013.

Early stage R&D by emerging economies

Another new approach, the Lead Optimization Latin America (LOLA) project, was launched with the aim of building upon and enhancing the research and development potential in the Latin American region, with first agreements established with UNICAMP (University of Campinas, Brazil) and with USP (University of São Paulo, São Carlos campus, Brazil). With an international collaborative approach, this 'virtual laboratory' sets a precedent for all emerging neglected disease endemic countries. For the first time, DND*i*'s early stage R&D activities are established in Latin America. Access is increasingly being gained to compound libraries of large international pharmaceutical companies, which also support the group, providing expertise in medicinal chemistry and professional advice, and training on drug discovery.

In 2013, DND*i* screened **over 217,000 compounds** in assays for leishmaniasis and Chagas disease and pursued compound optimization in several new lead series.

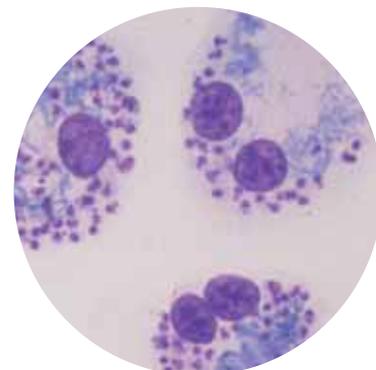
SCREENING

• **Main partners:** AbbVie (formerly Abbott), USA; Anacor, USA; Astellas, Japan; AstraZeneca, Sweden; Bayer, Germany; Bristol-Myers Squibb, USA; Celgene, USA; Drug Discovery Unit (DDU) at the University of Dundee, UK; E.I. du Pont de Nemours, USA; Eisai Co. Ltd, Japan; Glaxo-SmithKline, Tres Cantos, Spain; Institut Pasteur Korea (IPK), South Korea; Institute of Medical Microbiology, Immunology, and Parasitology, Hospital University of Bonn, Germany; 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; Northwick Park Institute for Medical Research, UK; Pfizer, USA; Pfizer Animal Health, USA; Sanofi, France; 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; TI Pharma, The Netherlands.

Screening for kinetoplastids

Screening core diversity libraries aims to address the low hit rate observed in visceral leishmaniasis (VL) and Chagas disease (albeit to a lesser extent), as well as the significant drop-out seen in early hit profiling and hit-to-lead development. High-throughput screening (HTS) of core



diversity libraries from several pharmaceutical companies (Sanofi, AbbVie, MSD, Pfizer, AstraZeneca and Bristol-Myers Squibb) have been completed against *Leishmania donovani* and *Trypanosoma cruzi* in collaboration with screening partners (University of Dundee and Institut Pasteur Korea). This has resulted in the identification of several new starting points that are currently being followed up in hit profiling, annotation, and hit-to-lead programmes.

A new high-throughput screening assay – the cidal axenic *L. donovani* model – has been developed in collaboration with the University of Dundee. This assay is amenable to high/very high throughput, suitable for the screening of very large collections (more than 1,000,000 compounds), and is used together with the previously developed axenic *L. donovani* assay. Adequate screening capacity is a key element of DNDi's discovery strategy, enabling the screening of large libraries or compound series and therefore lead to a quicker identification of hits/leads for optimization.

GlaxoSmithKline have screened their global compound library (a total of 1,800,000 compounds) for VL and Chagas disease and negotiated agreements with DNDi and others to access their results, and to explore the hits as potential candidates for further optimization.

To increase screening capacities, in August 2013, DNDi and Institut Pasteur Korea (IPK) signed a new research agreement by which DNDi will employ IPK's visual-based high-throughput screening technology in order to accelerate identification of promising drug candidates for leishmaniasis and Chagas disease.

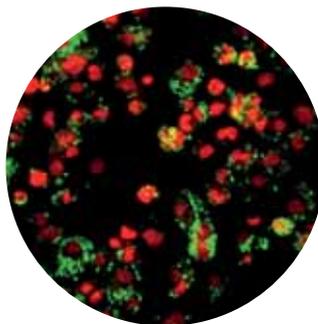
Screening of repurposing libraries for filarial diseases

- **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

Libraries of compounds, including registered drugs and compounds which have entered clinical trials for animal and human health, have been sourced from several companies for screening against adult *Onchocerca* parasites. Over 7,000 compounds were screened in 2013 and around 50 have shown activity against the parasite. Those with appropriate pharmacokinetic profiles are being screened in rodent models of the disease. While most will probably not be suitable for repurposing as macrofilaricidal drugs, they will be a rich resource for developing new clinical candidates because they come from well advanced research programmes within the companies. They will also lead to an understanding of new drug targets.

Mining of annotated compound collections

Discovery activities are typically associated with high attrition rates, especially in the case of candidates not associated with any pre-clinical data other than *in vitro* efficacy. In order to lower this attrition rate, mining of well-annotated chemical compound libraries aims to identify promising new active starting points for which data on chemistry, early preclinical profiling, druggability, and possibly even targets and modes of action are already available. From libraries originating from collaborating pharmaceutical and biotechnology companies, promising compound classes are identified by sampling a subset of representative compounds and testing for antiprotozoal activity. Examples of successful classes identified as part of DNDi's discovery programme include oxaboroles (Anacor Pharmaceuticals), and nitroimidazoles (TB Alliance and other compound sources). Several compound sets, based on inhibitors of a specific target or specific chemical classes, were accessed in 2013, such as various anti-infective sets from AstraZeneca, a kinase-biased collection from Celgene, and bioavailability collections from Sanofi and AbbVie.



Compound re-purposing

Proactive acquisition and investigation of compounds from selected series, associated with a significant level of available information (biological activities, pre-clinical dossier, published data, and safety profile, among others) enables identification of candidates with potential for further development – ideally ready to enter into pre-clinical or later stage without further optimization – for the target diseases. A successful example of this strategy is fexinidazole. DNDi extended and applied this strategy in collaboration with its pharmaceutical partners, including Astellas and AstraZeneca.

Reference screening centres

The Swiss Tropical and Public Health Institute (Swiss TPH) and the University of Antwerp (LMPH) serve as reference

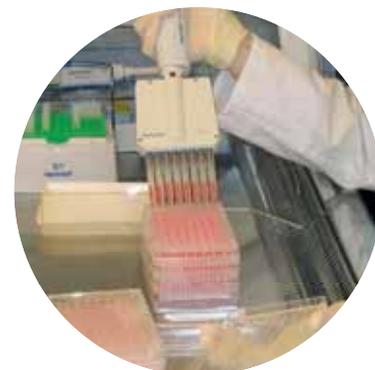
screening centres to ensure that screening methodologies are comparable, and that *in vitro* and *in vivo* assays at different sites and with different groups meet the same standards. The centres also provide expert parasitology advice that ensures the quality of DNDi's data and work.

LEAD OPTIMIZATION

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

DNDi's strategy for its lead optimization (LO) consortia is to advance new chemical classes identified through screening programmes, as well as to develop backup compounds that can rapidly replace front-runner compounds in case of failure. These consortia bring together expertise in chemistry, biology, drug metabolism, pharmacokinetics (DMPK), *in vivo* screening, drug safety assessment, and pre-formulation. Optimization efforts are focused on improving, for example, lead compound properties for absorption into the bloodstream following oral dosing, distribution of a compound to the site of infection, modification of structural motifs in the compound that are prone to breakdown or clearance, and which increase tolerability, and safety for the patient.

At DNDi, discovery efforts focus on four main series for lead optimization at any one time, in addition to further profiling of promising hit series for LO. In 2013, nitroimidazole and oxaborole compounds were each undergoing optimization for both leishmaniasis and Chagas disease, with an additional two series issued from the Broad Institute of the NIH library for Chagas disease only.



HUMAN AFRICAN TRYPANOSOMIASIS (HAT)

SLEEPING SICKNESS



The battle is not over until it is won

Sleeping sickness, or human African trypanosomiasis, threatens millions of people in 36 countries across sub-Saharan Africa. The Democratic Republic of the Congo bears the brunt, accounting for 83% of all cases. In the 1960s there were less than 5,000 patients suffering from the disease in the whole of the continent. However, the end of the 20th century – with internal conflict, competing health priorities, and decolonization – witnessed a halt in the successful control methods, and the number of cases reported rose steeply, peaking in 1998 with over 37,000 cases reported in that year. Nowadays, thanks to the combined efforts of WHO, National Sleeping Sickness Control Programmes, NGOs and other partners, the disease has once more been brought under control, and since 2010 the number of reported cases has fallen below 8,000. The WHO has laid out a roadmap to eliminate the disease as a public health problem by 2020, when less than one case per 10,000 inhabitants in at least 90% of endemic foci is expected.⁽¹⁾ Maximizing efficiency through a 'WHO network' of partners and stakeholders⁽²⁾ in order to achieve elimination is currently underway.

The most advanced stage of the disease is determined after multiple and complex diagnostic procedures, including a painful lumbar puncture, and is treated with a combination of oral and intravenously administered drugs. Nifurtimox-eflornithine combination treatment (NECT), introduced by DNDi and partners in 2009, was the first improved treatment option for patients with advanced sleeping sickness to be developed in 25 years, and has reduced the time required to spend in hospital during administration, from 14 to 10 days. By the end of 2012, NECT, which features on the WHO Essential Medicines Lists for adults and children, was being used to treat 96% of late-stage *T.b. gambiense* HAT patients in endemic countries, thus virtually replacing the previous and

toxic arsenic-based treatment, melarsoprol. The latter, however, is still the first-line treatment for the less common *T.b. rhodesiense* HAT.

To contribute to the WHO elimination goal, a 'test and treat' strategy that would be implemented at the primary healthcare level is on the horizon, with potential simple oral pills for both the early and late stage as well as both types of HAT, that are currently in development, along with new rapid diagnostics, which together would remove the need for painful and dangerous lumbar punctures.

This would mean that rural health centres, rather than hospitals, will play an increasingly important role, especially as the number of reported cases continues to dwindle.



Ideal Target Product Profile for HAT

A new treatment for adults and children:

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

(1) Control and surveillance of human African trypanosomiasis: report of a WHO technical committee (2013). World Health Organization. (2) http://www.who.int/neglected_diseases/HAT_roll_out_strategy_2013/en/#

→ FACT SHEET

WHAT IS THE IMPACT OF HAT?

The number of reported cases in 2012 was fewer than 8,000, but the actual number of cases is estimated to be 20,000.⁽¹⁾ Fatal if untreated, the disease affects mainly those living in remote areas with limited access to adequate health services. The disease is found in 36 countries in sub-Saharan Africa, but 8 countries report 97% of all cases (see map), and over two-thirds of those are reported in the Democratic Republic of the Congo.⁽²⁾ Almost eliminated in the 1960s, transmission increased again as a result of war, population displacement, poverty, and the collapse of adequate support to the control activities conducted within health systems. Recent successes and an impressive drop in the number of reported cases call for renewed hope, but there is still work to be done, as some areas are not covered by surveillance and control efforts.

HOW IS HAT TRANSMITTED?

HAT is transmitted to humans by two sub-species of the parasite *Trypanosoma brucei* (*T. b.*) through the bite of the tsetse fly: *T. b. gambiense* (West and Central Africa, responsible for the vast majority of cases) and *T. b. rhodesiense* (East Africa). Man is the essential reservoir for *T. b. gambiense*.

WHAT ARE THE SYMPTOMS?

HAT occurs in two stages:

→ **Stage 1:** the haemolympathic stage – includes non-specific symptoms like headaches and bouts of fever (and generally goes undiagnosed without active HAT surveillance).

→ **Stage 2:** the later, neurologic stage – occurs when the parasite crosses the blood-brain barrier and is characterized by serious sleep cycle disruptions, paralysis, progressive mental deterioration, and ultimately, without effective treatment, death.

A lumbar puncture is needed to differentiate between the two stages to choose an appropriate treatment.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

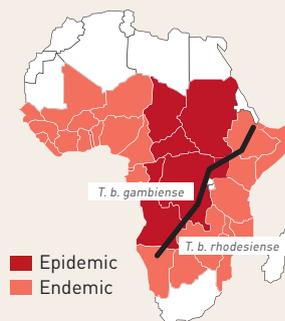
Available treatments have limitations, are difficult to administer, often toxic, and are stage-specific.

→ **Stage 1:** pentamidine and suramin, require injections and are ineffective for stage 2.

→ **Stage 2:** NECT (nifurtimox-eflornithine combination therapy), available since 2009, is a simplified therapy option for stage 2 *T. b. gambiense* sleeping sickness, with only 14 injections of eflornithine over 7 days and 10 days of oral treatment with nifurtimox. While not the most appropriate treatment to support elimination efforts as it requires a hospital setting, NECT does provide a major improvement in case management.

Melarsoprol, still the only drug available for stage 2 *T. b. rhodesiense*, is a toxic arsenic derivative that causes pain and fatal encephalopathies in up to 5% of patients who receive it,⁽³⁾ and is increasingly ineffective, with reports of drug resistance and treatment failure.

Eflornithine, today rarely used alone, is difficult to administer as treatment requires trained health staff and an extended hospital stay (56 intravenous infusions taking two hours each to administer, over 14 days, 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 was included on the WHO Essential Medicines List (EML) in 2009, and extended to the EML for children in 2013. **Since June 2013, all countries endemic to *T. b. gambiense* are using NECT as first-line treatment for second stage HAT, with the exception of Nigeria.**

As a medium-term strategy, DNDi initiated a compound mining effort to identify existing chemical compounds with potential against kinetoplastid diseases. This resulted in the rediscovery of fexinidazole, which completed Phase I clinical development in 2011. **Fexinidazole entered a pivotal Phase II/III study** in 2012 and is currently recruiting patients in the DRC. Two complementary studies will examine efficacy and safety in adults with stage 1 and early stage 2 HAT, and children aged 6-14 years. Sanofi is the industrial partner for this project.

In order to build a strong pipeline for long-term drug discovery, DNDi initially established a **HAT Lead Optimization Consortium** resulting in the identification of the **Oxaborole SCYX-7158**. SCYX-7158 successfully progressed through pre-clinical development, entering **Phase I clinical** development in early 2012, which is nearing completion. Other backup compounds were evaluated by the consortium and remain available for further development if necessary.

In addition, DNDi supports the **HAT Platform** (see page 47) that was launched in Kinshasa, Democratic Republic of the Congo (DRC) in 2005. The HAT Platform is a clinical research and access-supporting network that brings together key players in the fight against sleeping sickness from Angola, the Central African Republic, Chad, DRC, Republic of the Congo, Sudan, South Sudan, Uganda and those involved in HAT from the international research arena.

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

→ **An oral, safe, effective treatment to be used for both stage 2 and stage 1 HAT**

(1) Control and surveillance of human African trypanosomiasis: report of a WHO expert committee (2013); WHO, Geneva, Switzerland (2) Eliminating human African trypanosomiasis: where do we stand and what comes next? Simarro PP, Jannin J, Cattand P (2008) PLoS Med 5: e55. doi:10.1371/journal.pmed.0050055. (3) Clinical description of encephalopathic syndromes and risk factors for their occurrence and outcome during melarsoprol treatment of human African trypanosomiasis. Blum J, Nkunku S, Burri C. (2001) Trop Med Int Health;6:390-400.

SCYX-2035811

2013 OBJECTIVE:
Progress a backup
nitroimidazole into
pre-clinical development

- **Partners:** TB Alliance, USA; University of Auckland, New Zealand; SCYNEXIS Inc., USA; Pace University, USA; Wuxi AppTech, China
- **Project start:** June 2011

The nitroimidazole backup programme for HAT (see Annual Report 2012) identified SCYX-2035811 as a suitable candidate for further exploration. In the mouse acute model, SCYX-2035811 has shown excellent activity at doses down to 5 mg/kg for 4 days. Following careful pharmacokinetic analysis of plasma and brain levels, a study in the stage 2 mouse model of HAT was designed. Unfortunately, none of the doses tested (12.5, 25, and 50 mg/kg once daily for 7 days) were sufficient to provide cures in this study and further work on this compound has been put on hold, notably as there are currently other active HAT research projects, including a substantial programme at the Novartis Institute of Tropical Diseases. DNDi will continue to monitor research in this field, and reinvest if deemed necessary.

**SCYX-1608210
and SCYX-1330682**

2013 OBJECTIVE:
Select an oxaborole for
pre-clinical evaluation

- **Partners:** Anacor Pharmaceuticals Inc., USA; Pace University, USA; LMPH, Belgium; SCYNEXIS Inc., USA
- **Project start:** April 2009

Following extensive pharmacokinetic profiling of many possible back-up compounds to SCYX-7158 for HAT (previously known as the Oxaborole backup programme; see Annual Report 2012), two leads, SCYX-1608210 and SCYX-1330682, were prioritized. Based on available pre-clinical data, it is predicted that these two compounds will likely have shorter half-lives in humans than SCYX-7158. Both compounds have been shown to provide cures in the stage 2 mouse model of HAT. Given the encouraging progress of both fexinidazole (Phase II/III) and SCYX-7158 (Phase I), and as resources are limited, DNDi has chosen to place further development of these two back-up compounds on hold. Work will only recommence should problems be encountered with SCYX-7158 in clinical development.

SCYX-7158

2013 OBJECTIVE:
• Progress SCYX-7158
pre-clinical programme
• Manufacture SCYX-7158

tablet formulation; evaluate paediatric formulations • Complete SCYX-7158 Phase I programme • IMPD preparation and study site preparation for pivotal efficacy study

- **Partners:** Anacor Pharmaceuticals Inc., USA; SCYNEXIS Inc., USA; Advinus Therapeutics, India; Penn Pharma, UK; BaseCon, Denmark; Optimed, France; PhinC, France; Cardiabase, France; SGS Cephaac, France; Patheon, UK
- **Project start:** January 2010

**84
healthy
volunteers
recruited
out of 136**

SCYX-7158 belongs to a unique boron-based chemical class, the oxaboroles, which was originally provided by Anacor Pharmaceuticals (a biopharmaceutical company in Palo Alto, California, USA) and screened for activity against *T. brucei* at the University of California San Francisco. A unique collaboration between DNDi, Anacor Pharmaceutical, and SCYNEXIS (a drug discovery and development company based in Research Triangle Park, North Carolina, USA), within a consortium that also included Pace University (USA) and the Swiss Tropical and Public Health Institute, enabled the identification of SCYX-7158, selected as a promising pre-clinical candidate in late 2009. In pre-clinical studies, SCYX-7158 was shown to be safe and efficacious to treat stage 2 of the disease, as it is able to cross the blood-brain barrier. Pre-clinical development progressed successfully in 2010.

Batches of drug substance and drug product (capsules) were produced according to current good manufacturing practices (cGMP) and supplied for the Phase I clinical trial. In 2012, a robust tablet formulation was also developed in order to supply Phase II/III clinical trials, with manufacturing and release of clinical tablets (40 and 160 mg unit doses) completed in September 2013. The latter demonstrated comparable pharmacokinetics to capsules in a Phase I study and the formulation is considered suitable for future clinical studies.

A GLP (Good Laboratory Practice) reproductive toxicity package was initiated in 2013 and expected to be completed in 2014. A dose-finding experiment showed that the drug was not teratogenic up to 40 mg/kg/day.

Following clearance by the French Ethics Committee and Regulatory Authority, SCYX-7158 entered First-in-Human studies in March 2012 and became DNDi's first entity resulting from lead optimization efforts to enter early clinical development.

The Phase I study in healthy volunteers of sub-Saharan origin was temporarily halted in 2013 after the first dose of SCYX-7158 showed a longer than expected half-life in human plasma, triggering the need for additional studies in dogs. The study was re-started in the same year, testing single ascending doses of treatments. Safety profiling in additional cohorts is ongoing.

**NECT – Nifurtimox-
Eflornithine Combination
Therapy**

2013 OBJECTIVE:
• Completion of clinical
related activities • Inclusion
of NECT on the WHO Essential
Medicines List for children

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

• **Project start:** May 2004

**Over
13,000
treatments
distributed in
12 countries
(representing
99% of stage 2
cases)**

NECT was developed by Epicentre, MSF, DNDi, Swiss TPH, and the national HAT control programmes of the Republic of the Congo and DRC, as a combination of eflornithine and nifurtimox. It

quickly became first-line treatment for the neurological, 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.

In September 2012, DNDi and its partners concluded the follow-up of patients included in the 'NECT-Field' study, launched in 2009. This Phase IIIb study further documented the safety, effectiveness, and ease-of-use of NECT in real-life conditions, in specific populations such as children, pregnant and breastfeeding women. A total of 630 patients were enrolled in the study, including 100 children, 13 pregnant women, and 34 breastfeeding women.

NECT was included on the WHO Essential Medicines List in 2009, and extended to the Essential Medicines List for children in April 2013. Since June 2013, Angola recommended NECT as first line treatment, making it now available in all endemic countries with the exception of Nigeria, which does not have a functional HAT control programme. These countries account for 99% of all reported HAT cases. In 2013, nearly 96% of all stage 2 HAT patients were treated with NECT. All receive free supplies from WHO via drug donations by Sanofi and Bayer.

Fexinidazole for HAT



2013 OBJECTIVE: Manufacture additional tablet supplies • Develop tablet scale-up, process validation, and registration plan in partnership with Sanofi • Develop an integrated paediatric formulation plan and initiate in 4Q 2013 • Continue recruitment in pivotal study

- **Partners:** BaseCon, Denmark; Bertin Pharma, France; Cardinal Systems, France; Cardiabase, France; Médecins Sans Frontières, and other HAT Platform members; PhinC Development, France; Programme National de la Lutte Contre la Trypanosomiase Humaine Africaine (PNLTHA) DRC; RCTs, France; Sanofi, France; Swiss Tropical and Public Health Institute (Swiss TPH); SGS, France; Theradis Pharma, France
- **Project start:** April 2007



Fexinidazole is the first success of the extensive compound mining efforts pursued by DNDi within the nitroimidazole project initiated in 2005.

206 patients recruited out of 510 at 9 sites

This drug entered Phase I first-in-human studies⁽¹⁾ in September 2009 and Phase II/III in October 2012. This single pivotal Phase II/III study aims to prove the safety

and efficacy of fexinidazole, with NECT as the active comparator. The study was initiated and is conducted by DNDi in collaboration with the Swiss TPH and the human African trypanosomiasis national control programmes of the Democratic Republic of the Congo (DRC) and Central African Republic (CAR), in addition to MSF. DNDi is co-developing the drug with Sanofi: DNDi is responsible for pre-clinical, clinical, and pharmaceutical development, while Sanofi is responsible for the industrial development, regis-

tration, and production of the drug at its manufacturing sites. A safe API manufacturing process, that can be commercialized, has been developed in collaboration with Sanofi, who are now preparing for scale-up and registration.

By the end of 2013, 206 patients had been recruited at eight sites in DRC and one in CAR. Patient inclusion in CAR was temporarily stopped in December 2013 due to insecurity and conflict in the country. A strategy to accelerate the availability of fexinidazole will be submitted to the regulators. Two new complementary trials were ready for launch by the end of 2013, one for early second stage and first stage adults and another for children between 6 and 14 years of age.



Bill Gates, with Dr. Margaret Chan (WHO) and Christopher Viehbach (Sanofi), speaks about sleeping sickness and the urgent need for new rapid diagnostic tests and an oral treatment ('Uniting to Combat NTDs: A Conversation on Progress' event, Institut Pasteur, Paris, April 2013).

(1) Tarral A. et al. (2014) Determination of an Optimal Dosing Regimen for Fexinidazole, a Novel Oral Drug for the Treatment of Human African Trypanosomiasis: First-in-Human Studies. *Clinical Pharmacokinetics*, February 2014 DOI 10.1007/s40262-014-0136-3.

LEISHMANIASIS

A Global Disease with Regional Challenges

Leishmaniasis is a complex disease caused by more than 20 species of the *Leishmania* parasite, with over a million new cases occurring every year.⁽¹⁾ It breaks out in foci across tropical and temperate regions around the world, in areas where the sandfly, responsible for its transmission, lives. In anthroponotic leishmaniasis (transmission between humans by the sandfly) humans are the only reservoir, whereas animals such as dogs or rodents, also act as an important reservoir in zoonotic leishmaniasis (transmission from animals to humans by the sandfly).

Cutaneous leishmaniasis (CL) is the most common manifestation of the disease, with between 700,000 and 1.2 million new cases every year.⁽²⁾ Although it is generally not fatal, the unsightly skin lesions it causes lead to ostracism by the local community, and economic loss.

Visceral leishmaniasis, or kala-azar, is deadly if not treated, and accounts for 200,000 to 400,000 new cases and 20,000 to 40,000 deaths each year. Characteristically, the disease causes fever, weight loss, enlarged spleen and liver, and anaemia. In addition, following treatment for visceral leishmaniasis (VL), a non-itching or painful skin rash may develop from six months to two years or more after the apparent cure. This post-kala-azar dermal leishmaniasis (PKDL) occurs mainly in East Africa and on the Indian subcontinent, and is thought to be a reservoir for transmission. An additional phenomenon is constituted by asymptomatic carriers, who do not seem to develop the disease, despite having been in contact with the parasite. Current treatments for VL are not optimal as nearly all still require injections or intravenous infusions. Adequate monitoring and control are key if the WHO goal of eliminating anthroponotic VL from the Indian subcontinent by 2020⁽³⁾ is to be achieved, particularly as the role of PKDL and asymptomatic VL patients as disease reservoirs is poorly understood.

People living with HIV are prone to VL infection, whether they are prior asymptomatic carriers of VL who become symptomatic or due to new VL infections. In these cases, VL infection can accelerate the onset of AIDS. There are also concerns that HIV/VL co-infection may increase the transmission of leishmaniasis.

Some key endorsers of the London Declaration have undertaken to sustain, expand, and extend certain drug access programmes to ensure the necessary supply of drugs and other interventions to help control VL and other neglected diseases.



While the last decade has seen improvements in the treatment, diagnosis, and prevention of leishmaniasis notably in South Asia, supported by the development of liposomal amphotericin B, paromomycin, and miltefosine, response to treatment differs among regions (e.g. East Africa, Latin

Ideal Target Product Profile for VL

A new treatment for adults and children:

- Efficacious against all species of parasite in all regions
- Active against resistant strains
- At least 95% efficacy
- Short course (1/day for 10 days oral; or 3 shots over 10 days)
- Easy to use: oral or intra-muscular, requiring no monitoring
- No contraindications
- No interactions. Compatible for combination therapy
- Safe in pregnant and breastfeeding women
- For immunocompetent and immunosuppressed patients
- Affordable
- Adapted to tropical climates (minimum three-year shelf-life)

(1) WHO Fact sheet No 375, January 2014. (2) Alvar J, Vélez ID, Bern C, Herrero M, Desjeux P, et al. (2012) Leishmaniasis Worldwide and Global Estimates of Its Incidence. PLoS ONE 7(5): e35671. doi:10.1371/journal.pone.0035671. (3) Sustaining the drive to overcome the global impact of neglected tropical diseases: second WHO report on neglected diseases (2013). World Health Organization.

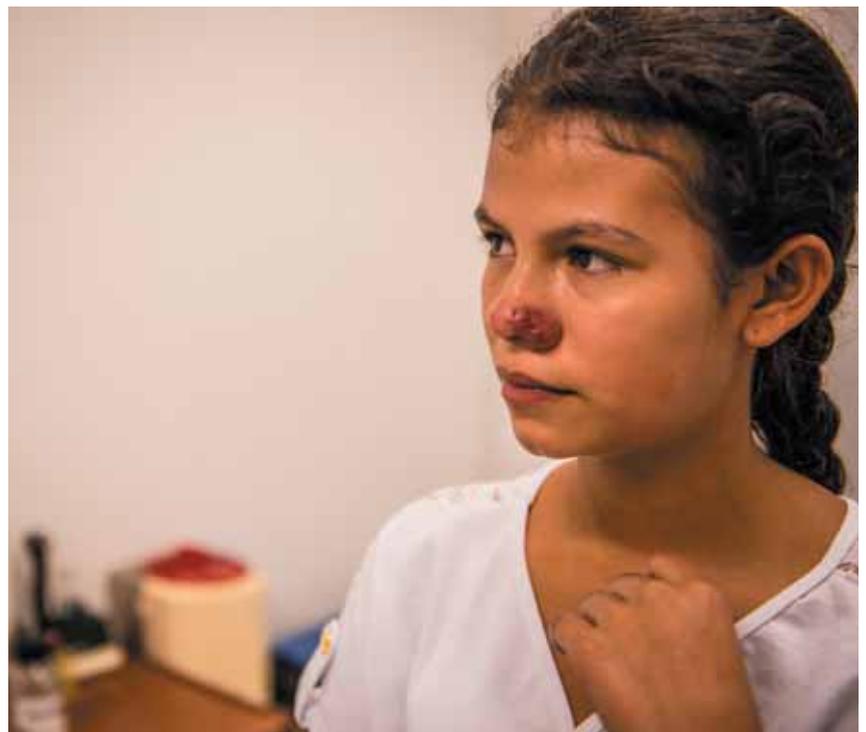
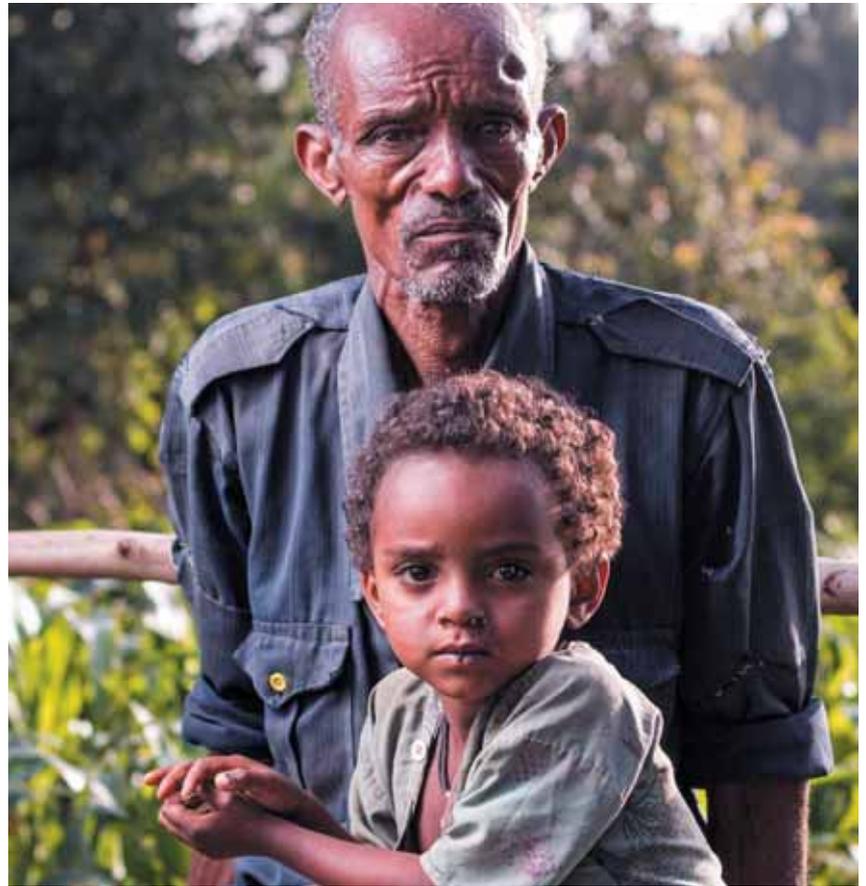
America, South Asia). DNDi's strategy seeks to develop new treatments that appropriately address the patient needs, specific to each affected region.

In an effort to address the unmet health needs of developing countries, in 2013 the WHO called for 'demonstration projects' (see page 51) to provide evidence on innovative mechanisms to fund and coordinate research and development for diseases disproportionately affecting developing countries, as recommended by the Consultative Expert Working Group (CEWG). The 'Visceral Leishmaniasis (VL) Global R&D Access Initiative' proposed by DNDi and partners, was one of four proposals selected in early 2014 to move forward. The proposal seeks to develop safe and effective oral treatments for VL patients, and potentially for asymptomatic carriers and PKDL patients, as well as diagnostics for the detection of asymptomatic carriers. In addition, the development of a shared open-access database to identify determinants of treatment effectiveness was proposed.⁽⁴⁾

Ideal Target Product Profile for CL

A new topical or oral treatment:

- Efficacious against all species of *Leishmania*
- At least 95% efficacy
- Easy to use: short course (14-28 days), requiring no monitoring
- No interactions. Compatible for combination therapy
- Leaving minimal scarring
- Safe in pregnant and breastfeeding women
- Affordable
- Adapted to tropical climates (minimum three-year shelf-life)



(4) The Visceral Leishmaniasis (VL) Global R&D & Access Initiative (2013) Drugs for Neglected Diseases initiative. http://www.who.int/phi/implementation/VL_global_R_D_access_initiative.pdf

➔ FACT SHEET

WHAT IS THE IMPACT OF LEISHMANIASIS?

A total of 98 countries and 3 territories on 5 continents reported endemic leishmaniasis transmission. Among parasitic diseases, morbidity and mortality caused by leishmaniasis are surpassed only by malaria and lymphatic filariasis. It is estimated that 350 million people are at risk of the disease, most of them children. The annual incidence is estimated at approximately 0.7 to 1.3 million CL cases and 0.2 to 0.4 million VL cases, with a case-fatality rate of 10% for visceral leishmaniasis per year (i.e. 20,000 to 40,000 deaths per year).⁽¹⁾ However, mortality data are extremely sparse and generally represent hospital-based deaths only, so actual figures are expected to be higher. Co-infection with other infectious diseases is an increasing concern: HIV-VL co-infection has been reported in 35 countries worldwide.

HOW IS LEISHMANIASIS TRANSMITTED?

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

CL is most frequently caused by *Leishmania major*, *L. tropica*, *L. infantum*, and *L. aethiopica* in the Old World (Africa, Europe, Asia), and *L. braziliensis*, *L. mexicana*, and related species in the New World (notably the Americas). Mucocutaneous leishmaniasis (MCL) can develop as a complication of CL. Depending on the species of *Leishmania*, the life cycle can be anthroponotic (transmitted from human to animal) or zoonotic (transmission from animal to human). In the latter case, animals act as a reservoir for the disease.

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

PKDL occurs during, or more often after, recovery from VL. It is caused by *L. donovani* and is

believed to be a parasite reservoir for human VL.

WHAT ARE THE SYMPTOMS?

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

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

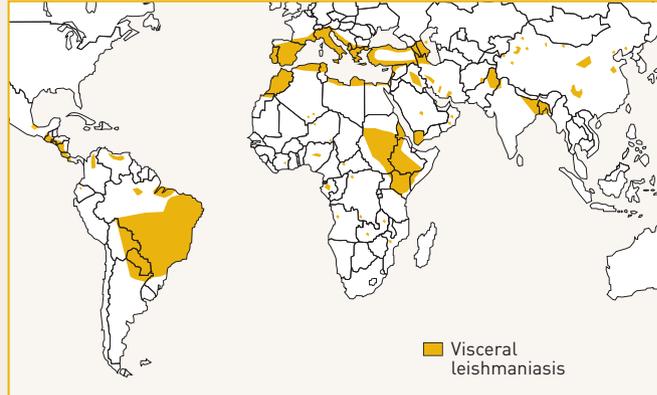
Mucocutaneous leishmaniasis (MCL) is characterized by partial or total destruction of mucous membranes of the nose, mouth, and throat.

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

CURRENT TREATMENTS AND THEIR LIMITATIONS

Existing drugs for VL have serious drawbacks in terms of safety, resistance, stability, and cost.⁽²⁾ 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 well documented. Require a 30-day parenteral treatment for VL. Registered in South East



Asia, Latin America, and some Mediterranean and African countries.

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

→ **AmBisome®**: a liposomal formulation of amphotericin B, it is much safer and highly efficacious. A single infusion of 10mg/kg has shown a 96.4% cure rate in Asia.⁽³⁾ However, high cost and the need for a cold chain limit its widespread use.⁽⁴⁾ 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.

→ **Miltefosine**: oral drug registered for use in India for VL, but expensive⁽⁵⁾ and requires 28-day treatment. Major limitations include low compliance, with risk of resistance, and contraindication in pregnancy and mandatory contraception for women of child-bearing age for the duration of therapy and 3 months beyond. A recent study in Asia indicated an emerging lack of efficacy in monotherapy in the region.⁽⁶⁾

→ **Paromomycin (PM)**: a low-cost parenteral formulation that requires 3 weeks of painful intramuscular administration and is associated with some degree of renal and ototoxicity with limited efficacy as monotherapy in East Africa.

In 2010, DNDi and LEAP partners delivered the **SSG&PM combination therapy for East Africa** (see page 28) that is recommended as first-line treatment for VL in the region by the WHO Expert Committee on the Control of Leishmaniases. SSG&PM has been included in the national guidelines of Sudan, South Sudan, Ethiopia, and in Kenya and it is in the process of being adopted in some of these countries. PM is registered in Uganda (2011) and Kenya (2013), and is in the process of being registered in Sudan and Ethiopia.

In India, a Phase III trial demonstrated the efficacy of combination therapies of already registered drugs: liposomal

(1) *Leishmaniasis Worldwide and Global Estimates of Its Incidence*. Alvar J. et al., (2012) PLoS ONE 7(5): e35671. doi:10.1371/journal.pone.0035671 (2) *Structures, Targets and Recent Approaches in Anti-Leishmanial Drug Discovery and Development*. Seifert K., *Open Med Chem J.* 2011; 5:31–39. doi: 10.2174/1874104501105010031 (3) *Comparison of short-course multidrug treatment with standard therapy for visceral leishmaniasis in India: an open-label, non-inferiority, randomised controlled trial*, Sundar S. et al., *The Lancet* 2011, Feb 5;377(9764):477–86. doi: 10.1016/S0140-6736(10)62050-8. *Epub* 2011 Jan 20. (4) *Through the WHO, significant cost reduction of both AmBisome® and miltefosine is available for the public sector of key endemic countries as of 2007*. (5) *Ibid.* (6) *Increasing Failure of Miltefosine in the Treatment of Kala-azar in Nepal and the Potential Role of Parasite Drug Resistance, Reinfection, or Noncompliance*, Rijal S. et al., *Clin Infect Dis.* 2013 Jun;56(11):1530–8. doi: 10.1093/cid/cit102. *Epub* 2013 Feb 20.

amphotericin, miltefosine, and paromomycin. AmBisome® monotherapy and combination therapies are recommended by the WHO Expert Committee on the Control of Leishmaniasis. DNDi is collaborating with the National Control Programmes of India and Bangladesh, MSF, the Bihar State Health Society, and the Indian Council for Medical Research to assess the effectiveness and safety of these new treatments at the Primary Health Care level and facilitate their introduction for the treatment of VL in South Asia.

In Latin America, DNDi is participating in a study sponsored by the Brazilian Innovation Agency (FINEP) to evaluate the safety and efficacy of Glucantime®, AmBisome®, and amphotericin B as monotherapies, and of AmBisome®-Glucantime® combination to treat VL patients. The national guidelines for VL were revised in 2013 based on the safety interim data for AmBisome® in this trial.

Existing treatments for CL are



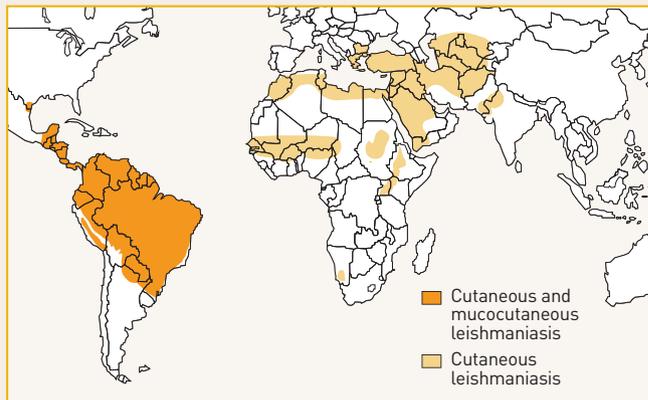
not satisfactory. Many treatment regimens are associated with significant failure rates and considerable toxicity. Relapses are common and there are increasing reports of drug resistance emergence.

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

→ Alternative treatments: **Liposomal amphotericin-B**, not fully tested on CL. Even if efficacious, cannot be deployed widely because of cost and delivery requirements.

Miltefosine, potentially teratogenic and has side effects that make it unsuitable to treat CL. Registered in Colombia. Other treatments, such as thermotherapy and cryotherapy are used in certain clinics, but are expensive.

→ A promising approach is to combine **chemotherapy with immune-modulation**: initial elimination of parasites with chemotherapy, followed by modification of the patient's immune response by an immune-enhancing agent (either a **therapeutic vaccine** or an appropriate adjuvant) could lead to quick recovery and control of persisting parasites. Therapeutic vaccines have yielded some



positive results for CL. Several chemical immunomodulators have been tested for cancer and

other diseases, and could be useful for CL therapy.

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?

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

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

In the **medium term**, DNDi is assessing fexinidazole, also under evaluation for the treatment of HAT and soon Chagas disease, for the treatment of primary VL patients.

DNDi's **long-term** strategy for VL is to bring new candidates into clinical development through its lead optimization programme with the ultimate goal of developing an oral combination treatment.

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

In addition, DNDi supports the **Leishmaniasis East Africa Platform (LEAP)** (see page 46) that aims to geographically extend all currently available VL drugs in East Africa and to develop new therapies suitable for the region, as well as to build and sustain capacity in the region for conducting clinical trials.

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

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

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

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

Nitroimidazole backup



2013 OBJECTIVE:
Select backup candidates for VL-2098 for the treatment of VL

- **Partners:** TB Alliance, USA; Auckland University, New Zealand; Laboratory of Microbiology, Parasitology and Hygiene (LMPH), University of Antwerp, Belgium; WuXi AppTech, China
- **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. The TB Alliance granted rights to DNDi to develop a class of potential anti-TB compounds that also show significant promise for treating other neglected diseases, such as VL.

Within TB Alliance's nitroimidazole library, VL-2098 was identified as a candidate with potent efficacy against VL (see below). A focused programme is ongoing to identify a backup pre-clinical candidate in case VL-2098 does not successfully complete pre-clinical testing.

Over 200 analogues have been prepared so far. Two backup compounds originating from two different scaffolds, meeting targets set at the beginning of the project, have now been selected and are being further profiled for *in vivo* efficacy and safety. In addition, data generated during this programme were used to establish preliminary pharmacokinetic/ pharmacodynamic (PK/PD) analysis for this series of compounds.

Oxaleish



2013 OBJECTIVE:
Select an oxaborole for pre-clinical evaluation

- **Partners:** Anacor Pharmaceuticals, USA; SCYNEXIS, USA; LMPH, University of Antwerp, Belgium; WuXi AppTech, China; Sandexis, UK; LSHTM, UK
- **Project start:** 2009

DNDi and Anacor have been working together over the last few years to identify oxaborole backups, initially for the HAT programme, and this has expanded to include both leishmaniasis and Chagas disease. DNDi-2035804 has been shown to produce excellent reductions in parasitaemia in the hamster model of VL using *L. infantum*. A 60g batch of API has been prepared and is being used to support detailed efficacy, pharmacokinetics, and safety profiling of this lead compound.

VL-2098



2013 OBJECTIVE:
Complete reproductive toxicology (male fertility in rat models) • Resume toxicology/safety activities as well as CMC activities

- **Partners:** TB Alliance, USA; Advinus Therapeutics, India; Endolytics, USA; Huntingdon Life Sciences, USA and UK; Accelera, Italy; Aptuit, Italy; Selcia, UK; Pharmorphix, UK
- **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. Safety testing with administrations at several multiples of the efficacious dose is ongoing. It is expected to reach completion of these studies, and to be proposed as a clinical candidate late in 2014.



Anfoleish (Cutaneous Leishmaniasis)



2013 OBJECTIVE:
Develop a topical anti-parasitic treatment containing amphotericin B for the treatment of CL

- **Partners:** PECET (Program for the Study and Control of Tropical Diseases), Universidad de Antioquia Medellin, Colombia; Humax Pharma, Colombia
- **Project start:** September 2011

The rationale for development of a topical formulation of amphotericin B was to provide a treatment to be applied locally at the CL lesion, with high anti-parasitic effect, but without the systemic toxicity associated with amphotericin B. Anfoleish was selected by DNDi for clinical development after completion of pre-clinical assessments. In November 2013, the DNDi scientific advisory committee approved the conduction of an open-label,

randomized, non-comparative, two-arm exploratory study which encompasses a two-step approach. The initial approach will be to determine the safety and PK of Anfoleish, when applied as a directly observed treatment two or three times per day for four weeks in 30 randomly assigned patients (15 per arm) with uncomplicated CL. If no safety or tolerability issues are identified, 50 additional patients will continue to be randomly allocated to receive Anfoleish, two or three times a day for four weeks. Initial efficacy will be measured by the percentage of subjects with initial clinical cure at day 90.

If this trial shows that Anfoleish is efficacious against *L. braziliensis*, a multi-country Phase III study will be planned in Latin America.

Fexinidazole for VL



2013 OBJECTIVE:
Initiate a Phase II proof-of-concept study in Sudan

- **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
- **Project start:** July 2010

Fexinidazole has shown potent activity against *L. donovani in vitro* and *in vivo* in a VL mouse model. It was assessed in three Phase I studies in healthy volunteers and was shown to be safe when given as a single dose or as repeated dosing after 14 days. This Phase II proof-of-concept study will evaluate fexinidazole for the treatment of primary VL patients in Sudan and started enrollment in late 2013. If successful, it will be followed by a Phase II/III programme in South Asia, East Africa, and Brazil.

HIV/VL for Africa



2013 OBJECTIVE:
Initiate HIV/VL co-infection study in Ethiopia and conduct two interim analyses

- **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
- **Project start:** September 2011

This study will evaluate the efficacy of a combination regimen of AmBisome® with miltefosine, and of AmBisome® (at a higher dose) monotherapy in Ethiopian patients co-infected with VL and HIV. A secondary objective is to assess relapse-free survival 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.

New VL treatments – Latin America



2013 OBJECTIVE:

Complete 50% patient recruitment

- **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
- **Project start:** February 2011

356 patients recruited out of 426 at 5 sites

About 90% of VL cases in Latin America occur in Brazil, and most of them affect children. In 2011, Brazil reported 3,894 new cases with a fatality rate of 6.7%. DNDi is supporting the implementation of a Phase III clinical trial sponsored by the Brazilian Ministry of Health, to assess treatments for VL. The primary objective of the study is to assess the efficacy and safety of amphotericin B deoxycholate, AmBisome®, and AmBisome® combined with Glucantime®, as compared to the first-line treatment, Glucantime®, for the treatment of VL patients in Brazil. The study progressed well during 2013, with 5 active sites and a total of 356 patients recruited (out of 426 total), and is expected to be completed by 2014. Evidence provided by this project will guide policies on the treatment of VL caused by *L. infantum* in Brazil. The national guidelines for VL were revised in 2013 based on the interim safety data for AmBisome® in this trial.

New VL treatments – Africa



2013 OBJECTIVE

Assess the efficacy and safety of miltefosine in East Africa

- **Partners:** Kenya Medical Research Institute (KEMRI), Kenya; Institute of Endemic Diseases (IEND), University of Khartoum, Sudan; Addis Ababa University, Ethiopia; Gondar University, Ethiopia; University of Makerere, Uganda; LSHTM, UK; Slotervaart Hospital, The Netherlands Cancer Institute, The Netherlands; Royal Tropical Institute (KIT), The Netherlands; Ministries of Health of Ethiopia, Sudan, Kenya, and Uganda; MSF; i+solutions, The Netherlands; LEAP; Institute of Tropical Medicine-Antwerp, Belgium
- **Project start:** November 2010



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

The LEAP 0208 Study, coordinated by DNDi and LEAP, to assess combinations of existing drugs to treat VL in Africa, aimed to evaluate the safety and efficacy of miltefosine monotherapy, AmBisome®-SSG, and AmBisome®-miltefosine combination treatments. Recruitment started in Kenya and Sudan in 2010 and ended in March 2012. Miltefosine, a drug originally developed for the treatment of breast cancer metastasis, is the only orally-administered drug against VL. It is registered and used in India and in some countries in Latin America.

The trial collected safety, efficacy, and pharmacokinetic data on miltefosine to geographically extend its use into East Africa. In addition, combination treatments of AmBisome® with either miltefosine or SSG were evaluated. Efficacy results were below the expected 91% of the current first line treatment with SSG&PM (AmBisome®+SSG, 87% cure rate after 6 months follow up; AmBisome®+miltefosine, 77%; miltefosine, 72%). Important PK/PD findings were obtained in this study related to the under exposure of miltefosine in children.

The slower parasite clearance when given a single infusion of AmBisome® as compared with multiple doses was proven earlier (LEAP AMBI 0106). Following discussions with experts and LEAP principal investigators, and taking into account the high price of hypothetical treatment (which would not fulfill the target product profile), the decision was taken to not proceed to a Phase III trial of any combination. The project is rephrasing priorities in order to study the PK of miltefosine in children treated following allometric dosing.

The results of the LEAP AMBI 0106 trial that aimed to determine the minimum dose of AmBisome® which is efficacious, safe, and cost-effective, to treat VL in Africa, were published in January 2014.⁽¹⁾

(1) Safety and Efficacy of Single Dose versus Multiple Doses of AmBisome® for Treatment of Visceral Leishmaniasis in Eastern Africa: A Randomised Trial. Khalil et al (2014) PLoS Negl Trop Dis. DOI: 10.1371/journal.pntd.0002613.

Generic AmBisome®



OVERALL PROJECT OBJECTIVE:

To have pre-qualified generic AmBisome® by 2017

- **Partners:** MSF
- **Project start:** November 2013

With the patent on AmBisome® ending in 2016 in the US, and having already expired in Europe, a market for generic formulations has opened up. Several producers in India and other countries are in the process of developing generics of AmBisome®; however, MSF's analysis of product dossiers suggests that there are very few generics of liposomal amphotericin B developed with the same composition, physico-chemical

characteristics, and quality-assurance as AmBisome®, and there are other formulations of liposomal amphotericin B of potentially bad quality. 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 liposomal amphotericin B is deemed necessary as this product is still expected to be the main-stream treatment for the next decade, and full dependency on Gilead has proven problematic in the past (batch recall in 2013). Gilead offers AmBisome® at a non-profit price of \$16.24/vial, but generic competition may bring the price down further. The aim of the project is to make a quality-assured generic of AmBisome® available.

SSG&PM



2013 OBJECTIVE:

Support registration of PM in Ethiopia and Sudan • MSF, DNDi, and Sudanese MOH sites complete treatment of 3,000 patients with SSG&PM combination

- **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
- **Project start:** November 2004

3,000 patients recruited out of 3,000

23,000 patients treated in East Africa since 2010

In 2010, DNDi and LEAP successfully showed that the combination of SSG and PM (17 days) was as efficacious as SSG monotherapy (30 days), with

the advantage of being shorter course, therefore lessening the burden on patients and health systems, and was more cost effective. Since then, DNDi and LEAP have worked with local ministries of health to ensure recommendation and uptake of the new treatment following its recommendation as first-line therapy for VL patients in East Africa by the WHO Expert Committee on the Control of Leishmaniases. First registration of PM was obtained in Uganda at the end of 2011, and registration was obtained in Kenya in January 2013. The registration process is underway in Sudan and Ethiopia. Nonetheless, implementation has already begun in the region, as the treatment was recommended. In addition, it has been included in the national VL guidelines of Sudan, South Sudan, Kenya, and Ethiopia. SSG&PM treatment has been rolled out in South Sudan in public health structures during the recent massive outbreak, as well as in MSF centres.

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 initiated in 2011, with recruitment of 3,000 patients completed in November 2013. SSG&PM is also being used to treat VL patients in South Sudan as part of its national programme.

New VL treatments – Bangladesh



2013 OBJECTIVE:

Advocate for policy change to include combinations • Complete 6 month follow-up

- **Partners:** Ministry of Health and Family Welfare, Bangladesh; International Centre for Diarrhoeal Disease Research (ICDDR,B), Bangladesh; Shaheed Suhrawardy Medical College and Hospital (ShSMC), Bangladesh; GVK Biosciences, Bangladesh
- **Project start:** July 2010

The Phase III trial conducted by DNDi and its partners in 2010 in India demonstrated the efficacy of combination therapies based on AmBisome®, miltefosine, and paromomycin.

602 patients recruited out of 602

This two-step Phase III study (first in hospital settings, then in primary healthcare centres) is using these combination therapies in Bangladesh. The last of 602 patients was enrolled in September 2013; six months follow-up will be complete in April 2014 and results will be available later in the year.

New VL treatments – India



2013 OBJECTIVE:

Significant progress in the implementation 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; Institute of Tropical Medicine-Antwerp, Belgium; MSF
- **Project start:** December 2006



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

900 patients recruited out of 900 (pilot phase)

Over 6,000 patients treated in pharmacovigilance study (since 2011)

To facilitate the introduction of these new treatments for VL in South Asia, DNDi is carrying out effectiveness studies that are being implemented in the region, including a pilot project in the Bihar State of India implementing combination therapies at the primary healthcare level, and single-dose AmBisome® at the hospital level. The project is monitoring pharmacovigilance as well as treatment effectiveness of the different treatment options when used outside a clinical trial by the public sector. The study began in 2012 in two districts

in India. On December 10, the Steering Committee met to evaluate the results. Data was presented on 900 patients enrolled in the pilot phase, of which 467 had completed a 6 month follow up. At the close of the year, a total of 1,122 patients had been enrolled, including 973 at hospitals and 149 PHCs. With the completion of this pilot phase, the Steering Committee recommended entering the implementation phase, which aims to treat 6,000 more patients. The trial is expected to end in 2015 and results will be available in 2016.

CHAGAS DISEASE

American trypanosomiasis



Securing access to current treatments while researching better options

The WHO estimates that about 7 to 8 million people are infected with this potentially life-threatening disease. It predominantly affects people in Latin America, but is now spreading to other continents due to population flows. Today, only an estimated 1% of those affected are treated. *Trypanosoma cruzi* parasites are mainly transmitted by contact with the faeces of infected blood-sucking triatomine 'kissing' bugs, but infection can also occur through eating food contaminated by infected insects, blood transfusions, organ transplants, and from an infected mother to her baby during pregnancy or childbirth. Newborns are included among the many who are not diagnosed with the infection and so do not receive treatment.

Benznidazole is one of two drugs currently used to treat Chagas disease, and LAFEPE and DNDi have successfully developed a formulation suitable for children up to the age of two.

Although it is currently the best available treatment option, benznidazole does have frequent side effects in adults, and so DNDi is also working with partners to develop new improved treatments and regimens, with decisions taken in 2013 to pursue studies on fexinidazole and alternative dosing of benznidazole. Drug development is a challenging process, all the more so for diseases such as Chagas where reliable animal models are lacking. Two potential new compounds from the same drug class, posaconazole and E1224, had shown promise *in vitro* and *in vivo*, but produced disappointing results when tested as monotherapies in clinical trials. It is vitally important that the correct tools and decision-making processes are in place to maximize the available opportunities and keep development costs to a minimum. The data from the E1224 trial (which also tested benznidazole), the first ever Phase II clinical trial to take place in Bolivia, provided clear efficacy and safety information for both compounds and will be valuable in guiding further drug development.

Recently, progress has been made towards improving the availability of current treatments for Chagas disease patients. In December 2012,

the Mundo Sano Foundation and DNDi launched a collaboration agreement to work together on the Mundo Sano-led drug consortium's (notably ELEA) vital second source of benznidazole for children affected by Chagas disease. The agreement focuses on drug production, patient access, and on securing affordability and accessibility to patients. In addition, the Global Chagas Disease Coalition brings together DNDi and major partners – including the Sabin Vaccine Institute and Texas Children's Hospital Center for Vaccine Development and National School of Tropical Medicine at Baylor College of Medicine (USA), the Mundo Sano Foundation (Argentina), CEADES (Bolivia), and ISGlobal (Spain) – with the support of Doctors Without Borders (MSF), the International Federation of People Affected by Chagas Disease (FINDECHAGAS), and the Health Institute of the Carlos Slim Foundation.



The aim of the Coalition is to address patients' needs by boosting access to existing health tools and treatments, supporting integrated vector-control prevention measures, and expanding global efforts to stimulate innovation for new and improved tools to treat and control Chagas disease.⁽¹⁾ Such action is urgently needed by the 99% of Chagas patients who are not accessing treatment today, despite increasing evidence of the impact of treatment even in the adult chronic stage of the disease.

Ideal Target Product Profile for Chagas Disease

A new treatment for both acute and chronic phases:

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

(1) Declaration of the Global Chagas Disease Coalition. PLOS Blogs. October 21, 2013.

→ FACT SHEET

WHAT IS THE IMPACT OF CHAGAS DISEASE?

Chagas disease is endemic to 21 countries in Latin America, where 100 million people are at risk. It is estimated that 8 million people are infected, leading to approximately 12,000 deaths every year in the region⁽¹⁾ and substantial economic burden.⁽²⁾ There are approximately 55,000 new cases each year.⁽³⁾ Increased migration and population movements have changed the epidemiology and geographic distribution of Chagas disease, which is now found outside Latin America, including in the United States, Europe, Australia, and Japan.

HOW IS CHAGAS DISEASE TRANSMITTED?

Chagas disease is related to infection by the kinetoplastid protozoan parasite *Trypanosoma cruzi*, most commonly transmitted by a triatomine vector known as the 'kissing bug'. Other routes of transmission include blood transfusion, organ transplantation, as well as congenital and, less often, oral routes through ingestion of contaminated food or beverages, especially in Amazonia.

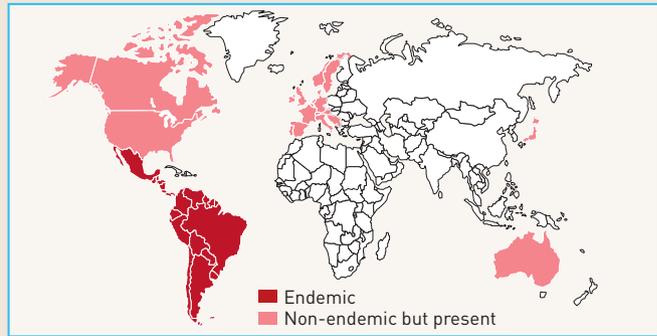
WHAT ARE THE SYMPTOMS?

The disease has two clinical phases:

→ **The acute phase** (fatal for 2-8% of children),⁽⁴⁾ often asymptomatic or unrecognized due to non-specific symptoms, such as fever, malaise, and enlarged lymph nodes, spleen, and liver. In less than half the cases, first visible signs can be a skin lesion or a purplish swelling of one eyelid (known as Romaña's sign). These symptoms spontaneously resolve in 4-6 weeks.

→ **The chronic phase**, which can be divided into two stages:

- The chronic and asymptomatic 'indeterminate' stage, during which patients can transmit the parasite to others, especially through vertical transmission or transfusion, while showing no signs of the disease, and which may last decades after infection.
- The chronic, symptomatic stage, developing later in up to 30% of infected patients, causes cardiopathies, digestive tract pathologies, and nervous system irregularities.⁽⁵⁾ Chagas disease is the leading cause of infectious heart disease (cardiomyopathy) in Latin America.



WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

Current treatments, **benznidazole and nifurtimox**, are effective against the acute phase of infection, and while there is increasing evidence of their efficacy against the chronic phase of the disease, broad use of these drugs is limited due to safety and tolerability issues. Drawbacks

include long treatment periods (60-90 days), dose-dependent toxicity, and a high drop-out rate of patients due to side-effects. There is currently no approved treatment for chronic disease with target organ involvement. In 2011, DNDi and partners produced a paediatric dosage form of benznidazole to fill the treatment gap for this population.

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?

DNDi's **short-term** goal was to make better use of existing treatments, for example through the development of a paediatric dosage form of benznidazole – a goal which was achieved. The treatment is registered in Brazil (2011), Argentina (2012), and Paraguay (2013), 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 manufactured solely by LAFEPE. Collaborative activities will continue to support greater treatment availability and adoption by countries.

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 in monotherapy and combination treatment are being explored. Fexinidazole, currently 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 page 48), which was launched in 2009.

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

- An effective and safe oral therapy for the treatment 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

(1) http://new.paho.org/hq/index.php?option=com_content&task=view&id=5856&Itemid=4196 (2) *Lancet Infect Dis.* 2013 Apr;13(4):342-8. doi: 10.1016/S1473-3099(13)70002-1. Epub 2013 Feb 8. (3) *Estimacion cuantitativa de la enfermedad de Chagas en las Americas.* Montevideo, Uruguay: Organizacion Panamericana de la Salud, 2006. (4) Parada H, Carrasco HA, Anez N, Fuenmayor C, Inglessis I. Cardiac involvement is a constant finding in acute Chagas' disease: a clinical, parasitological and histopathological study. *Int J Cardiol.* 1997. 60: 49-54. (5) http://www.msfaaccess.org/sites/default/files/MSF_assets/NegDis/Docs/NEGDIS_report_Chagas_UpdateOnProgress_ENG_2006.pdf

Nitroimidazole



2013 OBJECTIVE:

Finalize assessment of the nitroimidazole series (TB Alliance/University of

Auckland series, fexinidazole) for its potential for Chagas disease

- **Partners:** University of Auckland, New Zealand; TB Alliance, USA; Centre for Drug Candidate Optimisation (CDCO)/Monash University, Australia; Epichem, Australia; Murdoch University, Australia; Federal University of Ouro Preto (UFOP), Brazil; Institut Pasteur Korea (IPK), South Korea
- **Project start:** April 2012

Lead optimization activities have provided a better understanding of the essential features for a drug to be efficacious for the treatment of Chagas disease. Compounds issuing from the VL-2098 back-up programme (nitroimidazooxazine series) showing activity against *T. cruzi* *in vitro* are being further evaluated in *in vivo* models of Chagas disease.

Oxachagas



2013 OBJECTIVE:

One optimized lead for Chagas disease by the end of 2013

- **Partners:** Anacor Pharmaceuticals, USA; SCYNEXIS, Inc., USA; Murdoch University, Australia; Wuxi AppTech, China; Sandexis, UK; LMPH, Belgium
- **Project start:** May 2011

DNDi is pursuing several oxaborole series optimization projects for kinetoplastid diseases, including Chagas disease. Following significant (between 5 and 10 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 parasitaemia and increases in mouse survival to that observed with benznidazole, but did not produce a complete, or sterile, cure. Further profiling of oxaborole candidates are planned for new mouse models once validated, which are under development to include clinical insights into compound profiling resulting from analysis of data from the proof of concept trial of E1224 (see below).

Biomarkers



2013 OBJECTIVE:

- Identification of biomarkers to be used in clinical trials
- Finalize analysis of PCR

sampling study • Assess biomarker candidates for use in Phase III and additional studies • Complete pharmacokinetics component and treatment phase • Optimize PCR method extraction step

- **Partners:** Médecins Sans Frontières (MSF); Universidad Mayor de San Simon, Bolivia; Universidad Autónoma Juan Misael Saracho, Bolivia; Barcelona Centre for International Health Research (CRESIB), Spain; Dr Mario Fátala 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
- **Project start:** February 2010

An important hurdle for the development of new drugs for chronic Chagas disease has been the lack of clear and early markers that can indicate first treatment parasitological outcome and later indicate definite cure. To date, the only definite outcome is seroconversion, which may take several years. The project evaluates new early markers of treatment response in chronic Chagas disease. The initial focus is on the optimization of sampling procedures and validation of DNA quantification through polymerase chain reaction (PCR), considered as the state of the art to evaluate parasitological outcome. The TRAENA project in Argentina, a placebo-controlled clinical study of benznidazole in adult patients with chronic Chagas disease, offers the opportunity to correlate serological response and PCR outcomes with long follow-up. In the longer-term, DNDi is working towards identifying new biological markers to evaluate lytic antibodies, T-cell assays, multiplex serodiagnostic assays, and gene expression profiling. The PCR sampling study, in collaboration with MSF, was finalized in 2013 and preliminary results of the E1224 and TRAENA studies presented at the 62nd ASTMH conference in November 2013.

In the context of the E1224 study, markers of treatment response, such as conventional and non-conventional serology, multiplex serodiagnostic assays, selected pro-thrombotic factors, and apolipoprotein A1, were measured.

A project with Geneva University Hospitals and McGill University to assess the use of proteomic signatures and other biomarkers as potential tests of efficacy in serum samples of nifurtimox-treated Chagas patients highlights the inadequacy of serology to differentiate between treatment failure and



ongoing immunological response after treatment. Further studies are needed to establish the real potential of the markers identified so far. Serum samples of cohort patients (adult and children) treated with benznidazole and other drugs have been identified for follow-up studies to further validate the markers identified so far and exclude any treatment-specific data. Among the existing studies, DNDi is collaborating with University of Georgia and Texas Biomedical Research Institute in a Wellcome Trust funded, non-human primate study, to further determine PCR and other markers as sensitive tools that can consistently differentiate parasitological cure from treatment failure.

Another study is underway in collaboration with McGill University and the University Hospitals of Geneva. DNDi is a member and funder of the NHEPACHA network of investigators created for the long-term cohort evaluation of potential biomarkers.

K777 (completed)



2013 OBJECTIVE:

- Complete 28-day toxicity study in non-human primates
- Complete IND package

- **Partners:** University of California San Francisco (UCSF), USA
- **Project start:** September 2010

K777 is a vinyl sulfone cysteine protease inhibitor, which inhibits cruzain, a key protease required for the survival of *T. cruzi*. K777 was originally characterized by the Sandler Center for Research in Tropical Parasitic Disease at UCSF and has since been shown to be safe and efficacious in animal models of acute and chronic Chagas disease. The main objective of the project was to perform the required pre-clinical studies (safety pharmacology and toxicology) in order to complete the IND package for clinical evaluation of K777 for the treatment of Chagas disease. Safety pharmacology studies were completed, and no effects on electrocardiogram (ECG) or respiratory function were observed, even at the high dose. Dose Range Finding/Maximum Tolerated Dose (DRF/MTD) in non-human primates and a 28-day toxicity study was scheduled to be performed in 2013, but on the recommendation of the DNDi Scientific Advisory Committee in mid-2013, this project was stopped due to tolerability findings at low dose in primates and dogs.

Fenarimol (completed)



2013 OBJECTIVE:
Non-regulatory pre-clinical review

- **Partners:** Centre for Drug Candidate Optimisation (CDCO)/Monash University, Australia; Epichem, Australia; Murdoch University, Australia; Federal University of Ouro Preto (UFOP), Brazil; Institut Pasteur Korea (IPK), Korea
- **Project start:** December 2011

Two interesting candidates from the fenarimol series of compounds were identified through lead optimization efforts. In 2013, the project was in its non-regulatory pre-clinical phase, with further profiling of candidates, before nominating one candidate for progression into regulatory pre-clinical development. The objective was to perform Good Laboratory Practice (GLP) safety studies, as well as Chemistry, Manufacturing, and Control (CMC) studies on the selected candidate compound, in order to file a formal investigational new drug (IND) application and move the candidate to first-in-man studies. However, given the lack of sustained efficacy of azoles (E1224 and posaconazole) in clinical trials for Chagas diseases, this project has been stopped.



Fexinidazole for Chagas



2013 OBJECTIVE:
Decision to proceed to clinical evaluation of fexinidazole for Chagas disease

- **Partners:** Platform of Integral Care for Patients with Chagas Disease, Tarija y Cochabamba (Bolivia); Universidad Mayor de San Simon, 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; JSS Medical Research, Canada; Cardiabase, France; CREAPHARMA, France
- **Project start:** December 2013

Fexinidazole was in pre-clinical development as a broad-spectrum antiprotozoal drug by Hoechst in the 1970s-1980s, but its clinical development was not pursued. Recently, fexinidazole was 'rediscovered' and selected for development by DNDi as a new drug candidate for HAT, VL, and Chagas disease. Fexinidazole and its metabolites (M1 and M2) have previously been described as effective and superior to benznidazole or nifurtimox *in vitro* and in animal models against *T. cruzi* strains.

In January 2013, an expert panel convened by DNDi and including clinicians, cardiologists, and toxicologists from the endemic countries reviewed the safety data on fexinidazole for Chagas disease. The panel fully supported the proof-of-concept evaluation of the compound in adults with chronic indeterminate disease. A clinical candidate meeting was held in June 2013 to review all available efficacy, safety, and PK data on fexinidazole and metabolites (including data from current DNDi clinical studies for HAT). The lack of mutagenic potential (genotoxicity) and encouraging safety profile of fexinidazole, combined with its documented activity in acute and chronic models of Chagas disease supported nomination as a clinical candidate and the proof-of-concept (PoC) evaluation of this compound in Chagas disease was planned.

The Phase II PoC trial aims to determine whether at least one of six dosing regimens of orally administered fexinidazole is efficacious and safe compared to placebo, in clearing *T. cruzi* parasitaemia, and will be conducted in Bolivia. The sites of the Platform for Integral Care of Patients with Chagas Disease in Cochabamba and Tarija were selected as study centres for this project. The efficacy and safety results from this clinical trial will inform the decision of whether to proceed to Phase III.

Paediatric dosage form of benznidazole



2013 OBJECTIVE:
• Ensure paediatric benznidazole availability in Latin American endemic

countries • Ensure a second source of manufactured drug

- **Partners:** Laboratório Farmacêutico do Estado de Pernambuco (LAFEPE), Brazil; Hospital de Niños Ricardo Gutiérrez, Argentina; Instituto Nacional de Parasitología Dr M Fatala Chabén, Argentina; Hospital de Niños de Jujuy, Argentina; Ministério 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 Endemio-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

- **Project start:** May 2011

Until recently, adequate treatment options for children with Chagas disease were lacking: benznidazole was only available as an adult formulation. In July 2008, DNDi and LAFEPE entered a joint development programme that led to the determination and production of the most appropriate paediatric dosage formulation, strength, and dosing regimen of benznidazole.

A population pharmacokinetic study involving 81 children aged 0 to 12 years with Chagas disease was conducted across multiple sites in Argentina to gain more information on pharmacokinetics, treatment safety, and efficacy. Results were presented at the 62nd ASTMH in November 2013. All children showed complete parasitic clearance after treatment and, in Buenos Aires, children were assessed 12 months later and were still clear of *T. cruzi* parasites. The study also showed that children have lower blood levels of parasites than previously documented in adults, thus suggesting that there may be room for improvement and reduction of adult dosing regimens.

The paediatric formulation, adapted for babies and children up to two years of age, was registered in Brazil (2011), Argentina (2012), Bolivia (2013), and Paraguay (2013). In July 2013, the treatment was included on the WHO's 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, and to work to lower the price of the product to bring affordable treatments to Chagas patients.



Azole E1224



2013 OBJECTIVE:

To conclude Proof-of-Concept (PoC), Phase II evaluation for E1224 in adults with chronic indeterminate Chagas disease with the release of top-line report Q3 2013 for strategic decision on development of the drug

- **Additional partners:** Center for Tropical & Emerging Global Diseases, University of Georgia, USA; Cardinal Systems, France; Bioclinica, USA; Quantitative Solutions, USA
- **Project start:** February 2010

231 adult patients
recruited
out of 231
at **2** sites

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

The study evaluated the potential of E1224 as a treatment for Chagas disease and explored promising biomarkers of therapeutic response in Chagas disease (see also 'Biomarkers' project). This randomized, multicentre, placebo-controlled, safety and efficacy study evaluated three oral dosing regimens of E1224 and the standard dosing regimen of benznidazole (5mg/kg/day). The preliminary results, released in November 2013 at ASTMH, indicated that the experimental drug candidate E1224 was effective at clearing the parasite that causes Chagas disease at the end of the treatment course, but there was limited sustained efficacy one year after treatment as a single medication, as well as some safety issues at the highest dose. The current, standard therapy for Chagas, benznidazole, was shown to be very effective in the long term but continued to be associated with safety and tolerability concerns. While development of E1224 as monotherapy has been stopped, the focus has been shifted to exploring its use in a combination treatment for Chagas disease (see below).

Key findings from the project:

- At treatment completion, PCR-determined eradication rates of the Chagas parasite were 79-91% for E1224; 91% for benznidazole; 26% for placebo.
- 12 months after treatment, 8-31% of patients treated with E1224 maintained parasite clearance compared with 81% with benznidazole and 8.5% placebo.



- **Partners of the 3 projects:** Eisai Co. Ltd, Japan; Platform of Integral Care for Patients with Chagas Disease, Spain/Bolivia; Universidad Mayor de San Simon, Bolivia; Universidad Autónoma Juan Misael Saracho, Bolivia; Collective of Applied Studies and Social Development (CEADES), Bolivia; NUDFAC – Nucleus of Pharmaceutical and Cosmetics Development, Brazil; Centre de Recerca en Salut Internacional de Barcelona (CRESB), Spain; National Council of Scientific and Technological Research (INGEBI-CONICET), Argentina

New benznidazole regimens



OVERALL OBJECTIVE:

Evaluation of new treatment regimens of benznidazole for the adult patients with chronic Chagas disease, to reduce exposure and improve tolerability, while maintaining efficacy

- **Additional partner:** Instituto Nacional de Epidemiología Dr Fátala Cháben, Argentina
- **Project start:** December 2013

The E1224 proof-of-concept trial carried out in 2013 also showed that benznidazole, the standard treatment for Chagas, had sustained efficacy, but that it continued to be associated with side effects that resulted in treatment discontinuation. An expert meeting will be organized in 2014 to review the available data in support of the evaluation of benznidazole-sparing (shorter courses) regimens for Chagas disease. Proof-of-concept evaluation of new treatment regimens of benznidazole, for the treatment of adult patients with Chagas disease, will be initiated aiming to determine if the safety and tolerability issues of benznidazole can be managed by reduced doses and treatment duration.



New combinations



OVERALL OBJECTIVE:

Decision to proceed with proof-of-concept clinical evaluation of E1224/benznidazole combination treatment

- **Additional partner:** LAT Research, Argentina
- **Project start:** December 2013

DNDi and Eisai Co. Ltd undertook the development of E1224, the prodrug of posaconazole, in 2009. Following on from the results of the E1224 proof-of-concept trial in 2013, the decision was taken to evaluate the potential of azole + benznidazole combinations for the treatment of adult patients with chronic Chagas disease. The aim is to increase efficacy, and reduce the dose and duration of existing treatment (and potential impact on reduction of toxicity). In addition, combining drugs has the potential to delay development of resistance to the individual components of the combination. A Phase I drug-drug interaction study will be performed in 2014, to assess the safety and pharmacokinetics interaction of E1224 and benznidazole in healthy normal volunteers. Depending on the results, a decision will be taken as to whether to proceed to proof-of-concept evaluation of this combination treatment in adult patients with chronic Chagas disease.

Project
of the year
2013

PAEDIATRIC HIV



Accelerating ARV development and access for children

There have been huge increases in the number of adult patients treated for HIV infections over the last decade. Tragically, however, children have not benefited from the same level of treatment coverage. At best, only one-third of children who need paediatric antiretroviral therapy (ART) actually receive it, compared to 64% of all adults. Of the 3.4 million children currently estimated to be living with HIV, most live in sub-Saharan Africa and were infected by their HIV-positive mothers during pregnancy, childbirth, or breastfeeding. Over 700 children become newly infected every day and some 500 die each day of the disease. Without treatment, half of these children will die before their second birthday and 80% will have died before the age of five. Despite efforts to reach the goal of eliminating new paediatric HIV infections by 2015, the World Health Organization (WHO) has forecast that in 2020, 1.9 million children will be living with HIV, with an estimated 1.6 million in need of antiretroviral treatment.⁽¹⁾ More needs to be done to narrow, even close, the treatment gap.

For a number of years now, the WHO has recommended diagnosis and antiretroviral treatment for all children below the age of two, regardless of their clinical or immunological status. The guidelines for treating patients were consolidated and updated in June 2013, and now recommend immediate treatment of all children who are infected with HIV up to the age of five years.⁽²⁾ In addition, for children with HIV who are younger than three years of age, a regimen based on lopinavir/ritonavir (LPV/r), such as those currently under development by DNDi, should now be used as first-line ART regardless of previous exposure to non-nucleoside reverse transcriptase inhibitors, which may have been used to prevent mother-to-child transmission of the virus during pregnancy and childbirth.

A further complication for many of those infected with HIV is that they are frequently, and more easily, also infected with tuberculosis

(TB), particularly in sub-Saharan Africa. These children have a particularly poor prognosis. Unfortunately, the drugs needed to combat TB have significant drug-drug interactions with those used to treat HIV. The levels of lopinavir for example, are decreased below therapeutic levels in children also treated with the anti-TB drug rifampicin. This negative interaction requires new or adapted treatments, such as ritonavir 'boosters', to increase the bioavailability of the protease-inhibitor component of the anti-HIV treatment.

A 'Paediatric HIV Roundtable with Industry' was organized by DNDi in Dakar, Senegal, in October 2013, following on from the Conference on Paediatric Antiretroviral Drug Optimisation (PADO) organized by WHO. The discussions led to a jointly endorsed call to action among participants of both meetings to donors, stakeholders, industry, national regulatory bodies, researchers and decision makers, in order to ensure funding and accelerate the development of, and access to, paediatric formulations of ARVs that can be effectively administered for newborns to up to adolescents, a truly neglected population.⁽³⁾

Ideal Target Product Profile for Paediatric HIV

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

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

(1) http://www.who.int/hiv/pub/guidelines/arv2013/arvs2013supplement_march2014/en/ (2) <http://www.who.int/hiv/pub/guidelines/arv2013/en/> (3) 'Refocusing Research and Development of Paediatric HIV Treatments on the Needs of Children in Resource-Poor Settings: A Paediatric HIV Roundtable with Industry & Joint Call to Action on Paediatric HIV'. DNDi (2013). Downloaded from http://www.dndi.org/images/stories/diseases_portfolio/DNDi_Paediatric_HIV_roundtable.pdf

→ FACT SHEET

WHAT IS THE IMPACT OF PAEDIATRIC HIV?

At the end of 2012, an estimated 3.3 million children below the age of 15 were living with HIV, more than 90% of whom were in sub-Saharan Africa. An estimated 260,000 children under 15 years of age died of AIDS-related illness in 2012. In low- and middle-income countries, access to treatment has expanded to reach an estimated 647,000 HIV-infected children under the age of 15. Still, only 34% of HIV-positive children are estimated to be on antiretroviral therapy (ART), compared to 64% of all adults.⁽¹⁾

HOW IS PAEDIATRIC HIV TRANSMITTED?

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

WHAT ARE THE SYMPTOMS?

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

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

The 2013 WHO guidelines⁽²⁾ 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 ART combination that includes protease inhibitors, regardless of whether or not they have been exposed to ARVs through prevention of mother-to-child transmission (PMTCT). The combination of a **boosted protease inhibitor with two nucleoside reverse transcriptase inhibitors** (NRTIs) is considered by many experts as the most effective first-line therapy for infants and children, regardless of prior exposure to ARVs. However, this combination therapy



is not being widely used. According to a WHO survey performed in 45 countries, 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 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 of 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.⁽³⁾

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

- Develop and register two solid first-line 4-in-1 LPV/r-based fixed-dose combinations (FDCs) with 2 NRTIs. All components of the combination will be developed in the form of taste-masked granules, stable with no need for refrigeration, presented in a single unit with appropriate strengths to accommodate weight-band dosing.
- Develop and register a stand-alone ritonavir booster formulation that can be added to any PI-based paediatric ARV regimen and can be used to counteract the negative drug-drug interactions between PIs and rifampicin-containing TB treatments.

As a **short-term strategy**, DNDi will start 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. 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 as part of this short-term strategy.

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

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

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

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

(1) Global report: UNAIDS report on the global AIDS epidemic 2012, Geneva, 2013. (2) WHO: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. June 2013, Geneva. (3) Lallemand M et al., (2011) Paediatric HIV - A Neglected Disease? *N Eng J Med* 365

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



2013 OBJECTIVE

- Availability of clinical batches of optimized LPV/r granules, 4-in-1 LPV/r based FDCs and stand-alone RTV granules ('booster' for TB/HIV co-infection) to be used in adult bio-equivalency and paediatric phase II/III studies •

Perform, as needed, bioequivalence studies in healthy human volunteers using all components of the 4-in-1 FDC and optimized RTV granules • Initiate a clinical study to evaluate the efficacy, safety, feasibility, and acceptability of the optimized 4-in-1 LPV/r FDC or optimized LPV/r pellets together with NRTI dispersible tablets in children in Africa and Asia



- **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 • **Project start:** December 2011

Previously referred to as 'Improved PI for first-line treatment', this project aims to improve the formulation of PI-based first-line treatment for young infants and children living with HIV.

The development plan includes putting together all four drugs needed for the treatment of HIV in children into a single unit, also known as a fixed-dose combination (FDC), which is heat-stable, well taste-masked, solid, does not contain alcohol or inappropriate solvents and, most importantly, is easy to dose (using WHO-recommended weight band dosing) for the caregiver. The two FDCs in development are AZT/3TC/LPV/r and ABC/3TC/LPV/r.

The challenge of defining the dosage strengths of paediatric multidrug combinations is that for each component metabolic pathway and elimination routes differ, and that the mechanisms involved in absorption, distribution, metabolism, and excretion do not mature at the same rate over the period from birth to adolescence. DNDi executed a meta-analysis of the paediatric PK data available for LPV, ABC, ZDV, and 3TC to model the pharmacokinetics of each drug and performed simulations using the original FDA dosing recommendations, the 2010 WHO weight band dosing, and its subsequent modifications. The proportions of children above efficacy targets and the proportion of children at risk of toxicity for each of the weight bands were estimated. The modelling results of the ARVs (for LPV/r, ABC, 3TC, and AZT) were shared with WHO paediatric experts. The new 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,⁽¹⁾ under 'urgently needed ARV drugs for children recommended by the Paediatric ARV Working Group'. A paediatric pharmacokinetic expert group has been created to determine the optimal weight band dosing of LPV/r and NRTIs in order to deliver all components in a FDC. These doses are modelled using WHO weight band recommendations.

The new 2013 WHO guidelines, incorporating this dosing, were launched on the 30 June 2013, during the International AIDS (IAS) Conference in Kuala Lumpur, Malaysia. These guidelines recommend that:

- ART should be initiated in all children infected with HIV below 5 years of age, regardless of WHO clinical stage or CD4 count; and
- A LPV/r based regimen should be used as first-line ART for all HIV-positive children younger than 3 years of age, regardless of prior NNRTI exposure.

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 two new 4-in-1 FDCs and the stand-alone RTV booster are expected to be tested in healthy human volunteers in 2014.

Partnership
of the year
2013



2013 OBJECTIVE

- Availability of clinical batches of RTV granules
- Pharmacokinetics, safety,

and acceptability of superboosted LPV/r in liquid formulation for TB/HIV patients

- **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
- **Project start:** May 2012

37 patients
recruited
out of 90
at 4 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 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 by the end of 2013, four sites in South Africa had recruited 37 of the expected total of 90 patients for this study. A fifth site had obtained ethics approval and the sixth site was still pending ethics approval at the close of 2013.

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



(1) Consolidated Guidelines on The Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for A Public Health Approach, June 2013. WHO (2013).

FILARIAL DISEASES

Aiming for rapid control and patient cure

Filariasis is a group of infectious diseases caused by certain thread-like parasitic worms of the helminth (nematode) family: lymphatic filariasis (LF, or elephantiasis), onchocerciasis (river blindness), *Loa loa* (loiasis, or African eyeworm), and mansonelliasis. LF and onchocerciasis have the highest disease burdens of the filarial diseases. Infecting over 150 million people around the world and placing a billion people at risk, particularly in Africa and Asia, filariae are transmitted to humans through the bites of flies and mosquitoes. While rarely fatal, filarial diseases inflict life-long disabilities on patients, such as massively swollen limbs and genitals; blindness; chronic, debilitating pain, including regular acute attacks; severe, intense itching; disfigurement; and skin discoloration ('leopard skin'), resulting in depression and social stigmatization.

Lymphatic filariasis alone is the second cause of chronic disability worldwide. Generally, patients with filaria are often incapacitated by pain or poor limb function and thus cannot work or take care of their families or themselves. Social stigmatization because of their condition often leads to abandonment, isolation, and lack of support from others. In short, filarial diseases slowly destroy the lives of patients who become infected – physically, economically, and socially.

Control strategies for filarial diseases have for decades revolved around mass drug administration (MDA) of donated medicines, through programmes such as the African Programme for Onchocerciasis Control (APOC) and the Global Programme to Eliminate Lymphatic Filariasis (GPELFI). These programmes have been in place for over 20 years and rely on MDA of safe anti-parasitic drugs: ivermectin for onchocerciasis; ivermectin, albendazole, and diethylcarbamazine (DEC) for LF. Through these programmes, WHO has set goals of eliminating LF (defined as 70% of countries verified free of LF and 30% engaged in post-intervention surveillance activities) and controlling onchocerciasis by 2020.⁽¹⁾

However, shortcomings with the currently available drugs call into question whether these

long-running filarial control strategies, which differ according to disease and are not active in low-endemic areas, will truly wipe out filaria, and whether all infected patients are adequately being identified and are receiving effective treatment. First, current drugs kill mainly juvenile worms (microfilariae), which are transmitted *via* insect vectors, but do not kill adult worms (macrofilariae), which continue to produce new microfilariae in the body. Because of this, MDA must be carried out repeatedly for many years until the adult worms die out naturally and no longer produce new worms. For LF MDA, patients are treated once or twice a year for 4-6 years, while for onchocerciasis, MDA must be done for 10 or more years.



Second, current drugs pose life-threatening side effects in the LF and onchocerciasis patients who are co-infected with *Loa loa*. A small percentage of patients with *Loa loa* have very high levels of microfilariae, and treatment with current drugs can result in the sudden, massive death of these juvenile *Loa loa* worms that overwhelms the body and causes serious adverse reactions including brain damage (encephalopathy) and kidney failure, both of which can be fatal.⁽²⁾ Because of this side-effect risk, MDA with current drugs is considered unacceptable in areas where the *Loa loa* prevalence exceeds 20%.⁽³⁾

Therefore, a drug that can kill the adult onchocerciasis and LF worms (macrofilaricide) is
(to be continued page 39)

Ideal Target Product Profile for Filarial Diseases

A new treatment for adults and children:

- **Macrofilaricide:** Efficacious against the adult form of worms
- **Oral,** short-course treatment
- **No side-effects** following death of worms
- **Safe** in pregnant and breastfeeding women
- **Affordable**
- **Adapted to tropical climates** (minimum three-year shelf-life)

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

➔ FACT SHEET

WHAT IS THE IMPACT OF FILARIAL DISEASES?

Onchocerciasis (river blindness): An estimated 25 million people are infected worldwide,⁽¹⁾ with 99% of cases in 31 African countries. Foci also occur in some areas of Latin America (Brazil, Ecuador, Guatemala, Mexico, Venezuela) and Yemen.⁽²⁾ Approximately 123 million people are at risk of infection. Onchocerciasis is the world's second-leading infectious cause of blindness.⁽³⁾ The WHO estimates that about half a million people are blind due to onchocerciasis, and almost a million have different degrees of visual impairment. In endemic areas, children are exposed from birth, and infection can lead to growth retardation and weight loss.

Lymphatic filariasis (LF; elephantiasis): Over 120 million people are infected globally, with about 40 million disfigured or incapacitated by LF.⁽⁴⁾ More than 1.4 billion people in 73 countries are at risk of infection. An estimated 25 million men suffer genital disease, and over 15 million people have lymphoedema (swelling). The infection is usually acquired in childhood, but its debilitating manifestations usually occur later in life. After mental illness, LF is the second most common cause of long-term disability worldwide.

Loiasis (*Loa loa*; African eyeworm): An estimated 14.4 million people live in high-risk areas where *Loa loa* prevalence is >40%, and 15.2 million live in intermediate areas of 20-40% prevalence. The number of people at high risk varies considerably between countries. Patients infected with *Loa loa* only are not usually treated, but onchocerciasis and LF patients can be co-infected with *Loa loa* worms and, where such co-infection does exist, there is significant risk of severe adverse events (SAEs) with ivermectin treatment. This limits the use of ivermectin in mass drug administration (MDA) programmes in co-endemic

areas, and is an impediment to achieving WHO elimination goals for LF and onchocerciasis.

HOW ARE FILARIAE TRANSMITTED?

The thin, thread-like parasitic roundworms (belonging to the superfamily of *Filarioidea* nematodes) that cause filarial diseases are transmitted by flying insect vectors to humans:

→ Onchocerciasis is caused by *Onchocerca volvulus*, a parasitic worm that can live for 15 years in the human body. The disease is contracted through the bite of an infected female blackfly, which transmits microfilarial worms (larvae) from one person to another. After mating, a female worm releases about 1,000 new microfilariae larvae per day. Larvae develop into adult worms and settle into fibrous nodules in the human body close to the surface of the skin or near the joints. Formation of fibrous nodules in the eye leads to blindness.

→ LF is caused by *Wuchereria bancrofti*, transmitted to humans by various mosquito species. When a mosquito with infective larvae bites a person, the parasites are deposited on the person's skin and then enter the body. The larvae then migrate to the lymphatic vessels where they develop into adult worms, damaging the lymphatic system.



The worms live for 6 to 8 years and produce millions of larvae (microfilariae) that circulate in the blood.

→ Loiasis is caused by *Loa loa*, the adult worms of which can live for up to 17 years, during which time they release millions of larvae into the human body. These macrofilariae migrate throughout the body just under the skin and sometimes cross into the subconjunctival tissue of the eye where they can easily be seen. They are transmitted through the repeated bites of deerflies (also known as mango flies or mangrove flies).

WHAT ARE THE SYMPTOMS?

Onchocerciasis causes eye lesions leading to visual impairment and permanent blindness. It also causes intense itching, body pain, rashes, development of nodules, and skin disfigurement and discoloration.

Chronic LF leads to lymphoedema (tissue swelling, principally of the legs and genitals), elephantiasis (skin/

tissue thickening), and massive fluid accumulation (hydrocele) in the testes. Patients also suffer acute attacks of body pain. Physical disfigurement results in social stigma, as well as financial hardship from loss of income and increased medical expenses. LF and onchocerciasis can cause immense socioeconomic burdens of isolation and poverty.

Loiasis leads to recurrent episodes of itchy swellings and to 'eyeworm', the visible migration of the adult worm across the surface of the eye, which resolves after a few days but is itchy, painful, and causes light sensitivity. Subcutaneous migration of the worm causes tender, itching Calabar swelling, usually on the limbs and near the joints. Other symptoms include generalized itching, muscle and joint pain, and fatigue.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

Current treatments for onchocerciasis and LF are based

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?

DNDi's strategy is to develop a new drug with macrofilaricide (drug that kills adult worms) activity for use as a safe and field-adapted macrofilaricidal drug for patient case management and possibly later MDA. As a **medium-term strategy**, we are assessing emodepside, a potent antihelminthic drug currently used in combination with praziquantel to treat parasitic worms in cats and dogs, as a potential 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.

By 2015, DNDi aims to develop for testing a new, short-course oral macrofilaricide drug candidate, for use in case management and possibly later for MDA, and in regions of LF and onchocerciasis co-infection with *Loa loa*.

(1) <http://www.cdc.gov/parasites/onchocerciasis/epi.html> (2) <http://www.who.int/mediacentre/factsheets/fs374/en/> (3) http://www.who.int/blindness/partnerships/onchocerciasis_home/en/index.html (4) <http://www.who.int/mediacentre/factsheets/fs102/en/>

on mass drug administration (MDA) of antiparasitic drugs through programmes directed by the WHO. WHO recommends MDAs for onchocerciasis at least once yearly for 10-15 years, and for LF once yearly for at least 5 years. The drugs used in MDA programmes are **ivermectin** for onchocerciasis; and for LF, **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). The antibiotic drug doxycycline, while unsuitable for use in MDA programmes because of its relatively long treatment duration (4-6 weeks), shows promise for use in case management.

MDA drugs kill juvenile worms (microfilariae), but not adult worms (macrofilariae). By killing microfilariae, they can temporarily prevent vector-borne transmission (until the adult worms produce more microfilariae larvae), and induce temporary sterilization of adult worms, preventing re-population with new microfilariae for a few months. 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 LF 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.

needed. A new, safe, short-course macrofilaricidal drug could be used in individual patient treatment (case management) at the end of MDA (known as 'mopping up'), when the incidence rate is too low to justify initiating a new MDA round. It could also be used in screening and treatment programmes, which need to be scaled up, and in low-endemic areas. It could ultimately be used in MDA programmes to help eliminate the disease in the community with just one or two rounds of MDA treatment: patients could be cured within 1-2 years, rather than potentially up to 12-15 years. If sufficiently safe, the new drug would enable the treatment of patients in areas of *Loa loa* co-infection.

Emodepside



2013 OBJECTIVE:
Plan pre-clinical development as a potential macrofilaricide

- **Partners:** Bayer, Germany; Astellas, Japan; University Hospital of Bonn, Germany
- **Project start:** March 2013

Emodepside is a semi-synthetic product (originating from 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 anthelmintic used in combination with praziquantel (Profender®) for the treatment of parasitic worms in cats and dogs. Emodepside shows outstanding activity against filarial parasites. DNDi is looking to pursue its pre-clinical development for use in humans as a macrofilaricide treatment, and plans to review its potential as a candidate for clinical development.



(1) Zahner H, Schares G. (1993) Experimental chemotherapy of filariasis: comparative evaluation of the efficacy of filaricidal compounds in *Mastomys coucha* infected with *Litomosoides carinii*, *Acanthocheiloneema viteae*, *Brugia malayi* and *B. pahangi*. *Acta Trop.* 52:221-66. (2) Dominguez-Vazquez A et al. (1983) Comparison of flubendazole and diethylcarbamazine in treatment of onchocerciasis. *Lancet.* 22:139-43.

Flubendazole (completed)



2013 OBJECTIVE:
Complete pre-clinical development of flubendazole in collaboration with Johnson & Johnson

- **Partners:** Johnson & Johnson, USA; AbbVie, USA; Michigan State University, USA; University of Buea, Cameroon; McGill University, Canada
- **Project start:** April 2011

This project aimed to develop flubendazole as a safe, highly efficacious, and field-usable macrofilaricidal drug candidate for the treatment of onchocerciasis and LF. Flubendazole belongs to the benzimidazole class of molecules. Developed by Janssen Pharmaceuticals (a pharmaceutical company of Johnson & Johnson) in the mid-1970s, it is a potent and efficacious anti-helminthic drug for gastrointestinal nematode infections in swine, poultry, companion animals, and humans. In Europe, flubendazole is marketed for human use as Fluvermal.

In several animal models⁽¹⁾ and in a small-scale human clinical trial for onchocerciasis, in which the drug was administered parenterally,⁽²⁾ flubendazole showed very specific potency against the adult stage of the worm. Despite this selective potency, it has not been considered as a treatment for filarial infections, as all of the current formulations have very low bioavailability and these oral forms would not provide sufficient systemic exposure.

The first step of this project was to develop, with the help of AbbVie, a new pre-clinical formulation of flubendazole that allows oral absorption.

All data generated by DNDi has been made available to Johnson & Johnson in order to facilitate pre-clinical development of flubendazole as a macrofilaricide. DNDi will continue to support Johnson & Johnson by establishing the pharmacokinetic/pharmacodynamics relationship of flubendazole in different animal models of filariasis.

MALARIA



Striving for increased access to ACTs

The last decade has seen increased investment, research, and implementation efforts that have resulted in dramatic changes in the malaria control landscape over the past five years. Ambitious targets had aimed to reduce the number of malaria deaths worldwide to near zero by the end of 2015, whilst also reducing the number of cases to one quarter of those observed at the beginning of the current millennium, together with elimination in at least eight to ten new countries since 2008, including the entire WHO European Region. Despite such goals, still over 200 million cases of malaria occur each year with well over half a million deaths, mainly in Sub-Saharan Africa. Eliminating malaria will require effective preventive measures, through vector control, vaccines or chemoprevention, together with rapid diagnosis of populations at risk, and safe and effective treatment of affected patients.

The development of an effective vaccine has been slow, although some progress has been made. In 2013, the most clinically advanced vaccine candidate (RTS,S) was shown to almost halve the number of malaria cases over 18 months in young children aged between 5 and 17 months at the time of their first vaccination. However, infants (6-12 weeks at time of first vaccination) responded less well, with the number of cases only reduced by a quarter. Research and development is being pursued in this area.

In Southeast Asia, decreases in the rates of parasite clearance with some artemisinin-based combination therapies (ACTs) are indicative of the development of resistance, sometimes for both partner drugs. This is a matter for great concern, as currently there is no other drug class to replace artemisinins for treatment. The Medicines for Malaria Venture (MMV) is currently collaborating with Oxford University on a non-artemisinin based compound, OZ439. If demonstrated effective in resistant zones, it could become part of a new combination therapy to replace ACTs. In addition, in April 2014 MMV and GlaxoSmithKline announced the start of a Phase III programme to evaluate tafenoquine, awarded Breakthrough Therapy designation by the FDA, a potential single-dose treatment for *P. vivax* malaria. In this serious form of the

disease, a single infectious bite can lead to the parasite remaining dormant in the liver for periods ranging from weeks to years, from where it triggers relapses. The only currently available treatment for the eradication of the liver stage parasite is primaquine, but it is rarely used because of the risk of haemolysis in glucose-6-phosphate dehydrogenase (G6PD) deficient patients, limited access to G6PD tests, and poor compliance with its 14 day course of treatment. Although G6PD deficiency is also a concern with tafenoquine, its single-dose treatment would be a significant improvement on the lengthy treatment time needed with primaquine.

In zones of highly seasonal malaria, such as the Sahel sub-region of Africa, WHO currently recommends, for seasonal chemoprevention, the combination of amodiaquine (AQ) and sulfoxadine-pyrimethamine (SP) in regions where

P. falciparum malaria is sensitive to both

antimalarial medicines. By administering a full course of AQ+SP at monthly intervals throughout the rainy season, a constant therapeutic dose is maintained, and 75% of children under the age of five have been shown to be protected. However, adequate monitoring will be essential in order to detect any possible resistance developing in a timely fashion and to fully assess the pharmacovigilance risks for such a broad preventive treatment in a large population of children.

For many years, WHO has recommended ACTs, where a fast-acting artemisinin-based drug is combined with a much slower-acting drug from a different class, for the treatment of uncomplicated *falciparum* malaria. DNDi and partners have developed two ACT treatments in fixed-dose combinations, artesunate with amodiaquine (ASAQ) and artesunate with mefloquine (ASMQ). In Africa, however, a recent study⁽¹⁾ found no evidence of slow clearance after treatment with ASAQ or comparator ACTs over a ten-year period. ASAQ was found to maintain very good levels of efficacy in the countries where it has been used. By the end of 2013, 280 million treatments of ASAQ had been distributed. These, and all available ACTs recommended by WHO, are essential in the control of the disease.



(1) *Plasmodium falciparum* clearance in clinical studies of artesunate-amodiaquine and comparator treatments in sub-Saharan Africa, 1999-2009' ZWANG et al., (2014) *Malaria Journal* 13:114 doi:10.1186/1475-2875-13-114.

ASAQ Winthrop



2013 OBJECTIVES:

- Diversify ASAQ suppliers by transferring technology to a partner in Africa
- Facilitate

implementation of ACTs in FDC, in general, and specifically ASAQ, in all countries where it could benefit patients and abide local practices

- **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
- **Project start:** January 2002

Over 280 million treatments distributed

in 35 countries by end 2013

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. In 2010, ASAQ Winthrop obtained WHO authorization for a three-year shelf life, giving the product the longest shelf life of any pre-qualified FDC artemisinin-based treatment available for malaria.

In partnership with Sanofi, MMV, and National Malaria Control Programmes, high-quality data on ASAQ effectiveness and safety in the field is being collected, as part of a Risk Management Plan (RMP). This was the first RMP submitted to the WHO, and the first to be set up entirely in Africa. It is expected to contribute to building capacity to



monitor drug safety and efficacy in sub-Saharan African countries and could set the precedent for further real-life assessment studies of new ACTs. Together with partners, DNDi is also working on the transfer of technology to a second manufacturer in Africa, Zenufa, based in Tanzania.

By the end of 2013, 280 million treatments had been distributed in Africa

ASMQ FDC



2013 OBJECTIVES:

Clinical studies:

- Continue the key multi-centre comparative study conducted in three African countries

Technology transfer and registration:

- Inclusion on the WHO Essential Medicines List
- Support activities for pre-qualification by WHO and PAHO
- Continue registration authorization and facilitate implementation for ASMQ FDC in Asia
- Reduce the cost of MQ to decrease the price of ASMQ FDC

- **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
- **Project start:** January 2002

Over 1.2 million treatments distributed

in 4 countries by end of 2013

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. ASMQ FDC was registered in Brazil in March 2008. 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, and the product was registered in India in 2011. Both Farmanguinhos and principally Cipla supplied treatments in response to a large request from Venezuela in 2013 (over 382,000 treatments). ASMQ FDC was registered in Malaysia in March 2012, in Myanmar in October 2012, in Vietnam in late 2013 for the low-strength FDC, and in Tanzania in December 2013. Following the initiative by the WHO Prequalification of Medicines



Programme to set up a collaborative procedure in 2013 between Prequalification and interested National Medicines Regulatory Authorities (NMRAs), aiming to accelerate the review of the registration files of some products, Cipla and DNDi agreed to take part in this new process for ASMQ FDC. This involved the use of the Prequalification assessment for the evaluation, by the countries, of the regulatory files. The response of the NMRAs was to be provided within 90 days.

Phase IIIB study in children:

940 patients recruited out of 940 by end 2013 at 4 sites in 3 countries

Additional clinical studies are ongoing that will provide information of ASMQ FDC use in children, adults, and pregnant women in Africa. According to WHO recom-

mendation, AS+MQ could be considered for use in some countries in Africa. To provide key information on the efficacy and tolerability of ASMQ FDC, DNDi is sponsoring a multicentre Phase IIIB study in Tanzania, Burkina Faso, and Kenya to assess efficacy, safety, and pharmacokinetics of ASMQ FDC compared to artemether-lumefantrine in children below the age of 5 with uncomplicated *P. falciparum* malaria. Patient follow-up was completed in October 2013 and the study results are expected in Q3 2014. The admission of Farmanguinhos/Fiocruz into the PAHO Strategic Fund in April 2013 will allow procurement by South American national control programmes.

The FDC of ASMQ was included in the WHO Essential Medicines Lists for adults and children in April 2013, in line with current treatment guidelines.

The development of low-cost mefloquine with Medicines for Malaria Venture (MMV) is still under discussion, and the possible future inclusion of ASMQ in their portfolio is being considered.

EUR 23.2 million to maintain a robust pipeline to support long-term objectives

R&D EXPENDITURE BY DISEASE 2012-2013



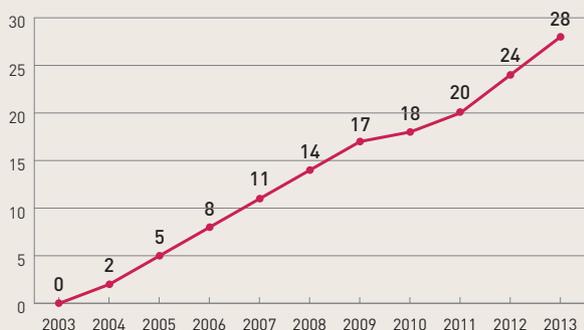
Overall R&D expenditure (EUR 23.2 M) was stable (+2%; EUR 0.4 M) compared to 2012. Percentage breakdown of 2013 R&D expenditure per disease with the following highlights:

- HAT:** With a total of EUR 5.8 M, HAT investments increased (+ EUR 0.8 M) because clinical activities for fexinidazole grew in 2013 (+ EUR 0.7 M), with 6 new clinical trial sites opened in DRC, reaching a total of 9 operating sites. The SCYX-7158 project finalized pre-clinical activities as well as the Phase I study (84 patients enrolled in 2013), thus incurring an increase of EUR 1.2 M in expenditures. The NECT study was completed in 2013 (- EUR 0.1 M). Screening and lead optimization efforts were redirected towards VL and Chagas disease (- EUR 1 M).
- Leishmaniasis:** This disease area remains the most substantial R&D expenditure (33%) approaching Business Plan projections. The overall EUR 0.1 M expenditure decrease in 2013 (EUR 6.8 M in 2012 against EUR 6.7 M in 2013) resulted from delays in authorization to operate in certain endemic countries, which postponed implementation of clinical activities for a few months, thus incurring a decrease in clinical expenditure of EUR 0.4 M, mainly in India. Pre-clinical activities increased by EUR 0.1 M, notably for the safety evaluation of VL-2098. Screening and lead optimization work focused more intently on VL, leading to an increase from 43% to 50%.
- Chagas disease:** Projects remained stable in 2013 (+ EUR 0.1 M), with EUR 4.8 M (23%) of R&D expenditure. A new activity, fexinidazole for Chagas disease, started at the end of the year, with mainly CMC costs (EUR 0.1 M). Biomarker activities, particularly the non-human study, which began in Q4 2012 were fully implemented during the entire year, incurring an increase of EUR 0.6 M. The benznidazole study was completed in early 2013 (- EUR 4 M), with access activities taking over this activity in 2014 only. Regarding pre-clinical activities, the fenarimol study was completed in 2012, incurring little cost in 2013 (- EUR 0.1 M) and the K777 study terminated mid-year (- EUR 0.1 M).
- Portfolio expansion:** the two new diseases areas represent 10.5% compared to 8.6% in 2012. This increase (+ EUR 0.4 M, +24%) is the most significant of the DNDi portfolio.
 - Filaria:** Project expenditure increased only by 10% (+ EUR 0.1 M). Two activities are ongoing: The flubendazole project hand-over to J&J engendered a significant decrease of 50% of costs (from EUR 0.6 M to 0.3 M EUR in 2013). Screening work, including high-throughput screening for the development of an oral formulation, doubled between 2012 and 2013 (from EUR 0.4 M to EUR 0.8 M).
 - Paediatric HIV:** Project expenditure increased by EUR 0.3 M. Two activities are ongoing: Clinical 'superboosting' study (ritonavir for superboosting LPV/r) in South Africa (EUR 0.55 M) and formulation development of the 4-in-1 with Cipla Ltd. as industrial partner (EUR 0.55 M).
- Malaria:** Expenditure decreased by 57% (- EUR 0.8 M), in line with the Business Plan. Three activities are still ongoing: Some access activities have been handed over to partners such as MMV, therefore access activities decreased by EUR 0.3 M. The recruitment for the ASMQ clinical trial Phase IV in Africa was completed in 2013 and the expenditure decreased by EUR 0.1 M. The ASAQ transfer of technology to Zenufa was temporarily placed on hold in 2013 for logistical reasons, thus causing an expenditure decrease of EUR 0.4 M.

Consolidation and steady increase of partnerships with research companies

CUMULATIVE NUMBER OF NEW PARTNERSHIPS ESTABLISHED WITH RESEARCH COMPANIES

Number of partnership agreements signed per year



By end 2013, 28 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, at no cost.



Development and translation increase with the advancement of several new compounds to clinical development

R&D EXPENDITURE PER R&D STAGE



Overall R&D expenditure increased by 2% (+ EUR 0.4 M) between 2012 and 2013 to reach a total of EUR 23.2 M. The most important fluctuation relates to growth of translational projects (Pre-clinical; Phase I; Phase IIa/PoC: + 40%) and the progress (+10%) of development projects (total + EUR 3 M).

- **Research:** Screening and lead optimization activities decreased (- EUR 1.1 M) due to restructuring of partnership models (shift of partners). Screening activities for filaria increased (+ EUR 0.4 M) with new partners involved.
- **Translation:** Expenditure increase between 2012 and 2013 (+ EUR 2.4 M) is due to:
 - Progress of SCYX-7158 in Phase I for HAT (+ EUR 1.3 M).
 - Start of two new fexinidazole projects: one for VL and one for Chagas disease (+ EUR 0.4 M).
 - The Biomarker project for Chagas disease, which started Q4 2012, was implemented during 12 months in 2013 (+ EUR 0.7 M).
- **Development:** The progression of fexinidazole for HAT Phase IIb/III clinical study (+ EUR 0.7 M) with 8 clinical sites in DRC and 1 in CAR is the major achievement in 2013.

Expenditures for New VL treatments in Bangladesh, Africa, and Latin America are decreasing (- EUR 0.2 M) since these studies completed recruitment and are preparing their final reports and next steps.

- **Implementation:** Project costs decreased by 42% (- EUR 1.9 M) in 2013 compared to 2012. With six projects in implementation (the first one entered in 2007), various stages have been reached:
 - Completion: NECT clinical sites closed end 2012, preparation of final study report (- EUR 0.1 M).
 - Transfer to partners: ASAQ and ASMQ access activities increasingly being handled by partners (- EUR 0.8 M).
 - Project delays: partners awaiting authorization to start implementation studies - VL combo study in Asia (- EUR 0.6 M) and paediatric benznidazole in Latin America (- EUR 0.4 M).

Leveraging partners' resources

IN-KIND CONTRIBUTIONS 2006-2013



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 8 years amounts to EUR 23 M, and has increased ten-fold, reflecting DNDi's investment in building strong partnerships. The 27% increase in 2013 compared to 2012 (+ EUR 1.6 M) is largely due to the flubendazole macrofilaricide project (EUR 4.1 M). More than 50% of the contribution relates to pharmaceutical and formulation development (reformulation for human use and New Chemical Entities, NCEs).

The monitoring required to value in-kind contributions is a continual process aimed at improving accuracy. For instance, 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. To illustrate this contribution, the total compounds screened in 2012 was consolidated and compared with 2013, showed a 51% increase (+73,887 compounds), without a major increase in the number of partners.

NUMBER OF COMPOUNDS SCREENED

