

# 2017 disease & project updates

## **39 ongoing projects on 7 diseases**

Read on for more information on our R&D portfolio across seven disease areas: sleeping sickness, leishmaniasis, Chagas disease, filarial diseases, mycetoma, paediatric HIV, and hepatitis C. This section shares the impact of these diseases on patients, and provides an overview of the disease burdens and treatment gaps, followed by a 2017 update on our 39 active projects (from research to development), acknowledging our many partners.



# Leishmaniasis



“

*There is so much prejudice against the disease. One day, when I was sick, a woman even refused to get in the same bus as me.*”

Moacir

**Moacir** in his garage, living with the disease for the past 26 years, Brazil

An unusual case, Moacir has had cutaneous leishmaniasis in its most aggressive form for over 26 years. His feet were so badly affected that he couldn't wear shoes on his wedding day, so he and his wife decided to get married barefoot. The whole family is affected by the social stigma of his disease.

Moacir has gone through countless treatments and suffered greatly from drug toxicity, including a heart attack, loss of one kidney, and high blood pressure. He continues to relapse.

Until recently, pentavalent antimonials like sodium stibogluconate (SSG) were the mainstay of treatment for VL and CL despite numerous drawbacks (toxic, difficult to administer, expensive, and even poorly effective in many regions).

Alternatives exist for VL, partly thanks to DNDi's work to optimize regimens based on existing medicines. As a result, the shorter combination of SSG with paromomycin is now the standard VL treatment in East Africa, while single-dose AmBisome is the first-line treatment in South Asia, with paromomycin-miltefosine as second line. These treatments are better than SSG monotherapy, but they remain sub-optimal, as they still have issues with toxicity, administration, affordability, and

access. The ongoing need for effective new treatments that are safe and (ideally) all-oral remains the basis for DNDi's long-term R&D strategy.

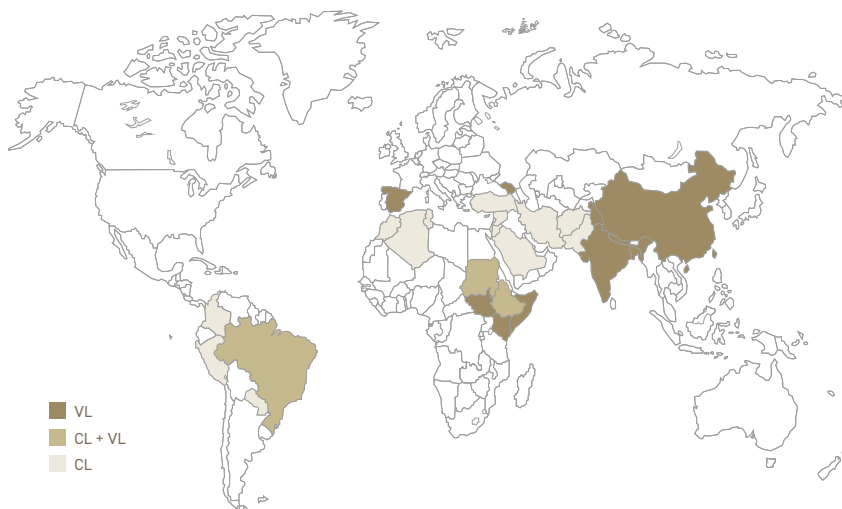
Research needs in leishmaniasis are further complicated by specific unresolved scientific questions. While the VL case load is falling to such a degree that elimination targets appear to be within reach in South Asia, the role in *Leishmania* transmission played by PKDL patients and possibly asymptomatic carriers must be clarified if elimination is to be sustained. Better treatments also need to be developed for patients co-infected with HIV, as current options are unsatisfactory, requiring long and often repeated courses of treatment, due to a high risk of relapse.

- Parasitic disease transmitted by sandfly bite
- Leishmaniasis can be zoonotic (transmitted from animals to humans) or anthroponotic (humans are only a reservoir), depending on the *Leishmania* parasite
- Multiple forms, including: visceral (VL), also known as kala-azar, fatal without treatment; cutaneous (CL); mucocutaneous (MCL); and post-kala-azar dermal leishmaniasis (PKDL), mostly affecting individuals after treatment for VL
- PKDL may play a role in disease transmission
- Children represent a significant proportion of VL patients
- VL in people living with HIV is a growing concern
- Treatment depends on disease type, co-infections, parasite species, and geography

**1** BILLION people around the world at risk

**50,000–90,000** new cases of VL annually

**20,000–30,000** deaths due to VL annually



**90% of new VL cases reported occur in seven countries:**

Brazil	Somalia
Ethiopia	South Sudan
Kenya	Sudan
India	

**The majority of CL cases reported occur in nine countries:**

Afghanistan	Pakistan
Algeria	Peru
Brazil	Saudi Arabia
Colombia	Syria
Iran	

**50%**  
UNDER 15 YEARS OLD  
of VL patients in India, Sudan, and Brazil

**90%**  
NEW CASES  
occurred in seven countries

#### DNDi aims to deliver:

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



## Screening

**OBJECTIVE:** Use high throughput screening to identify novel hit series for leishmaniasis from synthetic compound collections accessed from partners or acquired from commercial suppliers, and expand screening activities to natural products that are a promising source of novel active series

More than 20 novel series were identified in 2017 and are now being progressed.

## Leish H2L

**OBJECTIVE:** Identify new lead series from current ongoing hit-to-lead activities by taking advantage of the optimization consortia and screening platforms for leishmaniasis

The process of hit-to-lead optimization is ongoing with multiple series from several pharmaceutical companies and with hits from libraries purchased from commercial vendors and screened by DNDi to be advanced if promising activity can be shown in pre-clinical models.

## Booster H2L

NEW!

**OBJECTIVE:** Speed up the process and cut the cost of finding new treatments for leishmaniasis by bringing together pharmaceutical companies in a multilateral, simultaneous, and non-competitive search process

The Drug Discovery Booster was launched in 2015 to circumvent early-stage commercial barriers between pharmaceutical participants, allowing DNDi to search millions of unique compounds simultaneously in the hunt for new treatment leads.

In 2017, two new companies - AbbVie and Merck - signed on to the Drug Discovery Booster, joining Takeda, Eisai, Shionogi, AstraZeneca, and Celgene.

To date, 32 iterations of the booster have been launched around 16 distinct seed compounds. Ten hit series have been identified, four of which will enter into proof-of-concept *in vivo* efficacy studies by Q1 2018.

## Daiichi-Sankyo LH2L (leishmaniasis hit-to-lead)

NEW!

**OBJECTIVE:** Identify at least one - possibly two - progressable lead series meeting DNDi lead stage criteria for visceral leishmaniasis

Current hit-to-lead efforts of the series identified from the Daiichi Sankyo Pharma Space Library focus on Chagas disease (see p. 52), but the project team submits any newly synthesized molecules to a *Leishmania* cross screen to assess potential.

## Towards new-generation treatments for leishmaniasis

DNDi's recent efforts to develop modern treatments for leishmaniasis through its discovery pipeline are bearing fruit. DNDi and partners (GSK, DDU and Wellcome Trust at University of Dundee, Novartis, Pfizer, Takeda, and Celgene) have built an unprecedented portfolio of ten new chemical classes (four lead series, four pre-clinical candidates, and two clinical candidates) with different mechanisms of action against *Leishmania* parasites.



## DNDI-5421 & DNDI-5610

**OBJECTIVE:** Maintain back-up candidate oxaboroles that could replace the drug candidate DNDI-6148, if needed

These two compounds from the oxaborole class serve as back-ups to DNDI-6148. Their further development is currently on hold and will only recommence should problems be encountered with the development of DNDI-6148.

## Aminopyrazoles

**OBJECTIVE:** Select a pre-clinical candidate from the aminopyrazole series for the treatment of leishmaniasis

DNDI-5561 was nominated as a new pre-clinical candidate from the aminopyrazole series in October 2017. Four back-up compounds are well advanced and offer similar profiles to DNDI-5561. Additional studies, including preliminary toxicology assessments, are being planned to further understand the safety profiles of these compounds and to identify the best back-up to DNDI-5561. DNDi developed this aminopyrazole series from a high-throughput screening hit from a Pfizer compound library.



## RESEARCH

**CGH VL series 1**

**OBJECTIVE:** Select a pre-clinical candidate from the Celgene Global Health VL series for the treatment of VL

DNDi's collaboration with Celgene Global Health continues to explore the potential of this series to deliver a pre-clinical candidate. Compounds with much improved physical properties, including improved aqueous solubility, were identified in 2017.

**Leish L205 series**

NEW!

**OBJECTIVE:** Progress a compound from the 205 series towards candidate selection and nomination for further pre-clinical development for VL

Following proof-of-principle with the 205 series for VL, compounds from this series have shown a 100% parasite load reduction in liver and spleen in a VL murine model. Further characterization of this series is ongoing. Over 400 compounds have been synthesized to date in this lead optimization programme for Chagas disease and leishmaniasis.



## TRANSLATION

**DNDI-0690 nitroimidazole**

**OBJECTIVE:** Progress DNDI-0690, a nitroimidazole compound, through clinical development for the treatment of leishmaniasis

DNDI-0690, a nitroimidazooxazine for the treatment of VL and possibly CL, was selected for pre-clinical development in September 2015. A full pre-clinical toxicology and safety studies package was completed in 2017, and the decision to progress to a Phase I single ascending dose study in healthy volunteers is anticipated in early 2018.



## TRANSLATION

**DNDI-6148**

**OBJECTIVE:** Progress DNDI-6148, an oxaborole compound, through clinical development for the treatment of leishmaniasis

DNDi and Anacor have been working together over the last few years to identify oxaborole compounds, initially for the HAT programme, but this work has now expanded to include both leishmaniasis and Chagas disease. DNDI-6148 has emerged as a promising lead candidate for VL and CL, and by the end of 2015, studies including exploratory toxicology necessary for possible progression to pre-clinical development had been successfully completed. In January 2016, DNDI-6148 was nominated as a pre-clinical candidate for the treatment of VL and possibly CL.

The pre-clinical toxicology package was completed in 2017, and the decision was made to progress to Phase I single ascending dose in healthy volunteers in parallel with additional toxicological investigations.

**DNDI-5561**

NEW!

**OBJECTIVE:** Progress DNDI-5561, a selected aminopyrazole compound, to Phase I clinical studies for the treatment of VL

This project is the continuation of the optimization of the aminopyrazole series for VL. With the funding of the Japanese GHIT Fund, DNDi and partner Takeda worked with the objective of delivering an anti-parasitic aminopyrazole drug, as well as back-up candidates. DNDI-5561 is the front-running second-generation aminopyrazole.

Following positive results from efficacy and safety studies, DNDI-5561 was selected as a pre-clinical candidate in October 2017.

**GSK3186899 / DDD853651  
& GSK3494245 / DDD1305143**

NEW!

**OBJECTIVE:** Progress pre-clinical development of compounds for leishmaniasis

In April 2017, DNDi and GSK entered into an agreement for the pre-clinical development of two compounds for leishmaniasis which were discovered by GSK in collaboration with the Drug Discovery Unit (DDU) at the University of Dundee, following some co-funding by the Wellcome Trust.





## CpG-D35 for CL

**OBJECTIVE:** Demonstrate the suitability of CpG-D35, an immunomodulator to stimulate the innate immune system to fight the parasitic infection responsible for CL, as an adjunct to drug therapy, for progression to Phase 1 clinical studies

CpG-D35 is being developed as a combination therapy for the treatment of complicated CL and PKDL in partnership with GeneDesign. *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.

In 2017, final results of the pre-clinical *in vivo* efficacy study showed an improved outcome for CpG-D35, either alone or in combination with pentavalent antimony (glucantime). These results supported the completion of the pre-clinical package and initiation of the preparation of clinical supplies for a Phase I study.



## New CL combination therapies

**OBJECTIVE:** Further explore opportunities to maximize existing approved treatment approaches for CL when used in combination

When administrated alone, current CL treatments (antimonials, miltefosine, and thermotherapy) have well-established safety and efficacy profiles which are not satisfactory. Using a combination of therapeutic approaches may reduce efficacy rates, reduce treatment duration, and reduce the rate of adverse events. A combination of one single application of thermotherapy at 50°C for 30 seconds with a three-week course of oral miltefosine is being tested in a Phase II study in Colombia and Peru to gain information about safety and efficacy.

In 2017, recruitment of patients continued in Peru with the inclusion of 41 patients, and the study started in Colombia with the inclusion of 21 patients (out of a target of 130 patients). An interim analysis is planned in early 2018 once 65 patients have completed the Day 90 follow-up visit.



## New treatments for HIV/VL

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

Patients with VL and HIV co-infection are very difficult to manage. They have a high rate of treatment failure, a higher risk of death, and multiple episodes of relapse.

In 2014, a randomized non-comparative Phase III study testing both AmBisome monotherapy (regimen currently recommended by WHO) and a combination of AmBisome and miltefosine was initiated at two sites in Ethiopia for the treatment of HIV/VL co-infection. After 59 patients had been enrolled, recruitment was interrupted, as efficacy at the end of treatment was lower than expected. Patients who had not achieved cure at the end of treatment were given a second cycle of the same treatment and efficacy was measured again at the end of this second cycle.

Despite an initial disappointing result, the efficacy of the AmBisome and miltefosine combination used within a strategy of prolonged treatment for patients difficult to cure, gave promising results.

In 2017, results were presented to the Ethiopian authorities and WHO, to promote the implementation of the combination of AmBisome and miltefosine as first-line treatment for HIV/VL co-infected patients, using the strategy of one or two treatment cycles. A scientific paper will be published in 2018 to open discussion with other stakeholders to support new recommendations for treating HIV/VL co-infection.

In India, DNDi is the technical partner with the Rajendra Memorial Research Institute (RMRI) in a study sponsored by MSF and launched in the state of Bihar in 2017. This Phase III study will test AmBisome monotherapy and AmBisome in combination with miltefosine in 150 patients. Recruitment is expected to be completed by early 2018. Results will inform the national road map of kala-azar elimination in India.



## New treatments for PKDL

**OBJECTIVE:** Determine the safety and efficacy of two treatment regimens for patients with PKDL

PKDL is present mainly in two regions. In East Africa, the disease affects approximately 55% of patients previously treated for VL, a few months after VL therapy, and self-heals in 80% of cases within six months. Due to the nature of the disease and toxicity of the currently available treatments, only certain patients are targeted for treatment. In South Asia, where PKDL occurs in around 5-15% of treated VL cases many months or even years after VL therapy, the recommendation is to treat all patients.

Early treatment of PKDL patients has a benefit for the individual, but could also be a critical element of any VL public health and elimination strategy, as PKDL patients are believed to constitute a potential reservoir of infection for VL.

In late 2017, recruitment started for a Phase II study in Asia to test both AmBisome monotherapy and a combination of AmBisome and miltefosine, with six patients enrolled in clinical sites in India (RMRI in Patna and KAMRC in Muzzafarpur), while a clinical site in Bangladesh is preparing for initiation. The target recruitment of 110 patients is expected to be completed by January 2019.

A Phase II study to test both AmBisome in combination with miltefosine, and paromomycin in combination with miltefosine is under preparation in Sudan. Target recruitment will be 110 patients over two years.

A PKDL infectivity study – studying the ability of a pathogen to establish a horizontal infection, that is not from parent to child – in Bangladesh completed the recruitment of 65 patients and results are under analysis. In Sudan, the preparation of an insectarium for infectivity studies continues.

## New VL treatments in Latin America

**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, supporting the Brazilian Ministry of Health and its partners

The Brazilian Ministry of Health is reviewing its treatment policy with regard to the adoption of AmBisome as first-line treatment for VL following the presentation of previous trial results to the Ministry in 2016.

## Miltefosine/paromomycin combination for Africa

**OBJECTIVE:** Assess the safety and efficacy of a miltefosine/paromomycin combination compared to the current standard VL treatment

A Phase III study to compare two different durations (14 and 28 days) of combination regimens of miltefosine and paromomycin with the current standard VL treatment – sodium stibogluconate (SSG), and paromomycin – in both paediatric and adult patients has begun in East Africa – replacing the toxic SSG with oral miltefosine treatment in a combination.

In 2017, the study protocol went through a joint review facilitated by WHO-AVAREF (African Vaccine Regulatory Forum), with representatives from AVAREF, the National Ethic Committees, and regulatory authorities from Ethiopia, Kenya, Sudan, and Uganda. A clinical site was initiated in Dooka, Sudan in December 2017 and the first patient recruited in January 2018. Clinical sites in Kenya (Kacheliba) and Ethiopia (Gondar) are about to be initiated, followed by additional sites in Uganda and Kenya.





# Human African trypanosomiasis



“

*He was weak, he slept all day – even during meals. I knew that when people sleep all the time, they could have sleeping sickness so we went to the hospital.*”

Placide's mother

**Placide**, sleeping sickness patient, Democratic Republic of Congo

In 2011, Placide suffered a severe bout of sleeping sickness that came close to killing him. He was diagnosed with stage-2 HAT - when the parasites attack the brain - and was treated with NECT, which required more than two weeks in hospital. He was cured, but his family and doctors believe he has long-term neurological effects from the illness.

“There is still something not ‘right’ with him. He is very anxious and can’t continue at school, I’ve had to pull him out. He doesn’t have any friends,” said his mother.

Asked if he remembers his treatment, Placide nods and points to his lower back, where he received a lumbar puncture.

Today Placide is 11 years old and sits in his family’s courtyard, endlessly chipping away at a piece of wood, not far from the site of DNDi’s Phase III clinical trial for fexinidazole, a new oral therapy that will treat both stages of the disease, doing away with the need for lumbar puncture prior to treatment.

In 2009, DNDi and its partners delivered the combination therapy nifurtimox-eflornithine (NECT) which replaced earlier toxic treatments for HAT. NECT is now used to treat 100% of stage-2 g-HAT patients and has contributed to a dramatic reduction in HAT cases. However, the treatment is difficult to ship and administer, patients must undergo a lumbar puncture to confirm the disease stage, and must remain hospitalized for the full duration of treatment.

The development of new all-oral treatments would enable patients to be treated immediately, potentially at home, and would provide the tools needed to reach and sustain HAT elimination. If successful, this would represent a fundamental shift in disease management.



- Caused by two subspecies: *Trypanosoma brucei gambiense* (g-HAT, comprising 98% of reported cases) and *T. b. rhodesiense* (r-HAT)
- Humans are a reservoir for g-HAT; animals are a reservoir for r-HAT
- Transmitted by the bite of a tsetse fly
- Occurs in two stages: stage-1, often un- or misdiagnosed due to non-specific symptoms

(headaches, chills), and stage-2, the late stage where the parasite crosses the blood-brain barrier, causing serious neurological disorders including sleep cycle disruptions, neurological manifestations, and progressive mental deterioration

- Fatal without effective treatment
- WHO Roadmap objective: to eliminate HAT as a public health issue by 2020

13  
MILLION

estimated to live in  
areas at moderate to  
very high risk

61  
MILLION

people at risk

53  
CASES

of r-HAT reported  
in 2016



24  
COUNTRIES

g-HAT endemic  
in West &  
Central Africa

13  
COUNTRIES

r-HAT endemic  
in Eastern and  
Southern Africa

1,447  
CASES

of g-HAT reported  
in 2017

#### DNDi aims to deliver:

- Safe, effective, and orally administered drugs to replace current first-line HAT treatments, and to simplify current case management
- The goal is to develop two drugs effective for both stage-1 and 2, and both subspecies of the parasite



## SCYX-1330682 & SCYX-1608210

**OBJECTIVE:** Maintain back-up candidate oxaboroles to replace the drug candidate acoziborole, if needed

To ensure future development options if needed, DNDi continues to provide support and advice to researchers working on the discovery of new candidates for HAT, and maintains two back-up candidates from the oxaborole class, both having demonstrated cure for stage-2 of the disease in a murine model.



## Acoziborole (SCYX-7158)

**OBJECTIVE:** Develop and register acoziborole as a new, single-dose, oral treatment for the treatment of stage-2 HAT caused by *T.b. gambiense* (g-HAT), that is also safe and effective for stage-1 HAT

Following its identification as a hit compound in the Anacor chemical library, acoziborole became DNDi's first new chemical entity resulting from its own lead optimization programme to enter clinical development. A Phase I study was completed in 2015 and determined the therapeutic dose at 960 mg, to be administered as a single dose of three tablets, with a favourable safety profile. A pivotal Phase II/III trial started in the last quarter of 2016 in seven clinical sites in the Democratic Republic of Congo (DR Congo).

In 2017, recruitment continued in the DR Congo with the inclusion of 76 patients (out of a target of 210) at eight clinical sites, including new sites in Bandundu and Kinshasa (Roi Baudouin Hospital), in addition to Katanda, Isangi, Dipumba, N'gandajika, Masi Manimba, and Kwamouth. One site (Bolobo) was closed in December 2017. Three more sites will open in 2018, including one in Guinea. The submission of a regulatory dossier to the European Medicines Agency under Article 58 is planned for 2021.



## DEVELOPMENT

### Fexinidazole: On the regulatory pathway with the European Medicines Agency

**OBJECTIVE:** Develop and register fexinidazole as a new all-oral treatment for the treatment of stage-1 and stage-2 HAT caused by *T.b. gambiense* (g-HAT) in adults and children

In the 1970s, Hoechst (now part of Sanofi) initiated but did not pursue the pre-clinical development of fexinidazole, an anti-parasitic drug. In 2005, the compound was identified by DNDi as showing activity against the parasite that causes sleeping sickness. Pre-clinical studies began in 2007. In 2009, DNDi and Sanofi concluded a collaboration agreement for the development, manufacturing, and distribution of fexinidazole, with DNDi responsible for pre-clinical, clinical, and pharmaceutical development, and Sanofi responsible for the industrial development, registration, production, and distribution of the drug. Phase I studies began in 2010, and a Phase II/III pivotal clinical study started in 2012, led by the National HAT Control Programme (PNLTHA) of the Democratic Republic of Congo (DR Congo) and supervised by DNDi.

Between 2012 and 2016, the open label randomized pivotal Phase II/III clinical trial compared the efficacy and safety of fexinidazole – a 10-day all-oral treatment – with today's first-line treatment, nifurtimox-eflornithine combination therapy (NECT) – 14 intravenous infusions of eflornithine over seven days together with three times a day oral nifurtimox for ten days and requiring hospitalization – in meningo-encephalitic (stage-2) g-HAT patients. 394 patients were recruited across 10 sites in the DR Congo and Central African Republic.

Results confirmed a treatment success rate of 91.2% for fexinidazole, versus 97.6% for NECT, 18 months after the end of treatment. The results show that fexinidazole is effective within a predetermined acceptability margin, set following a survey with practitioners, based on the significant advantages of having a first-line treatment that is oral. There were no major differences in safety. The results were published in *The Lancet*<sup>1</sup> and presented at the European Congress on Tropical Medicine and International Health in October 2017.

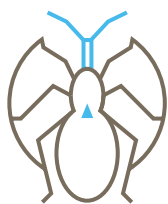
Two additional complementary cohorts with fexinidazole were completed in 2016, one including 230 adult patients with stage-1 and early stage-2 disease, and another including 125 children between six and 14 years, both at sites in the DR Congo. Follow-up of these patients was completed in 2017, with results to be published in 2018.

In January 2018, DNDi's industrial partner Sanofi submitted a regulatory dossier to the European Medicines Agency (EMA) under Article 58 for the treatment of *T.b. gambiense* HAT (stages-1 and 2) in adults and children above the age of six and above 20kg. By involving the WHO and regulators from the DR Congo and Uganda in the EMA process, the use of Article 58 will enable faster in-country implementation of fexinidazole.

A further Phase IIIb trial to obtain more information about special populations not included in previous fexinidazole studies (including pregnant and lactating women, and patients with poor nutritional status or chronic diseases) started in 2016 and is ongoing at seven sites in the DR Congo, of which two were newly opened in 2017. Patients are treated either in hospital or at home, based on pre-determined clinical and social criteria, thereby also providing preliminary information about treatment compliance and final effectiveness in ambulatory patients. Three additional sites will be opened in 2018, including one in Guinea.



<sup>1</sup> Mesu, Victor Kande Betu Ku et al. Oral fexinidazole for late-stage African *Trypanosoma brucei gambiense* trypanosomiasis: a pivotal multicentre, randomised, non-inferiority trial. *The Lancet*, Volume 391, Issue 10116, 144-154. November 2017.



## Chagas disease



“

*Finally, the doctors realized Yerko had advanced Chagas disease. His heart had enlarged and had difficulty pumping blood. (...) It was too late to reverse the damage.*”

Yerkos' wife, Raquel

**Yerko**, on his wedding day with his wife Raquel, and with his guitar, died of Chagas disease at 44 years old, Bolivia.

Yerko spent his early years in rural eastern Bolivia in a traditional house with walls made of adobe bricks and a roof of palm leaves – materials that provided perfect hiding places for *vinchucas*, or kissing bugs, which bite at night and transmit the parasite that causes Chagas disease. Yerko moved to the city with his family when he was just eight, but by then he already had Chagas.

Like many with this “silent” disease, it would be many more years before Yerko was diagnosed. He married, had three children, sang and played the guitar, and worked as a pharmacy clerk while studying to become a pharmacist. But his health had begun to deteriorate. By the time he was finally diagnosed, Yerko had advanced Chagas disease, and he died aged 44, leaving a huge void in his family and community.

Current treatments for Chagas disease (benznidazole and nifurtimox) are more than 40 years old, and while they show good efficacy in specific cases (those in the acute phase, and in children), the drug regimens are long and have substantial side effects, and their efficacy is difficult to assess for patients in the chronic stage. Improved treatment options are needed for all stages of Chagas infection. At the same time, access to existing treatments is poor, due to a lack of clear guidelines and policies supporting treatment options, and to the limited availability of medicines.

In 2017, the US Food & Drug Administration (FDA) approved benznidazole to treat children, the first drug ever approved by the FDA to treat Chagas disease, which will catalyse registration in endemic countries in Latin America that have not yet registered the drug (see p. 32).



- *Trypanosoma cruzi* parasite transmitted by the bite of a triatomine vector known as the 'kissing bug'; congenital transmission, blood transfusion, organ transplantation, or ingestion of contaminated food also possible
- Endemic in 21 countries in Latin America but also in Europe, North America, Japan, and Australia
- Occurs in two phases: the acute phase, with no or unspecific symptoms in most cases, lasts for

about two months after infection, and the chronic phase, where the parasites are hidden mainly in the heart and digestive muscles, which may take decades to show symptoms

- Up to 30% of chronically infected people develop cardiac problems and up to 10% develop digestive or neurological issues, or mixed alterations
- Can lead to sudden death due to cardiac complications



■ Endemic countries  
■ Non-endemic countries but present

70  
MILLION

people at risk,  
mainly in Latin  
America

12,000

deaths annually

6–8  
MILLION

people infected

<1%  
OF PEOPLE

with Chagas have  
access to diagnosis  
and treatment

### DNDi aims to deliver:

- Alternative regimens of existing drugs (lower doses, shorter treatment duration, and combinations):
  - A new benznidazole monotherapy
  - A new benznidazole and fosravuconazole combination therapy
  - A new fexinidazole monotherapy
- A safe and effective new drug treatment for chronic Chagas patients, ideally also effective for acute Chagas patients, including children, and safe to use during pregnancy
- An early test of cure and/or markers of therapeutic response



## Screening

**OBJECTIVE:** Use high throughput screening to identify novel hit series for Chagas disease from synthetic compound collections accessed from partners or acquired from commercial suppliers, and expand screening activities to natural products that are a promising source of novel active series

More than 20 novel series were identified in 2017 and are currently being progressed.

## Chagas H2L

**OBJECTIVE:** Identify new lead series from ongoing hit-to-lead activities by taking advantage of optimization consortia and screening platforms for Chagas disease

A new discovery cascade was implemented in 2017, comprising new *in vitro* and *in vivo* models. If promising activity is demonstrated, the identified series will then be advanced to full lead optimization programmes.



## Booster H2L

NEW!

**OBJECTIVE:** Speed up the process and cut the cost of finding new treatments for Chagas disease by bringing together pharmaceutical companies in a multilateral, simultaneous, and non-competitive search process

The Drug Discovery Booster was launched in 2015 to circumvent early-stage commercial barriers between pharmaceutical participants, allowing DNDi to search millions of unique compounds simultaneously in the hunt for new treatment leads.

In 2017, two new companies - AbbVie and Merck - joined the Drug Discovery Booster, which included already Takeda, Eisai, Shionogi, AstraZeneca, and Celgene, bringing the total to seven participants.

To date, 32 iterations of the booster have been launched around 16 distinct seed compounds. Ten hit series have been identified, four of which will enter into proof-of-concept *in vivo* efficacy studies by Q1 2018.

## Daiichi-Sankyo LH2L/CH2L

NEW!

**OBJECTIVE:** Identify at least one – possibly two – progressable lead series meeting DNDi lead stage criteria for visceral leishmaniasis and/or Chagas disease

Three *T. cruzi* active series with marginal activity against *Leishmania* were identified from a high-throughput screening of 40,000 members of the Daiichi Sankyo Pharma Space Library. Current medicinal chemistry efforts of this hit-to-lead collaboration focus on one series that was confirmed as the most promising chemotype in terms of activity and selectivity profile. To date, over 100 analogs to this series have been synthesized and tested for *T. cruzi* and *Leishmania* activities at Institut Pasteur Korea, leading to the identification of four preferred molecules nominated to proceed with pharmacokinetics studies. This project was initiated in April 2017 for a duration of 18 months.



## TRANSLATION

### Chagas C205 series

NEW!

**OBJECTIVE:** Optimize leads issued from the hit-to-lead 205 series, and identify pre-clinical candidates with the potential to fulfill the target product profile for Chagas disease

Following curative activity *in vivo* observed for several lead compounds of the 205 series, work in 2017 concentrated on better understanding the necessary parameters for obtaining cure in animals, in particular by testing different regimens and doses while exploring further optimization. Further characterization of this series is ongoing, and compounds are being profiled for candidate nomination. More than 400 compounds have been synthesized by this programme to date.

### Biomarkers

**OBJECTIVE:** Identify and evaluate new biological markers of therapeutic efficacy in chronic Chagas disease

The only measurable treatment outcome currently available is the disappearance of anti-Chagas antibodies. In adults, this can take several decades. Pre-clinical studies started in 2016 and were ongoing in 2017 to identify and validate potential biological markers of therapeutic response in Chagas patients. In addition, through the Ibero-American network NHEPACHA, DNDi is fostering work on testing four biomarkers to assess the response to Chagas treatment.



### New benznidazole regimens

**OBJECTIVE:** Evaluate new therapeutic regimens of benznidazole – the standard treatment for Chagas disease – as monotherapy or in combination with fosravuconazole – for the treatment of adult patients with chronic Chagas disease

Benznidazole, the standard treatment for Chagas, has sustained efficacy until 12 months post-therapy, but it is associated with side effects that can result in treatment discontinuation. The proof-of-concept “BENDITA” study was developed based on results from two previous clinical trials conducted by DNDi. A proof-of-concept trial carried out in 2013 showed that fosravuconazole (previously known as E1224), an azole-class antifungal drug discovered by the Japanese pharmaceutical company Eisai, was safe and effective at clearing the parasite, but its 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.

The “BENDITA” study aims to improve safety, tolerability, and compliance whilst maintaining or increasing efficacy compared to current regimens for chronic indeterminate Chagas disease patients. The trial used different doses, dosing frequency, and treatment duration of benznidazole as monotherapy or in combination with fosravuconazole. The trial has been conducted in three sites in Bolivia, with recruitment completed in July 2017. The primary efficacy parameter is sustained parasitological response at six months. The final assessment will include 12 months of follow-up, with final results available in early 2019.

### Fexinidazole

**OBJECTIVE:** Evaluate efficacy and safety of short-course and low-dose regimens of fexinidazole in adults with chronic Chagas disease

A Phase II proof-of-concept study of fexinidazole initiated in 2014 in Bolivia was interrupted due to safety and tolerability issues. Analyses of key outcomes demonstrated high efficacy findings at the lowest dose tested for all treatment durations, with safety concerns about treatment at high doses tested for more than 14 days. Acceptable safety and tolerability were found at low doses and short treatment durations.

From this conclusion, a new Phase II proof-of-concept study using shorter and lower-dose treatment regimens started in October 2017 at four sites in Spain (three in Barcelona, one in Valencia) with a fifth site to be opened in Madrid. The target conclusion date is mid-2019. This is the first time DNDi conducts a clinical trial for Chagas disease outside Bolivia and Latin America.





## Mycetoma



*I can't do my daily activities. I've been late to school. I have no crutches and I don't own a wheelchair, which I need to borrow. It is very difficult to walk.*

Amasi

A friend of **Amasi**, infected with mycetoma for over a year, pushes her around the village in a borrowed wheelchair, Sudan.

Amasi is 18 years old and has been infected with mycetoma for over a year. She lives in the village of Shadida Agabna, in Gezira State, a region south of Khartoum, Sudan that is heavily affected by mycetoma.

According to the Mycetoma Research Centre, in Khartoum about 20-25% of mycetoma patients are children. They often drop out of school and are unable to remain among their peers.

Stigma and shame can keep them hidden. In Amasi's case, her peers lend a hand, pushing her around the village in a borrowed wheelchair and contributing collectively to her care.

More than a dozen people in Amasi's village have had amputations due to mycetoma. Patients must travel long distances to the nearest city, Wad Medani, or even to Khartoum for surgery.

Due to the lack of safe and effective treatments for the fungal version of mycetoma, amputation is often the best (and only) chance patients have.

And all because of a simple thorn prick.

Eumycetoma is more difficult to treat than the bacterial form of the diseases.

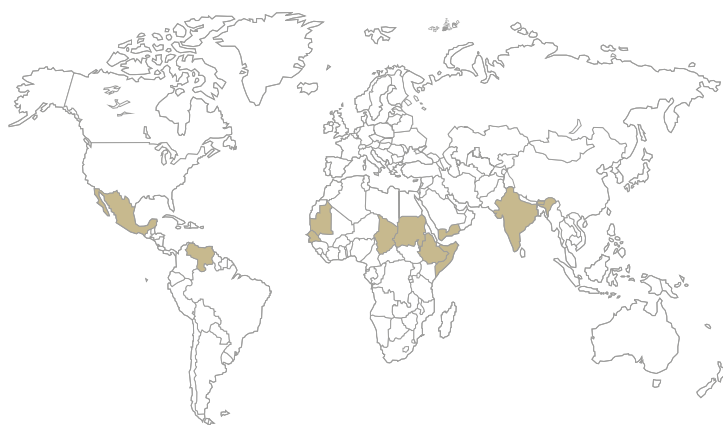
Treatments are long, toxic, often ineffective, and expensive. The cure rate using available antifungals is only 25-35%, and treatment is often followed by surgical removal of the remaining mass, or may lead to amputation.

In 2016, WHO added mycetoma to the list of the 18 neglected tropical diseases, increasing the likelihood of better monitoring and research funding, although mycetoma remains among the most neglected of neglected diseases. An effective, safe, and affordable treatment appropriate for use in rural settings is urgently needed.



Patients often have recurrent lesions after treatment that may result in amputation.

- Slow-growing infection with fungal (eumycetoma) and bacterial (actinomycetoma) forms
- Eumycetoma, mainly endemic in Africa, is more difficult to treat
- Mycetoma is endemic in tropical and subtropical regions. The 'mycetoma belt' includes Chad, Ethiopia, Mauritania, Senegal, Somalia, and Sudan, as well as India, Mexico, Venezuela, and Yemen
- Attacks skin, deep muscle, and bone, and is believed to enter the body via thorn pricks or lesions on the feet
- Affects poor people in rural areas – in particular, young males aged between 15 and 30
- Causes devastating deformities, often resulting in amputation; if left untreated, it becomes chronic and can be fatal
- No global surveillance, so limited epidemiological data; the Mycetoma Research Centre in Khartoum, Sudan, has recorded over 8,200 patients since 1991



■ Mycetoma belt

The 'mycetoma belt' includes Chad, Ethiopia, Mauritania, Sudan, Senegal, and Somalia, as well as India, Mexico, Venezuela, and Yemen.

Global burden:

unknown

### DNDi aims to deliver:

- A new, safe, effective, and affordable treatment for patients with eumycetoma



## DEVELOPMENT

### Fosravuconazole

**OBJECTIVE:** Study the efficacy of fosravuconazole as a potential new, safe, and affordable treatment for patients with eumycetoma

Fosravuconazole (formerly known as E1224 in DNDi's portfolio), an orally bioavailable azole developed by the Japanese pharmaceutical company Eisai, is under development for Chagas disease by DNDi (see p. 53). It could also be an effective and affordable treatment for eumycetoma. Its pharmacokinetic properties are favourable and its toxicity is low.

After receiving regulatory and ethical approval in March 2017, the Mycetoma Research Centre, a WHO Collaborating Centre,

began recruiting patients into the first-ever double-blind, randomized Phase II/III clinical trial for eumycetoma. The clinical trial, which plans to recruit 138 patients, evaluates the efficacy of the anti-fungal fosravuconazole in moderate lesions in comparison with the current treatment, itraconazole.

The primary objective of this single-centre study conducted in Sudan is to demonstrate the superiority of fosravuconazole over itraconazole after 12 months' treatment. By the end of 2017, 20 patients had been enrolled into the trial, a pace of enrolment that was slower than anticipated. In 2018, a satellite site will be established to screen more patients and refer them for treatment and care.



## Filarial diseases



“

*I depend totally on my wife, she feeds and dresses me, and on my son. After I lost my sight we couldn't send any of our children to school.* ”

Akoyo

**Akoyo's son guides his father everywhere since he went blind, Democratic Republic of the Congo.**

Fisherman Akoyo went blind in 2011, as a result of river blindness. He lives in the remote village of Babagulu in the Democratic Republic of the Congo.

The creeping blindness had begun a year earlier, and it eventually robbed him of his livelihood and the means to send his children to school.

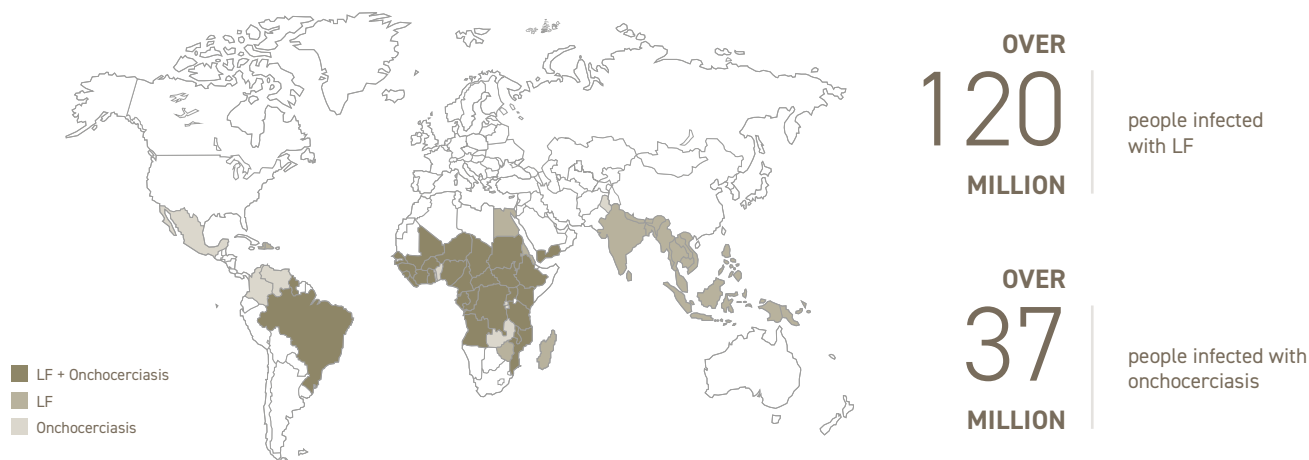
Ironically, Akoyo had once fought against the disease that eventually robbed him of his sight, as a volunteer distributing drugs to prevent transmission of river blindness.

Akoyo's village is one of many in the region devastated by river blindness, a neglected tropical disease transmitted by the bite of the blackfly. The river nearby makes it a perfect breeding ground for the blackflies that infect people with the filarial worms that cause river blindness.

Community leaders estimate that up to 3% of the community is blind. Akoyo's son Aito also has the tell-tale nodules on his torso and forehead, some the size of golfballs – painless, but a clear sign that he, too, is infected.

Existing treatments for filarial diseases take years to be effective because they only kill juvenile worms, not the adult worms, which continue to reproduce. Mass drug administration (MDA) programmes, typically using ivermectin, must therefore be repeated once or twice a year for over a decade until the adult worms die of natural causes. Despite many rounds of MDA, the disease has not yet been eliminated and a short-course treatment that kills adult worms and reduces the number of MDA cycles is needed to fulfill this goal. There are also serious safety issues with using ivermectin to treat people infected with loiasis. In addition, suboptimal responses to standard treatment in onchocerciasis patients may be indicators of drug resistance.

- Filarial diseases from parasitic nematode worms are transmitted to humans by blood-sucking insects
- There are three filarial diseases: lymphatic filariasis (LF, also known as elephantiasis), onchocerciasis (also known as river blindness) and loiasis (also known as *Loa loa*, or African eye-worm)
- Filarial diseases are rarely fatal but inflict hardship and misery on millions of people. Onchocerciasis and lymphatic filariasis cause life-long disabilities such as blindness, severe itching, dermatitis, and swollen limbs and genitals
- Lymphatic filariasis is endemic in 54 countries worldwide
- Onchocerciasis is endemic in 31 African countries



947  
MILLION people at risk of LF

169  
MILLION people at risk of onchocerciasis

#### DNDi aims to deliver:

- A new oral, short-course macrofilaricide treatment, with potential application to treat both onchocerciasis and lymphatic filariasis, and allow for treatment in regions co-endemic for *Loa loa*



## RESEARCH

### Screening

**OBJECTIVE:** Identify new drug candidates, by accessing and evaluating registered drugs, pre-clinical and clinical candidates, focused sets and libraries with known anthelmintic activity from animal and human health companies

In 2017, well-characterized libraries of compounds that had been extensively optimized for other indications were provided to DNDi by several pharmaceutical companies

for screening. Early screening of 530 compounds has been completed with Salvensis, Merck Sharp & Dohme, University of Carolina, AbbVie, and others. From this initial screen, a full lead optimization programme has been undertaken in collaboration with Celgene with further exploration of identified hits (505 compounds). This effort will continue through 2018, with the aim of delivering a pre-clinical candidate for filarial diseases.



## Macro-filaricide 3

**OBJECTIVE:** Develop a third macrofilaricide candidate for filarial diseases

Following a drug repurposing strategy, screening of compounds against *Onchocerca gutturosa* and *Onchocerca lienalis* identified several candidates from compound libraries provided by pharmaceutical companies. These compound collections are well-characterized chemical series which have been extensively optimized for use in other indications. Although the project was quite successful, none of the identified candidates had a drug profile with utility for filarial diseases.

Screening of compounds from several more companies yielded further candidates. These companies are conducting a hit-to-lead and lead optimization programme, which aims to develop a drug candidate for filarial indications. DNDi has contributed to this effort by providing biological resources, expertise, and the target product profile to select the best candidates.

In 2017, candidates from four distinct chemical series were evaluated through the lead optimization effort conducted in collaboration with Celgene while others were evaluated through the Macrofilaricide Drug Accelerator (MAC DA) led by the Bill & Melinda Gates Foundation as part of efforts to develop a third microfilaricide candidate for development.



## Oxfendazole

**OBJECTIVE:** Develop a macrofilaricide for filarial disease

Oxfendazole is currently under development for treatment of neurocysticercosis and trichuriasis. Taking advantage of pre-clinical work already available in the public domain, DNDi is exploring the possibility of repurposing oxfendazole as a macrofilaricidal treatment for filarial indications.

### ABBV-4083 (TylAMac)

**OBJECTIVE:** Develop ABBV-4083 as an anti-Wolbachia therapy and assess its macrofilaricidal efficacy

ABBV-4083 is a derivative of Tylosin, a veterinary antibiotic that targets the worm-symbiont Wolbachia. The compound is currently in early clinical development by AbbVie for the treatment of filarial diseases. ABBV-4083 is orally available, induces a robust anti-Wolbachia effect in several *in vivo* models, demonstrates clear superiority over doxycycline, and is effective after a shorter dosing regimen. Preliminary safety and toxicology profiling of this compound suggests a favourable safety profile.

Toxicology studies were completed in 2017, and an oral formulation was developed. In December, AbbVie began the first human trial of ABBV-4083 to test the drug's safety in healthy volunteers and assist in the selection of doses for future trials. This Phase I study, conducted at AbbVie's Clinical Pharmacology Research Unit in Chicago, US is expected to be completed in 2018.

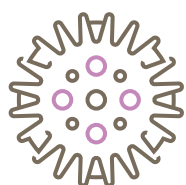
## Emodepside

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

Originating from the Japanese pharmaceutical company Astellas, emodepside has been developed and is currently commercialized by Bayer Animal Health as an anti-helminthic veterinary drug for cats and dogs. DNDi has a collaboration agreement with Bayer to jointly develop emodepside for the treatment of onchocerciasis in humans. DNDi is responsible for clinical development, and Bayer for pre-clinical, pharmaceutical development, manufacturing, registration, and supply of the drug at the lowest sustainable price.

Emodepside entered into Phase I studies in 2016, which continued throughout 2017 with 116 healthy volunteers recruited by the end of the year. The single ascending dose study was completed and the multiple ascending dose study will be completed in 2018.





## Paediatric HIV



“

*I faced a lot of difficulties with the medicine. I really had to battle in order for my baby to take them. It's heart-breaking to give a child four medicines at a time.*”

Sani

Sani, with her one-year old daughter Mel who is co-infected with HIV and TB, South Africa

Sani and her husband Brian knew they were going to have a child that was going to be HIV-positive. In addition to living with HIV, their baby Mel had also contracted tuberculosis (TB) and required multiple medicines.

While Sani and her husband Brian were able to obtain treatment for Mel, the available HIV therapy for infants was a foul-tasting lopinavir/ritonavir solution containing 40% alcohol and requiring refrigeration.

One of their biggest challenges was administering the medicine every day.

Despite major efforts to increase the number of children on HIV treatment and a continuing reduction in mother-to-child transmission of HIV, many of the two million children living with HIV are still being left behind. In 2016, only 43% of children living with HIV received antiretroviral therapy. While this is an important increase from 15% in 2009, it remains an unacceptably low level of treatment access for a vulnerable population.

One major challenge that contributes to this treatment gap is the suboptimal paediatric formulations available today. These formulations have not been designed with children's needs in mind: the only available version of lopinavir/ritonavir (LPV/r) is a bitter-tasting syrup that requires refrigeration and contains 40% alcohol.

Children struggle to take the medicine, often spitting or vomiting it back up, while caretakers in many sub-Saharan countries are forced to store the treatments buried in sand to keep them cool.

An improved first-line therapy for children under three years of age would be safe, easy to administer, well-tolerated and palatable, heat-stable, readily dispersible, and dosed once daily or less.

It is also important for any paediatric HIV treatment to be compatible with TB treatment, because children living with HIV are often co-infected with TB. In 2016, based on the interim results of a DNDi-sponsored study, WHO revised its guidelines to recommend 'superboosting' of ritonavir in HIV/TB coinfected children.

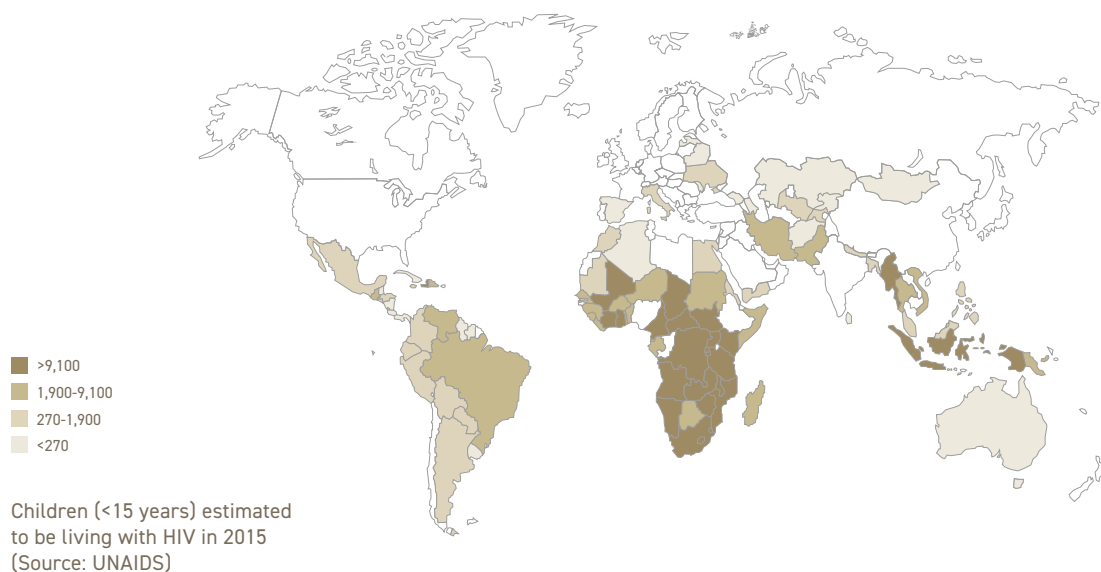
- 90% of infected infants acquire HIV from their mothers, during pregnancy, delivery, or through breast-feeding
- Effective treatments can prevent HIV transmission from a mother to her child, but not all HIV-infected pregnant women have access to these treatments

- Without treatment, 1 in 3 children die in their first year of life; and half before they reach their second birthday
- Only 43% of children (< 15 years) living with HIV are on antiretroviral medication
- Opportunistic infections such as tuberculosis are common

2.1 MILLION children living with HIV in 2016

90% in sub-Saharan Africa

OVER 300 HIV-related child deaths every day



160,000 children newly infected with HIV in 2016

#### DNDi aims to:

- Develop an improved, first-line, child-friendly “4-in-1” therapy for infants and young children – a lopinavir/ritonavir-based, fixed-dose formulation in combination with two nucleoside reverse transcriptase inhibitors
- Introduce lopinavir/ritonavir pellets until better-adapted 4-in-1 products are available



## TRANSLATION

### A “4-in-1”: Towards a substantially improved treatment option for children



**OBJECTIVE:** Following the work that led to the registration of a “2-in-1” lopinavir/ritonavir (LPV/r) fixed-dose combination, develop and register a solid, taste-masked, first-line LPV/r-based fixed-dose formulation with two nucleoside reverse transcriptase inhibitors (NRTIs), lamivudine and abacavir

Together with Cipla Ltd. and with the support of Unitaids, DNDi has developed a solid first-line 4-in-1 fixed-dose combination (abacavir/lamivudine/lopinavir/ritonavir) using the World Health Organization-recommended treatment regimen for infants and young children.

The 4-in-1 formulation, in the form of a capsule containing solid taste-masked granules, will be a great improvement over the current high-alcohol content LPV/r syrup and will not require refrigeration. It will be adequately dosed based on a child's weight, according to weight bands. In addition, caregivers will no longer have to worry about whether their children can swallow a capsule, as the granules within the capsule can easily be mixed with soft food or breast milk.

Preliminary pharmacokinetic studies in healthy human volunteers were conducted in 2017 with a final 4-in-1 formulation. Bioequivalence studies in healthy human volunteers will be performed in 2018, enabling regulatory filing. Safety, acceptability, and efficacy data on this new formulation will also be generated in sub-Saharan Africa to provide evidence for worldwide scale-up. The objective is to submit the 4-in-1 dossier for registration in late 2018.



## DEVELOPMENT

### LPV/r pellets + dual NRTI

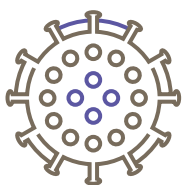
**OBJECTIVE:** Evaluate the effectiveness of LPV/r pellets in addition to AZT/3TC (or ABC/3TC) paediatric fixed-dose combination tablets in an implementation study in HIV-infected infants and young children who cannot swallow pills

Up until 2015, the only available version of LPV/r was a bitter-tasting syrup that requires refrigeration and contains 40% alcohol. In June of that year, the U.S. Food and Drug Administration approved an oral pellet formulation of LPV/r, developed by the Indian generic pharmaceutical company Cipla Ltd., which can be administered to young children with food and does not require refrigeration.

In September 2015, and with the support of Unitaids, DNDi launched the LIVING Study to provide early access to and demonstrate the effectiveness, safety, and acceptability of this new “2-in-1” LPV/r pellet formulation with more than 800 patients across Kenya. The study was expanded to additional sites in Uganda, and then to Tanzania in

2017. This study tested the use of these pellets in the field in combination with a class of ARVs known as nucleoside reverse transcriptase inhibitors (NRTIs), namely zidovudine/lamivudine (AZT/3TC) or abacavir/lamivudine (ABC/3TC). The study is intended to demonstrate the effectiveness, safety, and acceptability of LPV/r oral pellets in the field and pave the way for the 4-in-1. This study marks the first time that these pellets are being used in real-life settings and the findings will undoubtedly help programmes worldwide scale up treatment for HIV-infected children.

As of the end of 2017, 818 paediatric patients had been enrolled at 12 sites. Interim results were presented at the end of 2017 at the ICASA conference, showing that oral “2-in-1” pellets are effective, well tolerated, and well accepted by caregivers and children. Based on experience gained from introducing the 2-in-1, DNDi will work with health ministries, donors, and other HIV stakeholders to ensure that children will have access to the 4-in-1 when it is available.



# Hepatitis C



“

*I didn't feel anything in my body, but my heart! I've got hepatitis, oh my God, what about my kids, because my youngest one is just 5 years old.* ”

Jhuvi

Jhuvi, a hepatitis C patient, on her balcony, Malaysia

Jhuvi, a 39-year-old Malaysian businesswoman and mother of five children, learned that she had hepatitis C after donating blood. She believes that she contracted the disease when she got a tattoo while on vacation.

Jhuvi is now benefiting from treatment provided by the Malaysian Ministry of Health, thanks to the government's landmark decision to issue a “government use” licence to secure access to affordable treatment for hepatitis C.

Direct-acting antivirals (DAAs) have revolutionized the therapeutic landscape. With cure rates of 95%, these 8-to-12-week oral treatments have replaced less effective, injection-based 48-week regimens associated with side effects.

However, their price is a major barrier to access, even in high-income countries, so treatment rationing is common. Prices are also too high for countries to implement strategies that seek to identify asymptomatic people living with HCV, and “test-and-treat” strategies that could lead towards elimination.

A simple (i.e. that works for all patients, including those who are also living with HIV or inject drugs), pan-genotypic (i.e. effective for all genotypes), and affordable treatment would benefit many, particularly in countries unable to access generic HCV treatments.

Together with Egyptian manufacturer Pharco, DNDi has partnered with the Malaysian and Thai governments to test an affordable pan-genotypic combination therapy containing the drug candidate ravidasvir. Interim results released in April 2018 show a 97% cure rate, and promising results even in the hardest-to-treat cases.



- Hepatitis C virus (HCV) is transmitted through exposure to infected blood
- 55-85% of patients develop chronic infection, and of these, 15-30% are at risk of cirrhosis of the liver within 20 years

- HCV has six genotypes (GT), with GT1 most prevalent in the US, for example, and GT6 in South-East Asia
- Effective medicines are available, but their extremely high cost means that only 13% of HCV patients globally have had access to treatment

71  
MILLION

people have chronic HCV infection

OVER  
1.75  
MILLION

people newly infected every year

75%

of people living with HCV are in low- and middle-income countries



400,000

HCV-related deaths each year

#### DNDi aims to deliver:

- A safe, effective, and easy-to-use direct-acting antiviral regimen in an affordable combination, paving the way for a public health approach to HCV treatment



## Ravidasvir/sofosbuvir: Towards a pan-genotypic, simple, and affordable treatment

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

More than one million people are estimated to be chronically infected with HCV in Thailand and 400,000 in Malaysia, where genotypes 1, 3, and 6 are most common. Both countries were initially excluded from all global voluntary licensing agreements with drug companies.

In 2016, DNDi launched the "STORM-C-1" open label trial at eight sites in Malaysia and Thailand to assess the efficacy, safety, tolerability, pharmacokinetics, and acceptability of 12- and 24-week regimens combining the drug candidate ravidasvir with sofosbuvir in people living with the hepatitis C virus (HCV).

In stage one of this study, 301 chronically infected adults were treated with the ravidasvir/sofosbuvir combination for 12 weeks for patients without cirrhosis of the liver, and for 24 weeks for those with compensated cirrhosis.

Initial results published in April 2018 showed that after 12 weeks of treatment, 97% of those enrolled were cured (95% CI: 94.4-98.6). Cure rates were very high, even for the hardest-to-treat patients. Importantly, patients combining several risk factors were cured, and no unexpected safety signals were detected.

To further establish the pan-genotypic profile of ravidasvir, further data will be collected in Malaysia and Thailand, and other trials are envisioned in other parts of the world (for genotypes 2 and 5) and Ukraine (for vulnerable patient groups, including injecting drug users). Registration of ravidasvir will be pursued in Malaysia and other middle-income countries, including in Latin America.

DNDi's HCV programme includes work with Médecins Sans Frontières to develop and implement simpler models of care in specific target populations, as well as in large-scale treatment cohorts in Cambodia and Ukraine. The objective is to demonstrate that the challenges posed by HCV can be addressed through a public health approach.

## INTERIM CLINICAL TRIAL RESULTS FOR NEW HEPATITIS C TREATMENT

### STORM-C CLINICAL TRIAL

- 301 Patients recruited in six sites in Malaysia and Thailand
- Trial co-sponsored by Malaysian Ministry of Health
- Co-financed by Médecins Sans Frontières / Doctors without Borders
- Combination therapy with sofosbuvir and new drug candidate ravidasvir

### RAVIDASVIR

- NSSA inhibitor (suppresses viral replication)
- Licensed by Presidio Pharmaceuticals to Pharco Pharmaceuticals and DNDi
- A new chemical entity but to be priced like a generic in developing countries

### SVR 12

- Sustained Viral Response (SVR)
- Indicates that hepatitis C is undetectable for 12 weeks in patients

### PERCENTAGE OF PEOPLE CURED (SVR 12)

Overall	97%
Genotype 1	99%
Genotype 2	100%
Genotype 3	97%
Genotype 6	81%
Cirrhosis	96%
No Cirrhosis	97%
HIV co-infection	97%
No HIV co-infection	97%
Prior HCV treatment	96%
No prior HCV treatment	98%

Source: I. Andrieux-Meyer, S. Murad, et al. Poster LBP-032-ILC 2018.

## Where and when will the new combination be available?

### Ravidasvir: licences and territories

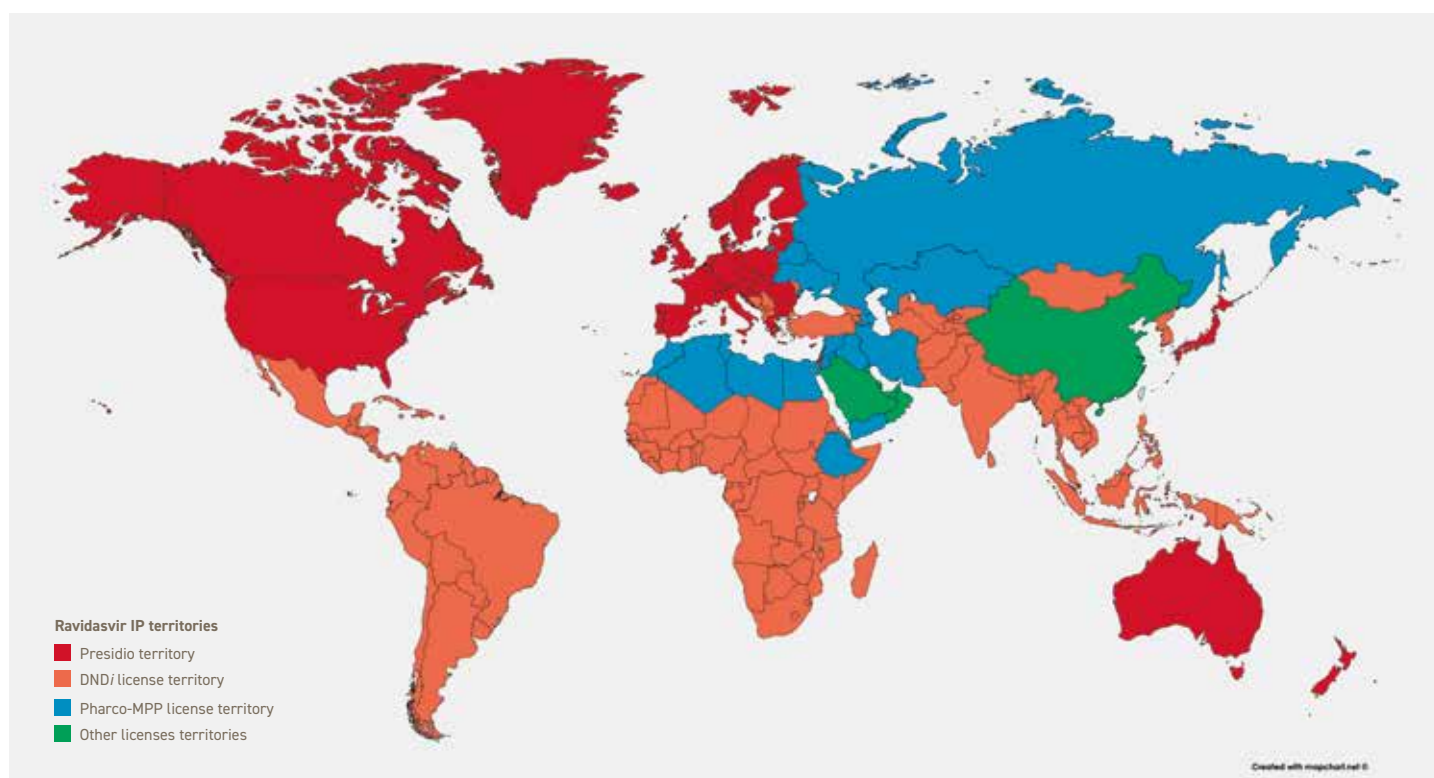
Patents on ravidasvir (RDV) are owned by Presidio, from whom DNDi secured non-exclusive licence rights for LMICs. DNDi also has an option to negotiate the licence rights for high-income countries.

Separately, Pharco sub-licensed RDV rights to the Medicines Patent Pool (MPP), opening up the possibility of generic competition in several countries that were not included in the DNDi licence, including high-prevalence LMICs such as Russia, Ukraine, Egypt, and Iran. According to the MPP, “combined, the MPP and DNDi agreements could potentially benefit countries where 85.3% of people live with hepatitis C in the 139 economies classified by the World Bank as low- and middle-income.”

### Overcoming access barriers

Securing access to sofosbuvir, the current backbone of DAA treatments, needs to be considered, particularly for countries excluded from pharmaceutical company voluntary licence schemes, in addition to other patented DAAs, such as daclatasvir, for which access is extremely limited in upper-middle and high-income countries due to the exclusion from Bristol Myers Squibb's preferential pricing structure.

In countries where, because of patenting and high pricing, affordability is the most limiting factor to access and scale-up DAAs, governments will need to take active steps. This includes making use of TRIPS flexibilities allowed under international trade rules, such as opposing patent applications, or issuing government use or compulsory licences, to overcome the barriers posed by granted patents.



In September 2017, Malaysia issued a “government use” licence enabling access to more affordable versions of sofosbuvir, an expensive and patented medicine to treat hepatitis C. This landmark decision will help the more than 400,000 people living with hepatitis C in Malaysia access sofosbuvir with important repercussions in the global efforts to secure access to expensive treatments.

Pharmaniaga (Malaysia) and Pharco (Egypt) signed a collaboration agreement with DNDi in November 2017 to manufacture and supply ravidasvir and sofosbuvir with the objective of selling the combination, once ravidasvir is registered, for USD 300 in the public sector in Malaysia, instead of USD 70,000.

# Main R&D Partners



## Leishmaniasis

AbbVie, USA; Accelera, Italy; Academic Medical Center in Amsterdam, The Netherlands; Addis Ababa University, Ethiopia; Advinus Therapeutics Ltd, India; Amatsi Aquitaine (formerly Bertin Pharma), France; Amudat Hospital, Uganda; Aptuit, Italy; Astellas Pharma Inc., Japan; AstraZeneca, Sweden and UK; Auckland University, New Zealand; BaseCon, Denmark; Bayer, Germany; Bioascent, UK; BioAster, France; Brasilia University, Brasilia, Brazil; Bristol-Myers Squibb, USA; Celgene Corporation, USA; Centre for Drug Candidate Optimisation, Monash University, Australia; Centro Nacional de Pesquisa em Energia e Materiais (CNPEM), LN Bio, Brazil; Charles River Laboratories (Wil Research), France and Netherlands; Crystallise!, Switzerland; Daiichi Sankyo Company, Limited, Japan; Daiichi Sankyo RD Novare Co., Ltd, Japan; Drug Discovery Unit, University of Dundee, UK; El du Pont de Nemours, USA; Eisai Co., Ltd., Japan; Epichem, Australia; Eurofins Cerep, France; Eurofins Panlabs Thailand, Thailand; Eurofins Panlabs, USA; Eurofins-Optimed, France; Foundation for Innovative New Diagnostics, Switzerland; GeneDesign Inc., Japan; Gilead Sciences, USA; GlaxoSmithKline, Spain and UK; Gondar University Hospital, Ethiopia; Griffith Institute for Drug Discovery, Griffith University, Australia; Hospital Sao José de Doencas Infecciosas, Fortaleza; Hypha Discovery Ltd, UK; Institut Pasteur Korea, South Korea; Institute of Endemic Disease, Khartoum University, Sudan; Institute of Medical Sciences, Banaras Hindu University, India; Institute of Microbial Chemistry, Japan; Institute of Tropical Medicine Antwerp, Belgium; Instituto de Física, Universidade de São Paulo, Brazil; Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, Peru; Instituto de Química, Universidade Estadual de Campinas, Brazil; Instituto de Salud Carlos III, Spain; International Centre for Diarrhoeal Disease Research, Bangladesh; Johnson & Johnson, USA; Kacheliba District Hospital, Kenya; Kala Azar Medical Research Centre, India; Kenya Medical Research Institute, Kenya; Kitasato Institute for Life Sciences, Japan; Laboratory of Microbiology Parasitology and Hygiene, University of Antwerp, Belgium; Lambda Therapeutic Research Ltd., India; LEAP Platform; London School of Hygiene & Tropical Medicine, UK; Makerere University, Uganda; Médecins Sans Frontières, Spain; Médecins Sans Frontières, The Netherlands; Medicines for Malaria Venture, Switzerland; Merck KGaA, Germany; Merck, USA; Ministry of Health, Neglected Tropical Disease Directorate, Ethiopia; Ministry of Health, Neglected Tropical Diseases Unit, Leishmaniasis Programme, Kenya; Ministry of Health, Neglected Tropical Diseases Unit, Leishmaniasis Programme, Sudan; Ministry of Health, Leishmaniasis Control Programme, Uganda; Montes Claros State University, Montes Claros, Brazil; Nagasaki University,

Japan; National Institute of Pathology, India; National Institutes of Health, USA; Netherlands Cancer Institute, The Netherlands; Northwick Park Institute for Medical Research, UK; Novartis, Switzerland and USA; Ohio State University, USA; Osaka University, Japan; Paediatric Hospital Joao Paulo II – FHEMIG, Belo Horizonte, Brazil; Pfizer Inc., USA; Pfizer Inc. (formerly Anacor Pharmaceuticals Inc.), USA; Piauí Federal University, Teresina, Brazil; Programa de Estudio y Control de Enfermedades Tropicales, Universidad de Antioquia, Medellín, Colombia; Programa Nacional de Leishmaniasis, Colombia; Rajendra Memorial Research Institute of Medical Sciences, India; Rene Rachou Research Center– Fiocruz-MG, Belo Horizonte, Brazil; Research Foundation of The Netherlands Cancer Institute, The Netherlands; Sandexis, UK; Sanofi Merial, USA; Sanofi, France; Sanofi-Aventis, France; Sara Pharm, Romania; Scynexis, USA; Sequella Inc, USA; Sergipe Federal University, Aracaju, Brazil; Shionogi & Co., Ltd., Japan; SK Hospital, Mymensingh, Bangladesh; Swiss Tropical and Public Health Institute, Switzerland; Syngene, India; Takeda Pharmaceutical Company Limited, Japan; TB Alliance, USA; TCG Lifesciences, India; The Broad Institute of M.I.T and Harvard, USA; Thermosurgery Technologies Inc, USA; UBC, Switzerland; Universidade Estadual do Rio de Janeiro, RJ, Brazil; University of Cape Town, South Africa; University of Gedaref, Sudan; University of Gondar, Ethiopia; US Food and Drug Administration, USA; Walter Reed Army Institute of Research, USA; WHO-NTD (Neglected Tropical Diseases department); WHO-TDR (Special Programme for Research and Training in Tropical Diseases); WuXi AppTech, China; Zoetis (formerly Pfizer Animal Health), USA



## Human African trypanosomiasis

Advinus Therapeutics Ltd, India; Aesica, UK; Amatsi Aquitaine (formerly Bertin Pharma), France; Aptuit, Italy; Avista Pharma (formerly SCYNEXIS), USA; Biotrial, France; Cardiabase, France; CBCO, DR Congo; Creapharm, France; Eurofins-Optimed, France; HAT Platform; Institut de Recherche pour le Développement, France; Institut National de Recherche Biomédicale, DR Congo; Institute of Tropical Medicine Antwerp, Belgium; Laboratory of Microbiology, Parasitology, and Hygiene, University of Antwerp, Belgium; Luxembourg Institute of Health, Luxembourg; Médecins Sans Frontières; National Control Programmes of the Democratic Republic of Congo, the Central African Republic, and of Guinea; Pace University, USA; Patheon, UK; Pfizer Inc., USA; Pfizer Inc. (formerly Anacor Pharmaceuticals Inc.), USA; PhinC, France; RCTs, France; Sanofi, France; SGS, Belgium; SGS, France; Swiss Tropical and Public Health Institute, Switzerland; Theradis Pharma, France; WHO-NTD (Neglected Tropical Diseases department)

Partners listed here include all those involved since the start of the project; for projects, see DNDi's R&D portfolio, from research through to development (see pp. 16-17).





## Chagas disease

AbbVie, USA; Astellas Pharma Inc., Japan; AstraZeneca, Sweden and UK; Barcelona Centre for International Health Research (CRESIB), Spain; Barcelona Centre for International Health Research, Spain; Barcelona Institute for Global Health (ISGlobal), Spain; Bayer, Germany; Bioascent, UK; Bioaster, France; Brazilian Biosciences National Laboratory, Brazil; Bristol-Myers Squibb, USA; Broad Institute of M.I.T and Harvard, USA; Celgene Corporation, USA; Centre for Drug Candidate Optimisation, Monash University, Australia; Centro de Chagas y Patología Regional, Hospital Independencia, Argentina; Centro Nacional de Pesquisa em Energia e Materiais, LN Bio, Brazil; Collective of Applied Studies and Social Development, Bolivia; Daiichi Sankyo Company, Limited, Japan; Daiichi Sankyo RD Novare Co., Ltd., Japan; Dr Mario Fátala Chabén National Institute of Parasitology, Argentina; Drug Discovery Unit, University of Dundee, UK; El du Pont de Nemours, USA; Eisai Co., Ltd., Japan; Epichem, Australia; Eurofins, France; FP Clinical Pharma – Ethel Feleder, Argentina; GlaxoSmithKline, Spain and UK; Griffith Institute for Drug Discovery (GRIDD), Griffith University, Australia; Hospital Clínic de Barcelona, Spain; Hospital de Niños Ricardo Gutiérrez, Buenos Aires, Argentina; Hospital General de l'Hospitalet Consorci Sanitari Integral, Barcelona, Spain; Infectious Diseases Data Observatory, University of Oxford, UK; Institut Pasteur Korea, South Korea; Institute of Microbial Chemistry, Japan; Instituto de Física, Universidade de São Paulo, Brazil; Instituto de Química, Universidade Estadual de Campinas, Brazil; Instituto Nacional de Parasitología Dr Fátala Cháben, Argentina; Johnson & Johnson, USA; Kitasato Institute for Life Sciences, Japan; Laboratorio ELEA PHOENIX, Argentina; Laboratory of Microbiology, Parasitology and Hygiene, University of Antwerp, Belgium; LAT Research, Argentina; London School of Hygiene & Tropical Medicine, UK; Luxembourg Institute of Health, Luxembourg; McGill University, Canada; Médecins Sans Frontières; Medicines for Malaria Venture, Switzerland; Merck KGaA, Germany; Merck, USA; Mundo Sano Foundation, Argentina; National Council of Scientific and Technological Research (INGEBI-CONICET), Argentina; NHEPACHA network; Northwick Park Institute for Medical Research, UK; Novartis, Switzerland and USA; Nucleus of Pharmaceutical and Cosmetics Development, Brazil; Pfizer Inc., USA; Pfizer Inc. (formerly Anacor Pharmaceuticals Inc.), USA; PhinC, France; Platform of Integral Care for Patients with Chagas Disease, Spain/Bolivia; Sandexis, UK; Sanofi Merial, USA; Sanofi, France; Sequella Inc, USA; Shionogi & Co., Ltd., Japan; Swiss Tropical and Public Health Institute, Switzerland; Takeda Pharmaceutical Company Limited, Japan; TB Alliance, USA; TCG Life Sciences, India; Texas Biomedical Research, USA; Unidad de Enfermedades Infecciosas, Sección de Salud Internacional y Consejo al Viajero, Valencia, Spain; Universidad Autónoma Juan Misael Saracho, Bolivia; Universidad Mayor de San Simón, Bolivia; Universidad San Martín, Argentina; University Hospitals of Geneva, Switzerland; University of Cape Town, South Africa; University of Georgia Research Foundation, USA; University of Texas at El Paso, USA; Vall d'Hebron University Hospital, Spain; Walter Reed Army

Institute of Research, USA; WHO-TDR (Special Programme for Research and Training in Tropical Diseases); WuXi AppTech, China; Zoetis (formerly Pfizer Animal Health), USA



## Mycetoma

Eisai Co., Ltd., Japan; Erasmus Medical Center, The Netherlands; Free University Amsterdam, The Netherlands; Institute of Endemic Diseases, Khartoum University, Sudan; Mycetoma Research Centre, Soba University Hospital, Khartoum, Sudan; Radboud University Medical Center, Nijmegen, The Netherlands



## Filarial diseases

AbbVie, USA; AWOL, UK; Analytical Services International, UK; Bayer, Germany; Bonn University Hospital, Institute of Medical Microbiology, Immunology and Parasitology, Germany; Celgene Corporation, USA; Hammersmith Medicines Research, UK; Imperial College, UK; Institut Bouisson Bertrand, France; Liverpool School of Tropical Medicine, UK; Mahidol University, Thailand; Merck, USA; National Museum of Natural History, France; Niche Science and Technology, UK; Northwick Park Institute for Medical Research, UK; Salvensis, UK; University of Carolina, USA; University of Health and Allied Sciences, Ghana; University of Washington, USA;



## Paediatric HIV

AbbVie, USA; Associated Medical Sciences/PHPT International Research Unit, Thailand; Baylor College of Medicine Children's Foundation, Uganda; Centre for Disease Control and Prevention/President's Emergency Plan for AIDS Relief, USA; Children of God Relief Institute-Lea Toto Project/Nyumbani, Nairobi, Kenya; Cipla Ltd., India; Clinton Health Access Initiative, USA; Department of Health, South Africa; Epicentre, Uganda; Gertrude's Children's Hospital, Kenya; Ifakara Health Institute, Tanzania; Institute of Tropical Medicine, Antwerp; Joint Clinical Research Centre, Fort Portal, Uganda; Joint Clinical Research Centre, Gulu, Uganda; Joint Clinical Research Centre, Kampala, Uganda; Kenya Medical Research Institute/FACES Project/St Lumumba Health Centre, Kisumu, Kenya; Kenyatta National Hospital, Kenya; Management and Development for Health, Tanzania; Mbagathi District Hospital, Kenya; Médecins Sans Frontières; Medical Research Council, UK; Ministry of Health, Kenya; Moi Teaching and Referral Hospital, Kenya; Necker Institute, France; Swiss Tropical and Public Health Institute, Switzerland; University of Nairobi, Kenya; various academic partners in South Africa, Kenya, Uganda, and Tanzania



## Hepatitis C

Associated Medical Sciences/PHPT International Research Unit, Thailand; Clinical Research Malaysia, Ministry of Health, Malaysia; Doppel Farmaceutici, Italy; Hospitals of Geneva, Switzerland; Hospital Kuala Lumpur, Malaysia; Insud Pharma/Elea, Argentina; Médecins Sans Frontières, Ukraine; Ministry of Health, Thailand; Ministry of Industry, Science and Technology, Thailand; Mundo Sano Foundation, Argentina; Pharco Pharmaceuticals Inc, Egypt; Pharmaniaga, Malaysia; Presidio Pharmaceuticals, USA