



R&D MODEL & PORTFOLIO

ADAPTED TREATMENTS FOR THE BENEFIT OF NEGLECTED PATIENTS

The R&D strategies developed by DNDi since its inception aim to address the immediate needs of patients by improving existing therapeutic options in the short term, whilst undertaking longer term research to identify and develop entirely new compounds which will be valuable adapted tools, particularly for elimination targets set by the World Health Organization. Although not necessarily breakthrough medicines, six new treatments have been delivered to date as a result of the short-term strategy, which have brought significant benefits to patients.

The year 2015 has been a turning point for DNDi, as long-term investments have now filled the drug development pipeline with thirteen new chemical entities (NCEs) included by the end of the year, the vast majority of which

are orally available compounds for systemic use. The most clinically advanced of these are for sleeping sickness: fexinidazole, which was identified from compound mining and is a ten day oral treatment, and SCYX-7158, which is entering

Phase II trials as a potential single-dose oral treatment and is the first molecule to arise from DNDi's lead optimization programme.

Leishmaniasis is a complex family of diseases, and the identification of new compounds has proved challenging. Compound libraries from a variety of sources have been screened and, despite the inevitable loss of compounds to attrition, NCEs from the nitroimidazole, oxaborole, and aminopyrazole chemical families are undergoing lead optimization to combat *Leishmania* infections, with the nitroimidazole VL-0690 selected to go forward to

pre-clinical development in 2015. Additional drug candidates have come from the drug discovery programmes of GSK/Dundee Drug Unit (two classes), and Celgene (one class). These six classes are also undergoing testing in animal models of CL. The three classes from the DNDi series have already shown efficacy against *L. major* in a mouse model of infection, with the aminopyrazole class showing sterile cure in animals. This is the first time this has been observed with a drug candidate. The NTD Drug Discovery Booster, a multilateral experiment launched in 2015, aims to speed up the discovery of new compounds for leishmaniasis and Chagas disease. The lack of clinical markers of disease, and of animal models capable of accurately predicting the translation of drugs from laboratory to patient, has proven to be a major obstacle in developing new drugs for Chagas disease.

A two-pronged approach aims to develop direct-acting or indirect-acting compounds for treating filarial diseases. Emodepside, used in veterinary healthcare, began its clinical evaluation in healthy volunteers in 2015 as a potential treatment for onchocerciasis. Additional NCEs are being sought by screening focused libraries with known anthelmintic activity from animal health companies and repurposing libraries from human health companies. Although drug repurposing is high risk, the wealth of information available for drugs which have already undergone clinical development can speed up the development process drastically, and new treatments reach patients faster. A macrofilaricide which indirectly leads to the death of the parasite by killing its *Wolbachia* symbiont entered the development pipeline in 2015.

This increased number of compounds in development has resulted in a concomitant increase in the number of clinical trials. At the end of 2015 more than 30 clinical trials were in preparation, on-going, or reporting results worldwide.

The extension of DNDi's portfolio with the new Business Plan 2015-2023 (see p. 6) led to the inclusion of two new diseases. Fosravuconazole, already available to DNDi because of its previous evaluation for Chagas disease, is the most promising drug candidate for fungal mycetoma and DNDi will begin recruiting 130 patients in Sudan in the first ever randomized clinical trial to be undertaken for eumycetoma. A combination of sofosbuvir with ravidasvir will be evaluated in 750 patients in Malaysia and Thailand as a potential public health tool to treat Hepatitis C.

DNDi
South
East
Asia

29 ongoing clinical studies in 2015, on 4 continents, for 7 diseases

Phase I
3 STUDIES

Phase II
11 STUDIES

Phase III
10 STUDIES

Phase IV
5 STUDIES

DNDi
DRC

Efficacy studies with fexinidazole in human African trypanosomiasis (HAT) patients in the Democratic Republic of Congo and Central African Republic will ultimately collect information from 750 adults and children above the age of 6 years with both stages of *gambiense* disease, including an evaluation of its ease of use under real-life conditions. A later study will examine its efficacy in patients with *rhodesiense* HAT.

DNDi
Africa

Fexinidazole is also being investigated for treating patients with the related kinetoplastid diseases – leishmaniasis and Chagas disease. A combination of fexinidazole and miltefosine for the treatment of visceral leishmaniasis (VL) patients in eastern Africa could be the first oral-only combination therapy for VL: an allometric dosing study of miltefosine to address drug underexposure in children was undertaken in 2015. Twelve month follow-up of efficacy and safety data of fexinidazole in adult Chagas disease patients was concluded in 2015, with the results expected in early 2016. A planned study in 270 adult patients with chronic

DNDi
Latin
America

Chagas disease aims to determine if the safety and tolerability issues of benznidazole can be managed by reduced doses and treatment duration, or by combination with fosravuconazole.

DNDi
Africa

DNDi is seeking to address the urgent need for better medicines for children living with HIV. In June 2015 lopinavir/ritonavir (LPV/r) pellets were awarded tentative approval for use by the U.S. Food and Drug Administration (FDA). This was followed by the initiation of an implementation study (the LIVING study) in 3,000 Kenyan children, which will provide information on their use as part of a combination treatment with AZT/3TC or ABC/3TC administered under normal living conditions. A "superboosting" study was undertaken in 96 African children infected with both HIV and tuberculosis (TB), aiming to compensate for the negative drug interactions between LPV/r and the TB-treatment rifampicin. The study was finalized in 2015 and results led the South African government to change its treatment guidelines for HIV/TB coinfecting children.

BUILDING A ROBUST PORTFOLIO

PROJECTS ARE DIVIDED INTO FIVE CATEGORIES:

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



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

› **New treatments developed from compounds with known antimicrobial/antiparasitic activities** aiming to maintain or improve efficacy and tolerability.

› **Compound repurposing for new indications of existing treatments in other diseases** (therapeutic switching).

› **Combinations or new formulations of existing drugs that are better adapted to field conditions and patient needs** (paediatric dosage forms, long-acting forms, new route of administration, fixed-dose combinations, co-packaging, or co-administration).

› **Geographical extension of existing treatments**, including completion of regulatory dossiers in new countries.



Implementation

Access

NECT

Nifurtimox-Eflornithine
Combination Therapy

SSG&PM

Africa

New VL Treatments

Asia

Benznidazole

Paediatric
Dosage form

Malaria

ASAQ FDC
ASMQ FDC

KEY R&D MILESTONES IN 2015

› DISCOVERY

- Successful implementation of NTD Drug Discovery Booster
- New series in H2L and lead optimization for leishmaniasis and Chagas disease
- Screening of 300,000 compounds from pharmaceutical and other libraries completed
- Two optimized lead candidates under review for VL with backup compounds in three different chemical classes – including one very potent for CL

› HUMAN AFRICAN TRYPANOSOMIASIS (HAT)

- Recruitment to three fexinidazole studies (pivotal late stage, early stage, children) completed
- Phase I study for SCYX-7158 completed

› LEISHMANIASIS

- DNDI-0690 nominated as new pre-clinical candidate for VL
- Miltefosine allometric dosing study recruitment completed in Africa
- Dose selection and decision to initiate drug-drug interaction study on fexinidazole/miltefosine as a potential oral combination in Africa
- Development of PKDL study for India and PKDL infectivity study in Bangladesh
- Study on new VL treatments in Latin America completed
- 12-month follow-up of VL-Asia study ongoing – collaboration with Kalacore for further implementation and pharmacovigilance monitoring

› CHAGAS DISEASE

- Drug-drug interaction study completed for E1224/benznidazole
- Development of study protocol for short-course benznidazole as well as benznidazole/E1224 combination

› FILARIAL DISEASES

- Pre-clinical development for emodepside completed

› PAEDIATRIC HIV

- Interim positive results for TB Superboosting study
- LIVING study on the implementation of pellets initiated in Kenya

› MALARIA

- ASAQ and ASMQ transferred to MMV
- ASAQ technology transfer to Zenufa: preparation of prequalification file
- >400 million ASAQ treatments delivered by Sanofi

TRANSMISSION

DNDi works on diseases that are transmitted in a variety of ways, from parasites living in two different hosts to viruses, worms, and a fungus. Curing these diseases requires not only an understanding of the infectious agents, but also an understanding of the interplay between infection, vector, and host.



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



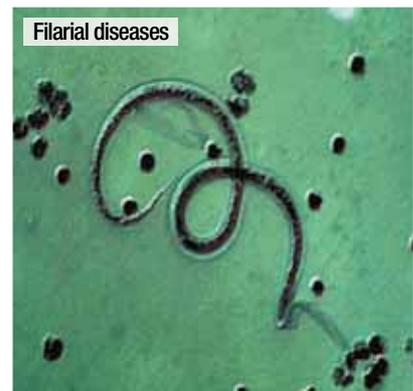
HAT is caused by two sub-species of kinetoplastid protozoan parasites: *Trypanosoma brucei (T.b.) gambiense* (West and Central Africa) and *T. b. rhodesiense* (East Africa). Parasites are transmitted to humans by tsetse flies.



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



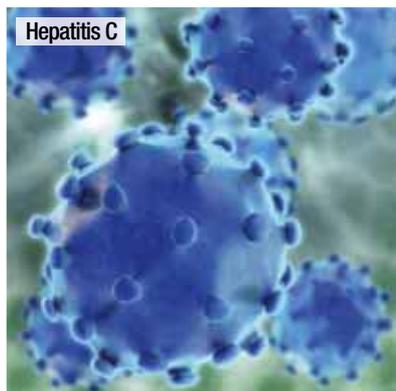
Malaria is caused by the *Plasmodium* parasite. Five species are involved: *P. falciparum*, *P. malariae*, *P. vivax*, *P. ovale* & *P. knowlesi*. They are transmitted from person to person by the bite of infected anopheline mosquitoes.



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



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



The **hepatitis C virus** exists in six genotypes that cause liver disease. It is a **blood-borne virus** that is commonly transmitted through **unsafe injection practices, contaminated medical equipment, and transfusion of unscreened blood**.



Mycetoma is a slow-growing **bacterial** (Actinomycetoma) or **fungal** (Eumycetoma) **infection**. The exact route of Eumycetoma infection is unknown but it is thought to enter the body after the skin has been pricked (e.g. by a thorn).

DISCOVERY

Drug discovery is a demanding process, particularly with the added constraints of working in a neglected area and within a limited budget. The standard “black box” approach involves screening compounds against parasites *in vitro*, to identify those which are able to kill the parasite under laboratory conditions.

Having identified initial hits, analogous compounds are synthesized and evaluated to identify even more potent molecules in a process known as hit-to-lead. The most promising of these undergo further optimization in order to maximize antiparasitic activity, increase tolerability and safety, and optimize the amount of time a compound stays in the body.

With compounds undergoing clinical development for HAT, DNDi's screening and lead optimization efforts are currently focused on identifying compounds for Chagas and leishmaniasis.

The mini-portfolio approach for filarial disease treatments aims to identify: (1) direct-acting compounds – by screening libraries from ani-

mal health companies and repurposing compounds for human use, and (2) indirectly-acting compounds – which kill the symbiotic *Wolbachia* bacteria – in partnership with the anti *Wolbachia* consortium (A-WOL) at the Liverpool School of Tropical Medicine, UK.

The NTD Drug Discovery Booster was launched in 2015 as an experiment aimed at speeding up the process and cutting the cost of finding new treatments for Chagas disease and leishmaniasis (see p. 21).

Medicinal chemistry with partners in the North and South

Over the last decade, DNDi has worked with academic and industrial medicinal chemistry partners who

are organized geographically into two consortia, in Australia (LO AUS) and the United States (LO US).

In 2013 we began building a new consortium in Latin America (LOLA), providing support and mentoring for young scientists in the region (see below). The consortia undertake hit-to-lead and lead optimization activities for visceral leishmaniasis and Chagas disease (see Leish H2L p. 29, and Chagas H2L p. 38), with HAT activities on hold in case of any future need.



A Latin American consortium for leishmaniasis and Chagas disease drug discovery



The Chemistry Team of Prof. Dr. Luiz Carlos Dias (centre), UNICAMP.

The “Partnership of the Year 2015” was awarded to LOLA, a Latin American Lead Optimization Programme. The LOLA project uses an international collaborative approach, working with UNICAMP (University of Campinas), Brazil, and with partners in the USA (AbbVie) and Europe (LMPH, University of Antwerp, Belgium) to carry out early stage drug discovery and sets a precedent for all emerging neglected disease endemic countries.

SCREENING

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

OVERALL OBJECTIVE:

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

2015 OBJECTIVE: Focus high throughput screening on identification of novel hit series for VL and Chagas disease by screening larger size compound libraries, exploring new “chemical space” and open source drug discovery initiatives

During 2015, over 300,000 compounds (representing more than 820,000 wells) were evaluated, with a focus on visceral leishmaniasis

in Chagas patients. A new *in vitro* protocol for *T. cruzi* amastigotes which can differentiate between CYP51 inhibitors (such as azoles and other scaffolds) and benzimidazole by determining time kill and percentage kill profiles was developed in collaboration with Swiss TPH. This assay has been integrated into our discovery cascade and is routinely used to profile and prioritize non-CYP51 *T. cruzi* hits. Over 50 novel VL and Chagas active scaffolds were identified in 2015 from screening efforts.

DNDi has actively collaborated with MMV on the development of a “Pathogen Box”- a collection

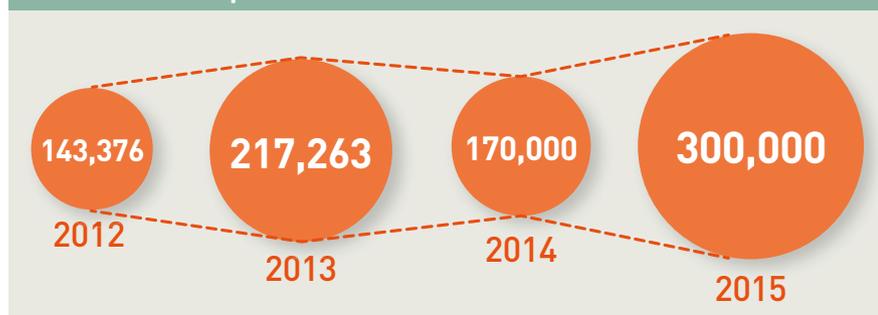
Medium throughput screening

for kinetoplastids – leishmaniasis, Chagas disease, and HAT (*Trypanosoma brucei*)

PARTNERS: The Swiss Tropical and Public Health Institute (Swiss TPH), Switzerland; the Laboratory of Microbiology, Parasitology, and Hygiene (LMPH), University of Antwerp, Belgium; and the Walter Reed Army Institute of Research (WRAIR), USA

MAIN COMPOUND LIBRARIES: AbbVie, USA; Anacor Pharmaceuticals Inc., USA; Astellas Pharma, Japan; AstraZeneca, UK; Celgene, USA; Daiichi Sankyo, Japan; Eisai Co. Ltd, Japan; GSK, Tres Cantos, Spain; Institut Pasteur Korea, South Korea; London School of Hygiene and Tropical Medicine (LSHTM), UK; Medicines for Malaria Venture (MMV), Switzerland; Merck, USA; Microbial Chemistry Research Foundation, Japan; Pfizer Ltd, UK; University of Dundee, UK; Sanofi, France; Takeda Pharmaceutical Company Ltd, Japan; TB Alliance, USA

Number of compounds screened



and Chagas disease, in five DNDi-Partner screening centres. This includes several chemical collections and sets of chemical analogues of hits/hit series from pharmaceutical and biotechnology companies. Commercial compound libraries from Axxam, Bioscent, and SPECS have been screened, together with TB Alliance’s “Active” and MMV’s “Biofocus” collections.

Drug candidates which target the enzyme CYP51 are very common hits in *T. cruzi* screens. However, recent clinical studies with fosravuconazole and posaconazole have shown that this is not a valid drug target

of 400 drug-like compounds for multi-purpose screening – and has supplied a number of “hit” compounds for the kinetoplastids for consideration; seventy of these 400 compounds show activity against kinetoplastids.

High throughput screening (large-size libraries)

for leishmaniasis (*Leishmania*) and Chagas disease (*Trypanosoma cruzi*)

PARTNERS: The Institut Pasteur Korea, South Korea, and the Drug Discovery Unit, University of Dundee, UK

Screening for filarial diseases

OVERALL OBJECTIVE:

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

2015 OBJECTIVE: Identify 1-2 new candidates

With the limited throughput of phenotypic screening against filarial nematodes, screening large chemical libraries is not possible, and DNDi has negotiated access to smaller focused chemical series that are more likely to give rise to drug candidates. These include indications sets (compounds that have progressed to pre-clinical or clinical research but failed to reach the market); well-annotated sets of compounds (e.g. bioavailable sets or compounds which have been through lead optimization); chemical series from veterinary anti-infective research programmes; or orthologous sets (compounds directed against human targets

with similar gene sequences to the parasites).

In total over 17,000 compounds have been provided by the companies and organizations listed below, in addition to the commercial MicroSource library. This effort yielded a considerable number of hits in the low micromolar range. However, further work is needed to make optimized antifilarial drugs before progressing any candidate into preclinical development. Resources for this project are mainly dedicated to profiling molecules

from the optimisation programmes undertaken by AbbVie and Celgene.

PARTNERS: The Hospital of Bonn, Institute for Medical Microbiology, Immunology & Parasitology (IMMIP), Germany; the Muséum National d'Histoire Naturelle Paris, France; and the Northwick Park Institute for Medical Research (NPIMR), UK



MAIN COMPOUND LIBRARIES: AbbVie, USA; AstraZeneca, UK; BASF, Germany; Bristol-Myers Squibb (BMS), USA; Celgene, USA; GSK, Tres Cantos, Spain; E.I. DuPont Nemours, USA; Epichem, Australia; Janssen, Belgium; Mercachem, The Netherlands; Merck, USA; Merck Serono, Germany; MMV, Switzerland; National Institutes of Health (NIH), USA; Novartis Centre de la Recherche Santé Animale, Switzerland; Sanofi, France; TB Alliance, USA; WuXi AppTech, China

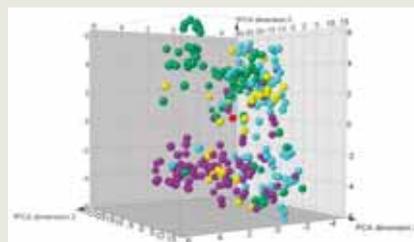
NTD Drug Discovery Booster to speed up compounds identification

OVERALL OBJECTIVE: Speed up the process and cut the cost of finding new treatments for leishmaniasis and Chagas Disease

OBJECTIVE 2015: Implement the NTD Drug Discovery Booster project with 3-6 pharmaceutical companies

More than 1,600 analogues tested

The NTD Drug Discovery Booster was launched in 2015 as an experiment aimed at speeding up the process and cutting the cost of finding new treatments for Chagas disease and leishmaniasis. Initially, the project brought together DNDi and four pharmaceutical companies: Eisai Co Ltd, Shionogi & Co Ltd, Takeda Pharmaceutical Ltd, and AstraZeneca plc.



The chemical universe around a DNDi lead molecule (red) is explored through sharing of molecules in pharma companies databases (green, cyan, yellow, purple spheres).

DNDi supplies active “seed” compounds used by each company for *in silico* searches of chemical libraries for structurally-related compounds and entirely novel chemical scaffolds. The most interesting compounds are selected and undergo further testing *in vitro* to assess potency. In a multilateral, simultaneous search process across the pharmaceutical companies, DNDi accesses millions of compounds, generated over decades of research. Identification of novel chemical entities acts as a starting point for optimization of potential treatments or cures for these diseases. The innovation of the Drug Discovery Booster not only lies in the multilateral and cross-company comparative approach, but also in the iterative nature of the search, in which companies continue to examine their compound libraries for better compound matches as the search is refined. This will significantly reduce the time it will take to find new, promising treatment leads.



NTD Drug Discovery Booster meeting in Tokyo with partners' representatives, November 2015.

By the end of 2015, six seed compounds had been submitted to the Booster for the first round of *in silico* screening and then the identified analogues were tested *in vitro* by the Institut Pasteur Korea and showed improvements in potency or the identification of novel chemical scaffolds. Further iterations will seek to build on these initial results. Celgene joined the consortium in 2016, and it is hoped that more companies will join in the future.

PARTNERS: AstraZeneca, UK; Celgene, USA (since 2016); Eisai, Japan; Shionogi, Japan; Takeda Pharmaceutical, Japan



A sleeping sickness patient rests in the HAT ward in Katanda, Kasai, DRC.

› **Sleeping sickness** is usually deadly without treatment. Patient numbers have fluctuated with time, with disease outbreaks occurring intermittently, particularly when surveillance and control measures were relaxed. In the mid-1960s fewer than 5,000 cases were reported in the whole African continent, but the disease re-emerged, with a major epidemic from 1970, peaking in 1998 with over 38,000 cases detected. Since then, numbers have been falling consistently thanks to the combined efforts of WHO, National Control Programmes, NGOs, and Belgian and French bilateral aid. The most recent figures show that fewer than 3,000 new cases of *T.b. gambiense* HAT (g-HAT) were reported in 2015, the lowest figure ever recorded by WHO; 117 cases of *T.b. rhodesiense* (r-HAT) were recorded in 2014.

Available treatment options depend on the stage of the disease and the parasite subspecies causing the infection, making the invasive and feared lumbar puncture – to determine if the parasite has entered the brain – mandatory for every patient diagnosed. Nifurtimox-eflornithine combination therapy (NECT), developed by Epicentre, MSF, DNDi, and partners for treating stage 2 g-HAT, replaced melarsoprol, a highly toxic arsenic-containing drug which killed 1 in 20 patients. Eflornithine was initially introduced as a slow-infusion treatment administered 56 times (every 6 hours for 14 days). In NECT, the number of eflornithine infusions is reduced to 14, in combination with orally administered nifurtimox, shortening the time spent in hospital and reducing the burden on resources. For stage 1 disease, pentamidine (discovered in 1940) remains the current treatment for g-HAT and suramin (discovered in 1920) for r-HAT. The arsenic-derivate melarsoprol is still the only treatment available for stage 2 r-HAT.

WHO aims to eliminate g-HAT as a public health problem by 2020. A paradigm shift in diagnosis and treatment is therefore needed, with patients screened at home, referred to a nearby centre for diagnostic confirmation

and sent back home with an oral treatment, obviating the need for staging of the disease by lumbar puncture. This will require a simple, reliable, rapid test, coupled with a safe and effective treatment that is easy to administer for both disease stages in g-HAT and r-HAT.

DNDi has advanced oral candidates for HAT treatment in clinical development that are new chemical entities: fexinidazole, a 10-day treatment, and SCYX-7158, a potential single-dose treatment. The fexinidazole pivotal trial in adults with stage 2 g-HAT, and additional trials in adults with stage 1 disease and in children with both disease stages, had finished recruitment by the beginning of 2016. In addition, an implementation study to determine safety and efficacy in a 'real world' setting will provide further data on the use of fexinidazole for treating outpatients, including at home. This will inform HAT endemic countries on

the widest possible use of the drug and guide treatment policy. A study is planned for fexinidazole in r-HAT. SCYX-7158 has completed studies in healthy human volunteers and DNDi will start recruiting patients into a phase II/III trial in 2016.

During recruitment into the fexinidazole trials in the DRC, mobile teams from the National Control Programme for HAT, supported by DNDi, travel to endemic villages to identify infected people who are then sent to specialized district hospitals for diagnosis confirmation and treatment. Mobile teams tested approximately 25% of the nearly 4 million people screened for g-HAT in the entire country in 2014 and 2015. As such, DNDi is making a real contribution to the control and elimination of HAT through the work of mobile teams and conduct of clinical trials.

With the exciting prospect of wiping out this deadly disease, it is vital that funding is maintained to sustain elimination efforts and avoid previous scenarios where control and surveillance lapsed and the disease re-emerged.

Sustained disease elimination requires new tools

13.1 million people were estimated to live in areas at moderate to very high risk in 2012 (more than one case per 10,000 population)

Disease is caused by two subspecies of *Trypanosoma brucei* (*T. b.*) *gambiense* (g-HAT; 98% of reported sleeping sickness cases) and *T. b. rhodesiense* (r-HAT), and occurs in two stages: the early stage has non-specific symptoms and is often un- or misdiagnosed, and the late stage, where the parasite crosses the blood-brain barrier, causing serious neurological disorders including sleep cycle disruptions, paralysis, and progressive mental deterioration. Without effective treatment, the disease usually leads to death. A lumbar puncture is needed to differentiate between stages in order to choose the appropriate treatment.

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

TREATMENT OF STAGE 1 HAT

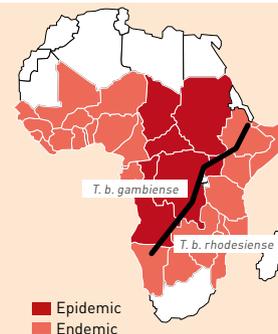
Pentamidine (1940) for g-HAT and **suramin** (1920s) for r-HAT, require injections and are ineffective for stage 2.

TREATMENT OF STAGE 2 HAT

NECT – nifurtimox-eflornithine combination therapy (2009): for stage 2 g-HAT, requires 14 slow intravenous infusions of eflornithine of 2 hours each over 7 days, together with three times a day oral nifurtimox for 10 days. Requires specialized hospital administration and trained staff. Since its addition to the EML, NECT is first-line treatment for stage 2 g-HAT.

Eflornithine (1981): today seldom used alone, requires an extended stay in hospital during administration (56 intravenous infusions – four times per day, over 14 days).

Melarsoprol (1949): No longer used for g-HAT. Remains the only drug available for stage 2 r-HAT – a toxic arsenic derivative that causes pain and fatal encephalopathy in up to 5% of patients who receive it.



T. b. gambiense
is endemic
in

24 countries
of West and Central Africa
• Less than 3,000
new cases reported (2015)

T. b. rhodesiense
is endemic
in

13 countries
of Eastern and Southern
Africa • 117 cases (2014)

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 option for sleeping sickness** in 25 years: nifurtimox and eflornithine combination therapy (NECT). NECT is included on the WHO Essential Medicines Lists (EML) for adults (since 2009) and children (since 2013), and virtually all *T. b. gambiense* endemic countries are now using NECT as first-line treatment for stage 2 g-HAT.

As a medium-term strategy, DNDi initiated a compound mining effort to identify existing chemical compounds with potential against kinetoplastid diseases, resulting in the rediscovery of fexinidazole. After a complete Phase I programme, DNDi engaged in g-HAT patient studies. Inclusion into a **pivotal Phase II/III study** in stage 2 g-HAT is complete and patient follow-up is ongoing. Two complementary studies will examine efficacy and safety in adults with stage 1 and early stage 2 g-HAT, in children aged 6-14 years, and a third one is being planned for r-HAT

patients. Additional information will be obtained from a study in special population groups and to provide preliminary evidence on treatment compliance and effectiveness in ambulatory patients. Sanofi is the industrial partner.

In order to build a strong pipeline for **long-term drug discovery**, DNDi established a HAT Lead Optimization Consortium resulting in identification of the oxaborole **SCYX-7158**, which successfully progressed through pre-clinical development. **Phase I clinical** development was completed in 2015 and preparations are underway for a prospective Phase II/III efficacy study in patients, to be initiated in 2016. Other backup compounds were evaluated by the consortium and remain available for further development if necessary.

In addition, DNDi supports the **HAT Platform** (see p.59) that was launched in Kinshasa, Democratic Republic of the Congo (DRC) in 2005. The HAT Platform is a clinical research and access-supporting network for HAT endemic countries that brings together key players in the

research on sleeping sickness in endemic countries and those involved in HAT from the international research arena, with partners having a role in developing HAT health policy participating in the Platform.

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

By 2018, DNDi aims to deliver from its HAT-specific portfolio: An oral, safe, effective treatment to be used for both stage 2 and stage 1 HAT.

RESEARCH



SCYX-1608210 and SCYX-1330682

PROJECT START: April 2007 and April 2009 respectively

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

2015 OBJECTIVE: Retain as a back-up compound in case of future need

Extensive pharmacokinetic profiling of possible oxaborole compounds led to the selection of SCYX-1608210 and SCYX-1330682, which demonstrated cure in the stage 2 mouse model of HAT, as a backup for SCYX-7158 in case of need. Given the current success of other projects for HAT, further development was put on hold in 2013 and will only recommence should problems be encountered with SCYX-7158 in clinical development.

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

TRANSLATION



SCYX-7158

PROJECT START: January 2010

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

2015 OBJECTIVE: Complete single-ascending dose study in healthy human volunteers

An oxaborole originally provided by Anacor Pharmaceuticals was found to be active against HAT parasites at the University of California San Francisco, and further investigated by a consortium consisting of DNDi, Anacor, SCYNEXIS, Pace University, and Swiss TPH. Compound optimization over two years and examination of over 1,000 compounds produced SCYX-7158 which was selected as a promising pre-clinical candidate for g-HAT in late 2009. In pre-clinical studies, SCYX-7158 was shown to be safe and efficacious in treating a brain form of the disease in animals, when administered orally in a single dose.

In March 2012, SCYX-7158 became DNDi's first new chemical entity resulting from its own lead optimization programme, to enter clinical development. SCYX-7158 was found to have an unusually long half-life when tested in healthy volunteers. This Phase I study was finalized in March 2015 and results were presented later that year at the European Congress on Tropical Medicine and International Health in Basel. The single-dose treatment will be tested in patients with stage 2 g-HAT in a Phase II/III trial, planned to start in the Democratic Republic of the Congo in 2016. The study will use several sites already active in fexinidazole development with addition of new sites selected from high-prevalence g-HAT areas. Patients will be followed up for 18 months after treatment to ensure long-lasting cure, with a preliminary evaluation of data performed after the first 12 months.

PARTNERS: Anacor Pharmaceuticals Inc., USA; Advinus Therapeutics Ltd, India; SCYNEXIS Inc., USA; Institut de Recherche pour le Développement (IRD), France.



DEVELOPMENT



Fexinidazole

PROJECT START: April 2007

OVERALL OBJECTIVE: Develop and register fexinidazole as a new oral drug for the treatment of HAT caused by *T. b. gambiense* (g-HAT), ideally also to be used for *T. b. rhodesiense* (r-HAT)

2015 OBJECTIVES:

- Complete recruitment of the pivotal Phase II/III study of fexinidazole versus the reference treatment (NECT)
- Complete recruitment of the studies in adults with stage 1/early stage 2 g-HAT and in children above 6 years of age and over 20 kg weight (both stages)

749 patients recruited at 10 sites

Fexinidazole, the result of successful compound-mining efforts pursued by DNDi in 2005, entered clinical

development in September 2009 and is being co-developed with Sanofi: DNDi is undertaking clinical and pharmaceutical development whilst Sanofi is responsible for the industrial development and production. Fexinidazole is the most advanced oral candidate under development for HAT. DNDi aims to evaluate and register it as a treatment for a wide range of patients, specifically in adults and children over 6 years of age and 20 kg body weight with either stage of disease.

The pivotal study compares fexinidazole in patients with late stage g-HAT versus NECT, and completed inclusions of all 394 patients between October 2012 and April 2015. The 18 month follow-up period will end in 2016, and results processed for regulatory submission in Q3 2017. Additional safety and efficacy data from the two complementary studies will also be included; the first reached 230 early stage adult patients and the second 125 children aged 6-14 years (approximately equal numbers of early stage and late stage patients) in an open, non-comparative study, using the same

regimen with doses adapted to children's weight. In total therefore, information collected from 749 individuals will be included in the safety database.

More information from special population groups not included in trials to date, such as pregnant and breastfeeding women, patients with poor nutritional status or with chronic diseases, will be obtained in a planned Phase IIIb trial. This will also include a cohort of outpatients and will provide preliminary information about treatment compliance and use on an outpatient basis.

The protocol for a study to be undertaken in r-HAT patients is being finalized, sites in Uganda and Malawi have been identified, and the study is planned to commence in 2017.

The submission of a regulatory dossier to the European Medicines Agency (EMA) under Article 58 is planned for 2017, for the treatment of g-HAT with fexinidazole. This provision allows the EMA's Committee for Medicinal Products for Human Use (CHMP) to give scientific opinions, in co-operation with the World Health Organization (WHO), on drugs to prevent or treat diseases of major public health interest and intended exclusively for markets outside the European Union. It aims to ensure faster WHO prequalification of medicines by removing barriers to simultaneous prequalification. A Risk Management Plan to further monitor safety and efficacy in the field is under preparation in collaboration with Sanofi and WHO.

PARTNERS: Sanofi, France; Swiss Tropical and Public Health Institute (Swiss TPH), Switzerland; Institute of Tropical Medicine (ITM) – Antwerp, Belgium; Médecins Sans Frontières; Institut de Recherche pour le Développement (IRD), France; Institut National de Recherche Biomédicale (INRB), DRC; HAT Platform; National Control Programmes of the Democratic Republic of Congo and the Central African Republic.

IMPLEMENTATION



NECT: Nifurtimox-Eflornithine Combination Therapy

PROJECT START: May 2004

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

2015 OBJECTIVE: Prepare the field for change of policy and implementation

365 NECT kits distributed, sufficient to treat 1,460 patients

NECT, a co-administration of intravenous eflornithine and oral nifurtimox, was developed by Epicentre, MSF, DNDi, Swiss TPH, and the national HAT control programmes of the Republic of the Congo

and DRC. After inclusion in the WHO Essential Medicines List in 2009, it quickly became the first-line treatment for

second stage g-HAT. NECT has been a game-changer in the treatment of sleeping sickness – it has reduced the number of eflornithine infusions required, compared to when it is used as a monotherapy, from 56 to 14. More importantly, however, it has had a major impact on patients, by removing the fear of treatment they had when the only option was melarsoprol, a product so toxic that it killed up to 5% of all patients who received it. NECT is available in all endemic countries, who receive free supplies from WHO via drug donations by Sanofi and Bayer.

In 2015, 365 NECT kits containing four treatments each were distributed in all disease endemic countries, sufficient to treat 1,460 patients with second stage g-HAT.

MAIN PARTNERS: Epicentre, France; Médecins Sans Frontières (MSF), Holland; Swiss Tropical and Public Health Institute (Swiss TPH), Switzerland; Ministry of Health, Republic of Congo; HAT Platform; National Trypanosomiasis Control Programme, DRC



Visceral leishmaniasis patients waiting to see a healthcare worker at the Kala-Azar Medical Research Centre (KAMRC), Muzaffarpur, Bihar, India.

› **Leishmaniasis** affects the poorest of the poor and has strong links with malnutrition, low-quality housing, and lack of resources. Some 350 million people around the world are at risk of developing leishmaniasis in one of its many forms. There are more than 20 species of *Leishmania* parasite, transmitted to humans by approximately 30 species of phlebotomine sand flies found throughout the tropics and subtropics, as well as in temperate zones.

One of the two most common forms of disease, visceral leishmaniasis (VL) or kala-azar, is fatal without treatment. There are 200,000-400,000 new cases per year, albeit with a large reduction recently in South Asia. The WHO's roadmap for elimination - published in 2012 and supported by the London Declaration the same year - targets elimination of kala-azar as a public health problem by the end of 2020 in South Asia.

Surprisingly, the response of visceral leishmaniasis to treatment is not homogenous across continents, nor even within the same region, and different drugs and/

or regimens are needed, particularly in eastern Africa. Intermediate results from an implementation trial which was underway in India, carried out by DNDi and partners, led the government to change its treatment guidelines in 2014, abandoning miltefosine monotherapy in favour of single-dose Ambisome® as first-line and a combination of paromomycin/miltefosine as second-line treatment. These changes were subsequently also taken up by the governments of Bangladesh and Nepal. Similarly in Latin America, the interim results of an implementation trial carried out by DNDi with partners in Brazil led to Ambisome® being included as second-line treatment after Glucantime®, with the final results now suggesting it would be more suitable as first-line treatment. In addition, Ambisome® alone or in combination with miltefosine is being evaluated in Ethiopia for treating VL patients who are co-infected with HIV.

Post kala-azar dermal leishmaniasis (PKDL) is a complication of VL. Treating PKDL patients, which may

also remove a reservoir for reinfection and outbreaks, is likely to be key for sustained elimination of the disease. The safety and efficacy of Ambisome® alone or in combination with miltefosine will be assessed for treating PKDL patients in India and Bangladesh, whilst patients in Sudan will receive Ambisome® or paromomycin in combination with miltefosine.

Cutaneous leishmaniasis, although not life-threatening, is more common than the visceral form and is the cause of serious socio-economic problems in populations with already limited resources. Initial approaches will explore opportunities to better use the existing treatments in combination, together with the development of a topical formulation for small numbers of ulcerated, uncomplicated CL lesions. However, an oral treatment will

be needed to treat multiple or large lesions, to be selected from compounds at early clinical stages or from the DNDi discovery programme. PKDL and complicated forms of CL may be treatable with an immune modifier combined with chemotherapy.

DNDi has recently identified new chemical entities from its drug discovery efforts and it is hoped that these, together with other leads expected to emerge from the NTD Drug Discovery Booster, launched in 2015, will lead to a generation of safe and effective oral treatments for VL and CL.

DNDi is a member of the consortium for the Control and Elimination of Visceral Leishmaniasis, known as KalaCORE, which aims to tackle VL in South Asia and East Africa by supporting national efforts and coordinating with national VL control programmes.

Following the acceptance of a joint submission in 2015 by DNDi and the Instituto de Salud Carlos III (ISCIII), a Madrid-based WHO collaborating Center for leishmaniasis for 19 years, the 6th World Congress on Leishmaniasis will take place in Toledo, Spain from 16 to 20 May 2017, with some 1500 attendees expected (see www.worldleish2017.org).

Multiple approaches needed to address a complex family of diseases

What are the current treatments and their limitations?

Existing drugs have serious drawbacks in terms of safety, resistance, stability, and cost. They have low tolerability, long treatment duration, and are difficult to administer. These drugs are used either as monotherapy or in combination for the various forms of leishmaniasis.

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 has been reported. Serious cardiotoxicity leading to death is well documented. In monotherapy, they require a 30-day parenteral treatment for VL. For CL: intramuscular injections for 21 days; in the Old World, generally 1-2 intralesional applications per week for 3-7 weeks, sometimes alternating with cryotherapy (not used in the New World). Registered in South East Asia, Latin America, and some Mediterranean and African countries.

Amphotericin B deoxycholate: only an alternative treatment for VL in areas with high rates of unresponsiveness to antimonials where no other options are available. Need for hospitalization, constant renal monitoring of patients, 28-day duration of treatment, and infusion-related adverse events are notable drawbacks. Amphotericin B displays dose-limiting toxicity. Registered in South Asian countries and some countries in Africa and Latin America.

AmBisome®: a liposomal formulation of amphotericin B, which is comparatively much safer and highly efficacious. A single infusion of 10mg/kg has shown a 96.4% cure rate in Asia. However, high cost and the need for a cold chain limit widespread use. Registered for VL in India, USA, and Europe and used as a second-line drug for the treatment of VL in East Africa at higher doses than in India and for VL in Brazil. It is also used to treat PKDL cases in Sudan. A donation to WHO facilitates free distribution of AmBisome® to the three countries involved in the elimination strategy in South Asia for primary VL patients, and as a rescue treatment for African VL. It is not properly evaluated for cutaneous leishmaniasis (CL).

Miltefosine: an oral drug administered twice daily, registered for use in India for VL, and requires 28-day treatment. Major limitations include low compliance, risk of resistance, contraindication in pregnancy, and mandatory contraception for women of child-bearing age for the duration of therapy and three months beyond. A recent study in Asia indicated an emerging lack of efficacy of monotherapy in the region, probably associated with drug underexposure in children, and the same has been observed in Africa. For CL, currently approved for lesions caused by three *Leishmania* species. Miltefosine is not registered in many endemic countries and is consequently not available.

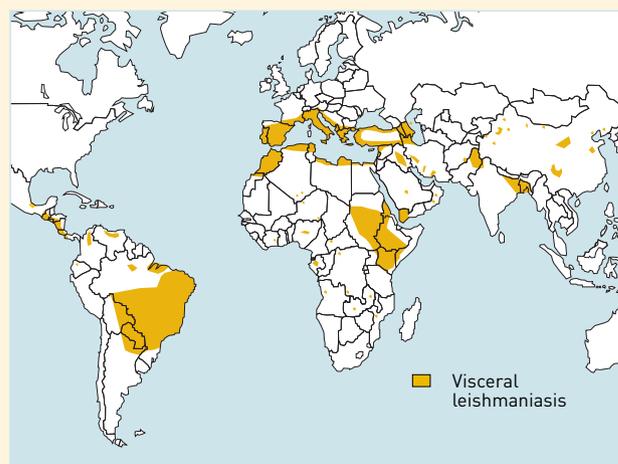
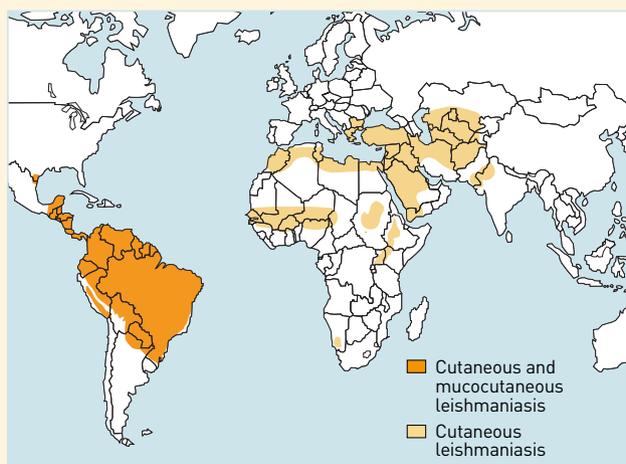
Paromomycin: a low-cost parenteral formulation that requires three weeks of painful intramuscular administration is also highly efficacious in Asia but is associated with some degree of renal and ototoxicity; limited efficacy as monotherapy in East Africa.

350
million people
at risk in

98
countries

0.7-1.2
million cases
of CL annually

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



WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?

VISCERAL LEISHMANIASIS

Improved treatment options for VL patients in some areas have already been delivered. DNDi's **short-term approach** has been 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, and the geographical extension of existing drugs in other countries and regions. In 2010, DNDi and LEAP partners **delivered the SSG&PM combination therapy for East Africa**, now recommended as first-line treatment for VL in the region. In **India**, a Phase III trial demonstrated the efficacy of combination therapies of already-registered drugs (see p. 35). In 2014, based on the evidence generated by this trial and one conducted by Sundar *et al.*, the government of **India** recommended use of single-dose AmBisome® as a first option and paromomycin/miltefosine combination as the second option for treatment instead of using miltefosine as monotherapy, with the same policy change also taken up in Bangladesh and Nepal. DNDi later collaborated with the National Control Programmes of India and Bangladesh, MSF, the Bihar State Health Society, and the Indian Council for Medical Research to assess the effectiveness and safety of these new treatments at the primary healthcare level and facilitate their introduction. In **Latin America**, DNDi is participating in a study sponsored by the Brazilian Innovation Agency (FINEP) to evaluate the safety and efficacy of Glucantime®, AmBisome®, and amphotericin B as monotherapies, and of

AmBisome®/Glucantime® combination to treat VL patients. The national control programme has extended the use of AmBisome® as second-line treatment based on the interim safety data from this trial.

Leishmania and HIV co-infection is a growing problem, difficult to manage clinically due to poor response to treatment with frequent relapses of disease, and is eventually fatal. DNDi is working with partners towards better treatment for HIV/VL co-infected patients in **Africa and Asia**.

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

The role of **Post-Kala Azar Dermal Leishmaniasis** (PKDL, a common complication of VL) in infectivity is poorly understood and treatment options remain limited, requiring long and often repeated courses of treatment including with antimonials. It is a particular problem in Sudan and Bangladesh, and needs to be addressed if VL is to be controlled. DNDi is working with partners to facilitate additional research in epidemiology, diagnosis, pathogenesis, and treatment.

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

In addition, DNDi supports the **Leishmaniasis East Africa Platform** (LEAP) (see p. 58).

A new VL treatment for adults and children based on a new chemical entity would ideally be **efficacious against all species of Leishmania in all regions as well as against resistant strains, have at least 95% efficacy, be short course** (once a day for 10 days oral; or 3 shots over 10 days), **easy to use**, compatible for **combination therapy, safe** in pregnant and breastfeeding women and for immunocompetent/immunosuppressed patients, **affordable**, and adapted to tropical climates. The TPP for the combination treatment will be reviewed in 2016.

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

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

CUTANEOUS LEISHMANIASIS

For CL, DNDi's objective is to develop short, safe, efficacious, affordable, and field-adapted treatments, at least for lesions caused by *L. tropica* and *L. braziliensis*. As a **medium-term** strategy, DNDi is developing a topical treatment based on amphotericin B. In addition, we aim to improve treatment strategies using currently available treatment modalities and will be evaluating a single application of heat therapy combined with a short course of oral miltefosine. In the **medium to long**

term, DNDi aims to develop an oral drug and an immune-modulator for use in combination with chemotherapy. This novel approach aims to initially eliminate parasites with chemotherapy, followed by enhancement of the patient's immune response with an immune-stimulating agent.

A new topical or oral treatment for CL would ideally be **efficacious against all species**, show at least **95% efficacy**, be **easy to use, short course** (14-28 days), compatible for combination therapy,

produce **minimal scarring**, be **safe** in pregnant and breastfeeding women, **affordable**, and **adapted to tropical climates**.

By 2020, DNDi aims to deliver from its CL-specific portfolio:
A safe, effective, and shorter-course treatment for CL

RESEARCH



Leish H2L

(Leishmaniasis Hit to Lead)

PROJECT START: On-going

OVERALL OBJECTIVE: Identify new leads series from current ongoing Hit-to-Lead activities by taking advantage of the optimization consortia platform screening of compounds for VL

2015 OBJECTIVE: Progress two new chemical classes into lead optimization

Hit to lead is a dynamic phase in the drug discovery cascade in which small molecule hits from high throughput screens are evaluated and undergo limited optimization to identify promising lead compounds. Series from a number of different partners have shown activity against *L. donovani*; work on these series to bring forward suitable candidates for lead optimization is on-going.



A notable success in January 2015 was the successful advancement of the aminopyrazole series from the hit to lead stage into the next lead optimization stage. This early work has recently been published in *J. Med. Chem.* In addition, the NTD Drug Discovery Booster project commenced in April 2015 working with four pharmaceutical companies: Eisai, Shionogi, Takeda, and AstraZeneca and has so far conducted hit expansion on six different hits which are being developed for leishmaniasis and Chagas disease.

A number of pharmacokinetic and pharmacodynamic studies have been conducted in animal models of VL using existing and experimental drugs to build improved PK/PD models and ameliorate the translation of new drugs from discovery into clinical studies.

MAIN PARTNERS: Epichem, Australia; UNICAMP (University of Campinas, Brazil); Centre for Drug Candidate Optimization, Monash University, Australia; TCG Lifesciences, India; Sandexis, UK; WuXi AppTech, China; Laboratory of Microbiology, Parasitology and Hygiene, University of Antwerp, Belgium; London School of Hygiene and Tropical Medicine, UK; Griffith University, Australia; GSK, Tres Cantos, Spain; Sanofi, France; Anacor Pharmaceuticals Inc., USA; Merck, USA; AstraZeneca, UK; AbbVie, USA; Pfizer, UK.

Oxaborole

(previously known as Oxaleish)

PROJECT START: January 2010

OVERALL OBJECTIVE: Select an oxaborole for pre-clinical evaluation

2015 OBJECTIVES:

- Select an oxaborole for pre-clinical evaluation
- Complete profiling of lead oxaboroles

DNDi and Anacor have been working together over the last few years to identify oxaborole compounds, initially for the HAT programme, and this has expanded to include both leishmaniasis and Chagas disease. DNDI-6148 has emerged as a promising lead candidate and by the end of 2015, studies including exploratory toxicology necessary for possible progression to pre-clinical development had been successfully completed. It is anticipated that pre-clinical development of DNDI-6148 will commence following a review meeting in January 2016. Approximately four additional oxaborole compounds continue to be developed behind DNDI-6148 as potential back-ups in case an insurmountable issue should be identified.

MAIN PARTNERS: Anacor Pharmaceuticals Inc., USA; Laboratory of Microbiology, Parasitology and Hygiene, University of Antwerp, Belgium; London School of Hygiene and Tropical Medicine (LSHTM), UK; Wuxi AppTech, China; Sandexis, UK

Aminopyrazoles

PROJECT START: February 2012

OVERALL OBJECTIVE: Select an aminopyrazole for pre-clinical evaluation

2015 OBJECTIVE: Identify compounds suitable for pre-clinical evaluation

Compound mining of well-annotated chemical compound libraries has been used to identify a new class of compounds active against VL. In June 2014, the first *in vivo* proof of concept for VL series 12 (aminopyrazoles) from Pfizer was achieved in the hamster early curative model of VL. An initial compound gave 93% and 95% reductions in parasitaemia in liver and spleen respectively after five days oral dosing at 50mg/kg BID, with a subsequent compound showing even better *in vivo* activity (>99% reduction in parasitaemia in both liver and spleen). The project moved into the lead optimization stage in January 2015, with GHIT Fund support and expert scientific assistance from Takeda from April 2015. Further compounds are being designed and tested. Profiling of current and new leads in a panel of drug sensitive and drug resistant strains of *Leishmania*, exploration of the *in vivo* dose response, rat pharmacokinetics, and initial *in vitro* safety assays are all underway. A full lead optimization programme is ongoing and we aim to select an optimized lead in 2016.

MAIN PARTNERS: Takeda Pharmaceutical Company Ltd, Japan; Wuxi AppTech, China; Laboratory of Microbiology, Parasitology and Hygiene, University of Antwerp, Belgium; London School of Hygiene and Tropical Medicine, UK; Pfizer, UK; Sandexis, UK

TRANSLATION



VL2098 (completed)

PROJECT START: July 2010

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

2015 OBJECTIVE: Decision on whether or not to move the candidate forward

VL-2098 was chosen for development from a selection of 70 nitroimidazoles belonging to four chemical sub-classes as a very potent and safe molecule. An in-depth evaluation of its efficacy, pharmacokinetic, and early safety profile showed the compound to be potent against *L. donovani in vitro* and efficacious in acute and chronic VL animal models after oral dosing. However, toxicology and pharmacokinetic studies performed in three animal species indicated a link between dose, length of treatment, and testicular toxicity. Further studies of longer duration were undertaken in order to determine the safety margin, but as it was not possible to establish any therapeutic window between plasma exposures in the most sensitive animal model and efficacious exposures in the two rodent species, the decision was taken to close the project in early 2015.

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

Fexi sulfone (completed)

PROJECT START: January 2015

OVERALL OBJECTIVE: Investigate the potential of developing fexinidazole sulfone as a treatment for VL

2015 OBJECTIVE: Take decision on whether to develop fexinidazole sulfone

Oral fexinidazole is under development as a treatment for our kinetoplastid diseases, and is most advanced for HAT. When absorbed it functions as a pro-drug for the rapidly formed sulfoxide (M1) and sulfone (M2) metabolites which are 10x more active than fexinidazole itself in *in vitro* tests and also exhibit a higher drug exposure at all dose levels. Fexinidazole sulfone was considered for development as a drug to replace fexinidazole, and the dossier was reviewed in 2015. In October 2015 the decision was taken not to progress fexinidazole sulfone as there was no clear advantage over fexinidazole; the latter continues to undergo evaluation for VL in combination with miltefosine.

PARTNERS: None

DNDI-0690

PROJECT START: September 2015

OVERALL OBJECTIVE: Progress and evaluate a nitroimidazole as a potential treatment for VL

2015 OBJECTIVE: Select a compound to progress from the nitroimidazooxazine backup programme

Following the termination of the VL-2098 project in early 2015, the decision was taken to progress with lead compounds from two sub-series previously identified from the nitroimidazooxazine backup programme (DNDI-8219 and DNDI-0690) which had good efficacy *in vivo*, better solubility, and lower potential for cardiotoxic effects. A 14-day toxicity evaluation carried out in 2015 led to DNDI-0690 nomination as a pre-clinical candidate in September 2015. In addition, with other potential lead compounds for VL, DNDI-0690 was profiled *in vitro* against CL-causing strains of *Leishmania* at the London School of Hygiene & Tropical Medicine and the Walter Reed Army Institute of Research and showed good to excellent activity, consistent with their activity against *L. donovani* and *L. infantum*.

MAIN PARTNERS: London School of Hygiene and Tropical Medicine (LSHTM), UK; TB Alliance, USA; Auckland University, New Zealand; Laboratory of Microbiology, Parasitology and Hygiene (LMPH), University of Antwerp, Belgium; WuXi AppTech, China; Aptuit, Italy; Accelera, Italy



TRANSLATION



Fexinidazole/Miltefosine Combination

PROJECT START: 2013

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

2015 OBJECTIVES: Initiate allometric dosing study of miltefosine in children. Prepare for a drug-drug interaction study on fexinidazole-miltefosine

30 paediatric patients recruited at 4 sites

Fexinidazole has shown potent activity against *L. donovani* *in vitro* and *in vivo* in a VL mouse model, and studies in healthy volunteers found it to be safe

when given as a single dose or as repeated dosing after 14 days. Furthermore, fexinidazole is in late stage development for HAT with a good safety profile.

A Phase II proof-of-concept study initiated in 2013 assessed the safety and efficacy of fexinidazole for the treatment of primary VL adult patients in Sudan, and enrolled 14 patients. All patients showed clinical improvement during treatment and the majority had parasite clearance (by microscopy) at the end of treatment. Three patients remained cured until 6 months follow-up, however the response was not sustained in other patients and relapses were observed. The study was interrupted in 2014 as it failed to show conclusive efficacy in

the majority of patients. Miltefosine is the only other oral drug currently available and will be evaluated in combination with fexinidazole in Eastern Africa. A previous study carried out in Africa indicated miltefosine was underdosed in children as compared to adults, and that dose adjustment was required. A study to assess safety and efficacy of miltefosine using an allometric dosing in children with VL was initiated in Kenya and Uganda in June 2015, recruitment completed in September, and patient follow up will end in 2016.

As the ultimate goal is to develop a combination of fexinidazole and miltefosine, a drug-drug interaction study in normal healthy volunteers to assess the pharmacokinetics and safety of the concomitant administration of fexinidazole and miltefosine has been prepared.

MAIN PARTNERS: Institute of Endemic Disease (IEND), Khartoum University, Sudan; Kenya Medical Research Institute (KEMRI), Kenya; Makerere University, Uganda; Amudat Hospital, Uganda; Leishmaniasis East Africa Platform (LEAP); Kacheliba District Hospital, Kenya; Uppsala University, Sweden; Utrecht University, The Netherlands; London School of Hygiene and Tropical Medicine (LSHTM), UK; Koninklijk Instituut voor de Tropen (KIT), The Netherlands; The Netherlands Cancer Institute, The Netherlands; PhinC, France; Centres d'Investigation Clinique des Centres Hospitaliers Universitaires de Clermont-Ferrand, Lille et Bichat-Claude Bernard, France; SGS, Belgium; Cardiabase, France; Optimed, France; UBC, Switzerland.



TRANSLATION



CpG-D35 (CL)

PROJECT START: June 2014

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

2015 OBJECTIVE: Advance the pre-clinical development of CpG-D35

CpG-D35 is being developed as a combination therapy for the treatment of complicated cutaneous leishmaniasis and post kala-azar dermal leishmaniasis (PKDL). *Leishmania* parasites are able to persist in host cells by evading or exploiting immune mechanisms. Modulating the immune response with CpG oligonucleotides may improve the effectiveness of chemotherapies. The project has four phases: production and characterization of GMP-grade CpG-D35, pre-clinical studies in two species to assess potential toxicities, Phase I clinical trials in healthy volunteers, and proof-of-concept clinical trials in patients for CpG-D35 and the combination of CpG-D35 with chemotherapy. In 2015 IND-enabling pre-clinical safety prerequisites and service providers for entry into Phase I proof-of-concept clinical trials were identified.

MAIN PARTNERS: US FDA, USA; National Institutes of Health (NIH), USA; Ohio State University, USA; Nagasaki University, Japan; University of Osaka, Japan; GeneDesign Inc., Japan

Anfoleish (CL)

PROJECT START: September 2011

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

2015 OBJECTIVE: Continue enrolment in the Phase Ib/II exploratory study and have an indication of the safety, PK, and efficacy

80 patients recruited at 1 site The rationale for development of a topical formulation of amphotericin B was to provide a treatment to be applied locally at the CL lesion, showing high anti-parasitic effect, but without the systemic toxicity associated with amphotericin B. A Phase Ib/II open-label, randomized, non-comparative, two-arm exploratory study is being conducted in Colombia. Initially planned to include only patients with CL caused by *L. braziliensis*, recruitment was widened to include patients with CL caused by *L. panamensis*. Enrolment of all 80 patients was completed in November 2015, and preliminary data on cure will be available in 2016.

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

MAIN PARTNERS: Humax Pharmaceutical, Medellin, Colombia; Programa de Estudio y Control de Enfermedades Tropicales, Universidad de Antioquia, Medellin, Colombia

New CL combination therapies

PROJECT START: June 2015

OVERALL OBJECTIVE: Develop an improved treatment for CL based on existing treatments used in combination

2015 OBJECTIVE: Obtain approval of the proposed study

The efficacy of currently available and approved CL treatment approaches (antimonials, miltefosine, and thermotherapy) is approximately 70-75% worldwide. The safety profiles of these approaches when administered alone is very well established. Using a combination of therapies may both improve this efficacy rate and reduce the length of treatment and rate of adverse events. A combination of one single application of thermotherapy at 50°C for 30 seconds with a 3 week course of oral miltefosine will be tested in order to gain information about safety and efficacy, with no anticipated safety problems and in a short period of time. The study protocol was finalized and submitted for review by local ethics committees in 2015; approval was received from Peru and Colombia in December 2015. It will be submitted to regulatory authorities in 2016 and patient enrolment is expected to begin the same year.

MAIN PARTNERS: Programa de Estudio y Control de Enfermedades Tropicales, Universidad de Antioquia, Medellin, Colombia; Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, Peru



DEVELOPMENT



New treatments for HIV/VL co-infection for Africa

PROJECT START: September 2011

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

2015 OBJECTIVE: Finalize recruitment into HIV/VL coinfection study and conduct three interim analyses

59 patients recruited at 2 sites

This study, initiated in 2014, aimed to evaluate the efficacy of a combination regimen of AmBisome® with miltefosine, and of AmBisome® (at a higher dose) monotherapy in Ethiopian patients co-infected with VL and HIV. The AmBisome® monotherapy arm was dropped due to lower than expected efficacy at the time of the first interim analysis in April 2015, and recruitment into the remaining combination arm was also interrupted after the 2nd interim analysis in July for the same reason. Efficacy and safety data for the treatment period is currently under analysis. All 59 patients recruited continue the 12 months follow-up with pentamidine prophylaxis. The final clinical trial report is expected in 2016.

In anthroponotic transmission areas (where disease is transmitted by the vector from human to animals), the WHO recommends secondary prophylaxis with drugs not given in treating primary VL cases to avoid resistance development. As part of the Africoleish consortium, the results from a separate study to assess pentamidine as prophylaxis to prevent VL relapses in HIV-VL population demonstrated monthly pentamidine infusions led to lower rates of VL relapses in HIV co-infected patients following one year of treatment.

MAIN PARTNERS: Gondar University Hospital, Ethiopia; Addis Ababa University, Ethiopia; London School of Hygiene and Tropical Medicine (LSHTM), UK; Institute of Tropical Medicine (ITM) – Antwerp, Belgium; Médecins Sans Frontières (MSF), The Netherlands; Uppsala University, Sweden; Gilead Sciences, USA; LEAP; The Netherlands Cancer Institute, The Netherlands; Utrecht University, The Netherlands; BaseCon, Denmark; UBC, Switzerland

New treatments for PKDL for Asia/Africa

PROJECT START: March 2015

OVERALL OBJECTIVE: Evaluate the role of PKDL in transmission and epidemiology of *Leishmania* parasites and to develop a new treatment

2015 OBJECTIVE: Carry out preparations for epidemiological, infectivity, and PK and treatment studies

DNDi is prioritizing the management of PKDL patients who are believed to constitute a reservoir of infection for visceral leishmaniasis in the Indian Sub-continent and East Africa. A synopsis has been developed for a Phase II clinical trial of AmBisome® alone or in combination with miltefosine, to assess the safety and efficacy for the treatment of PKDL patients in India and Bangladesh, and AmBisome® or paromomycin in combination with miltefosine for the treatment of PKDL in Sudan.

An infectivity study will also be conducted in both countries, to explore the role of PKDL as a potential reservoir of *L. donovani* parasites which can be spread by the sandfly. This is of particular concern in the period between epidemics, and the trial aims to ascertain if there is a need for chemotherapy for all PKDL patients to reduce transmission. It also aims to identify immunological biomarkers of infectivity in VL and PKDL cases. In preparation of the study, an insectarium was constructed at the SK hospital in Mymensingh, Bangladesh in 2015.

MAIN PARTNERS: International Centre for Diarrhoeal Disease Research (ICDDR,B), Bangladesh; Rajendra Memorial Research Institute of Medical Sciences (RMRIMS), India; Kala Azar Medical Research Centre, India; Institute of Medical Sciences, Banaras Hindu University, Varanasi, India; Safdarjung Hospital, Delhi, India; Uppsala University, Sweden; Institute of Endemic Disease (IEND), Khartoum University, Sudan; Ministry of Health, Sudan; LEAP



DEVELOPMENT



New VL treatments for Latin America

PROJECT START: February 2011

OVERALL OBJECTIVE: Assess the efficacy and safety of amphotericin B deoxycholate, AmBisome®, and AmBisome® combined with Glucantime®, as compared to the first-line treatment, Glucantime®, for the treatment of VL patients in Brazil

2015 OBJECTIVE: Complete VL trial

378 patients recruited at 5 sites (2 active in 2015)

More than 95% of VL cases in Latin America occur in Brazil, and most of them are children. In 2013, Brazil reported 3,253 new cases with a fatality rate of 6.7%. DNDi is supporting the implementation of a Phase IV clinical trial, sponsored by the Brazilian Ministry of Health, to assess current treatments used for VL in Brazil (Glucantime®, AmBisome®, and amphotericin B as monotherapies, and an AmBisome®/Glucantime® combination proposed by DNDi). In 2014, patient recruitment was stopped based on the interim analysis of 50% of the recruited patients, and the five trial sites concluded six months follow-up of the 378 patients enrolled in the study. Data management and sites close-out were finalized in 2015 and study results show that, although there is no statistically significant difference in efficacy between treatment arms, AmBisome® monotherapy shows a statistically better safety profile in terms of frequency and severity of adverse events, and early treatment suspension due to toxicity. These results, associated with a shorter administration time, suggest that AmBisome® monotherapy would be a more adequate first line treatment of VL in Brazil and in Latin America. All final results will be published in 2016. Follow-up discussions will be held with the Brazilian Ministry of Health and PAHO in 2016 for evidence-based policy changes in the treatment of VL patients in Brazil, and to discuss plans for further studies to improve efficacy with good safety profile for treatment of VL in Brazil. The Ministry of Health already changed treatment recommendations in 2013, expanding the use of AmBisome® monotherapy as a second-line treatment, based on interim safety data provided by the trial.

PARTNERS: BRAZIL: Rene Rachou Research Center – Fiocruz-MG, Belo Horizonte; Paediatric Hospital Joao Paulo II – FHEMIG, Belo Horizonte; Brasilia University; Montes Claros State University; Piaui Federal University, Teresina; Sergipe Federal University, Aracaju; Leishmaniasis Control Programme/Ministry of Health; Universidade Estadual do Rio de Janeiro; Hospital Sao José de Doencas Infecciosas, Fortaleza



IMPLEMENTATION



SSG&PM Sodium Stibogluconate/Paromomycin Combination Therapy

PROJECT START: April 2011

OVERALL OBJECTIVE: Include SSG&PM as the new first line treatment for primary VL in the national guidelines of countries in the region, disseminate results to the region's VL stakeholders and update registration status of SSG&PM

2015 OBJECTIVES: Renew retention of SSG&PM in the register for Kenya and Uganda and register SSG and PM in Ethiopia and Sudan

More than 10,000 patients treated

In 2010, DNDi and LEAP successfully showed that the combination of SSG and PM (17 days) was as efficacious as SSG monotherapy (30 days); this shorter course lessens the burden on patients and health systems, and is more cost effective. WHO recommended SSG&PM combination as first line treatment for primary VL in Eastern Africa in March of the same year, and a large Pharmacovigilance (PV) study was implemented in Sudan, Ethiopia, Uganda, and Kenya between April 2011 and May 2014. The PV study results showed a 95% cure rate at the end of treatment with the SSG&PM therapy with no new safety concerns.

SSG&PM is recommended as first-line treatment for VL in Sudan, Ethiopia, South Sudan, Somalia, and Kenya. SSG&PM has been included in the national guidelines of Sudan, South Sudan, Ethiopia, Somalia, and Kenya, and the guidelines are under review in Uganda. PM is registered in Uganda (2011) and Kenya (2013), and is in the process of registration in Sudan and Ethiopia.

MAIN PARTNERS: Ministries of Health of Uganda, Sudan, Kenya, and Ethiopia; Institute of Endemic Disease (IEND), Khartoum University, Sudan; Kenya Medical Research Institute (KEMRI), Kenya; Gondar University Hospital, Ethiopia; Addis Ababa University, Ethiopia; Arba Minch Hospital, Ethiopia; Makerere University, Uganda; Amudat Hospital, Uganda; LEAP; Médecins Sans Frontières (MSF), Switzerland and Holland; London School of Hygiene and Tropical Medicine (LSHTM), UK; IDA Foundation, The Netherlands

IMPLEMENTATION



New VL treatments - Asia

PROJECT START: July 2010 (Bangladesh)/December 2006 (India)

OVERALL OBJECTIVE: Develop one to two new (combination) treatments and support recommendations from the authorities in the main endemic countries. Provide evidence for adoption of combination treatment as a second line option in national policy in Bangladesh

2015 OBJECTIVE: Advocate for the adoption of combinations as second line treatment in Bangladesh

1,761 patients recruited at 12 sites in India

The Phase III trial conducted in India in 2008-2010 demonstrated the efficacy of combination therapies based on AmBisome[®], miltefosine, and paromomycin, and an additional study by Sundar *et al.* showed the efficacy of single-dose AmBisome[®] given as an intravenous infusion. To facilitate the introduction of these new treatments for VL in South Asia, DNDi conducted safety and effectiveness studies, including a pilot project in the Bihar State of India (2012-2015) implementing combination therapies at the primary healthcare level, and single-dose AmBisome[®] at the hospital level.

These regimes were observed to be safe and effective and, based on the study results, the Indian National Roadmap for Kala-Azar Elimination in August 2014 recommended use of single dose AmBisome[®] as a first option treatment for the

treatment of VL patients, with paromomycin and miltefosine as a second option at all levels; a policy also reflected in Bangladesh and Nepal. This removal of miltefosine monotherapy is an important policy change. The pilot study continued following up patients, documenting 12 month treatment outcomes, at the request of the national programme; this follow up was completed in September 2015. Site close out activities will be completed in January 2016.

In Bangladesh, a two-step Phase III study conducted from 2010-2014 in 602 patients (first in hospital settings, then in primary healthcare centres) used the same combination therapies as those tested in India. All tested treatments demonstrated excellent cure rates and were well tolerated by patients, in support of policy change in the country.

MAIN PARTNERS: INDIA: Indian Council of Medical Research (ICMR); Rajendra Memorial Research Institute of Medical Sciences (RMRIMS); Bihar State Health Society; National Vector Borne Disease Control Programme (NVBDCP); Kala Azar Medical Research Centre; GVK Biosciences; BANGLADESH: Ministry of Health and Family Welfare; International Centre for Diarrhoeal Disease Research (ICDDR,B); Shaheed Suhrawardy Medical College and Hospital; OTHER: Médecins Sans Frontières (MSF), Spain; London School of Hygiene and Tropical Medicine (LSHTM), UK; WHO-TDR, Switzerland; Institute of Tropical Medicine-Antwerp, Belgium





Health workers at the Mizque health care centre, Cochabamba, Bolivia.

› **Chagas disease** is endemic in 21 Latin American countries and in the USA, and is of increasing concern in Europe due to migrant populations. The asymptomatic nature of chronic disease means that it is difficult to know exactly how many people are infected, but current estimates are of 5.7 million people in Latin America alone, indicating that more than 6 million people are likely to be affected worldwide. It is the leading cause of infectious cardiomyopathy in the Western hemisphere. Chagas disease mostly affects those living in poverty, and to date less than 1% of people infected with *Trypanosoma cruzi* have access to diagnosis and treatment, despite the fact that more than one-half of Chagas disease sufferers live in Latin America's wealthiest countries – Argentina, Brazil, and Mexico. The only drugs developed which successfully kill *T. cruzi* parasites are nifurtimox and benznidazole, both more than 40 years old, and although effective, they are used as long treatment regimens and cause frequent side effects. Benznidazole is currently produced in Brazil and Argentina.

The benznidazole/fosravuconazole (E1224) trial carried out by DNDi and partners confirmed the long-term efficacy of benznidazole, although with the already observed side effects, and further trials are planned to evaluate shorter treatment courses and lower doses of benznidazole with and without fosravuconazole, aiming to maintain or increase efficacy and improve safety. In addition, the recently completed Merck-sponsored STOP Chagas trial in adults with asymptomatic chronic disease confirmed the efficacy of benznidazole and the lack of sustained effect by the azole class of compounds as treatment for Chagas. However, the BENEFIT (Benznidazole Evaluation for Interrupting Trypanosomiasis) trial showed benznidazole treatment was not effective in preventing progression of disease in patients with known Chagas cardiac involvement. These

results highlighted the importance of early diagnosis and treatment of Chagas patients. Fexinidazole is also being evaluated in adults with chronic indeterminate disease and early stage drug discovery efforts are aiming to identify entirely new chemical entities for development.

In response to the lack of access to treatments, DNDi proposed a project to assess the feasibility of scaling up treatment and access to benznidazole, in five countries in the Americas. Previous work undertaken has shown an important paradigm shift over the past two years, from discussing vector control to focusing on the urgent need to scale up access to diagnosis and treatment in Latin America. Throughout 2015, DNDi has worked closely with the Colombian Chagas National Control Programme, providing technical support to create the

enabling environment needed to scale up access to diagnosis and treatment for Chagas in Colombia. As a result of meetings and discussions between the Ministry of Health, the National Control Programme, and the Red Chagas Colombia

Improving treatments and access to medicines

programme, a comprehensive roadmap for Chagas has been developed which defines operational interventions – such as implementation of pilot projects in four different regions in the country, registration of benznidazole, and support for validation of a new national diagnostic protocol for Chagas disease – which are due to start in 2016. A project in Mexico will focus on short- and medium-term approaches to further assess the disease burden, raise awareness, and ultimately improve patient access by working with the Ministry of Health and other stakeholders. Furthermore, there is the aim to identify and address barriers to access diagnosis and treatment in the USA, as there are large numbers affected by Chagas disease in areas with large populations from endemic countries – such as in California, Florida, and Texas – who are excluded from the healthcare system.

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

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

What are the current treatments and their limitations?

Current treatments, **benznidazole and nifurtimox**, are effective against the acute phase of infection, and while there is increasing evidence of their efficacy in the chronic indeterminate phase of the disease, broad use of these drugs has been limited due to lack of guidelines and policies supporting implementation. Drawbacks include long treatment periods (60-90 days), dose-dependent toxicity, and a high drop-out rate of patients due to side-effects. There is currently no approved treatment for the chronic form of the disease with target organ involvement (chronic symptomatic stage).

Endemic in
21 countries

IN LATIN AMERICA

70 million
people at risk

5.7 million
people infected,
leading to approximately
7,000 deaths every year

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?

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

As a **medium-term** strategy, DNDi has been assessing known families of compounds, such as nitroimidazoles and the new triazole antifungals, for activity against *T. cruzi* in adult chronic patients. A proof-of-concept trial showed fosravuconazole (E1224) monotherapy did not show sustained efficacy, as measured by sustained parasite clearance one year after end of treatment. In contrast, the current regimen of benznidazole was very efficacious over the period of 12 months of follow-up. Alternative benznidazole regimens, including reduced dosing and duration of treatment in monotherapy, and combination treatment with fosravuconazole, are now being explored.

Fexinidazole, a non-genotoxic nitroimidazole currently in development for HAT and VL, is also being evaluated for treatment of adult indeterminate Chagas disease. Additionally, DNDi continues to search for potential biomarkers of treatment response to enhance clinical trial capabilities for evaluation of new compounds.

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

In addition, DNDi supports clinical research capabilities and access through the Chagas Clinical Research Platform (see p. 60), which was launched in 2009.

Ideally, a new treatment would target **both acute and chronic** phases of the disease, with activity against most parasite species in all endemic regions, with a better **safety** profile than existing drugs and non-inferior **efficacy** to benznidazole, being **easy-to-use** (oral, once-a-day for less than 30 days, requiring no hospitalization, and little or no monitoring), **affordable**, and **adapted to tropical climates**.

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

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

RESEARCH



Nitroimidazole

PROJECT START: April 2012

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

An opportunistic approach was undertaken to assess compounds issuing from the VL-2098 back-up programme (nitroimidazooxazine series) showing activity against *T. cruzi* *in vitro*, evaluating the most promising candidates in *in vivo* models of Chagas disease. Given the ongoing clinical development of fexinidazole for Chagas disease, further progression was put on hold and will only recommence if a need arises.

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

Chagas H2L (Chagas Hit to Lead)

PROJECT START: On-going

OVERALL OBJECTIVE: Identify new leads series from current ongoing Hit-to-Lead activities to move them into lead optimization

2015 OBJECTIVE: Identify new chemical series to progress into Hit-to-Lead and lead optimization stages

Multiple hits from screening with several pharmaceutical partners or from other sources have been progressed into hit confirmation and expansion studies. Several promising series, issued from the published hit list from "GSK kinetoplastid Boxes" and Celgene, have been identified and are currently moving into the hit-to-lead stage; one series showed Proof of Principle *in vivo* and is in Lead Optimization. In order to identify hit series with a different mechanism of action, the screening cascade has been modified to filter out potential CYP51 inhibitors (same mechanism of action as posaconazole or ravuconazole), and prioritizing trypanocidal compounds early on. The insights gained from additional *in vitro* assays, coupled with a new *in vivo* model based on BioLuminescent Imaging, was developed at the LSHTM. The model predicts the outcome of benznidazole and posaconazole in clinical trials, enabling compounds to be moved forward with more confidence.

Opportunities for new candidates to include in the pipeline are continually under review. Preliminary mapping and set-up of discovery activities are continuing in Latin America in accordance with the global DNDi strategy of empowerment of and funding from the regional offices.

MAIN PARTNERS: Centre for Drug Candidate Optimization, Monash University, Australia; Epichem, Australia; Griffith University, Australia; London School of Hygiene and Tropical Medicine, UK; WuXi AppTech, China; LNBio/CNPEM, Brazil; University of Campinas (UNICAMP), Brazil; AbbVie, USA; Sanofi, France; Sandexis, UK; Laboratory of Microbiology, Parasitology and Hygiene, University of Antwerp, Belgium; TCG Life Sciences, India; AbbVie, USA

TRANSLATION



Biomarkers

PROJECT START: 2010

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

2015 OBJECTIVES:

- Follow-up validation and characterization studies on selected markers identified through proteomic-based platforms and other studies
- Progress Non-Human Primate Study through 12 month assessment and immunosuppression phase

DNDi has been seeking to identify and/or evaluate biomarkers of therapeutic response to treatment, as the only measurable outcomes to date have been clinical benefit and seroconversion, and, with the exception of children, the latter can take several decades. The initial focus has been on optimizing blood sampling procedures and validation of DNA quantification through polymerase chain reaction (PCR), one of the key outcome measures in use for clinical trials in Chagas disease. The assessment of proteomic signatures in serum samples from nifurtimox-treated Chagas patients previously led to the identification of possible biological markers of therapeutic response. Children show faster seroconversion than adults. In 2015, analysis of sera from children treated with benznidazole was undertaken in order to evaluate a potential correlation between seroconversion and the presence or absence of biological markers. Early indications are that these can be used to classify patients as cured or not, and results of confirmatory experiments are expected in 2016.

DNDi is collaborating with the University of Georgia and the Texas Biomedical Research Institute in a Wellcome Trust funded, non-human primate study in naturally infected animals with chronic Chagas disease, to further determine PCR and other markers as sensitive tools to consistently differentiate parasitological cure from treatment failure. The dosing period of the non-human primate study in naturally infected animals with chronic Chagas disease ended in 2015, and a 12-month follow-up assessment was completed in August 2015. The study immunosuppression phase was initiated in October 2015 and will end in mid-2016, at which point blood and tissue sample PCR and assessment of other biomarkers will be undertaken to determine if they can differentiate parasitological cure from treatment failure.

DNDi is a member of the NHEPACHA network of investigators created for the long-term cohort evaluation of potential biomarkers.

MAIN PARTNERS: Texas Biomedical Research, USA; University of Georgia Research Foundation, USA; McGill University, Canada; 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 Texas at El Paso, USA; National Council of Scientific and Technological Research (INGEBI-CONICET), Argentina; NHEPACHA network; Universidad San Martín, Argentina

DEVELOPMENT



New benznidazole regimens/ combinations

PROJECT START: December 2013

OVERALL OBJECTIVE: Develop a new improved regimen of benznidazole and a benznidazole/fosravuconazole combination treatment regimen for chronic Chagas disease

2015 OBJECTIVE: Initiate plans for Phase II studies for simpler benznidazole monotherapy regime or in combination with fosravuconazole



Benznidazole, the standard treatment for Chagas, had sustained efficacy until 12 months post-therapy, but was associated with side effects that resulted in treatment discontinuation. A proof-

of-concept trial carried out in 2013 showed that fosravuconazole (previously known as E1224) had good safety and was effective at clearing the parasite, but efficacy was not sustained. A Phase I drug-drug interaction study, undertaken in 2014 in 28 healthy human volunteers in Buenos Aires, Argentina, assessed the safety and pharmacokinetic interactions of fosravuconazole and benznidazole administered separately and in combination: no major clinically relevant safety or tolerability issues were identified. A proof of concept study in approximately 270 patients with chronic Chagas disease will determine if the safety and tolerability issues of benznidazole can be managed by reduced doses and treatment duration, or by combining it with fosravuconazole. The protocol for this study, composed of eight arms with benznidazole in monotherapy or in combination with fosravuconazole at selected doses and treatment durations versus placebo, was finalized in 2015. Sites in Argentina, Bolivia, and Spain were identified, and patient recruitment is expected to start in 2016.

MAIN PARTNERS: ARGENTINA: Fundación Mundo Sano and ELEA; Administración Nacional de Laboratorios e Institutos de Salud (ANLIS); Instituto Nacional de Epidemiología Dr Fátala Chábén; Instituto de Investigaciones en Ingeniería Genética y Biología Molecular "Dr. Héctor N. Torres" - INGEBI-CONICET; Centro de Chagas y Patología Regional, Hospital Independencia, Santiago del Estero; Fundación Para el Estudio de las Infecciones Parasitarias y Enfermedad de Chagas (FIPEC); BOLIVIA: Collective of Applied Studies and Social Development (CEADES); Universidad Autónoma Juan Misael Saracho; Universidad Mayor de San Simón; SPAIN: IS Global, Centre de Recerca en Salut Internacional de Barcelona (CRESIB); Hospital General de Valencia; SPAIN/BOLIVIA: Platform of Integral Care for Patients with Chagas Disease; JAPAN: Eisai Co. Ltd

DEVELOPMENT



Fexinidazole

PROJECT START: December 2013

OVERALL OBJECTIVE: Evaluate fexinidazole for treatment of chronic Chagas disease

2015 OBJECTIVE: Conclude the 12-month assessments of the PoC Phase II and proceed to the data cleaning and analysis

47 patients recruited at 2 sites

Comprehensive pre-clinical results evaluation of fexinidazole supported its clinical evaluation in patients. A Phase II Proof-of-Concept trial was initiated in adult patients with chronic Chagas disease in Bolivia in 2014, but after recruiting 47 participants, the study was interrupted due to safety and tolerability issues. A safety review did not identify the same frequency or severity of adverse events for fexinidazole when used in other indications. Patient monitoring continued for 12 months post-treatment to assess if there was sustained suppression of parasites as assessed by PCR and the final study results are expected in early 2016.

MAIN PARTNERS: ARGENTINA: Instituto de Investigaciones en Ingeniería Genética y Biología Molecular "Dr. Héctor N. Torres" INGEBI-CONICET; BOLIVIA: Collective of Applied Studies and Social Development (CEADES); Platform of Integral Care for Patients with Chagas Disease, Tarija and Cochabamba; Universidad Autónoma Juan Misael Saracho; Universidad Mayor de San Simón; SPAIN: Centre de Recerca en Salut Internacional de Barcelona (CRESIB)



IMPLEMENTATION



Paediatric Dosage Form of Benznidazole

PROJECT START: May 2011

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

2015 OBJECTIVES:

- Ensure paediatric benznidazole is available in endemic countries in Latin America and together with ELEA
- Submit a regulatory dossier for second source of paediatric benznidazole

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 in children aged 0 to 12 years with Chagas disease was conducted and showed complete parasitic clearance in all children immediately after treatment. Sustained response at 12 months was assessed in a subset of patients with longer follow-up. The study also showed that children have lower

blood levels of benznidazole than previously documented in adults, suggesting that reduced adult dose regimen should be considered for evaluation. An easy to use and adapted paediatric dosage form was developed and registered in Brazil (2011), and subsequently included on the WHO Essential Medicines List for children (2013). The Mundo Sano Foundation and DNDi signed a collaboration agreement (2013) to deliver a second source of the treatment in partnership with ELEA. ELEA produced pilot and scale-up batches in 2014, and stability testing is underway. Submission for marketing authorization was carried out by ELEA in Argentina at the end of 2015, and will proceed in other endemic countries. Through this project, DNDi has also stepped up efforts to support the scale up of treatment with benznidazole for adult patients with Chagas disease.

MAIN PARTNERS: BRAZIL: LAFEPE; ARGENTINA: Fundación Mundo Sano and ELEA; Centro Nacional de Diagnóstico e Investigación de Endemo-epidemias (CeNDIE), Administración Nacional de Laboratorios e Institutos de Salud (ANLIS); Centro de Chagas y Patología Regional, Hospital Independencia, Santiago del Estero; Hospital de Niños de Jujuy; Hospital de Niños Dr. Ricardo Gutiérrez; Hospital Público Materno Infantil – Salta; Instituto Nacional de Parasitología Dr M Fátala Chabén; Ministry of Health; Ministerio de Salud, Provincia de Jujuy





Foot measurement of a lymphatic filariasis patient in Sukala, Satyavadi, Puri district, Odisha, India.

► **The helminth** worms responsible for causing parasitic disease in animals and humans are classified into three species – roundworms or nematodes (including filarial worms and soil-transmitted helminths), flatworms, and flukes. Filarial worms are spread by blood-feeding insect vectors, and invade different parts of the human body causing chronic disease. *Wucheria bancrofti*, *Brugia malayi*, and *B. timori* adult worms invade the lymphatic system, and *Onchocerca volvulus* and *Loa loa* form deep tissue and subcutaneous nodules.

Onchocerciasis is predominantly found in West and Central Africa where it causes river blindness, so-called because the black flies which spread disease breed in fast-flowing rivers and streams, and can produce blindness after many years of chronic infection. Before large control programmes started, blindness was highly prevalent in villages along rivers infested with blackflies, leading to the abandonment of fertile land, and increased poverty. An estimated 37 million people are infected with *O. volvulus* worms, which cause severe itching and may result in blindness or impaired vision.

Lymphatic filariasis (LF) is more widespread, found in tropical areas principally in Africa and Asia. Worms migrate to the lymph glands, resulting in swollen limbs and genitals, a disabling, painful, and highly stigmatizing affliction. Over 67 million people are infected and over 36 million are estimated to be clinically affected by the symptoms.

Loiasis, also known as African eyeworm because of the migration of the adult worm through the conjunctiva, has less direct impact, with symptoms not considered to be as severe. But loiasis infection has important implications

for LF and onchocerciasis control programmes using preventive mass drug administration (MDA) chemotherapy, as serious adverse events can occur in co-infected patients.

MDA programmes depend on donations from pharmaceutical companies, and although the drugs are effective in killing the different juvenile worms (microfilariae) of the *O. volvulus*, *W. bancrofti*, and *Brugia* worms, they do not kill adult worms (macrofilariae) which continue to reproduce during most of their long lifespan. MDA chemotherapy therefore needs repeating once or twice annually for over a decade. A short-course treatment that kills adult worms is needed to cure patients, and may also be useful in reducing the number of cycles of MDA to achieve disease control or elimination.

DNDi is aiming to develop a safe and effective field-adapted macrofilaricidal drug with its partners, based on drugs used to

treat animal helminth infections. A parallel approach is to target *Wolbachia*, a symbiotic intracellular bacterium present in *Onchocerca*, *Wucheria*, and *Brugia* worms, aiming to identify drugs which kill the *Wolbachia* and impact worm survival and reproduction.

The year 2015 was a defining one for filarial diseases. In October, one half of the Nobel Prize for Medicine was awarded jointly to William Campbell and Satoshi Omura for their discovery of the antifilarial drug ivermectin, used in MDA programmes. Meanwhile, the 20-year old African Programme for Onchocerciasis Control, considered to be one the most successful public health initiatives ever, closed at the end of the year. While both milestones bear testament to the progress made in treating these diseases, millions of people remain affected and in need of a curative treatment.

Treatments are needed for juvenile as well as adult worms

What are the current treatments and their limitations?

Current treatments for onchocerciasis and lymphatic filariasis are based on repeated mass drug administration (MDA) of antiparasitic drugs through programmes directed by the WHO. WHO recommends MDA for onchocerciasis at least once yearly for 10-15 years, and for lymphatic filariasis once yearly for at least five years. The drugs used in MDA programmes are **ivermectin** for onchocerciasis; **albendazole** for lymphatic filariasis; and **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).

A bite from an infected insect allows filarial larvae to pass into the blood and migrate through the human body. These mature into adults that produce microfilariae, which the insect ingests during a blood meal, and the cycle goes on. MDA drugs can prevent this vector-borne transmission for several months by killing mainly the microfilariae, and inducing a temporary sterilization of adult worms. However, because adult worms (macrofilariae) 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.



Ivermectin treatment is safe and has been used widely in MDA programmes. However, the use of ivermectin in patients co-infected with high levels of *Loa loa* microfilaria in the blood can result in safety issues such as the occurrence of encephalopathy that can be fatal if not properly managed. Additionally, a suboptimal response to ivermectin in patients with onchocerciasis has been reported which may be a sign of resistance development. Furthermore, the morbidity associated with onchocerciasis and LF infection (itching, dermatitis, lymphedema, and blindness) are only partially improved or prevented and require repeated treatment with the current drugs.

ONCHOCERCIASIS

37 million infected worldwide, with 99% cases in

31 African countries

746,000 visually impaired

265,000 blinded and more than 4 million suffering from severe itching

169 million were estimated at risk in 2014

LYMPHATIC FILARIASIS

Over **1.1 billion** people at risk worldwide, 57% in South East Asia region

Over **36 million** suffering from clinical illness (19.4 million with hydrocele, and 16.6 million with lymphedema)

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?

DNDi's strategy is to develop a new compound with macrofilaricide activity (to kill adult worms) for use as a safe and field-adapted macrofilaricidal drug for patient case management and possibly later MDA if needed.

As a **medium-term strategy**, DNDi is assessing emodepside which is commercialized by Bayer under license from Astellas as an anthelmintic veterinary drug for cats and dogs in combination with praziquantel (Profender®) and in combination

with toltrazuril (Procox®). DNDi has an agreement with Bayer to develop emodepside for the treatment of onchocerciasis.

Other compounds targeting *Wolbachia*, a worm symbiotic bacteria present in the parasites causing onchocerciasis and LF, will also be explored.

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.

DNDi aims to deliver a **safe, efficacious, affordable, and field-adapted macrofilaricidal drug** for onchocerciasis and/or lymphatic filariasis for the treatment of patients, and as a **possible alternative in mass drug administration programmes**.

TRANSLATION



Macrofilaricide 2

PROJECT START: March 2015

OVERALL OBJECTIVE: Develop a macrofilaricide effective against worm-symbiotic *Wolbachia* bacteria

Two derivatives of a veterinary antibiotic, which target the worm-symbiont *Wolbachia* bacterium, are currently in development for treatment of filarial diseases. These compounds can be delivered orally, induce a robust anti-*Wolbachia* effect in several *in vivo* models, demonstrate clear superiority over doxycycline, and are effective after a shorter dosing regimen. Preliminary safety and toxicology profiling of these compounds carried out in 2015 suggests a favourable safety profile. Upon successful completion of the necessary toxicology studies, expected in 2016, and development of an oral formulation, a Phase I single rising dose study in healthy human volunteers will be performed to determine the safety, tolerability, maximum tolerated dose, and pharmacokinetics of single oral doses of the selected compound. If appropriate pharmacokinetic characteristics are demonstrated and are suggestive of sufficient therapeutic margins, the safety, tolerability, and pharmacokinetics of multiple ascending doses of an oral formulation of the compound will be determined. To demonstrate proof of concept for filarial disease, a Phase Ib programme will be conducted in patients. This programme will be designed to provide data on which a collective decision can be made to proceed into Phase II studies in patients with either onchocerciasis or lymphatic filariasis.

MAIN PARTNERS: AbbVie, USA; Liverpool School of Tropical Medicine, UK



Emodepside

PROJECT START: March 2013

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

2015 OBJECTIVES:

- Complete pre-clinical package for first-in-human study
- Progress emodepside into first-in-human study

Emodepside is a semi-synthetic product (originated by Astellas and out-licensed to Bayer for animal and human use); its precursor is synthesized by a fungus living in the leaves of *Camellia japonica*. It is a potent antihelminthic drug used in combination with praziquantel (as Profender®) and in combination with toltrazuril (as Procox®) for the treatment of parasitic worms in cats and dogs. DNDi and Bayer Pharma AG are jointly developing emodepside for the treatment of onchocerciasis patients. DNDi will be responsible for the pre-clinical and clinical development of emodepside and Bayer for the pharmaceutical development, manufacturing, registration, and supply of the drug at the lowest sustainable price. The pre-clinical package to start Phase I studies was completed and recruitment into a single-ascending dose study was initiated in December 2015.

MAIN PARTNER: Bayer HealthCare, Germany

Filling knowledge gaps

As is frequently the case with neglected diseases, there are a number of knowledge gaps. DNDi partners are carrying out modelling studies aiming to quantify and characterize the future needs of patients suffering from onchocerciasis and lymphatic filariasis, and to provide information on the size and profile of target populations for the new treatments in development. There is also a need for reliable biomarkers of disease evolution which can assess the effect of new treatments as an alternative to existing invasive skin biopsies and nodulectomies. A new medical optical imaging technique is being evaluated, which aims to find an optical signature of live versus dead *O. volvulus* worms in subcutaneous nodules.

PARTNERS: Erasmus University, the Netherlands; CEA-LETI⁽¹⁾, France; REFODTE, Cameroon; Institut de Recherche pour le Développement, France.

(1) LETI a French state-owned research entity, (Commissariat à l'énergie atomique et aux énergies alternatives (CEA), Laboratoire d'Électronique et de Technologies de l'Information (LETI).



A mother of an HIV+ baby boy administering him bitter tasting ARV medication, Belville South, Cape Town, South Africa.

► **HIV** continues to be a major public health problem worldwide, particularly in sub-Saharan Africa, even though international efforts to combat HIV/AIDS since the turn of the millennium have led to an overall decrease in the number of new cases diagnosed and in the number of AIDS-related deaths. Children are the worst affected, and the majority of babies born with HIV are still not diagnosed or treated. Of the approximately 2.6 million children currently living with HIV, only 32% receive treatment. Although efforts in preventing mother-to-child transmission should reduce the market size of paediatric HIV in the long term, the increased testing of pregnant women and their children is paradoxically expected to increase the paediatric market in the short to medium term, and the need for paediatric treatment will continue to increase until at least 2020. Antiretroviral therapy is not able to cure the disease and needs to be taken for life, but it can control the virus and enable the patient to live a healthy life. Early treatment is essential, as without it 50% of children infected will die before their second birthday, and 80% before their fifth. Adapted paediatric treatments are needed for infants and young children that are safe, efficacious, and easy for the child to swallow, thus ensuring their best chance of survival to adulthood. Children in Africa are frequently also co-infected with

tuberculosis (TB), so HIV and TB treatments need to be compatible.

Antiretroviral treatments typically combine three or more drugs with different modes of action. The only approved protease inhibitor for young children, lopinavir boosted with ritonavir (LPV/r), comes as an unpleasant tasting oral solution with a high alcohol content. It also requires refrigeration, is difficult to store due to its large volume, and expensive, making it unsuitable for resource-

poor settings. DNDi and partners have been working on developing a taste-masked, solid LPV/r oral formulation adapted for infants and young children, which would ultimately be combined with two nucleoside reverse transcriptase inhibitors (NRTIs) into a single '4-in-1' unit or capsule.

As a first step, LPV/r has been formulated into pellets by Cipla Ltd., which received the U.S. Food and Drug Administration (FDA) tentative approval for use in June 2015. These pellets can be sprinkled onto food, are alcohol-free, do not require a cold chain, and are cheaper to transport, although they still have an unpleasant taste. As such, the formulation provides a better treatment option for children and is currently undergoing evaluation in DNDi's LIVING study in Africa, which will give valuable information on its use under normal living conditions.

Developing treatments for children living with HIV/AIDS

What are the current treatments and their limitations?

The 2013 WHO guidelines recommend early diagnosis and immediate treatment of HIV-positive infants and children under the age of five, regardless of immunological status; infants under the age of three should be treated with an antiretroviral treatment (ART) combination that includes protease inhibitors, regardless of whether they have been exposed to ARVs, for the prevention of mother-to-child transmission (PMTCT).

The combination of a **boosted protease inhibitor (PI) with two nucleoside reverse transcriptase inhibitors (NRTIs)**, ABC + 3TC or ZDV + 3TC, is considered by the WHO as the most effective first-line therapy for infants and children.

However, this combination therapy is not being widely used. According to a WHO survey performed in 45 countries, in 2010 only 12.2% of children with HIV were receiving a first-line treatment containing 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 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 with TB and HIV in infants and children are high. Drug-drug interactions between PIs in particular and rifampicin, one of the drugs used to treat TB greatly diminish the blood levels of PIs and hinder the efficacy of the antiretroviral (ARV) treatment. In order to counteract this interaction, extra ritonavir (RTV) needs to be added to the standard proportion of LPV/r. This is called 'superboosting'. The currently available ritonavir formulation suffers the same limitations as the current formulation of RTV with regard to taste, high alcohol content, and logistical constraints imposed by its short shelf-life.

2.6 million
children
below the age of 5
living with HIV/AIDS

More than **86%**
of all new infections in
sub-Saharan Africa

150,000
children
under 15 years of age
died of AIDS-related
illness in 2014
globally

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?

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

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

1. Develop and register **two solid first-line '4-in-1' LPV/r-based fixed-dose combinations (FDCs)** with two NRTIs. All components of the combination will be developed in the form of taste-masked granules, which are stable with no need for refrigeration, presented in a single unit with appropriate strengths to accommodate weight band dosing.
2. **Evaluate the superboosting strategy:** i.e. increasing the LPV:RTV ratio that can effectively and safely 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

Cipla's LPV/r-based pellets before the **'4-in-1' FDC** becomes available, 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 pellets to the LPV/r liquid formulation. These pellets are being used in combination with NRTI dispersible tablets in implementation studies (LIVING study), which started in 2015. In the **longer-term**, DNDi is working with Cipla, its industrial partner, on combining taste-masked LPV/r granules or pellets 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 order to address the needs of **HIV/TB co-infected** children, DNDi aims to assess the addition of ritonavir for superboosting LPV/r at a 1:1 LPV:RTV ratio. DNDi is conducting a study to establish the pharmacokinetics, efficacy, and safety of superboosted LPV/r in children in South Africa with the existing ritonavir solution. Interim results look promising for this approach and the study is being extended to include all solid formulations.

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

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

- Two new **'4-in-1'** paediatric formulations containing a PI (LPV/r) and two NRTIs (ABC or AZT and 3TC)
- One new regimen recommended to treat HIV/TB coinfection

TRANSLATION



Two '4-in-1' LPV/r based FDC granules

PROJECT START: 2012

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

2015 OBJECTIVES:

- Perform pilot comparative bioavailability studies of the most promising taste-masked LPV/r granule or pellet formulations in adult volunteers
- Perform as-needed bioequivalence studies in healthy human volunteers using all components of the '4-in-1' FDC

Pharmacokinetic modelling was carried out to determine drug dosages within potential '4-in-1' formulations, and the proposed dosing for the two '4-in-1' LPV/r based FDCs and RTV booster were incorporated into Annex 7 of the WHO's new Consolidated Guidelines on The Use of Antiretroviral Drugs for Treating and Preventing HIV Infection, under 'urgently needed ARV drugs for children recommended by the Paediatric ARV Working Group' in 2013.

New formulations of LPV/r pellets are required to optimize bioavailability and taste-masking, but this has proved to be very challenging. In 2015, three of the most promising formulations tested in previous *in vivo* studies were assessed, and were found to be highly bioavailable in Phase I studies in man. Additional bioavailability studies and standardized electronic tongue taste-testing (e-tongue) of granules with modified coatings and different polymers will be performed in 2016.

MAIN PARTNERS: Cipla Ltd., India; Department of Health, South Africa; UNITAID; President's Emergency Plan for AIDS Relief (PEPFAR), USA; Médecins Sans Frontières; Necker Institute, Paris; various academic partners in South Africa and Kenya; AbbVie, USA; WuXi AppTech, China



DEVELOPMENT



Superbooster therapy for paediatric HIV/TB co-infection

PROJECT START: 2012

OVERALL OBJECTIVE: Evaluate the pharmacokinetic enhancer/booster formulation to be added to any PI-based paediatric ARV regimen

2015 OBJECTIVES:

- Finish recruitment of the RTV superboosting study performed in South Africa (using LPV/r and RTV originator's liquid formulations)
- Ensure guideline change
- Prepare for the evaluation of superboosting with solid formulations (LPV/r granules/pellets plus RTV solid booster)

96 patients recruited at 5 sites

In Africa, a large proportion of HIV-positive infants and children are co-infected with tuberculosis (TB). Rifampicin is commonly used to treat TB in children, however it has negative interactions with protease inhibitors (PIs) included in treatments used to combat HIV infection: concomitant administration of rifampicin leads to a decrease in LPV/r exposure of up to 90%. To counteract this effect, the amount of ritonavir (RTV) in the LPV/r combination must be quadrupled in a procedure known as superboosting. A stand-alone RTV booster formulation is needed that can be added to any PI-based paediatric ARV regimen. Like LPV/r, RTV has a high alcohol content, is unstable, and completely unpalatable.

A pharmacokinetic study has been carried out in infants and young children co-infected with TB and HIV at five sites in South Africa to supplement existing information and evaluate the effect of the 'super-boosting' strategy. At the end of November 2015 all 96 patients had been included. Interim results show that LPV exposure during TB/HIV cotreatment using the superboosting approach is as good as that when children return to standard LPV/r based therapy. Superboosting was safe and well tolerated. This study is being extended to include all solid formulations. Results were shared with the South African government and WHO to support a change in guidelines for the management of TB/HIV co-infections in children. The South African government changed its guidelines in December 2015 and WHO is expected to do so by summer 2016.

MAIN PARTNERS: Department of Health and Department of Science and Technology, South Africa; Stellenbosch University and Tygerberg Children's Hospital, South Africa; Perinatal HIV Research Unit University of Witwatersrand, South Africa; Shandukani Research Centre, Wits Reproductive Health and HIV Institute, South Africa; Empilweni Services and Research Unit, Rahima Moosa Mother and Child Hospital, South Africa; Enhancing Care Foundation, South Africa; Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, South Africa.

DEVELOPMENT



LPV/r pellets with dual NRTI FDC

PROJECT START: 2014

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

2015 OBJECTIVES:

- Provide early access to the solid LPV formulation
- Gain knowledge on the acceptability of these LPV/r pellets in youngest infants in order to inform the choice of formulations for the '4-in-1s'

18 paediatric patients recruited at 3 sites

Cipla has developed LPV/r pellets in capsules which can be opened and administered orally to small children, allowing the drug to be sprinkled on food and offering the advantage, over the current liquid formulation of these drugs, of being alcohol-free. These pellets do not require a cold chain and are less costly in terms of weight of product for transport; however, their poor taste is still a barrier.

The implementation study aims to provide supportive clinical data on the feasibility, efficacy, safety, and PK of LPV/r pellet-based therapies in routine treatment settings in order to facilitate registration, recommendation in national guidelines, and adoption in treatment programmes in the countries concerned. The LIVING study started in Kenya in September 2015 and is planned to expand to Uganda, South Africa, Tanzania, Zimbabwe, and Zambia in 2016.

MAIN PARTNERS: Joint Clinical Research Centre (JCRC), Uganda; Baylor College of Medicine Children's Foundation, Uganda; Epicentre, Uganda; University of Nairobi, Kenya; Gertrude's Children's Hospital, Kenya; Kenya Medical Research Institute (KEMRI), Kenya; Associated Medical Sciences/PHPT International Research Unit (AMS-PHPT), Thailand; Department of Health, South Africa; Cipla Ltd., India; UNITAID; St Lumumba Health Centre, Kisumu, Kenya; Moi Teaching and Referral Hospital, Kenya; Ministry of Health, Kenya; Clinton Health Access Initiative (CHAI), USA





Rosalyn, Kamaal, and Mohd Rashid Bin Hashim: activists and community leaders living with hepatitis C, at the Hospital Selayang, Batu caves, Selangor, Malaysia.

› **Hepatitis C** causes chronic liver disease, including inflammation, cirrhosis, and hepatocellular carcinoma; an estimated 130-150 million people are chronically infected with HCV worldwide. This blood-borne virus is most commonly spread through unsafe injection practices, inadequate sterilization of medical equipment, and insufficient screening of blood products. HCV can also be transmitted sexually and from an infected mother to her baby, although this is less common. The virus exists with six major genotypes (GTs), but prevalence varies by region with GT1 most prevalent in high-income countries and GT3 in low- and middle-income countries (LMICs).

In the last few years, direct acting antivirals (DAAs) have revolutionized the therapeutic landscape. These well-tolerated oral treatments have a cure rate of 95% or more and are taken once daily for 12 weeks, replacing the less effective regimen of weekly pegylated interferon injections, frequently administered with twice-daily oral ribavirin for up to 48 weeks, a therapy associated with unpleasant side effects. R&D efforts have focused principally on registering a product for the lucrative market in high-income countries, with little data available on efficacy in populations carrying the genotypes that are predominant in LMICs. The price of drugs is a major barrier to treatment access, with sofosbuvir treatment costing \$84,000 in the US, for example, and \$94,000 when combined with ledipasvir.

A drug development strategy based on a public health approach

DNDi aims to meet the specific needs of patients in LMICs by developing a short-course, affordable, highly efficacious, safe, and all-oral pan-genotypic regimen that will enable countries to implement a “public health approach” to the epidemic. It aims to identify and treat not only those in immediate need of therapy but all those infected, in order to prevent the long-term morbidity and mortality associated with HCV, and to reduce further transmission of the virus. This approach will build on the lessons learned from efforts to scale up HIV/AIDS treatment in resource-limited settings, and includes simplified models of care that allow for decentralization to the primary healthcare level, task-shifting of clinical and nonclinical services, and reduced dependence on genotyping and other expensive and sophisticated laboratory monitoring.

In April 2016, in partnership with the governments of Malaysia and Thailand, DNDi and the Egyptian generic drug manufacturer Pharco Pharmaceuticals announced an agreement to test an affordable HCV regimen. Phase III clinical studies will evaluate sofosbuvir plus the drug candidate ravidasvir. The efficacy, safety, and pharmacokinetics of the sofosbuvir and ravidasvir combination will be evaluated in approximately 1,000 patients with various levels of liver fibrosis, different genotypes, and with/without HIV co-infection. The company has also agreed to supply the sofosbuvir plus ravidasvir combination at a price of less than \$300 per treatment course, both for and after the studies, if they are successful.

What is hepatitis C?

Hepatitis C is an inflammatory liver disease caused by infection with the hepatitis C virus (HCV). HCV is transmitted parenterally through exchange of body fluids, mostly through exposure to contaminated blood. Most patients are unaware of their infection status and furthermore, access to treatment remains beyond reach in most developing countries where the burden of disease is the greatest, and no vaccine is available.

The incubation period for hepatitis C infection lasts from 2 weeks to 6 months. Approximately 15-20% of people clear the infection spontaneously. While they have developed HCV-specific antibodies, after a few months HCV RNA can no longer be detected in their blood. However, about 75-85% of newly infected people develop chronic infection; HCV infects their liver cells and can cause severe inflammation of the liver with long-term complications. About 60-70% of chronically infected people develop chronic liver disease; 5-20% develop cirrhosis within the first two decades of infection and 5% liver cancer. In addition to liver disease, HCV persistent infection is associated with chronic fatigue, diabetes, depression, cryoglobulinaemia, and kidney disease.

Due to the high genetic heterogeneity of HCV, it is classified into six major genotypes. Disease expression and response to therapy may vary according to the genotype.

What are the current treatments and their limitations?

Up until 2011, pegylated-interferon with ribavirin was the standard treatment for chronic HCV, but management of the treatment is complex and many patients do not finish their 48-week treatment course because interferon is not well tolerated and can be difficult to access in some settings. Recent scientific advances have led to the development of new antiviral drugs for HCV, **the direct acting antivirals (DAAs)**, which have revolutionized the therapeutic landscape. In recognition of this, in 2016 the WHO updated its treatment guidelines to recommend that DAA regimens be used for the treatment of people with hepatitis C infection rather than regimens with pegylated interferon and ribavirin. DAAs are much more effective (with cure rates of >95% in clinical trials, including in previously hard-to-treat populations), safer, and better tolerated than existing therapies. Their use has simplified HCV treatment by decreasing the duration of treatment, simplifying monitoring and laboratory requirements, and increasing cure rates. However, despite the low cost of production, access to these treatments remains quite limited, due mostly to the high price charged by innovator pharmaceutical companies.

130-150

million people

globally have chronic HCV infection,

of which

85%

live in low- and middle-income countries

2.3

million people

suffer from HIV/HCV co-infection worldwide

500,000

deaths per year

from HCV-related liver diseases

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?

DNDi plans to enable the use of DAAs as a public health tool to treat HCV. A public health approach for resource-limited settings will be taken, including simplified models of care that allow for decentralization to the primary healthcare level, task shifting of clinical and non-clinical services, and reduced dependence on genotyping and other sophisticated lab monitoring.

DNDi is proposing a two-step project with a focus on:

1. Regional research & development (R&D):

In the **medium term**, DNDi and partners will conduct Phase III clinical trials in Malaysia, Thailand, and other countries to test the efficacy of a combination of sofosbuvir (SOF, already registered for HCV) + ravidasvir (RDV, a promising drug candidate) as a pan-genotypic treatment and public health for tackling the HCV epidemic.

2. Support affordable access:

An actively engaged Advisory Group has been created to advise the project on the rapidly-changing HCV treatment access landscape. There are many avenues for access, including but not limited to: developing alternative treatments with favourable licensing/access terms, patent oppositions, compulsory licensing, and voluntary licensing. Multi-stakeholder projects will be piloted in key countries.

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

Evidence for the safety, efficacy, and ease of use of direct-acting antiviral regimens to be used in an affordable combination as a public health approach

DEVELOPMENT



Sofosbuvir/Ravidasvir treatments

PROJECT START: Clinical trial to start 2016

OVERALL OBJECTIVE: Conduct Phase II/III clinical trials to test the efficacy of a combination of sofosbuvir + ravidasvir

OBJECTIVE 2015: Exploratory work

More than 1 million people are estimated to be chronically infected with HCV in Thailand and 400,000 in Malaysia (genotypes 1, 3, and 6). Both countries have been excluded from all global voluntary licensing agreements with drug companies that have developed effective treatments for HCV that include low and some middle income countries. In the short term, DNDi will focus on combining SOF – already registered for hepatitis C – and RDV – a drug candidate developed by Presidio and licensed to Pharco – to evaluate pan-genotypic activity in Thai and Malaysian populations. The study will assess, in real-world settings, the efficacy, safety, tolerability, pharmacokinetics, and

acceptability of a 12-week regimen containing SOF plus RDV in participants infected with HCV, regardless of the HCV genotype, source of transmission (including intravenous drug use), or HIV co-infection, and also in patients with compensated liver disease with or without cirrhosis. For participants with compensated liver cirrhosis, treatment duration will be 24 weeks. A total of 750 subjects will be enrolled, including up to 30% with compensated cirrhosis and up to 20% people who inject drugs, providing data on efficacy and safety of the SOF-RDV combination as well as on treatment compliance.

In 2015 the HCV project was undertaking exploratory work on assessing patient needs and project opportunities, recruitment of patients, and fund-raising.

MAIN PARTNERS: Pharco Pharmaceuticals, Inc., Egypt; Presidio Pharmaceuticals, Inc., USA; Clinical Research Malaysia (CRM), Ministry of Health, Malaysia





Almina, a mycetoma patient, showing her lesions to Prof Fahal and his team at the Mycetoma Research Centre, Sudan.

› **Mycetoma** is a truly neglected disease on every level. Although many suffer from this devastating infection, the global burden of disease is unknown, as those affected live in remote villages in the tropics and subtropics where there is no disease surveillance. The route of transmission is also unknown, and although it is thought that the infection may come from the soil or from animal dung, entering the body after the skin has been pricked, by a thorn for example, there have been no comprehensive studies to prove this theory.

Mycetoma was included in the official list of Neglected Tropical Diseases during discussions at the World Health Assembly in May 2016 – the 18th disease to be included – giving the disease the political prominence it so desperately needs. Such an important step will allow governments as well as other funding bodies to consider providing resources to set up research programmes for the development of new treatments and diagnostics to combat the disease.

Newly recognized as a neglected disease by WHO

What are the current treatments and their limitations?

There are two groups of microbial agents which cause disease. Actinomycetoma – the form caused by filamentous bacteria (actinomycetes) – responds well to antibiotics (amikacin and co-trimoxazole) and has a 90% cure rate. However eumycetoma – the fungal form – develops into a chronic skin infection which, without treatment, invades the surrounding tissue and bone. Children and young adults, particularly men working outdoors, are most at risk.

Early treatment has a higher chance of being effective, but patients live a long way from health centres and tend to present with advanced disease, if at all, by which time antifungal cure is only 25-35% effective. Treatment is most often followed by surgical removal of the remaining mass and there is a high chance of recurrence, often leading to multiple amputations and ultimately the loss of entire limbs, with the associated risk of complications and death. Current antifungals are expensive and cause serious side effects, and an effective, safe, and affordable curative treatment for use in rural settings is desperately needed.

Ketoconazole and **itraconazole** are the antifungal agents that are currently in use, however these have serious side effects. Concerns about liver toxicity have led the FDA and EMA to restrict the use of ketoconazole. Both the duration (twelve months) and cost of treatment are significant barriers to access for patients and health authorities in endemic areas, and as a result drop-out rates are high: at 10,000 USD per annum, the treatment represents between 50-100% of the average annual wage of patients.

A stigmatizing disease

that causes devastating deformities, often resulting in amputation and morbidity.

Basic epidemiological information

is missing for this very neglected disease.

The causative organisms of mycetoma are

endemic in tropical and subtropical areas of the 'mycetoma belt'.

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?

Recognizing an opportunity to test the effectiveness of fosravuconazole in treating mycetoma after experience with this drug as a Chagas agent, DNDi included its clinical testing for the disease in its Business Plan 2015-2023 as a short-term, pragmatic, mini-portfolio approach, and in 2016 will begin a clinical study in partnership with the Mycetoma Research Centre in Sudan.

DEVELOPMENT



Fosravuconazole

PROJECT START: September 2015

OVERALL OBJECTIVE: Conduct a randomized controlled clinical trial to investigate the efficacy of fosravuconazole compared to the current treatment, itraconazole.

Treating eumycetoma is a challenge. Currently, the antifungals ketoconazole and itraconazole are the only therapies available but these are expensive, ineffective, and have serious side effects. Patients often have to undergo amputation, and often more than once, sometimes resulting in death. Safe, effective antifungal agents that are appropriate for use in rural settings are urgently needed.

Fosravuconazole (E1224), an orally bioavailable azole that is under development for Chagas disease, may be an effective and affordable treatment for eumycetoma. Fosravuconazole, a prodrug, is rapidly converted to ravuconazole, which has been shown to have potent *in vitro* activity against one of the causative agents of eumycetoma, *Madurella mycetomatis*. Its pharmacokinetic properties are favourable and its toxicity is low. A randomized controlled trial will be conducted with the WHO Collaborating Centre on Mycetoma in Khartoum to study the efficacy of fosravuconazole in moderate lesions in comparison with the current treatment, itraconazole. The primary objective of this double-blinded, randomized, single-centre study (with an interim analysis at three months) will be to demonstrate superiority of fosravuconazole over itraconazole after 12 months treatment. The study is due to begin in 2016.

MAIN PARTNERS: Eisai Co. Ltd, Japan; Erasmus Medical Center, The Netherlands; Radboud University Medical Center, Nijmegen, The Netherlands; Mycetoma Research Centre (MRC), Soba University Hospital, Khartoum, Sudan; Institute of Endemic Diseases (IEND), Khartoum University, Sudan



Mustafa Alnour Athassan, a young university student aged 26, with mycetoma, sitting on the rickshaw he took to the Mycetoma Research Centre (MRC) in Khartoum, Sudan. Despite the treatments he received, the flesh-eating fungal disease continued to progress and his leg was amputated in July 2015. The disease unfortunately spread to his groin and lungs. He died in March 2016.





ASAQ and ASMQ, the two antimalarial treatments developed by DNDi and partners.

► **ASAQ and ASMQ**, fixed-dose combinations of artesunate (AS) with amodiaquine (AQ) or mefloquine (MQ), were the first projects to be undertaken by DNDi; their development was based on WHO recommendations for artemisinin-combination therapies to treat malaria in 2001. Their development was overseen by the Fixed-Dose Combination Therapy (FACT) Consortium, formed in 2002, with the aim of developing field-adapted formulations that would be easy to administer to all age/weight categories of patients, but particularly infants and young children, and which were able to withstand tropical conditions.

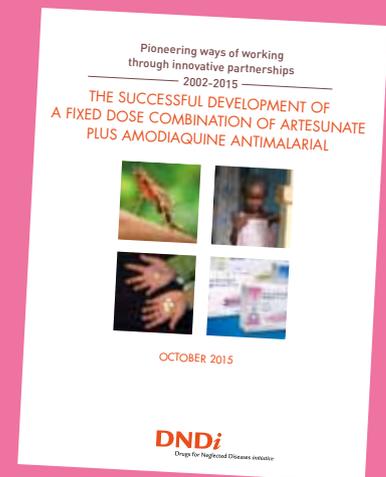
ASAQ-Winthrop®, a generic fixed-dose combination (FDC) of ASAQ, was the first product launched by DNDi in 2007 and was followed by ASMQ FDC the following year. Both feature on the WHO Essential Medicines Lists for adults and children.

The malaria projects were formally handed over to Medicines for Malaria Venture in May 2015, who will continue to implement these treatments in the field. Sanofi produces the generic ASAQ-Winthrop® in Morocco, and a commercial version, Coarsucam™. DNDi is finalizing the technology transfer of ASAQ-Winthrop® to a second manufacturer based in Tanzania, Zenufa, and an application for WHO prequalification will be submitted in 2016. Cipla Ltd., in India, manufactures prequalified

ASMQ FDC, following a successful technology transfer from the Brazilian manufacturer Farmanguinhos/Fiocruz. The shelf-life under tropical conditions for both products was extended from two to three years in March 2016.

By the end of 2015, more than 437 million treatments of ASAQ FDC produced by Sanofi had been distributed, and over 900,000 treatments of ASMQ FDC.

An innovative approach for the successful development of patient-adapted treatments



In 2016 DNDi published an analysis of the lessons learned during the development of ASAQ FDC. The development of ASAQ FDC was characterized by innovation in its development approach (with public and private partners), formulation development, partnership with a major pharmaceutical company, implementation strategy, Risk Management Plan, and choice of a regulatory strategy.

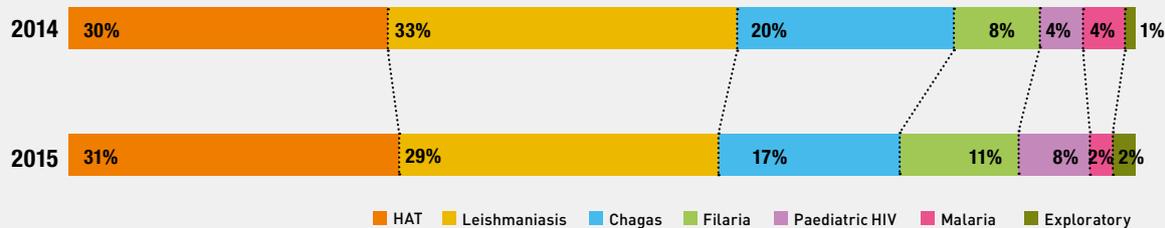
The document reviews the development of ASAQ FDC, and forms part of a broader reflection on DNDi's business model and the lessons learned over a decade since its creation in 2003.

1. www.dndi.org/ASAQreport



EUR 32.7 million: moving toward a more dynamic R&D portfolio while maintaining a robust Kinetoplastids disease pipeline

R&D EXPENDITURE BY DISEASE (2014-2015)



Overall R&D expenditures (EUR 32.7 M) increased by 18% (EUR 5.1 M) compared to 2014.

Percentage breakdown highlights of 2015 R&D expenditures per disease (screening and lead optimization expenditures are split and allocated towards disease expenditures)

• **Kinetoplastids diseases** remain at the heart of the portfolio with 77% of the expenses:

Human African trypanosomiasis (HAT)

With a total of EUR 8.7 M, HAT represents the most substantial R&D expenditure (31%). Investments increased due to the growth in clinical activities for fexinidazole (+EUR 1.6 M), with the Phase IIb/III clinical study and the two additional cohorts (for stage 1 & early stage 2 and for children) with 10 operational sites in the DRC plus the preparation of three new clinical trial sites. The SCYX-7158 project completed Phase I, with Phase II/III now being prepared (writing synopsis, getting scientific advice from EMA, meeting with CARSAC (Cameroon) to present and evaluate the protocol, and finally submission to the Ethics Committee in the DRC). More details on page 25, "Development".

Leishmaniasis

Overall expenditures remained stable between 2014 and 2015 at EUR 8.4 M. Some projects are entering into the portfolio or progressing, such as the preclinical work for VL with DNDI-0690 (+EUR 0.4 M), the CPG for CL project (+EUR 0.1 M), the preparation of clinical trial study for PKDL treatment (+EUR 0.1 M), the combination fexinidazole/miltefosine project, and the completion of the recruitment of 30 patients for the Miltefosine Allometric Study (+EUR 0.4 M). Other projects are completed, such as the preclinical package for VL-2098 (-EUR 0.7 M) and the VL Combo study in Asia (-EUR 0.2 M), or progressing in a different phase, like the VL India implementation (-EUR 0.2 M).

Chagas disease

Projects remained stable in 2015 (- EUR 0.2 M), accounting for a total of EUR 4.8 M (17%) of R&D expenditure. The screening and lead optimization work toward Chagas disease increased by EUR 0.7 M. The Chagas access projects (+EUR 0.2 M) are developing activities in Latin America and North America. The completion of the study of fexinidazole for Chagas and the closure of the E1224 project incurred a decrease of EUR 0.7 M. The biomarker project was put on hold due to safety issues at the end of 2015, which entailed a budget decrease of EUR 0.4 M.

• **Portfolio expansion:** The three new disease and exploratory areas represent 23%, compared to 17% in 2014. Their increase (+EUR 2.3 M, +55%) is the most significant of the DND portfolio.

Filaria

Project expenditures increased by 66% (+EUR 1.2 M). Screening work is ongoing and increased (+EUR 0.2 M) as well as the preclinical activities (+EUR 0.3 M), with two new candidates (oxfendazole and TylAMac). The flubendazole project was however closed in early 2015 (-EUR 0.8 M). The main increase is related to the Phase I for emodepside (+EUR 1.5 M).

Paediatric HIV

Project expenditure increased by 108% (+EUR 1.1 M). The implementation study for a "4-in-1" product (+EUR 0.3 M) is developing with three countries and 9 sites involved in the project, and 49 patients recruited in January 2016. The clinical 'superbooster' study (ritonavir for super boosting LPV/r) in South Africa (+EUR 0.1 M) is ongoing with the purchase of equipment (+EUR 0.7 M) for the formulation development of the "4-in-1" with Cipla Ltd as an industrial partner to enable the production of treatments for the implementation study.

Malaria

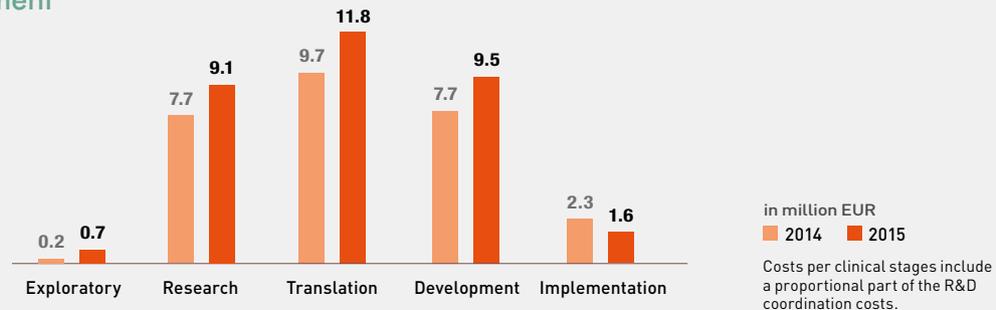
Handover to MMV is complete (-EUR 0.5 M), however the ASAQ technology transfer was still ongoing in 2015.

Dynamic portfolio - Exploratory and feasibility studies

Based on the new business plan objectives, and as a part of the 'dynamic portfolio' concept, various feasibility studies were undertaken in 2015 to evaluate the possibility of adding new projects to the portfolio, including for hepatitis C, anti-infectives, and mycetoma (+EUR 0.5 M).



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



Overall R&D expenditure increased by 18% between 2014 and 2015 to reach a total of EUR 32.7 M.

The most important fluctuation relates to growth of development projects (+23%), and the progress of translational projects including pre-clinical, Phase I, and Phase IIa/proof of concept (+22%). The R&D coordination & supervision costs (EUR 4.3 M) are included proportionally in the R&D expenditure per stage (+EUR 1.2 M).

Implementation

Projects costs decreased by 31% (-EUR 0.7 M) in 2015 compared to 2014.

With six projects in implementation (the first one entered in 2007), four projects are now terminated:

ASMQ for Malaria, NECT for HAT, and SSG&PM combination therapy for VL in Africa were finalized in 2014, with some expenses related to publication still ongoing (-EUR 0.4 M). The paediatric benznidazole for Chagas project was closed in 2015 (-EUR 0.1 M). The activity of New Treatments for VL in Asia is decreasing since the adoption of the treatment policy by the Indian Ministry of Health (-EUR 0.2 M).

Development

Projects costs increased by 23% (+EUR 1.8 M) in 2015 compared to 2014.

This progression is mainly due to the clinical activities for fexinidazole for HAT in the DRC. 88% of data concerning the 359 patients included in the fexinidazole Phase II/III clinical study have been cleaned. The complementary cohort trials, for stage 1 and early stage 2 in adults completed recruitment, with 230 patients and 95% of data cleaned. The clinical trial with children aged between 6 and 14 years completed recruitment, with 125 patients (last patient included mid-January 2016) and 95% of data cleaned. A total of 714 patients are thus included in the three clinical trials. Expenditures related to the HIV/VL co-infection and the new VL treatment in Latin America projects remain stable.

Translation

Leveraging partners' resources

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

The cumulated in-kind contribution over nine years amounts to EUR 30.3 M, reflecting DNDi's investment in building strong partnerships. The 11% increase in 2015 compared to 2014 (+EUR 0.3 M) is largely due to the support from several pharmaceutical companies towards the NTD Drug Discovery Booster experiment.

DNDi has access to pharmaceutical libraries that will allow the development of innovative medicines with new chemical entities. The pharmaceutical companies provide compound libraries for screening and lead optimization at no cost. It is difficult for companies to value such contributions given the number of internal and external collaborators involved in this important effort and the existence of many indirect and intangible contributions.

To illustrate this contribution, the total number of compounds screened in 2012, 2013, 2014, and 2015 was consolidated and compared; it showed an increase of 76% between 2014 and 2015 with 300,000 compounds

Expenditures increased by 22% (+EUR 2.1 M) in 2015 compared to 2014.

The three main drivers of this growth are the following:

- the paediatric HIV projects (+EUR 1.1 M), with development work including the bioequivalence CMC work, and equipment purchase with Cipla in order to select the best formulation for the "4-in-1";
- the filarial portfolio (+EUR 1.2 M), with the first-in-human Single Ascending Dose Study (SAD), the emodepside study, and the on-going evaluation - via pre-clinical activities - of opportunities from partners, including rifampicin, oxfendazole, and TylAMac;
- and the fexinidazole projects for Chagas disease: the Phase II study is on hold (-EUR 0.6 M), while the fexinidazole/miltefosine combination for VL in phase II is ongoing (+EUR 0.4 M).

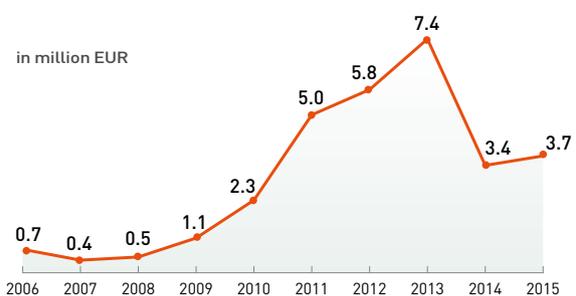
Research

Screening and lead optimization expenditure increased by 18% (+EUR 1.4 M) in 2015 compared to 2014.

This was mainly due to more work on PK, chemistry, efficacy studies, API scale up, and exploratory toxicity studies (+EUR 0.9 M). In addition, three series were in late-stage lead optimization instead of the usual two series and candidate selection stage [DNDi-0690; DNDi-6148]. The NTD Drug Booster project was also implemented during the entire year (+EUR 0.3 M) and a special effort was made for the Lead Optimization Latin America programme (LOLA), with an increase of chemist FTE from 1 to 4 during the last part of the year (+EUR 0.2 M). Screening and lead optimization efforts were entirely redirected towards leishmaniasis and Chagas disease.

Exploratory

In relation to the new business plan launched in 2015, exploratory activities were implemented for hepatitis C, mycetoma, and anti-infectives (+EUR 0.5 M).



screened (representing a total of more than 820,000 wells) in priority against visceral leishmaniasis and Chagas disease.

By the end of 2015, 34 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.