

2017 Annual Report

# Responding to Neglected Patients' Needs Through Innovation

**DNDi**

Drugs for Neglected Diseases *initiative*

# Vision

- To improve the quality of life and the health of people suffering from neglected diseases by using an alternative model to develop drugs for these diseases, and by ensuring equitable access to new and field-relevant health tools.
- In this not-for-profit model, driven by the public sector, a variety of players collaborate to raise awareness of the need to research and develop drugs for those neglected diseases that fall outside the scope of market-driven research and development (R&D). They also build public responsibility and leadership in addressing the needs of these patients.

# Mission

- To develop new drugs or new formulations of existing drugs for **people living with neglected diseases**. Acting in the public interest, DNDi bridges existing R&D gaps in essential drugs for these diseases by initiating and coordinating drug R&D projects in collaboration with the international research community, the public sector, the pharmaceutical industry, and other relevant partners.
- DNDi's **primary focus** has been the development of drugs for **the most neglected diseases**, such as human African trypanosomiasis (HAT, or sleeping sickness), leishmaniasis, and Chagas disease, while considering engagement in R&D projects for other neglected patients (e.g. malaria, paediatric HIV, filarial infections) and development of diagnostics and/or vaccines to address unmet needs that others are unable or unwilling to address.
- In pursuing these goals, DNDi enables R&D networks built on global collaborations. While harnessing existing support capacities in countries where the diseases are endemic, DNDi contributes to **strengthening capacities in a sustainable manner**, including through know-how and technology transfers in the field of drug R&D for neglected diseases.
- In order to address evolving needs of public health importance and maintain DNDi's commitment to delivering on the objectives of the current portfolio of diseases, **a dynamic portfolio approach** has been adopted. This enables DNDi to take on new disease areas with various operating models, while completing objectives in current diseases.

The Drugs for Neglected Diseases *initiative* (DNDi) is a collaborative, patient-needs driven, not-for-profit research and development (R&D) organization that develops safe, effective, and affordable treatments for the millions of people across the world affected by neglected diseases, notably human African trypanosomiasis (sleeping sickness), leishmaniasis, Chagas disease, filarial infections, paediatric HIV, mycetoma, and hepatitis C.

Launched in 2016 by the World Health Organization (WHO) and DNDi, the Global Antibiotic Research & Development Partnership (GARDP) aims to develop and deliver new treatments for bacterial infections where drug resistance is present or emerging, or for which inadequate treatment exists, while endeavouring to ensure sustainable access. GARDP is currently operating within DNDi, which provides its governance.

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# Message

## from the Chair of the Board and the Executive Director

**Dr Marie-Paule Kieny**  
Chair of the Board of Directors



**Dr Bernard Pécoul**  
Executive Director



DND*i* will be marking the 15<sup>th</sup> year since its founding in late 2018, an anniversary which comes at an exciting time in DND*i*'s growth. Our pipeline is maturing, and significant scientific milestones are on the cusp of being reached.

We have delivered seven treatments to date for five diseases. This illustrates the wisdom of having invested early on, not only in long-term projects to discover and develop new chemical entities (NCEs), but also in short-term projects that would have a more immediate impact on improving clinical care for patients. In the coming years, we anticipate being able to deliver further treatments based on new formulations, combinations, or regimens using existing drugs.

Our investments in drug discovery are beginning to bear fruit. DND*i*'s portfolio currently includes more than 20 NCEs that are adapted to the needs of patients. Some will contribute to supporting the sustainable elimination of several neglected tropical diseases (NTDs).

Most excitingly perhaps, fexinidazole, DND*i*'s first NCE, is today in the last stages of regulatory approval, submitted by our industrial partner Sanofi. If successful, 'fexi' will be the first all-oral treatment for sleeping sickness, eliminating the need for a lumbar puncture to differentiate the stages of the disease, and could facilitate the elimination of this old tropical disease, in line with WHO's ambitious targets.

For leishmaniasis, after more than a decade of research efforts and progress, a new path is opening up for the development of novel drugs. Two NCEs were nominated as pre-clinical candidates over the past year. DND*i* is gathering partners around a new shared objective, with the creation of a new consortium bringing together GlaxoSmithKline, Novartis, Celgene, Takeda, Pfizer, the University of Dundee, and the Wellcome Trust that will lead to a radical breakthrough for patients in coming years.

### Engaging with partners

First, we have broken new ground through our partnerships, contributing to Grupo Insud's successful registration of the first treatment to be approved in the US for Chagas disease. With Insud's non-profit partner Fundación Mundo Sano, we created a new far-reaching framework to work with countries, the Pan-American Health Organization and other groups to give a much-needed boost to the response to Chagas and put an end to the unacceptable situation where only 1% of infected people today have access to diagnosis and treatment. These efforts will be boosted by the sale of Insud's priority review voucher, the first time this scheme has been voluntarily put towards benefitting neglected patients.



Second, for hepatitis C, we have forged alliances with Pharco Pharmaceuticals, the Ministries of Health of Malaysia and Thailand, Doctors Without Borders (MSF), and the Foundation for Innovative New Diagnostics (FIND) that promise to have transformational outcomes. A decisive milestone was achieved in 2017 with the successful completion of our clinical trials in these countries, showing that ravidasvir is as safe and effective as the very best of existing treatments. Thanks to Pharco's pro-public health approach to pricing, the new drug could benefit countries currently blocked from accessing affordable options. Combined with MSF's and FIND's work to simplify models of care, DNDi is eager to work towards providing countries with what could be tools for a public health approach to the disease.

## The need for political leadership

Beyond all these initiatives, we are aware that a comprehensive approach to answering global health needs also requires strong political leadership, and the commitment of countries and global health leaders.

In that sense, the decision of the Malaysian government in September 2017 to issue a "government use" licence enabling access to more affordable versions of an expensive and patented medicine to treat hepatitis C must be applauded. This landmark decision is helping the more than 400,000 people living with hepatitis C in Malaysia to access treatment. It could also have an important impact on the global effort to secure access to effective and affordable treatments for this viral disease.

In a different vein, the ambitious programme on universal health coverage from the WHO Director-General, Dr Tedros, is appreciable and a matter of considerable relevance for both NTDs and antimicrobial resistance.

Last but not least, the G20 Ministers of Health Summit under Germany's presidency has pledged to invigorate research and development efforts to find new drugs. During a pledging event in Berlin to address this emerging global health concern, Germany also led on galvanizing support for the Global Antibiotic Research and Development Partnership (GARDP), created jointly by DNDi and WHO in 2016 to develop and deliver new or improved antibiotic treatments. Such support has allowed the concrete embodiment of DNDi's incubation of GARDP and the fast maturation of GARDP's programmes, swiftly moving from concept to action.

As DNDi prepares to celebrate its 15th anniversary this coming year, we will no doubt be looking back on the long journey we embarked on when the founding partners of DNDi refused to accept as a given that neglected populations must continue to be forgotten by medical innovation. Behind all the work we do to effectively address this challenge is a network of devoted staff, committed donors, and engaged partners who together make it all happen and possible.

On behalf of DNDi, we would like to simply express our sincere gratitude. Thank you!



Dr Marie-Paule Kieny



Dr Bernard Pécoul



## In memory of Whim Manogo

Whim joined DNDi Africa Regional Office in 2016 as Finance Manager and played an important role in the Nairobi office. He passed on after a short illness on 15 March 2018. We have lost a valuable, professional, optimistic, and friendly member of the DNDi team. Whim is deeply missed by his family, friends, and colleagues.



# 2017 highlights

## Partnering to maximize impact

Read about DND's key achievements in 2017 with:

- a recap of 2017 in numbers,
- a presentation of our activities worldwide,
- an update on R&D progress by phase of product development,
- a summary on the successful incubation of the antimicrobial initiative GARDP,
- an overview of our capacity-strengthening efforts,
- progress on increasing access to treatment, and
- policy, fundraising, and communications activities.

# 2017 in numbers

44  
R&D PROJECTS  
UNDERWAY

covering every  
stage of the R&D  
process

12

new R&D  
partnerships

221  
PEOPLE

working  
at DNDi  
*(core staff and  
consultants)*

869  
PEOPLE

working on  
DNDi projects  
in partner  
organizations

170,407  
COMPOUNDS  
SCREENED

to look for  
promising “hits”  
as potential  
drug candidates

3+2

3 COMPOUNDS  
advanced to pre-  
clinical stage, and  
2 CANDIDATES  
advanced to clinical  
development

21  
CLINICAL  
TRIALS

in progress in  
7 disease areas  
at 52 sites in  
15 countries

OVER  
2,500  
PATIENTS

enrolled in the  
clinical studies  
completed in 2017



666,917

PEOPLE

screened for sleeping sickness by 10 mobile teams in DR Congo and treated for a variety of diseases

685

PEOPLE

trained to support clinical research, from Good Clinical Practice to the use of new diagnostic technologies and processes

2

TECHNOLOGY  
TRANSFERS

in Malaysia and in Latin America – for the manufacture and supply of hepatitis C treatments

6

NATIONAL  
TREATMENT  
POLICIES

or guidelines revised to reflect the use of DNDi-delivered treatment, and 4 policy changes in progress

22

PEER-REVIEWED  
SCIENTIFIC  
PUBLICATIONS

on DNDi's research, of which 87% were open access publications

AROUND  
1,500SCIENTISTS,  
RESEARCHERS, AND  
POLICYMAKERS

met in Toledo, Spain, in May at WorldLeish6

*(co-organized by DNDi and the Instituto de Salud Carlos III, Madrid)*

EUR  
83.4  
MILLION

Multi-year funds secured for DNDi and GARDP in 2017

EUR  
6  
MILLION

Value of in-kind contributions from partners



# DNDi worldwide

## Closer to neglected patients and our partners

DNDi's regional offices are fundamental to our patient- and partnership-driven model, and essential to DNDi's strategy, identity, and credibility. Regional offices, which house half of DNDi staff, ensure the organization remains rooted in neglected disease-endemic countries, and provide all-important proximity to neglected patients, partners, clinicians, and researchers who best understand their needs and contexts. They also help DNDi influence disease policy at national level.

### DNDi India in 2017

- Support of Indian National Kala-azar Elimination Programme in building capacity to diagnose kala-azar and post-kala-azar dermal leishmaniasis (PKDL)
- Study to determine prevalence of PKDL in previously treated leishmaniasis patients
- Technical partner in an MSF study on kala-azar-HIV co-infection in Bihar, testing treatments with AmBisome monotherapy and AmBisome-miltefosine combination
- Start of a clinical trial for PKDL, testing AmBisome monotherapy and AmBisome-miltefosine combination
- Expansion of the Open Source Network project with an additional Indian university

### DNDi Latin America in 2017

- Completion of recruitment in the clinical study of new regimens of benznidazole monotherapy and in combination with fosravuconazole in Bolivia for the treatment of Chagas disease
- Start of a Phase II clinical study in Spain to test short courses of fexinidazole for Chagas disease
- Implementation of a new, simplified diagnostic algorithm and treatment for all patients with Chagas disease, including chronic patients, as part of the pilot Chagas Access Programme in Colombia
- Start of a clinical study on cutaneous leishmaniasis combining thermotherapy with miltefosine in Colombia and Peru

## DNDi North America in 2017

- Approval by the U.S. Food and Drug Administration (FDA) of Chemo Group's (now InSud Pharma) benznidazole for children with Chagas disease in close collaboration with Exeltis, Mundo Sano, and DNDi
- A DNDi-supported survey of almost 5,000 Latin American-born residents of Los Angeles County found that 1.24% tested positive for Chagas disease
- Advocacy at the UN High-Level Political Forum on Sustainable Development in New York and continued support for global health R&D in Washington, DC in a changing political environment
- A campaign to raise funds for African sleeping sickness secures over USD 500,000 in new private contributions that will help put the disease on the path to sustainable elimination

## DNDi Headquarters - Switzerland

- Strategic leadership and coordination of research and development, from drug discovery through clinical development and registration
- Administrative and support departments, including finance, human resources, IT, policy advocacy, communications, and fundraising
- About half of all DNDi staff
- Re-organization process started in 2017 to ensure structure keeps pace with evolution of DNDi portfolio.

## DNDi Japan in 2017

- NTD Drug Discovery Booster presented with Japanese pharmaceutical partners at the Annual Meeting of the Pharmaceutical Society of Japan
- Official side event on NTDs at the Universal Health Coverage Forum in partnership with Uniting to Combat NTDs, Nagasaki and St Luke's International Universities
- Renewed support of GHIT Fund to projects on leishmaniasis, Chagas disease, and eumycetoma

## DNDi South-East Asia in 2017

- After completion of patient recruitment in the sofosbuvir/ravidasvir clinical study for hepatitis C in Malaysia, start of recruitment in Thailand
- Approval by Malaysia of a "government use" licence to secure access to more affordable treatments for hepatitis C
- Agreement signed between pharmaceutical companies Pharmaniga (Malaysia) and Pharco Pharmaceuticals (Egypt), and DNDi to supply affordable hepatitis C treatment in Malaysia

## DNDi Africa in 2017

- Support for the first-ever clinical trial in eumycetoma, studying the efficacy of the anti-fungal drug fosravuconazole at the Mycetoma Research Centre, Sudan
- Preliminary evaluation of the paediatric HIV 'LIVING' study: high levels of viral suppression in infants and young children after 48 weeks of treatment
- Initiation of the first site for the miltefosine/paromomycin clinical trial in Sudan for visceral leishmaniasis (VL) in Eastern Africa
- Community meetings in Amudat, Uganda, and Kacheliba and West Pokot, Kenya to share findings of the miltefosine dosing clinical trial in children with primary VL
- Stakeholders' meeting in Addis Ababa, Ethiopia on clinical trial for HIV/VL coinfecting patients
- ISO 9001:2008 certification (quality management systems) received for Nairobi office

## DNDi DR Congo in 2017

- Support completion of fexinidazole clinical studies in adults (stage 1 and 2) and children with sleeping sickness
- Start of Phase IIIb study in seven clinical sites in DR Congo to generate information on fexinidazole in special population groups in in- and out-patients
- Start of Phase II/III study in nine clinical sites in DR Congo to test acoziborole as a single-dose treatment in patients with stage 1 or 2 sleeping sickness

## DNDi South Africa in 2017

- Opening of a new DNDi-GARDP joint liaison office in Cape Town
- Collaboration agreement with South African Medical Research Council

A woman in a white lab coat, blue surgical mask, and a colorful patterned hairnet is working in a laboratory. She is wearing white gloves and is focused on a task at a lab bench. A microscope is visible in the background.

# Research & development

## Portfolio maturing towards delivering innovative treatments

Given the urgency to provide better treatments for neglected diseases and neglected patients, DNDi's first research and development (R&D) strategies focused on developing new formulations, combinations, or regimens based on existing drugs. Seven new treatments have been delivered, and efforts continue to improve existing options for leishmaniasis, Chagas disease, and paediatric HIV.

As we approach the 15th anniversary of DNDi's experiment in public health-driven R&D, our portfolio has significantly matured. Our pipeline is strong and growing, with 20 new chemical entities (NCEs) for six out of the seven diseases in the portfolio. Our most advanced NCE, fexinidazole, has reached the very last steps before registration. Acoziborole, the first NCE arising from DNDi's own discovery and lead optimization efforts, is in late-stage clinical development, and the next wave of NCEs is now entering clinical development.

In addition, the Global Antibiotic Research & Development Partnership (GARDP), created jointly in 2016 by DNDi and WHO, started three R&D initiatives on neonatal sepsis, sexually-transmitted infections, and a Memory Recovery, Discovery, and Exploratory programme.

This maturation is the fruit of years of support from our donors and our investments, not least in innovative approaches to identify and select promising compounds, to build new alliances with partners, or to create new pathways to address neglected patient needs.

### New mechanisms

In the past four years we operated a strategic shift in our collaboration with partners, moving from bilateral to multilateral approaches to partnerships. This maximizes our chances of reaching high-quality drug hits, optimizes the



research capacity of multiple partners, and reduces time and costs. Examples include the Drug Discovery Booster, the Open Synthesis Network, and collaborations with other product development partnerships, such as Medicines for Malaria Venture with the Pandemic Response Box.

## New alliances

Further strengthening our virtual model, DNDi consolidated new alliances with a range of partners. This includes, for example, hit-to-lead optimization activities with Daiichi Sankyo, multilateral drug development activities with partners in Malaysia (Pharmaniaga), Egypt (Pharco), and Argentina (Elea/Insud) for HCV, and with US biotech Entasis Therapeutics for GARDP's gonorrhea programme.

Older alliances have taken new directions in 2017. Following the registration of benznidazole to treat Chagas disease in the US, our long-standing partnership with the Fundación Mundo Sano will develop new activities to boost access to treatment through a new Chagas Disease Regional Access Framework. For leishmaniasis, DNDi is gathering established partners around a new shared objective, with the creation of a new consortium to consolidate the strong pipeline of NCEs and hopefully leading to what would be

a radical breakthrough for patients in coming years, the development of an oral treatment based on combined NCEs.

## New pathways

Fruitful engagement with regulatory actors is critically important to ensure broader access. Together with Cipla, DNDi is working with the US FDA to obtain guidance for submission of new treatments for children living with HIV. We are also engaged in new mechanisms with Argentina and Malaysia to facilitate, review, and accelerate approvals of a new drug for hepatitis C. Lastly, by selecting the European Medicines Agency's Article 58 (intended for medicines that will be used outside the European Union) as a channel for the regulatory review of fexinidazole, DNDi and Sanofi, together with the World Health Organization, are able to involve two endemic countries (DR Congo and Uganda) in the evaluation of the regulatory dossier, in preparation for future in-country registration and uptake.

As regulatory capacity building gains momentum in new regions of the world, DNDi hopes to play a catalysing role in using these new mechanisms, favouring collaborative pathways for better and faster access to treatments, to bring the best science to the most neglected.



# Key R&D achievements in 2017



## DRUG DISCOVERY

The Open Synthesis Network project to crowdsource drug compound production grows to 12 university partners in Brazil, India, Switzerland, the UK, and the US. Two new partners join the NTD Drug Booster, all working collaboratively to accelerate drug discovery for leishmaniasis and Chagas, with 10 hit series identified and four novel series progressing into the discovery pipeline. A successful discovery programme results in the nomination of DNDI-5561 as a new pre-clinical candidate for leishmaniasis.



## HUMAN AFRICAN TRYPANOSOMIASIS

A regulatory dossier is submitted by Sanofi to the European Medicines Agency for fexinidazole as the first all-oral treatment for sleeping sickness, following results from the Phase II/III study which proved "fexi" to be safe and effective. The introduction of fexinidazole would be revolutionary as it would end the need for invasive lumbar punctures to stage patients and for systematic hospitalization.



## LEISHMANIASIS

DNDi and partners build up an unprecedented portfolio of 10 chemical classes, including four lead series, four pre-clinical candidates, and two clinical candidates to progress to Phase I, with the ultimate aim of developing two entirely new treatment combinations for both visceral and cutaneous leishmaniasis, in all regions. Meanwhile, studies begin in South Asia, Latin America, and East Africa to test new regimens for post-kala-azar dermal leishmaniasis, cutaneous leishmaniasis, and visceral leishmaniasis. And the results of a trial showing the efficacy of a potential new first-line regimen for HIV/VL co-infection are presented in Ethiopia.



## CHAGAS DISEASE

Insud's benznidazole is registered in the US, supported by DNDi. This is the first drug approved by the FDA to treat Chagas disease. Insud is granted a priority review voucher – 50% of revenue derived from its sale will support access to Chagas treatment, notably through the new Chagas Disease Regional Access Framework developed by DNDi and Fundación Mundo Sano. The search for better treatment options goes on, with recruitment completed in the Phase II study of new regimens of benznidazole, and benznidazole in combination with fosravuconazole in Bolivia, and a study launching in Spain to evaluate short-course fexinidazole regimens.



## FILARIAL DISEASES

DNDi continues to build a diverse portfolio of potential macrofilaricides (drugs that kill adult filarial worms) in order to provide a needed cure for patients. Phase I studies in healthy volunteers begin for both Bayer's emodepside, which targets adult worms, and AbbVie's antibiotic TylAMac, which targets the endosymbiotic bacteria (Wolbachia) that live in some filarial worms and are essential for the worms' survival.



## MYCETOMA

Patients are enrolled in Sudan in the first-ever double-blind, randomized clinical trial for eumycetoma (the fungal version of mycetoma), assessing fosravuconazole as a potential new treatment for this extremely neglected and disfiguring disease.



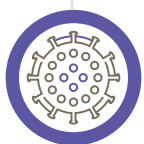
## PAEDIATRIC HIV

A first-line “4-in-1” fixed-dose combination of abacavir, lamivudine, lopinavir, and ritonavir granules is on track to be submitted for US FDA registration in late 2018 to radically improve treatment options for young children living with HIV. In the meantime, results from the LIVING study show that “2-in-1” lopinavir/ritonavir pellets improve treatment outcomes for children, and are well adopted by caregivers.



## GARDP

GARDP enters into partnership with Entasis to develop a novel, first-in-class antibiotic for gonorrhoea. A feasibility survey assesses and identifies potential sites for a neonatal sepsis observational study planned in 2018, as an epidemiology survey indicates high levels of drug resistance in neonatal units. Regulatory approval is granted to conduct a clinical trial to confirm dose and safety of fosfomycin, a drug not widely used in newborns with sepsis. GARDP’s memory recovery workstream reviews around 20 assets from pharmaceutical companies for their potential value for antimicrobial drug development.



## HEPATITIS C

Treatment is completed by all 301 patients in a Phase II/III trial combining ravidasvir and sofosbuvir in Malaysia and Thailand, with 97% cured overall and high cure rates for the hardest-to-treat (cirrhotic) patients. This means the combination is equivalent to the best therapies in use today, raising hope for alternative affordable options for countries unable to access generic treatments.



# DNDi R&D Portfolio

December 2017



RESEARCH				TRANSLATION		
	SCREEN	HIT TO LEAD	LEAD OPT.	PRE-CLINICAL	PHASE I	PHASE IIA/POC
HUMAN AFRICAN TRYPANOSOMIASIS			<div>● SCYX-1330682</div> <div>● SCYX-1608210</div>			
LEISHMANIASIS	Screening	<div>Leish H2L</div> <div>Booster H2L</div> <div>Daiichi-Sankyo LH2L</div>	<div>● DNDI-5421</div> <div>● DNDI-5610</div> <div>● Amino Pyrazoles</div> <div>● CGH VL Series 1</div> <div>● Leish L205 Series</div>	<div>● DNDI-6148</div> <div>● DNDI-0690</div> <div>● DNDI-5561</div> <div>● GSK3186899</div> <div>● DDD853651</div> <div>● GSK3494245</div> <div>● DDD1305143</div> <div>● CpG-D35 (CL)</div>		<div>New CL Combinations</div>
CHAGAS DISEASE	Screening	<div>Chagas H2L</div> <div>Booster H2L</div> <div>Daiichi-Sankyo CH2L</div>	<div>Biomarkers</div> <div>● Chagas C205 Series</div>			<div>New Benz</div> <div>● Regimens +/- Fosravuconazole</div> <div>● Fexinidazole</div>
FILARIAL DISEASES	Screening		<div>● Macro Filaricide 3</div>	<div>● Oxfendazole</div>	<div>● Emodepside</div> <div>● ABBV-4083</div>	
MYCETOMA						
PAEDIATRIC HIV					<div>Two '4-in-1' LPV/r/ABC/3TC</div>	
HEPATITIS C						
MALARIA	Malaria portfolio was transferred to MMV in 2015.					

● New Chemical Entity (NCE)





DEVELOPMENT		IMPLEMENTATION
PHASE IIB/III	REGISTRATION	ACCESS
<ul style="list-style-type: none"> <li>Acoziborole</li> </ul>	<ul style="list-style-type: none"> <li>Fexinidazole</li> </ul>	NECT Nifurtimox-Eflornithine Combination Therapy
New Treatments for HIV/VL New Treatments for PKDL MF/Paromomycin Combo for Africa	New VL Treatments Latin America	SSG&PM Africa New VL Treatments Asia
		Benznidazole Paediatric Dosage Form
<ul style="list-style-type: none"> <li>Fosravuconazole</li> </ul>		
	LPV/r Pellets with Dual NRTI	Superbooster Therapy Paediatric HIV/TB
<ul style="list-style-type: none"> <li>Ravidasvir/ Sofosbuvir</li> </ul>		
		Malaria FDC ASAQ
		Malaria FDC ASMQ

# 7 new treatments delivered, recommended & implemented since 2007



## 2007 **ASAQ\*** MALARIA

Partnership  
with Sanofi



- Once daily fixed-dose artemisinin-based combination for 3 days, in 4 dosage forms
- WHO prequalified (2008) and WHO Essential Medicines Lists (adults and children)
- Registered in 32 African countries, plus India, Ecuador, and Colombia
- 500 million treatments delivered since 2007
- Technology transfer to Zenufa (Tanzania)

## 2008 **ASMQ\*** MALARIA

Partnership with  
Farmanguinhos/Fiocruz  
(Brazil)



- Once daily fixed-dose artemisinin-based combination for 3 days, in 4 dosage forms
- WHO prequalified (2012) and WHO Essential Medicines Lists (adults and children)
- Registered in 11 countries in Asia, Latin America, and Africa
- South-South technology transfer to Cipla (India)

## 2009 **NECT** HUMAN AFRICAN TRYPANOSOMIASIS (HAT)

Partnership with MSF,  
Epicentre, national  
control programmes, and  
WHO



- First new treatment for HAT in over 25 years, replacing complex and toxic melarsoprol treatment that killed 5% of those treated
- 14 intravenous infusions of eflornithine over 7 days + oral nifurtimox 3 times/day for 10 days
- WHO Essential Medicines Lists (adults and children)
- First-line treatment in the 13 endemic countries in sub-Saharan Africa
- Free supply from WHO via drug donations by Sanofi and Bayer to endemic countries

\* Projects handed over to Medicines for Malaria Venture in 2015

## 2010 **SSG&PM** VISCERAL LEISHMANIASIS IN EAST AFRICA

Partnership with the Leishmaniasis East Africa Platform (LEAP), national control programmes, MSF, and WHO



- Intramuscular injection once per day for 17 days (instead of 30 days previously)
- Recommended by the WHO Expert Committee on the Control of Leishmaniases (2010) as safe and effective treatment for VL in East Africa
- Included in national treatment guidelines of Ethiopia, Kenya, South Sudan, Sudan, and Uganda

## 2011 **PAEDIATRIC BENZNIDAZOLE** CHAGAS DISEASE

Partnership with LAFEPE (Brazil) to develop the first paediatric treatment for Chagas (early 2018)



- Child-adapted dose of 12.5 mg per tablet twice daily for 60 days (children were previously treated with fractioned tablets designed for adults)
- WHO Essential Medicines List (children)
- Collaboration with Fundación Mundo Sano (FMS) and Laboratorio ELEA PHOENIX, Argentina to develop a second source
- Registered in Brazil (2011) and in Argentina (2018)

## 2011 **NEW VL TREATMENTS ASIA** VISCERAL LEISHMANIASIS IN ASIA

Partnerships with kala-azar actors in South Asia including the MoH, research institutes, NGOs, and WHO-TDR



- Better combination therapies for South Asia to replace treatments with severe side effects and growing drug resistance
- Recommended by the WHO Expert Committee on the Control of Leishmaniases (2010) as safe and effective treatments for VL in Asia (AmBisome single or multiple dose, and all combinations tested in DNDi's clinical trial)
- Policy change supported for the control and elimination of kala-azar in highly endemic countries (India, Bangladesh, Nepal)

## 2016 **SUPERBOOSTER THERAPY** PAEDIATRIC HIV

Partnership with Cipla



- More effective treatment for children co-infected with HIV and tuberculosis (TB)
- "Super-boosting" the dose of ritonavir, an antiretroviral used to treat HIV in children, counteracts negative interactions between common TB drug rifampicin and HIV therapy
- WHO revised its guidelines to recommend "superboosting" of ritonavir when treating co-infected children (2016)

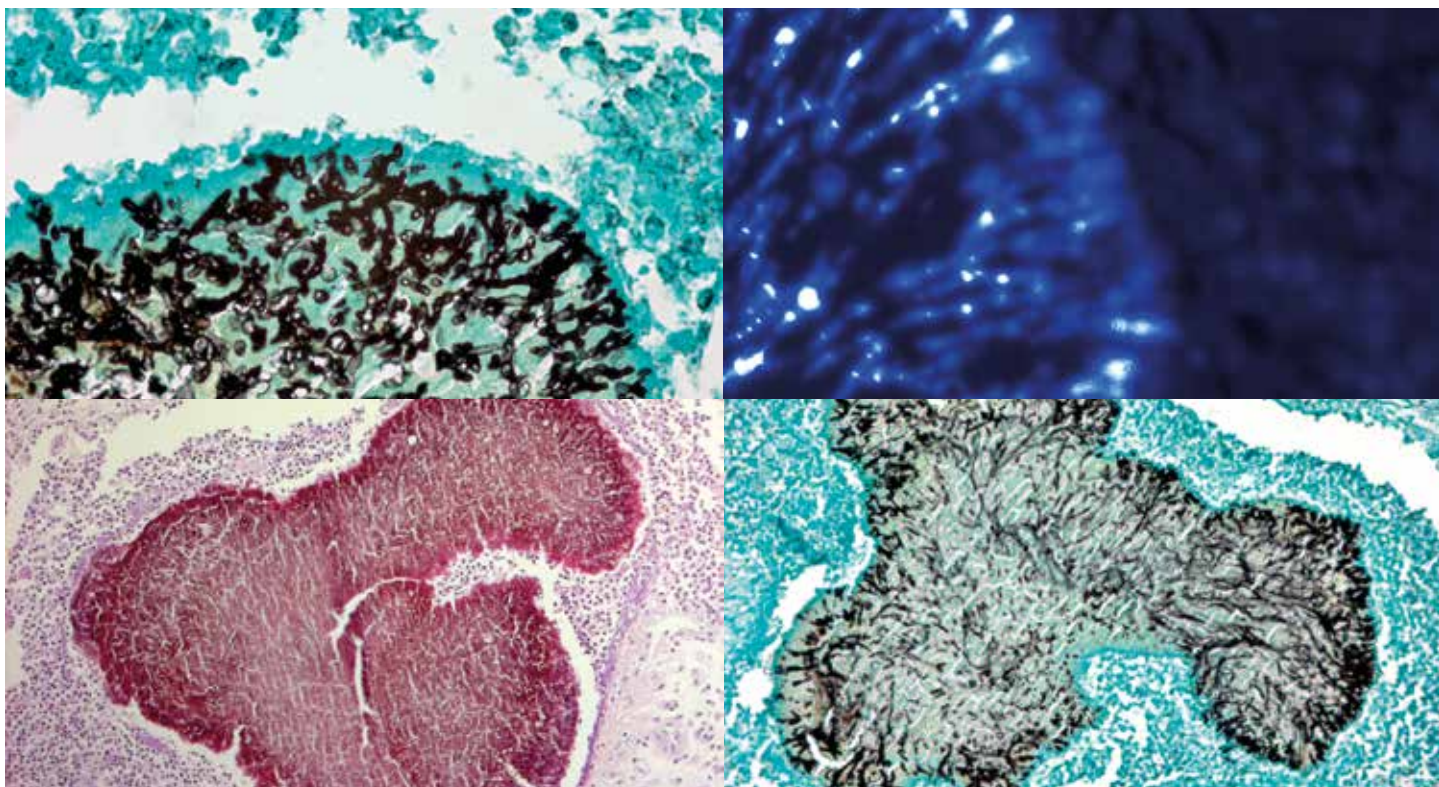
# Drug discovery and open approaches for increased efficiency

DNDi works through collaborations in all phases of drug research and development. In the very earliest stages of drug discovery, from molecule screening through to lead selection and optimization, this collaborative work takes place through key partnerships and drug discovery consortia that DNDi has gradually put in place over the last 15 years. Consortia are working on hit-to-lead and lead optimization activities for visceral leishmaniasis (VL) and Chagas disease with partners in the US, Canada, Europe, China, India, Japan, Korea, Australia, and finally Brazil where DNDi's first early-stage research programme, *Lead Optimization Latin America* (LOLA), was launched in a neglected disease-endemic country.

With many world-class research institutions and global pharmaceutical organizations, India is rich in both scientific knowledge and infrastructure. DNDi is building a *Lead*

*Optimization Consortium in India* (LOCI) with multidisciplinary drug discovery partners to focus on early-stage discovery and optimization of novel pre-clinical candidates against VL. Partners are being identified from across India with capabilities and expertise including medicinal and synthetic chemistry; parasitology screening; microbiology; structural biology; absorption, distribution, metabolism, and excretion (ADME) and pharmacokinetics; and toxicology.

Since 2015, DNDi has been exploring open innovation approaches to drug discovery, through which a variety of partners collaborate without the restraints of intellectual property. Open innovation at DNDi now ranges from working with university chemistry teaching labs, to a virtual Open Pharma community that supports the lead optimization of chemical compounds that could one day become new medicines.



*Madurella mycetomatis* in culture medium and in *in vitro* susceptibility assays.



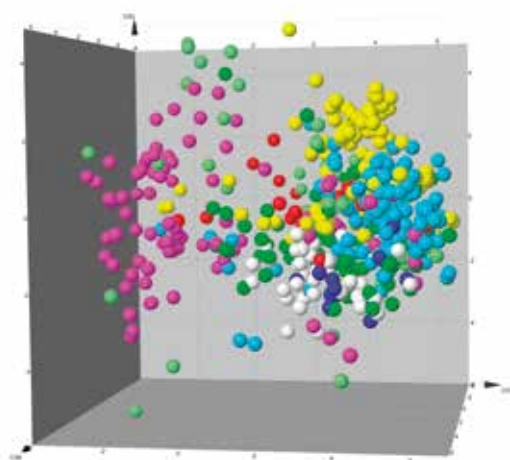
## NTD Drug Discovery Booster – speeding up drug discovery & cutting costs

With the addition of two new partners in 2017, and one so far in 2018, the NTD Drug Discovery Booster project now includes eight pharmaceutical company partners, all working in tandem to screen millions of compounds based on an active “seed” compound supplied by DNDi. The Booster aims to accelerate the process and cut the cost of finding new treatments for leishmaniasis and Chagas disease.

With the support of the Japanese GHIT Fund, the project brings together eight pharmaceutical companies: AbbVie, Astellas Pharma Inc., AstraZeneca plc, Celgene Corporation, Eisai Co., Ltd., Merck, Shionogi & Co., Ltd., and Takeda Pharmaceutical Limited.

By using a simultaneous search process across the eight global pharmaceutical companies, DNDi can access millions of unique compounds, generated over many decades of research, to screen for molecules that hold promise for further development as potential drug candidates.

The Booster has provided twelve hit series so far and compounds from four of these have been investigated for proof of principle. Two compounds demonstrated *in vivo* efficacy, and improved compounds are scheduled for profiling in 2018. Improved compounds from two other series will be investigated.



A « chemical space » projection of a representative booster screen demonstrates how each of the booster partners provides different yet complimentary answers to the same question (contributions coloured according to partner).

## Open Synthesis Network – crowdsourcing compound synthesis

The Open Synthesis Network (OSN) was launched in 2016 to harness the capacity of chemistry teaching labs to help discover new drugs for patients living with neglected diseases. Through OSN, DNDi engages master's and undergraduate students in research for leishmaniasis – and along the way introduces some of the best and brightest to the possibility of a career in medicinal chemistry. With the addition of six new partners in 2017, OSN now includes 12 universities in Brazil, India, Switzerland, Germany, the UK, and the US.

DNDi approaches universities with real problems from selected lead optimization programmes, and graduate and final-year undergraduate students are given the challenge of synthesizing proposed analogues as part of their practical training, rather than the more traditional synthesis of well-known substances such as aspirin, as is usual in chemistry teaching labs. Their compounds are tested and the data returned to the students, who may then propose further analogues for testing, thereby building up a rich source of information that may ultimately lead to the development of a life-saving drug.

Students are currently working on compounds that target *leishmania donovani* and *leishmania infantum*, the parasites that cause visceral leishmaniasis, as well as compounds focused on *trypanosoma cruzi*, the causative agent of Chagas disease. Any successful compounds that come from the OSN project will be evaluated further as part of DNDi's discovery pipeline, with the goal of developing oral drugs that are easy to administer and have fewer side effects than existing treatments.

Part of the network: Shobhaben Pratapbhai Patel School of Pharmacy & Technology Management at Narsee Monjee Institute of Management Studies (NMIMS), Mumbai, India; Indian Institute of Chemical Technology (IICT), Hyderabad, India; Imperial College, London, UK; Northeastern University, Boston, USA; Pace University, New York City, USA; Duke University, Durham, USA; Haverford College, USA; Indian Institute of Technology (IIT), Gandhinagar, India; Miami University, USA; University of Geneva, Switzerland; University of Washington Tacoma, USA; and the Federal University of Rio de Janeiro (UFRJ), RJ, Brazil.

# Translational research: joining forces for new chemical entities

Translational research transitions promising drug candidates from drug discovery programmes through early development stages, assessing safety and tolerability in human volunteers, to full and clinical development, evaluating drug efficacy and safety in patients through large-scale studies. In the first part of the translational phase, researchers assess the safety and tolerability of a drug in animals and investigate routes for large-scale production and suitable formulations for dosing, before moving for the first time to studies in healthy volunteers. They also investigate how the drug is metabolized and excreted, develop drug formulations, establish therapeutic dosing requirements, and study the risks of drug-drug interactions. A promising compound can then advance to proof-of-concept studies (POC) in limited numbers of patients to make a provisional assessment of whether the drug has the desired effect on the infectious disease.

Since the success rate for each compound in the translational phase is less than 20% – the average success rate is 55% in pre-clinical studies, 70% in Phase I studies and only 50% in POC studies<sup>1</sup> – it is critical that the research and development portfolio is filled with multiple drug candidates for each disease, to ensure the delivery of novel drugs. Hence the importance of collaborating with several partners, who are working on



## Identifying new drug combinations for an old disease

One of the biggest challenges for translation teams is identifying the best combination of drugs to treat specific diseases. Drug combinations can maximize treatment outcomes whilst shortening treatment duration and minimizing the potential for the development of drug resistance. Combination therapy is expected to be particularly beneficial for treating visceral leishmaniasis (VL), HIV/VL co-infection, post-kala-azar dermal leishmaniasis, and cutaneous and mucocutaneous leishmaniasis.

To identify potential drug combinations to be assessed in clinical trials, drugs that are antagonistic (i.e., no benefit from combining them) must be excluded to prioritize instead those that have additive or, ideally, synergistic effects (i.e., more effective than when used separately). To this end, in 2017 DNDi initiated an *in vitro* assessment of drug combinations using *Leishmania donovani* assay models in collaboration with DNDi's long-time partner, the Swiss Tropical and Public Health Institute (Swiss TPH). Exploration of new combinations *in vitro* is likely to be expanded to include new partners in 2018.



<sup>1</sup> Solomon N and Ridley RG. Virtual drug discovery and development for neglected diseases through public-private partnerships. *Nature Reviews, Drug Discovery*. 2003;2:919-928:5-15.

different chemical classes, to maximize chances to discover the best compound to be progressed through the portfolio.

2017 saw important progress with new chemical entities (NCEs) advanced to Phase I studies for the treatment of onchocerciasis (river blindness): ABBV-4083 (TylAMac) developed with AbbVie, and emodepside, jointly developed with Bayer. Emodepside was tested in three different Phase I studies in healthy volunteers, while toxicology studies were completed for TylAMac and a Phase I study was initiated (see p. 58). These two drug candidates represent hope for more effective treatment of filarial diseases, particularly in regions that are co-endemic for onchocerciasis and *Loa loa*, also known as African eye worm.

DNDi's leishmaniasis pipeline has become much stronger, with six compounds in pre-clinical development and one new combination (miltefosine with thermotherapy) for

cutaneous leishmaniasis in POC studies. DNDi and several partners have built this unprecedented portfolio of new chemical classes with different mechanisms of action against *Leishmania* parasites (see pp. 42-43). In 2017, one new compound, DNDI-5561 developed with Takeda, was nominated for pre-clinical development, and GlaxoSmithKline (GSK), the University of Dundee Drug Discovery Unit (DDU), and DNDi entered into an agreement for the pre-clinical development of two compounds developed by GSK in collaboration with DDU.

Two other compounds – DNDI-6148 (developed by DNDi, based on a “hit” molecule from Anacor, now Pfizer) and DNDI-0690 (developed by DNDi after its discovery within a collaboration with the University of Auckland) – completed pre-clinical development, with preparations underway for Phase I clinical studies in 2018. This pipeline is a strong basis for advancing towards new oral treatments for both visceral and cutaneous leishmaniasis.



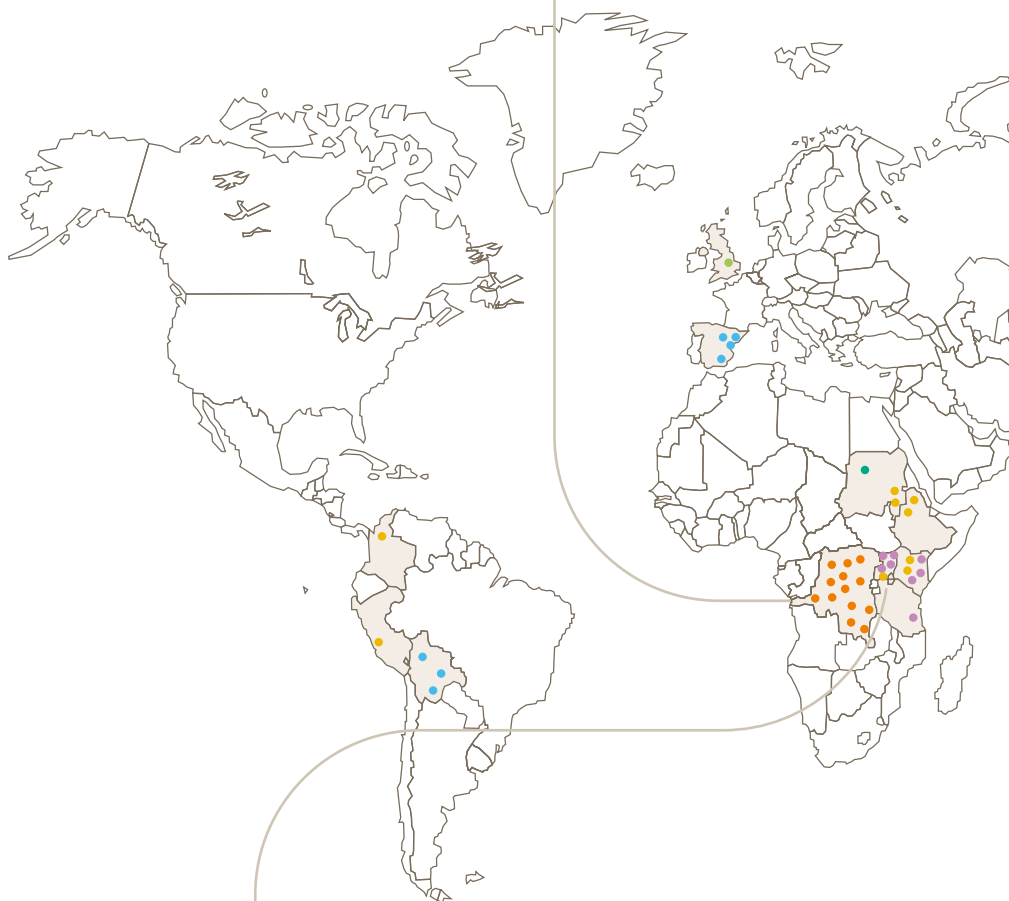
# 2017 clinical activities: 21 trials, 4,000+ participants

The year was rich in clinical activities. Six trials that treated over 2,500 people were completed, and five new studies were launched. DNDi and its partners conducted **21 studies at 52 active clinical sites in 15 countries**, including three studies in Phase I, seven studies in Phase II, ten studies in Phase II/III, and one study in Phase IV.

Studies ongoing or completed in 2017 involved more than 4,000 participants, in addition to hundreds of patients who were screened and received treatment but were not included in the trials. Nearly 1,000 leishmaniasis patients were treated at LEAP sites in East Africa, for example.

## DISEASES

- Human African trypanosomiasis
- Leishmaniasis
- Chagas disease
- Filarial diseases
- Mycetoma
- Paediatric HIV
- Hepatitis C



## Clinical trial data transparency

DNDi recognizes the importance of sharing data collected through its clinical trials for health research, and the ethical imperative to contribute to increasing scientific knowledge. As such, in May 2017, DNDi signed on to the WHO Joint Statement on Public Disclosure of Results from Clinical Trials and committed itself to WHO's standards on clinical trial transparency, including registering all clinical trials in a publicly available register, promptly reporting trial results 12 months after completion of the trial, and publishing findings in open access journals.

## HIV: Introducing oral pellets for children living with HIV

Since 2015, DNDi has been running the "LIVING" study in Kenya, Uganda, and Tanzania for an improved "2-in-1" oral pellet formulation, with 819 children enrolled by the end of 2017. Interim results show the 2-in-1 formulation is effective and well-tolerated by children, and highly acceptable to caregivers. By introducing the 2-in-1 oral pellets, which are an interim solution to replace bitter-tasting syrups, DNDi is paving the way for the more rapid introduction of a "4-in-1" fixed dose combination, on track to be delivered in 2019.



## Sleeping sickness: A study for the Congolese run by the Congolese

More than 200 people in the Democratic Republic of the Congo (DR Congo) have been actively engaged in DNDi's five-year clinical development effort for fexinidazole. This unprecedented effort generated data enabling Sanofi to submit a regulatory dossier to the European Medicines Agency. All data were collected by local health staff at nine clinical sites (DR Congo and Central African Republic), with 10 mobile teams from the Congolese National Sleeping Sickness Control Programme screening over 2 million people in remote villages – and more than 660,000 people in 2017 alone. All data (biological, quality assessment, follow-up) were collected and managed by Congolese partners.



## Hepatitis C: Enabling public health impact

DNDi conducted the STORM-C-1 open label trial to assess the efficacy, safety, tolerance, and pharmacokinetics of the drug candidate ravidasvir combined with sofosbuvir for the treatment of hepatitis C virus (HCV) in Malaysia. Interim results showed that 12 weeks after completing treatment, 97% of the 301 patients enrolled were cured.

## From Phase I to implementation

A list of all ongoing clinical trials sponsored by DNDi in 2017 is presented below. All studies are overseen by principal investigators from the countries where the studies take place and involve regional partners from public and private sectors.

### PHASE I

Research on safe dosage with healthy volunteers

#### Filarial diseases

- Emodepside single ascending dose for onchocerciasis (UK)
- Safety, tolerability, and PK of multiple-ascending doses of emodepside (UK)
- Relative bioavailability study of emodepside immediate release tablets and solution (UK)

### PHASE II a/PoC

Early safety and proof-of-concept in patients

#### HAT

- Acoziborole pivotal study in adults with stage 1 and stage 2 HAT (DR Congo)

#### Mycetoma

- Fosravuconazole proof-of-concept for eumycetoma patients (Sudan)

#### Cutaneous leishmaniasis

- Thermotherapy & miltefosine combination proof-of-concept (Colombia, Peru)

#### PKDL

- Short-course regimens for treatment of PKDL (Sudan)
- Short-course regimens for treatment of PKDL (India, Bangladesh)

#### Chagas disease

- Benznidazole new doses, improved treatment, and therapeutic associations (Bolivia)
- Fexinidazole proof-of-concept (Spain)

### PHASE IIb/III

Larger scale safety and efficacy trials

#### HAT

- Study of fexinidazole in special population groups, in in- and out-patients (DR Congo)
- Fexinidazole pivotal study (DR Congo)
- Fexinidazole study in adults with early-stage 1 + stage 2 HAT (DR Congo)
- Fexinidazole study in children with both stage 1 + 2 HAT (DR Congo)

#### Hepatitis C

- Ravidasvir/sofosbuvir combination therapy (Malaysia, Thailand)

#### Paediatric HIV

- Lopinavir/ritonavir pellets with dual NRTIs implementation study in infants and young children (Kenya, Uganda, Tanzania)

#### Visceral leishmaniasis

- Miltefosine/paromomycin Phase III trial for treatment of primary visceral leishmaniasis (VL) patients in Eastern Africa (Ethiopia, Kenya, Sudan, Uganda)

#### PKDL

- Infectivity study of PKDL patients (Bangladesh)

#### HIV-VL

- New treatments for HIV-VL co-infection (MSF study sponsored by DNDi) (India)
- New treatments for HIV-VL co-infection (MSF study sponsored by DNDi) (Ethiopia)

### PHASE IV

Post-registration trials for additional data

#### PKDL

- Follow-up study of PKDL patients (India)

# GARDP

## Start-up's first year sees rapid progress



Together with WHO, DNDi created the Global Antibiotic Research & Development Partnership (GARDP) in May 2016 to develop and deliver treatments in the fight against antimicrobial resistance, targeting important indications less likely to be developed by others.

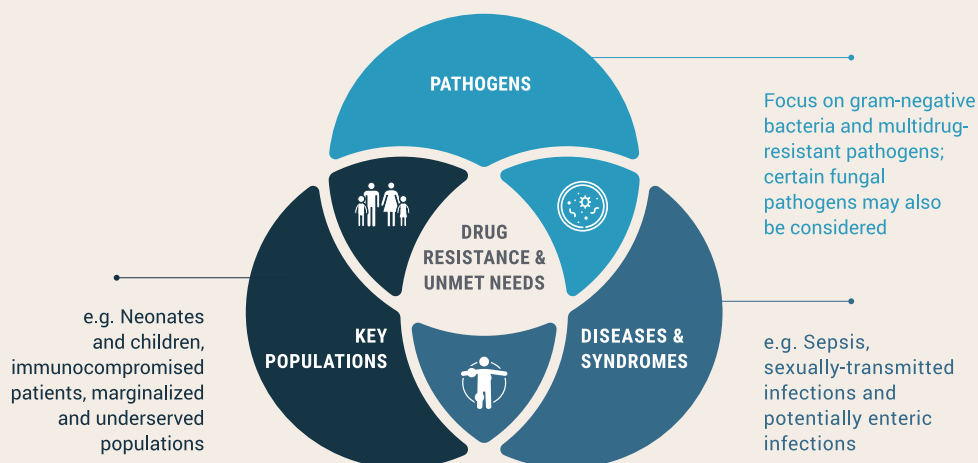
GARDP has benefited greatly from its unique parentage, capitalizing on DNDi's R&D know-how and WHO's technical expertise in a range of diseases. GARDP is an important element of the WHO's Global Action Plan on Antimicrobial Resistance that calls for new public-private partnerships to encourage R&D of new antimicrobial agents.

### Key achievements:

- Developed a business plan that prioritizes R&D strategies on global health priorities
- Secured EUR 56 million in additional funding (see pp. 36-37)
- Published a scientific roadmap and target product profiles for sexually-transmitted infections
- Partnered with Entasis Therapeutics to develop a novel, first-in-class antibiotic for drug-resistant gonorrhoea
- Conducted a survey on antibiotics used to treat late-onset sepsis in newborns, which indicates high levels of drug resistance in some settings
- Published a strategy to address antibacterial resistance in newborn babies
- Reviewed some 20 assets from several pharmaceutical companies and launched REVIVE, an online resource for the antimicrobial R&D community
- Established a country partnership with South Africa
- Opened a joint DNDi/GARDP office in South Africa
- Built a skilled team with expertise from a range of sectors and scientific networks

## Three programmes

GARDP's priorities are determined by considering the intersection between: WHO priority pathogens; specific populations' health needs; and individual diseases and broader syndromes. In addition to a paediatric platform to be launched in 2018 on paediatric antibiotics, GARDP's first Business Plan focuses on the following programmes of work:



### Neonatal sepsis

Every year, around 214,000 deaths in newborns are attributable to drug-resistant infections, which represent a major barrier to achieving the Sustainable Development Goal to reduce child mortality. A considerable challenge is the lack of evidence about appropriate treatment of drug-resistant infections in newborns.

GARDP hopes to develop this evidence base. An initial feasibility survey completed in 2017 shows high levels of drug resistance in neonatal units. GARDP will work on new and improved treatments for newborns, through partnerships including with St George's, University of London and the Paediatric European Network for Treatment of AIDS (PENTA) Foundation. A study on the pharmacokinetics of a potential drug candidate and a global observational study have been approved. Both are ready for implementation in 2018.

### Sexually-transmitted infections

With around 78 million new cases each year, gonorrhoea is one of the most common sexually-transmitted infections. Development of resistance is a major concern. In 2017, GARDP entered its first partnership agreement with Entasis Therapeutics on the development of zoliflodacin – a novel, first-in-class oral antibiotic that has high activity against drug-resistant gonorrhoea. In parallel to sponsoring a phase III clinical trial, including in the EU,

South Africa, Thailand, and the US, GARDP will carry out non-clinical activities to ensure zoliflodacin is effective against recent and geographically diverse strains of gonorrhoea.

If zoliflodacin receives regulatory approval, Entasis will grant GARDP a licence in 168 low- and middle-income countries. GARDP is committed to affordable and equitable pricing.

### Antimicrobial memory recovery and exploratory

This programme focuses on recovering knowledge, data, and assets of forgotten, abandoned or withdrawn antibiotics, and to identify new treatments. A memory recovery workstream is evaluating recovered molecules for their potential value for antimicrobial drug development. In 2017, some 20 assets were reviewed from several pharmaceutical companies.

GARDP has developed REVIVE, a digital space to facilitate learning and sharing good practice in the conduct of antimicrobial drug R&D. So far, more than 100 experts have engaged with REVIVE. A programme of webinars and workshops is planned for 2018.

The discovery and exploratory workstream supports pre-clinical research. This includes building a long-term portfolio of therapeutic interventions to address the ultimate and unavoidable development of resistance to any new therapy that is brought to patients.

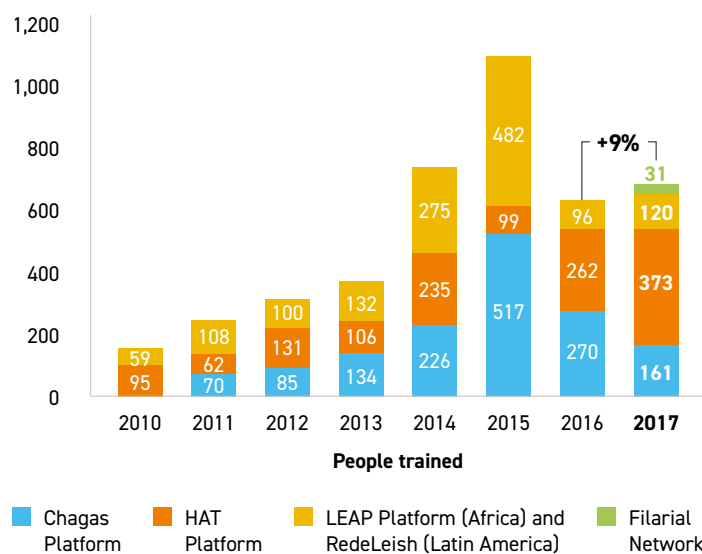
# Strengthening capacities

## Ensuring sustainable impact

As we work with endemic-country partners to conduct clinical trials, central to DNDi's mission and vision is the idea of strengthening existing clinical research capacities to ensure the sustainability of our work, and increasing endemic countries' ability to respond to their own research needs.

The disease-specific research platforms and networks created by DNDi and partners form a central part of this objective (see pp. 30-31). To date, platforms or networks have been established for leishmaniasis in both East Africa and Latin America, for Chagas disease, and for human African trypanosomiasis. A filarial clinical research network is also being set up, and efforts are underway to develop a network of researchers working in paediatric HIV. The platforms provide training, encourage knowledge sharing, and act as amplifiers for the scientific research led by regional scientists.

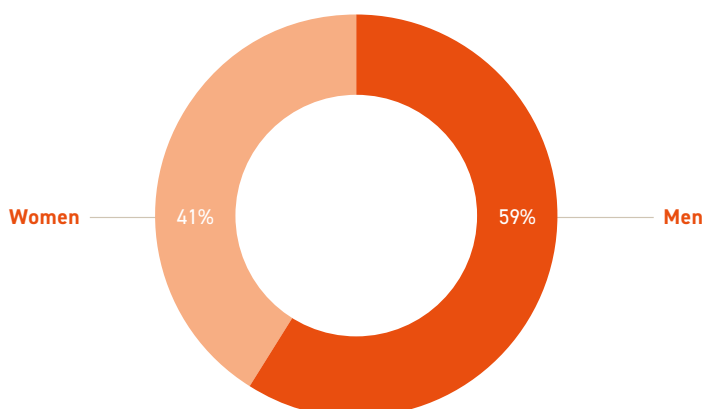
### 685 PEOPLE TRAINED IN 2017



The number of people trained between 2016 and 2017 increased by 9%, partly due to the addition of the filarial network.

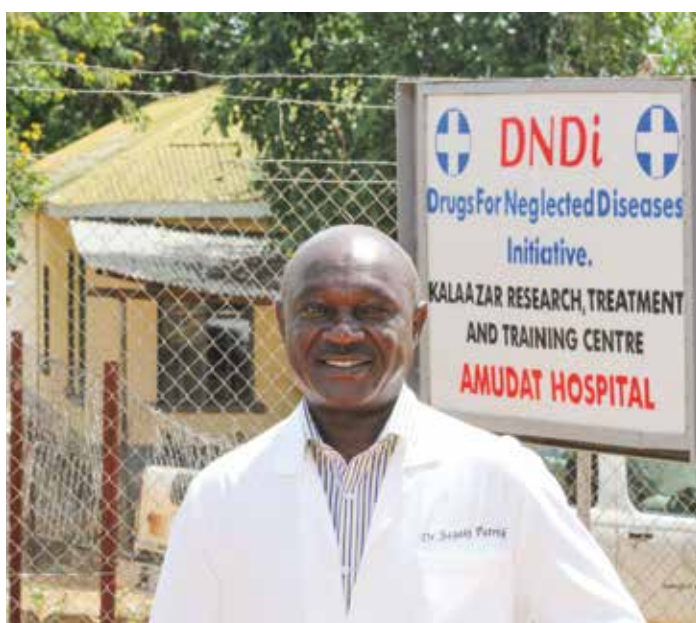


## PEOPLE TRAINED, BY GENDER



Gender-disaggregated data were collected for 553 out of 685 people trained.

Upgrading of infrastructure needed for clinical trials is also an essential component of this work. Seven new clinical trial sites were opened in 2017 where DNDi invested in improving power supply and telecommunications, rehabilitating buildings and equipment, including laboratories, and providing health commodities. Some of this is done outside the disease-specific research platforms. To enable the start of the first-ever clinical trial on mycetoma treatment, for example, DNDi supported training and infrastructure improvements for the new Research Unit set up by the Mycetoma Research Centre in Khartoum, Sudan. The new Research Unit, which has wards, a research laboratory, and a pharmacy, officially opened in July 2017.



## Filling the diagnosis gap for kala-azar in India

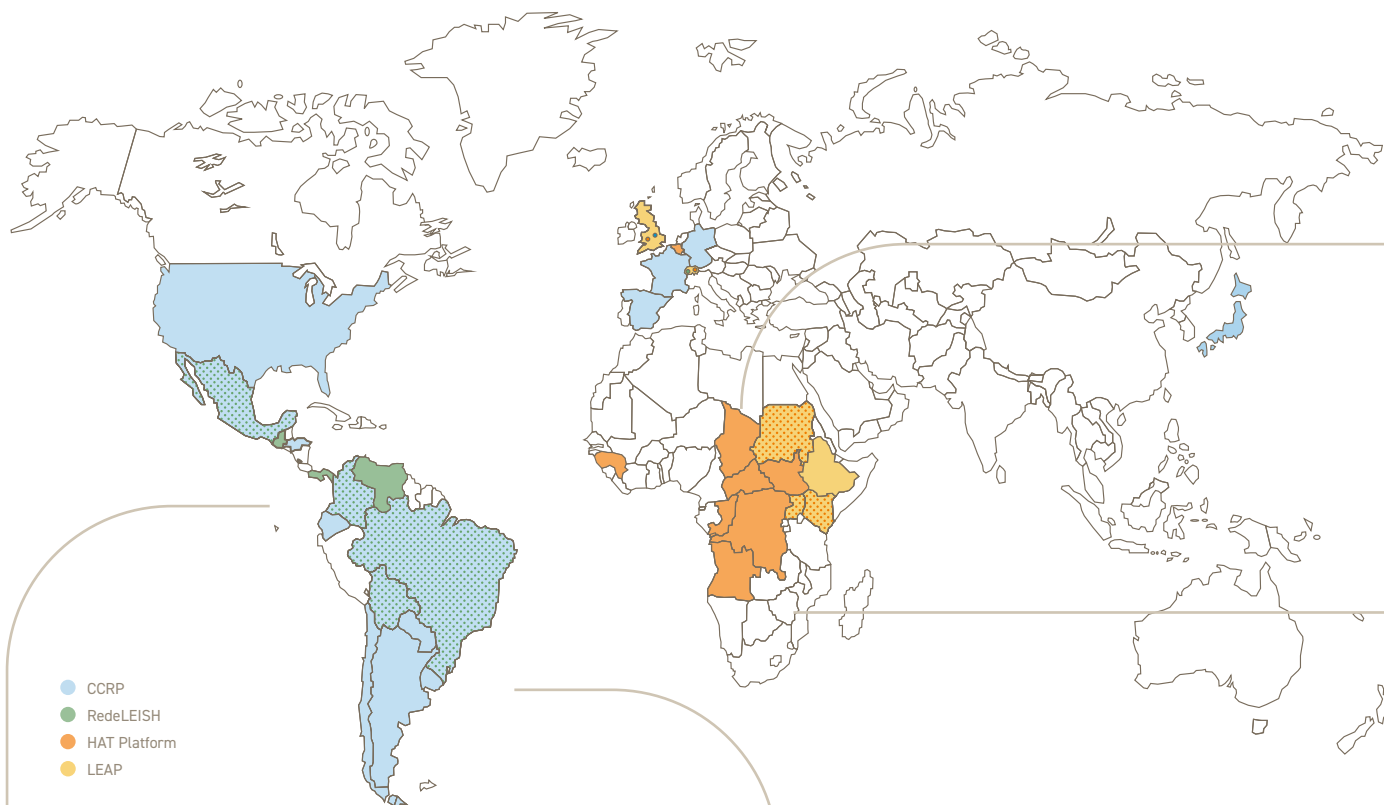
In 2017, DNDi supported the Indian National Kala-azar Elimination Programme by strengthening the capacity of five healthcare facilities in the state of Bihar (Purnia, Saharsa, Saran, Vaishali, and Muzzafarpur District Hospitals) to conduct parasitological diagnosis of visceral leishmaniasis.

The objective is to build the sites' capacity for confirmation of relapse, and diagnosis of post-kala-azar dermal leishmaniasis (PKDL) by microscopy. A lack of infrastructure and expertise at district-level treatment centres to perform parasitology of tissue aspirates for VL diagnosis results in missed cases and loss of patients, who are then not appropriately treated. With increased diagnostic capacity, the catchment areas for the five district hospitals can now appropriately treat patients and help prevent new outbreaks.

## The DNDi Data Centre in Nairobi aims for high-quality data

The management of data is critical to ensure high-quality clinical trials, from study design and implementation, through to reporting. In Eastern Africa, data management is led by the DNDi Data Centre in Nairobi, which trains for continuous improvement in data management to support high-quality study data and the rapid delivery of clinical trial results once the study is completed. Training includes development of data management plans, design of case report forms, database design and validation, data query management, and quality control. In 2017, the Data Centre trained more than 50 people, including personnel for DNDi paediatric HIV, visceral leishmaniasis (VL), and mycetoma clinical studies, as well as personnel for partners' studies, such as an MSF study on multi-drug-resistant tuberculosis in Uzbekistan, Belarus, and South Africa, and a WHO trial on Buruli ulcer in Ghana and Benin. The Data Centre also trained Kenya Ministry of Health staff on the DHIS2 platform for managing data related to VL surveillance.

# Platforms & Networks



## RedeLEISH

- Founded in 2014 in Rio de Janeiro, Brazil
- 139 members, from 62 institutions

### 2017 HIGHLIGHTS

- Launch of a manifesto, signed by 143 investigators and civil society representatives, for mucocutaneous leishmaniasis to raise the awareness of the scientific community and policy makers of the urgent need for more research for this very neglected form of leishmaniasis.
- Co-organization of the 'Brazilian Patients Forum against Infectious and Neglected Diseases' during the 53<sup>rd</sup> Brazilian Congress of Tropical Medicine (MedTrop).
- In coordination with TDR/WHO, supported efforts on the harmonization of criteria for clinical trials in cutaneous leishmaniasis and conducted a systematic review to assess therapeutic response and relapse rates.



## Chagas Clinical Research Platform (CCRP)

- Founded in 2009 in Uberaba, Brazil
- 424 members from over 150 institutions

### 2017 HIGHLIGHTS

- 7 clinical trial sites were active: 3 in Bolivia for the Phase II proof-of-concept BENDITA trial (to assess safety and tolerability of benznidazole with reduced doses and treatment duration, and in combination with fosravuconazole) and 4 in Spain for the Phase II proof-of-concept study of fexinidazole to treat Chagas.
- 161 people trained at 4 workshops/technical meetings in Colombia, Brazil, and the US.
- Discussions promoted by the Chagas Platform in Brazil are supporting the ongoing changes of the Brazilian national guidelines for the treatment of Chagas disease.

7  
CLINICAL  
SITES\*

161  
PEOPLE  
TRAINED

31  
MEMBERS

28  
PEOPLE  
TRAINED

## Filarial Clinical Research Network

- DNDi and its partners continue to work towards the launch of a clinical research platform on filarial diseases with key local, governmental, NGO, and academic representatives.

### 2017 HIGHLIGHTS

- The Network organized a workshop on onchocerciasis parasitological methods in Ghana. The objective was to reach a consensus on the evaluation and interpretation of microfilaria (juvenile worms) and macrofilaria (adult worms) in clinical studies. 28 experts attended the training.



## HAT Platform

- Founded in 2005 in Kinshasa, DR Congo
- 120 members from over 20 institutions

### 2017 HIGHLIGHTS

- 11 clinical trial sites were active and 2 in rehabilitation to conduct the Phase II/III study of acoziborole and the Phase IIIb study of fexinidazole. 10 mobile teams supported the screening of patients.
- Training activities increased, with 373 people trained (vs 262 in 2016) to address all aspects of ongoing clinical activities, including: training of investigators, nurses, and lab technicians; waste management; and training on diagnostic tools.
- Prepare for policy change and the development of national sleeping sickness treatment guidelines with fexinidazole in DR Congo.

11  
CLINICAL  
SITES\*

373  
PEOPLE  
TRAINED



## Leishmaniasis East Africa Platform (LEAP)

- Founded in 2003 in Khartoum, Sudan
- 60 members from over 20 institutions

### 2017 HIGHLIGHTS

- 5 clinical trial sites were active and 1 under construction in Ethiopia, Kenya, Uganda, and Sudan.
- Outside of the clinical trials, 1,084 people were treated and 2,898 were screened.
- 120 people were trained, including investigators, lab technicians, nurses, and pharmacists on Good Clinical Practice and protocols. Others received training on how to better communicate on their projects. Financial support for seven long-term trainings (Master's degrees or diplomas) was also provided.
- Following the dissemination of the HIV/VL study results, support for the development of a new policy by WHO.

5  
CLINICAL  
SITES\*

120  
PEOPLE  
TRAINED

## Our partners

### HAT Platform

National sleeping sickness control programmes, research institutions, and national laboratories of public health of the most affected endemic countries: Angola, Central African Republic, Chad, Democratic Republic of Congo, Guinea, Republic of Congo, South Sudan, Sudan, Uganda; Centre interdisciplinaire de Bioéthique pour l'Afrique Francophone (CIBAF); Drugs for Neglected Diseases initiative (DNDi), Switzerland; Eastern Africa Network for Trypanosomiasis (EANETT); Foundation for Innovative New Diagnostics (FIND), Switzerland; Institut de Recherche pour le Développement (IRD), France; Institut National de Recherche Biomédicale (INRB), DR Congo; Institut Pasteur Bangui, CAR; Institute of Tropical Medicine-Antwerp, Belgium; INZI Project, University of Edinburgh, UK; Juba University, South Sudan; Kenya Agricultural Research Institute - Trypanosomiasis Research Centre (KARI-TRC), Kenya; Médecins Sans Frontières (MSF); Swiss Tropical and Public Health Institute (Swiss TPH), Switzerland; Tropical Medicine Research Institute (TMRI), Sudan; University of Makerere, Uganda; WHO Department of Neglected Tropical Diseases, as observer.

### LEAP

Center for Clinical Research, Kenya Medical Research Institute, Kenya; Ministry of Health, Kenya; Institute of Endemic Diseases, University of Khartoum, Sudan; Federal Ministry of Health, Sudan; Addis Ababa University, Ethiopia; Gondar University, Ethiopia; Federal Bureau of Health, Ethiopia; Makerere University, Uganda; Ministry of Health, Uganda; MSF; London School of Hygiene & Tropical Medicine, UK; WHO; DNDi, Switzerland; FIND, Switzerland.

### CCRP

Over 150 institutions including: Pan American Health Organization (PAHO); Department of Neglected Tropical Diseases, WHO; Ministries of Health and National Control Programmes of high-burden endemic countries (Argentina, Bolivia, Brazil, Mexico, Paraguay, Honduras); MSF; International Federation of People Affected by Chagas Disease and patient associations. ARGENTINA: Hospital de Niños Ricardo Gutiérrez; Instituto Nacional de Parasitología Dr M. Fatalla Chabén; Hospital de Niños de Jujuy; Hospital Público Materno Infantil - Salta; Centro de Chagas y Patología Regional, Santiago del Estero; Consejo Nacional de Investigaciones Científicas y Técnicas; Fundación Mundo Sano, EAEA. BRAZIL: Instituto Oswaldo Cruz; Instituto de Pesquisa Evandro Chagas-Fiocruz; Centro de Pesquisas René Rachou-Fiocruz; LAFEP. BOLIVIA: Universidad Mayor de San Simón; Platform of Integral Care for Patients with Chagas Disease; Collective of Applied Studies and Social Development. COLOMBIA: Centro de Investigaciones en Microbiología y Parasitología Tropical, Universidad de los Andes; Centro Internacional de Entrenamiento e Investigaciones Médicas; Programa de Estudio y Control de Enfermedades Tropicales, Universidad de Antioquia (PECET); Red Chagas Colombia. FRANCE: Institut de Recherche pour le Développement. GERMANY: Bayer HealthCare. JAPAN: Eisai Co., Ltd. MEXICO: Instituto Carlos Slim de la Salud; Instituto Nacional de Salud Pública. SPAIN: ISGlobal and Barcelona Centre for International Health Research; Hospital Clinic Barcelona; Instituto de Parasitología y Biomedicina López Neyra; Consejo Superior de Investigaciones Científicas; Instituto Catalán de la Salud. SWITZERLAND: DNDi; Geneva University Hospitals. UK: The Global Health Network. USA: Merck; Sabin Vaccine Institute.

### RedeLEISH

BOLIVIA: Fundación Nacional de Dermatología (FUNDERMA), Universidad Mayor de San Simón. BRAZIL: Plataforma de Pesquisa Clínica - FIOCRUZ RJ, Centro de Pesquisa Gonçalo Moniz-FIOCRUZ BA; Universidade Federal da Bahia (UFBA); Universidade Federal do Piauí (UFPI); Centro de Pesquisa René Rachou-FIOCRUZ BH; Instituto Nacional de Infectologia - FIOCRUZ RJ; Fundação de Medicina Tropical Heitor Vieira Dourado; Ministério da Saúde; Instituto Evandro Chagas; Universidade do Estado do Pará (UEPA); Instituto Nacional de Pesquisa da Amazônia (INPA); Secretaria Municipal de Saúde Unidade Referência em Atenção Primária Drª Claudia Vitorino; Universidade de Brasília - Núcleo de Medicina Tropical (UnB); Universidade Federal de Mato Grosso/Hospital Universitário Júlio Müller; Universidade de São Paulo (USP); Universidade Federal do Pará (UFPA); Universidade do Rio de Janeiro (UFRJ); Universidade Federal do Ceará (UFC); Universidade de Pernambuco (UFPE); Laboratório do Estado de Pernambuco (LAFEP); Universidade Federal de Santa Catarina (UFSC). COLOMBIA: Centro Dermatológico Federico Lleras Acosta; Centro Internacional de Entrenamiento e Investigaciones Médicas (CIDEIM); Instituto Colombiano de Medicina Tropical; Instituto Nacional de Salud (INS); Programa de Estudios y Control de Enfermedades Tropicales (PECET); Ministerio de la Salud. GUATEMALA: Universidad del Valle. MEXICO: Universidad Nacional Autónoma de México. PANAMA: Instituto Conmemorativo Gorgas de Estudios de la Salud. PERU: Department of Parasitology, Public Health Training Program - U.S. Naval Medical Research Unit No. 6; Universidad Peruana Cayetano Heredia. SWITZERLAND: DNDi; FIND. VENEZUELA: Instituto Médico la Floresta. WHO. PAHO.

\*Sites belonging to platform/network members and used for DNDi studies

# Access

## Transitioning from registration to implementation



Since its creation, DNDi has delivered seven treatments across a range of diseases and supported their registration and introduction. From this experience, we have learnt that the transition from registration to access is one of the most challenging aspects of our mission. DNDi's access strategy relies on partnerships with health ministries, national control programmes, industrial partners, NGO allies, and others to reach neglected patients and communities, and achieve maximum public health impact.

### Chagas: Innovative partnerships to spur access

DNDi has long sought to mobilize energies and funds in a bid to address the unacceptable situation for Chagas disease, where less than 1% of infected individuals are diagnosed and even fewer receive treatment.

These efforts received a considerable boost in August 2017, when pharmaceutical company Insud, with DNDi's support, received a priority review voucher as a result of registering benznidazole for the treatment of Chagas disease with the US FDA. As part of the collaboration agreement between Insud and DNDi, half of the revenues from the sale of the PRV will be dedicated to increasing access to diagnosis, treatment and prevention throughout the Americas.

A Regional Access Framework for Chagas Disease has been developed by DNDi and Insud's corporate social responsibility partner Fundación Mundo Sano, to be implemented in collaboration with members of the Chagas Coalition. Countries can look to efforts made by the Colombian Ministry of Health, which, with DNDi technical support, launched a pilot project to boost diagnosis and treatment. Initial results show a more than tenfold increase in the number of patients screened and a radical reduction in the wait for a confirmed diagnosis. A second project in Guatemala seeks to replicate this success and demonstrate the feasibility of diagnosis and treatment at the primary care level.



## Fexinidazole: Using the regulatory process to pave the way for access

In December 2017, a few months after the conclusion of large-scale DNDi clinical trials, our industrial partner Sanofi submitted the registration dossier for fexinidazole as the first all-oral treatment for sleeping sickness. In a promising move for access, a submission was made to the European Medicines Agency under what is known as Article 58 (see p. 49).

If fexinidazole is registered in late 2018, regulatory approval will only be the first step. Translation into national policy and treatment guidelines will be needed as well as community awareness efforts and treatment knowledge for health providers.

## HIV: Preparing for the 4-in-1 by encouraging uptake of the 2-in-1

DNDi is working with Indian manufacturer Cipla to develop a “4-in-1”, a solid first-line fixed-dose combination combining four antiretrovirals (abacavir, lamivudine, lopinavir, and ritonavir), as granules contained in a capsule. Caregivers will be able to open the capsules and give the granules to children with soft food, breast milk, or milk and water. These granules will not require refrigeration, and they will be taste-masked and easy to dose across various weight bands. Submission for US FDA registration will be pursued in late 2018.

In the meantime, DNDi has been working with countries to increase access to an interim solution. The “2-in-1” lopinavir/ritonavir (LPV/r) pellets developed by Cipla are a better option for children than existing syrups as they are much easier for children to take and for caregivers to administer. To increase access to the 2-in-1, DNDi has been running an implementation trial known as the “LIVING” study in Kenya, Tanzania and Uganda. Interim results show very high levels of adherence and clinical improvement, as well as lower HIV viral loads, proving that better formulations can lead to better outcomes. The trial also aims to facilitate in-country adoption of optimized LPV/r regimens, which will ultimately help transitioning towards the 4-in-1, once it is available.

While some countries have experienced stock-outs of the 2-in-1 oral pellets due to production levels at Cipla that have not kept pace with the growing demand, Cipla plans to increase its production capacity in September 2018 if it receives FDA approval for scale-up processes. It is also hoped that additional suppliers will come on line by the end of the year. Building on the lessons learned with the 2-in-1, DNDi and Cipla have formed a working group to implement an access plan for the 4-in-1. This working group will identify priority countries for the introduction of the new formulation and key partners for the three key dimensions of access: sustained demand, financing, and supply.

## Hepatitis C: A public health approach for access

Although there are now several effective and safe treatment options for hepatitis C, access to affordable medicines is impossible for millions of people. Middle-income countries are the most affected. DNDi aims to bring a solution to this situation through multiple partnerships with widely different stakeholders who all share the common aim of increasing access to hepatitis C treatment.

DNDi has partnered with Pharco, an Egyptian pharmaceutical company, in the development of ravidasvir, a new chemical entity with potential effectiveness against all genotypes of the disease. In 2016, DNDi began working with the Malaysian Ministry of Health to introduce a public health approach within the framework of the country's National Strategic Plan on viral hepatitis. Clinical trials were launched in six Malaysian hospitals with the Ministry as co-sponsor of the trial. A similar partnership followed in Thailand.

Promising results suggest that the ravidasvir/sofosbuvir combination is comparable to the very best hepatitis C therapies available, with one radical difference: its price. Thanks to partnerships in Malaysia (Pharmaniaga) and Argentina (Insud/Elea), DNDi has secured a target price of USD 300 to 500 per treatment course, a fraction of the price of what is available today in countries where patent barriers block generic options, and which are excluded from pharmaceutical company discount schemes.

However, to use this drug combination, countries would also need access to affordable sofosbuvir. In September 2017, Malaysia issued a “government use” licence to source generic sofosbuvir, a move which has allowed it to accelerate access to affordable hepatitis C treatment in its public hospitals.



# Policy, Fundraising & Communications

## Putting patient needs at the centre



Key global health policy processes of the last several years have led to consideration of medical innovation and access at the highest levels of the global policy agenda in the last year. The Global Health Security Agenda launched in 2014 in the midst of the Ebola crisis; the WHO Global Action Plan on Antimicrobial Resistance (AMR), endorsed by the World Health Assembly in 2015; and the Sustainable Development Goals, adopted by all UN Member States in September 2015, including health goals with specific targets for R&D and access to essential medicines and vaccines – have all turned a global spotlight on the consequences of underfunding R&D for health, be it for neglected tropical diseases, viral diseases like HIV and HCV, or AMR.

### Towards sustainable elimination

In April, WHO convened the Neglected Tropical Diseases Summit to celebrate progress since the 2012 London Declaration and take stock of the coalition's achievements against the ambitious target of controlling or eliminating ten NTDs by 2020. Drug donations, the bedrock of the coalition, have provided a strong contribution, but critical innovation needs remain and must be met if we are to reach and sustain elimination. People living with or at risk from NTDs continue to need improved treatments for VL and Chagas, and curative solutions for lymphatic filariasis and river blindness. With the stagnation of financing of research for neglected diseases, and public-sector funding for R&D falling to its lowest level since 2007, DNDi will continue to push for a stronger R&D response to NTDs.

### Universal Health Coverage

WHO Director General Dr Tedros has declared universal health coverage (UHC) to be the priority for his mandate. This has important implications for NTDs, which are diseases of poverty affecting most countries. Delivering quality UHC depends on the availability of and access to safe, effective, and affordable medicines, underscoring the continued need for R&D for NTDs as a key component of the UHC agenda. NTD programmes provide entry points to some of the world's hardest-to-reach



At the NTD Summit in April, Dr Wilfried Mutombo, DNDi project coordinator for sleeping sickness, advocates for new tools to sustain elimination efforts.

communities, and many policymakers have identified the ability to address NTDs as a “litmus test” for UHC.

## AMR at the G20 summit

The Berlin Declaration that followed the first-ever G20 Health Ministers meeting in May 2017 cautioned that success in the fight against AMR cannot be achieved with current treatments. It recognized the importance of ‘reactivating the R&D pipeline through incentive mechanisms that avoid the reliance on high price/volume combinations’ to ensure sustainable access. It called for ‘broadening the voluntary financial support’ for initiatives, including GARDP, which ‘reinvigorate R&D in science and industry for antimicrobials’ (see p. 26-27).

## Alternative R&D models

DNDi contributes to key debates on the future of public health-oriented biomedical R&D. At the “1st World Conference on Access to Medical Products and International Laws for Trade and Health, in the Context of the 2030 Agenda for Sustainable Development” organized by the Government of India and WHO in New Delhi in November, DNDi presented on how alternative models for R&D could deliver innovation and access, pro-public health management of intellectual property, and the potential of open access approaches. The final recommendations supported alternative open, collaborative R&D models, with conditions ensuring a public return on public investment, and the need for sustainable R&D financing.

## Political leadership in action

2017 was marked by the Malaysian government’s decision to reaffirm its strong commitment to providing access to treatments for hepatitis C by issuing a “government use” licence enabling access to more affordable versions of sofosbuvir, an expensive and patented treatment for hepatitis C. This is a landmark decision for the more than 400,000 people living with hepatitis C in Malaysia (see p. 65).

## DNDi awarded the 2017 Geneva Innovation Prize

In recognition of its innovative and collaborative model, DNDi was awarded the Innovation Prize 2017 by the Geneva Chamber of Commerce, Industry and Services, the Department of Security and Economy, and the Office for the Promotion of Industries and Technologies.



DNDi’s Executive Director Dr Bernard Pécoul receives the Innovation Prize of Geneva from Juan Carlos Torres, President of Geneva Chamber of Commerce, Industry, and Services (CCIG), Frédérique Reeb-Landry, former Director General, CCIG, and Michel Balestra, President of the Jury.

## WorldLeish6: 1,500 leishmaniasis experts met in Toledo

In 2017, DNDi joined forces with the WHO Collaborating Centre for Leishmaniasis at the Instituto de Salud Carlos III, Madrid, to co-organize the 6th World Congress on leishmaniasis. The event attracted 1,500 scientific experts, health decision-makers, WHO, government representatives of endemic countries, and all major organizations involved in the fight against leishmaniasis. Among the outputs from the conference were a PLOS special collection dedicated to leishmaniasis; the ‘100 students’ initiative programme allowing students and young scientists from resource-limited settings to attend, and supporting professional development of a new generation of scientists; and the launch of a manifesto to raise awareness of the urgent need for more research on mucocutaneous leishmaniasis, a very neglected form of leishmaniasis.



World leishmaniasis experts Dr Ahmed Mudawi Musa and Prof Ahmed Mohamed El Hassan, Institute of Endemic Diseases, University of Khartoum, Sudan; and Prof C.P. Thakur, Emeritus Professor of Medicine, Patna Medical College, India at the closing session of WL6.



## Scientific publications

In 2017, DNDi staff members authored or co-authored 22 peer-reviewed publications. Of these, nine had a lead author or co-author from an endemic country, and 18 were published in an open access journal, in keeping with DNDi's commitment to open access.

### DNDi 2017 selected publications

Increasing access to comprehensive care for Chagas disease: Development of a patient-centered model in Colombia, by Marchiol A, Forsyth C, Bernal O, Valencia C, Cucunubá Z, Pachón E, Soto M, Batista C. *Pan American Journal of Public Health*, December 2017.

First external quality assurance program for bloodstream Real-Time PCR monitoring of treatment response in clinical trials of Chagas disease, by Juan C. Ramírez, Rudy Parrado, Elena Sulleiro, Anabelle de la Barra, Marcelo Rodríguez, Sandro Villarroel, Lucía Irazu, Cristina Alonso-Vega, Fabiana Alves, María A. Curto, Lineth García, Lourdes Ortiz, Faustino Torrico, Joaquim Gascón, Laurence Flevaud, Israel Molina, Isabela Ribeiro, Alejandro G. Schijman. *PLOS ONE*, November 2017.

Oral fexinidazole for late-stage African *Trypanosoma brucei* gambiense trypanosomiasis: A pivotal multicentre, randomized, non-inferiority trial, by Kande Betu Ku Mesu V, Mutombo Kalonji W, Bardonneau C, Valverde Mordt O, Blesson S, Simon F, Delhomme S, Bernhard S, Kuziena W, Fina Lubaki JP, Lumeya Vuvu S, Nganzobo Ngima P, Mahenzi Mbembo H, Ilunga M, Kasongo Bonama A, Amici Heradi J, Limaliza Solomo JL, Mandula G, Kaninda Badibabi L, Regongbenga Dama F, Kavunga Lukula P, Ngolo Tete D, Lumbala C, Scherrer B, Strub-Wourgaft N, Tarral A. *The Lancet*, November 2017.

Assessment of a pretomanid analogue library for African trypanosomiasis: Hit-to-lead studies on 6-substituted 2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazine 8-oxides, by Thompson AM, Marshall AJ, Maes L, Yarlott N, Bacchi CJ, Gaukel E, Wring SA, Launay D, Brailard S, Chatelain E, Mowbray CE, Denny WA. *Bioorganic & Medicinal Chemistry Letters*, October 2017.

Systematic review of clinical trials assessing the therapeutic efficacy of visceral leishmaniasis treatments: A first step to assess the feasibility of establishing an individual patient data sharing platform, by Bush JT, Wasunna M, Alves F, Alvar J, Olliaro PL, Otieno M, Hopkins Sibley C, Strub Wourgaft N, Guerin PJ. *PLOS Neglected Tropical Diseases*, September 2017.

Visceral leishmaniasis relapse hazard is linked to reduced miltefosine exposure in patients from Eastern Africa: A population pharmacokinetic/pharmacodynamic study, by Dorlo TPC, Kip AE, Younis BM, Ellis SJ, Alves F, Beijnen JH, Njenga S, Kirigi G, Hailu H, Olobo J, Musa AM, Balasegaram M, Wasunna M, Karlsson MO and Khalil EAG. *Journal of Antimicrobial Chemotherapy*, September 2017.

Efficacy and safety of available treatments for visceral leishmaniasis in Brazil: A multicenter, randomized, open label trial, by Romero GAS, Costa DL, Costa CHN, de Almeida RP, de Melo EV, de Carvalho SFG, Rabello A, de Carvalho AL, de Queiroz Sousa A, Leite RD, Soares Lima S, Alves Amaral T, Piovesan Alves F, Rode J, the Collaborative LVBrasil Group. *PLOS Neglected Tropical Diseases*, June 2017.

Safety and efficacy of short course combination regimens with AmBisome®, miltefosine, paromomycin for the treatment of visceral leishmaniasis (VL) in Bangladesh, by Rahman R, Goyal V, Haque R, Jamil K, Faiz A, Samad R, Ellis S, Balasegaram M, den Boer M, Rijal S, Strub-Wourgaft N, Alves F, Alvar J, Sharma B. *PLOS Neglected Tropical Diseases*, June 2017.

Infectivity of post-kala-azar dermal leishmaniasis patients to sand flies: Revisiting a proof-of-concept in the context of the kala-azar elimination program in the Indian subcontinent, by Molina R, Ghosh D, Carrillo E, Monnerat S, Bern C, Mondal D, Alvar J. *Clinical Infectious Diseases*, May 2017.

Safety and effectiveness of sodium stibogluconate and paromomycin combination for the treatment of visceral leishmaniasis in eastern Africa: Results from a pharmacovigilance programme, by Kimutai R, Musa AM, Njoroge S, Omollo R, Alves F, Hailu A, Khalil EAG, Diro E, Soipei P, Musa B, Salman K, Ritmeijer K, Chappuis F, Rashid J, Mohammed R, Jameneh A, Makonnen E, Olobo J, Okello L, Sagaki P, Strub N, Ellis S, Alvar J, Balasegaram M, Alirol E, Wasunna M. *Clinical Drug Investigation*, January 2017.

### GARDP 2017 publications

Tackling antimicrobial resistance in neonatal sepsis by Folgori L, Ellis SJ, Bielicki JA, Heath PT, Sharland M, Balasegaram M. *The Lancet Global Health*, November 2017.

Multidrug-resistant gonorrhoea: A research and development roadmap to discover new medicines by Alirol E, Wi TE, Bala M, Bazzo ML, Chen XS, Deal C, Dillon J-A, Kularatne R, Heim J, Hooft van Huijsdijnen R, Hook EW, Lahra M, Lewis DA, Ndowa F, Shafer WM, Tayler L, Workowski K, Unemo M, Balasegaram M. *PLOS Medicine*, July 2017.

# EUR 83.4 million secured in 2017, additional EUR 56 million pledged

The 2017 G-FINDER report<sup>1</sup> found that USD 3 billion was invested in neglected disease research and development in 2016, marking the third consecutive year of declining funding and the lowest level of public sector funding for neglected disease R&D since 2007. Nevertheless, largely thanks to the support of our regular donors, 2017 was an exceptional fundraising year, with more than EUR 72.7 million committed for DNDi.

## Commitments renewed for NTDs, HIV, HCV

Funds raised in 2017 for the neglected disease portfolio include increased support for the sleeping sickness programme from the Bill & Melinda Gates Foundation, as well as from private donors primarily from the US, through the HAT campaign launched last year, but also in Europe. Other noteworthy contributions include the first grant from the GHIT Fund secured for mycetoma, and from the European and Developing Countries Clinical Trials Partnership for a visceral leishmaniasis clinical trial in four African countries. In addition, the first grant entirely dedicated to DNDi's HCV programme was received from the Médecins Sans Frontières/Doctors Without Borders (MSF) Transformational Investment Capacity.

<sup>1</sup> G-Finder 2017, Neglected Disease Research and Development: Reflecting on a Decade of Global Investment  
<http://www.policycuresresearch.org/g-finder-2017>.



## Germany hosts pledging conference for GARDP

In May, the G20 Health Ministers cautioned that success in the fight against antimicrobial resistance (AMR) cannot be achieved with the current treatments. The Declaration welcomed and sought to build on initiatives such as GARDP, to 'reinvigorate research and development in science and industry for antimicrobials.'

The German Federal Ministry of Health and Ministry of Education and Research then hosted a pledging conference for GARDP in September 2017. A total of EUR 56 M was pledged by Germany, Luxembourg, Monaco, the Netherlands, South Africa, Switzerland, the United Kingdom, and the Wellcome Trust for the development of new and improved treatments to fight antibiotic resistance and contribute to ensuring healthy lives and well-being for all. Of this total, EUR 5.5 M was received in 2017.

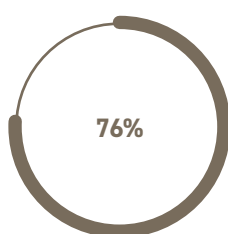
## Fundraising targets and achievements



● DNDi  
● GARDP

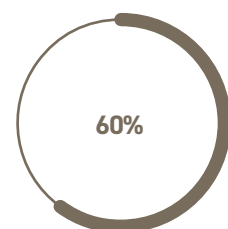
Since 2003, DNDi's cumulative income reached EUR 491 M, against a target of EUR 650 M by 2023. By the end of 2017, GARDP had EUR 64 M in commitments and pledges, almost 25% of the EUR 270 M total funding required to deliver GARDP's objectives by 2023.

## The importance of core funding



Core funding provides DNDi with financial stability and the flexibility to manage our scientific portfolio dynamically. Two of the three DNDi core funding donors, UK aid and the Swiss Agency for Development and Cooperation, renewed their support to DNDi in 2017.

## The importance of public sources



DNDi's 2017 fundraising successes also reinforced the importance of public funding, representing more than 60% of funds raised for DNDi and GARDP in 2017.

## Major contributions received in 2017

### UK aid, UK (2017-2021)

UK aid provided a grant of GBP 50 M to support DNDi activities, including all NTD clinical and discovery activities, and hepatitis C, and including GBP 3 M for GARDP.

### Swiss Agency for Development and Cooperation (SDC), Switzerland (2017-2020)

SDC provided a grant of CHF 8 M to support all DNDi activities, including NTD clinical activities, discovery activities, and hepatitis C.

### Global Health Innovative Technology Fund (GHIT Fund), Japan (2017-2019)

The GHIT Fund awarded more than JPY 897 M to DNDi and its partners through five different grants, including the first dedicated support to a clinical trial for mycetoma in Sudan (JPY 252 M).

### European and Developing Countries Clinical Trials Partnership (EDCTP) (2017-2020)

EDCTP provided EUR 5.5 M for the Afri-KA-DIA consortium, for an adapted, safe, effective combination treatment for visceral leishmaniasis, and improved diagnostic tools.

### MSF - Transformational Investment Capacity (2017-2020)

MSF provided DNDi with EUR 7.8 M, the first significant contribution to DNDi's hepatitis C programme with the objective of increasing access to care and treatment for HCV patients.

### Bill & Melinda Gates Foundation (2017-2019)

The Foundation approved a supplemental grant of USD 4.8 M for DNDi's HAT programme.



# 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.

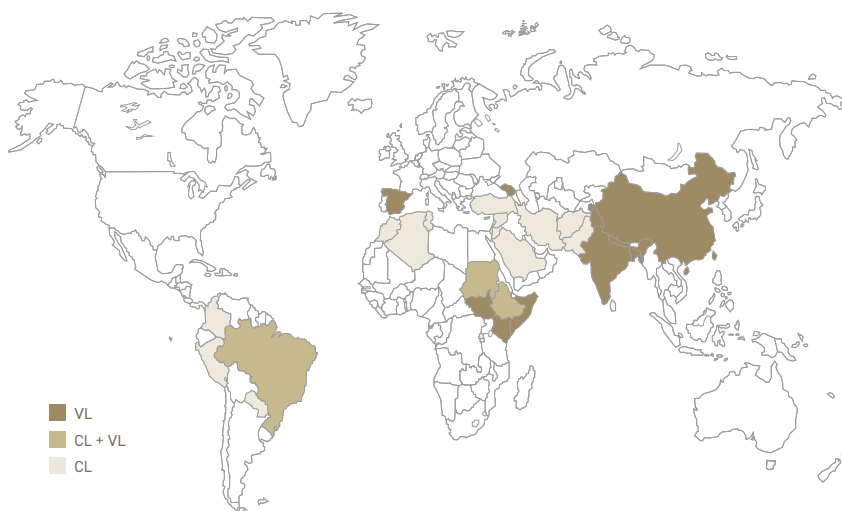


- Parasitic disease transmitted by sandfly bite
- Leishmaniasis can be zoonotic (transmitted from animals to humans) or anthroponotic (humans are only a reservoir), depending on the *Leishmania* parasite
- Multiple forms, including: visceral (VL), also known as kala-azar, fatal without treatment; cutaneous (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.

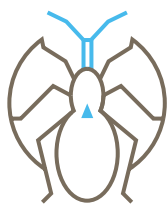
Two additional complementary cohorts with fexinidazole were completed in 2016, one including 230 adult patients with stage-1 and early stage-2 disease, and another including 125 children between six and 14 years, both at sites in the DR Congo. Follow-up of these patients was completed in 2017, with results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

### DNDí 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.

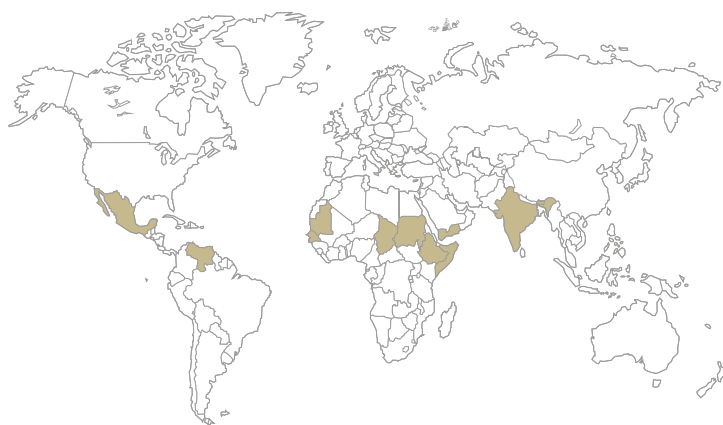
Eumycetoma is more difficult to treat than the bacterial form of the diseases.

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.

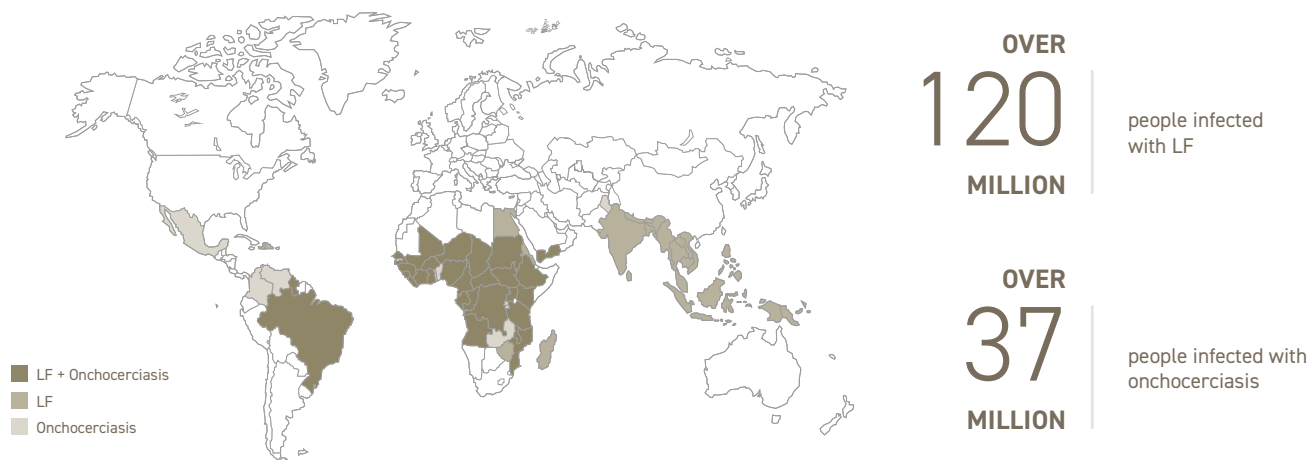
Akoyo's village is one of many in the region devastated by river blindness, a neglected tropical disease transmitted by the bite of the blackfly. The river nearby makes it a perfect breeding ground for the blackflies that infect people with the filarial worms that cause river blindness.

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.

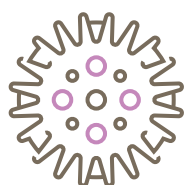
Toxicology studies were completed in 2017, and an oral formulation was developed. In December, AbbVie began the first human trial of ABBV-4083 to test the drug's safety in healthy volunteers and assist in the selection of doses for future trials. This Phase I study, conducted at AbbVie's Clinical Pharmacology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

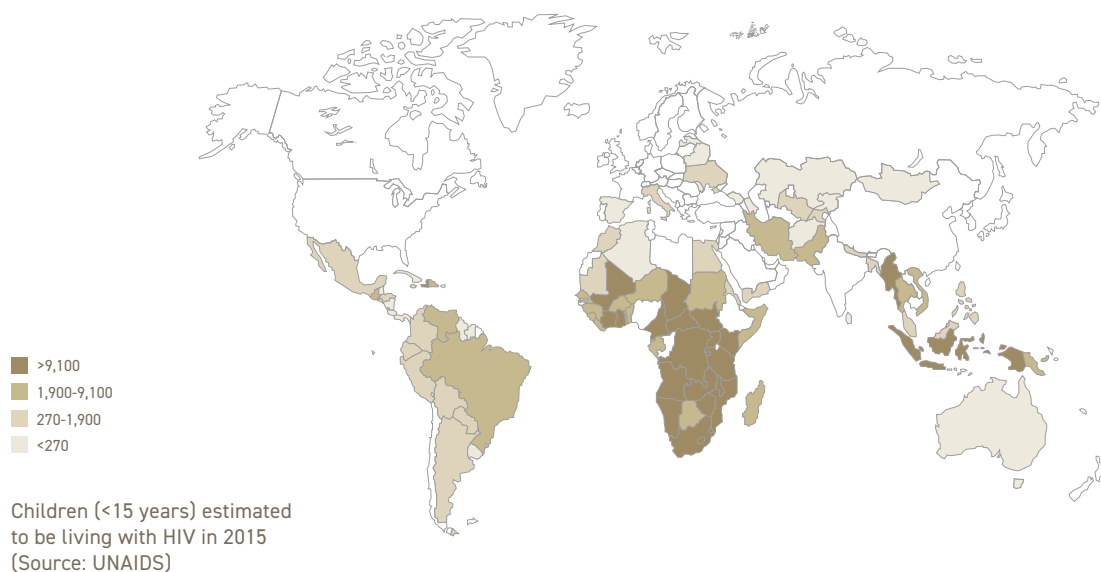
- 90% of infected infants acquire HIV from their mothers, during pregnancy, delivery, or through breast-feeding
- Effective treatments can prevent HIV transmission from a mother to her child, but not all HIV-infected pregnant women have access to these treatments

- 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 Unitaid, 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

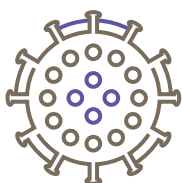
**OBJECTIVE:** Evaluate the effectiveness of LPV/r pellets in addition to AZT/3TC (or ABC/3TC) paediatric fixed-dose combination tablets in an implementation study in HIV-infected infants and young children who cannot swallow pills

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 Unitaid, 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

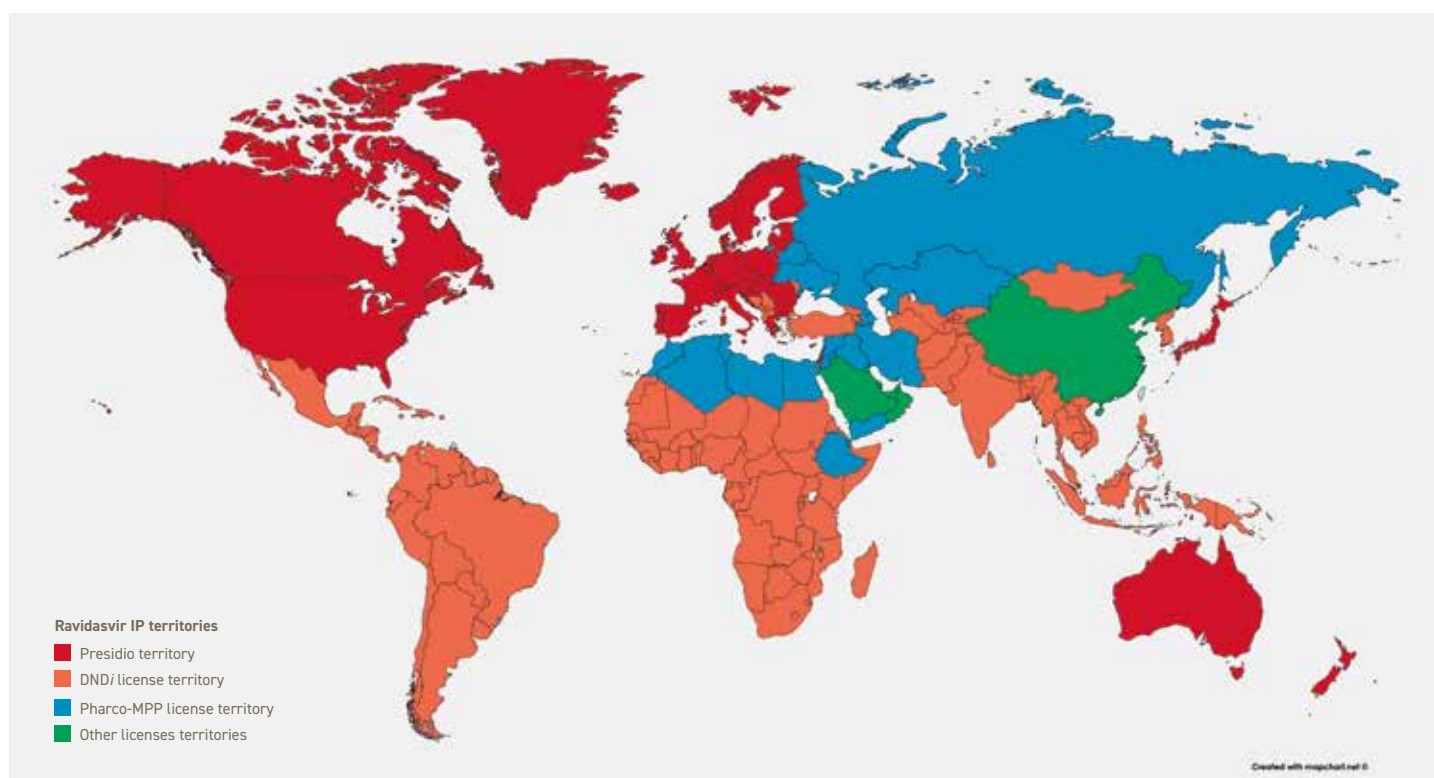
Patents on ravidasvir (RDV) are owned by Presidio, from whom DNDi secured non-exclusive licence rights for LMICs. DNDi also has an option to negotiate the licence rights for high-income countries.

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; Accelerera, 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; Piaui Federal University, Teresina, Brazil; Programa de Estudio y Control de Enfermedades Tropicales, Universidad de Antioquia, Medellin, 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







# 2017 financial and performance indicators

## **Accountability and transparency**

This section provides an extract of DND's 2017 Financial and Performance Report, including key performance indicators for expenditure, human resources, partnerships, and contributions.

# 2017 KEY FINANCIAL PERFORMANCE INDICATORS

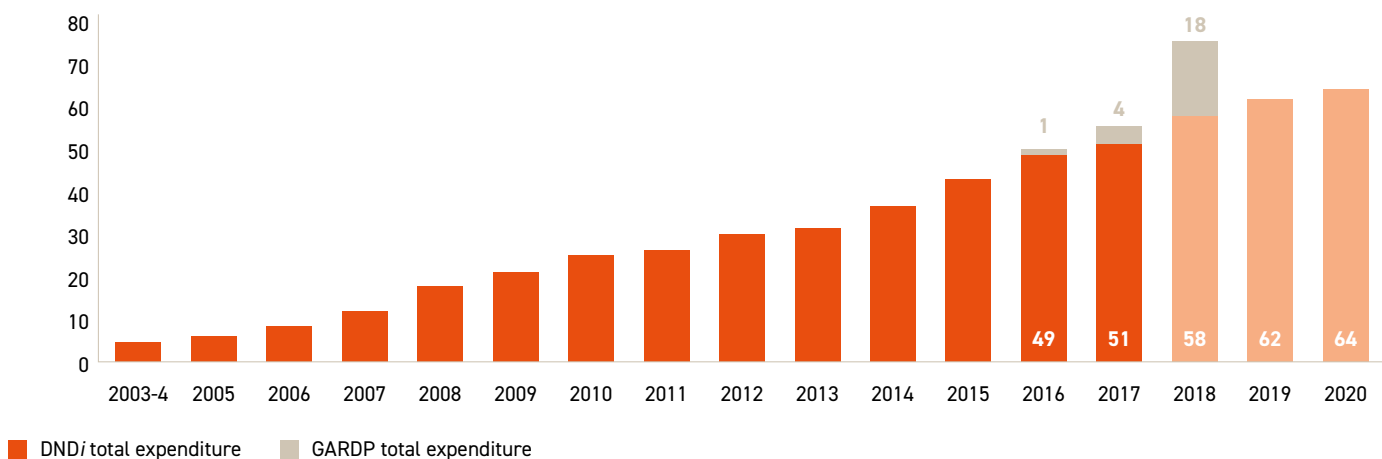
## EXPENDITURE

### Steady growth in spending, concentrated on R&D

- In 2017, expenditure amounted to EUR 55.6 M, up by 14% (+EUR 6.8 M) over 2016.
- Overall R&D expenditure (EUR 43.5 M) increased by almost 17% (+EUR 6.2 M) over 2016.
- The operating gain in 2017 (EUR 0.5 M) was largely negated by exchange rate losses (EUR 0.4 M).
- Since the inception of DNDi in 2003, the organization's expenditure totals EUR 364 M.
- The objective of DNDi's incubation of the Global Antibiotic Research & Development Partnership (GARDP) is that it becomes a separate legal entity by the end of 2018, so a GARDP forecast is not included from 2019.

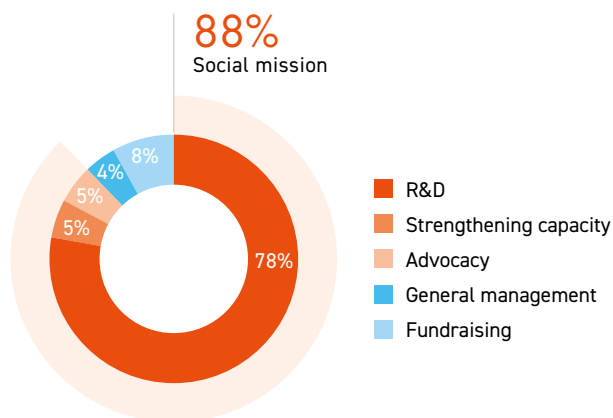
### Statement of activities 2003-2017 and forecast 2018-2020

In million EUR



### 88.4% of spending dedicated to the social mission

- The trend of DNDi's ratio of social mission to non-social mission spending improved slightly over the last three years, with the latter reduced from 12.3% in 2015 to 11.8% in 2016 and 11.6% in 2017.
- Social mission expenditure grew by 14% (+EUR 6.1 M), due to the significant growth of the most recently added diseases in the R&D portfolio: GARDP incubation (+265%, +EUR 2.4 M), hepatitis C projects (+93%, +EUR 0.8 M), and filarial disease projects (+35%, +EUR 1.3 M).
- Non-social mission expenditure grew by 12% (+EUR 0.7 M), proportional to social mission growth, to support project activities (number of full-time employees, office space, travel).



The main driver of the increase in global R&D spending in 2017 was GARDP activity (+EUR 2.4 M). Spending also increased for clinical activities, with a special effort to support hepatitis C (+EUR 0.8 M), filarial diseases (+EUR 1.3 M), and human African trypanosomiasis (+EUR 0.7 M) projects.

**Neglected tropical diseases accounted for 78.6% of R&D expenditure in 2017, as total spending on leishmaniasis, HAT, Chagas disease, filaria, and mycetoma increased by EUR 2.4 M.**

Early discovery activities (lead optimization and screening: EUR 6.1 M) have been split between leishmaniasis and Chagas disease budgets on a proportional basis.

### Leishmaniasis

- With a total of EUR 9.9 M spent in 2017, leishmaniasis represented the largest area of R&D expenditure by disease portfolio (26%). There was significant growth in the visceral leishmaniasis (VL) programme due to progression of new chemical entities: one new pre-clinical candidate (DNDI-5561) was nominated, and two clinical candidates (DNDI-6148 and DNDI-0690) were nominated in preparation for Phase I studies.
- There were numerous advanced clinical leishmaniasis activities in 2017, with seven studies and clinical trials ongoing on three continents for VL, HIV/VL, post-kala-azar dermal leishmaniasis, and cutaneous leishmaniasis.
- Lead optimization and compound screening activities were fewer but gained in effectiveness.

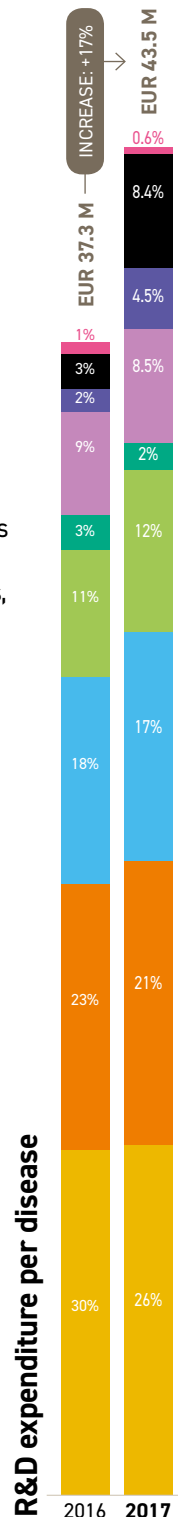
### Human African trypanosomiasis

- With a total of EUR 8.2 M, the HAT portfolio represented 21% of R&D expenditure, concentrated on clinical activities with five clinical trials ongoing.
- The fexinidazole project saw a slight decrease in 2017 (-EUR 0.1 M) with three trials (FEXI 004, 005, 006) completed. A regulatory dossier was submitted by Sanofi to the European Medicines Agency for an opinion under Article 58, while clinical study reports were in preparation and the Phase IIIb implementation study continued.
- Progress continued on the acoziborole Phase II/III trial.

### Chagas disease

- Chagas projects accounted for 17% of R&D expenditure in 2017 (EUR 6.4 M), with a spending increase over 2016 (+EUR 0.4 M) due to two ongoing clinical trials.
- The recruitment of patients in Bolivia for a proof-of-concept study for new benznidazole regimens/combinations was completed in 2017 (+EUR 0.6 M).
- A proof-of-concept study for fexinidazole for Chagas started patient recruitment in Spain (+EUR 0.5 M).

Leishmaniasis	HAT	Chagas
Filaria	Mycetoma	Paediatric HIV
HCV	GARDP	Malaria



- Investments in biomarker research decreased (-EUR 0.5 M) because the main study was completed in 2016, though activities are ongoing.
- Access spending decreased (-EUR 0.2 M), DNDI established strong partnerships to develop long-term access activities.
- Investment in lead optimization and compound screening activities remained stable.

### Filaria

- Filarial disease spending totalled EUR 4.8 M in 2017, accounting for 12% of R&D expenditure.
- 2017 saw progress in emodepside Phase I studies (+EUR 1.3 M) with three clinical trials ongoing.

### Mycetoma

- Mycetoma accounted for 2% of R&D expenditure in 2017 (EUR 0.9 M).
- Spending was concentrated on the recruitment of patients for the proof-of-concept study of fosravuconazole in Sudan (+EUR 0.4 M).

**Viral diseases accounted for 13% of R&D expenditure in 2017, as total spending on HIV and hepatitis C increased by EUR 1.2 M.**

### Paediatric HIV

- Paediatric HIV accounted for 8.5% of R&D expenditure (EUR 3.3 M).
- The LIVING study added a tenth clinical trial site, with 850 children enrolled by December 2017 (+EUR 0.5 M).
- The super-boosting study in TB-HIV co-infected children in South Africa was completed (-EUR 0.1 M).

### Hepatitis C virus (HCV)

- HCV accounted for 4.5% of R&D expenditure in 2017 (EUR 1.7 M).
- Spending increased with completion of the first stage of Phase III clinical studies (300 patients) in Malaysia and Thailand (+EUR 0.8 M).

### Antimicrobial resistance – GARDP

- GARDP accounted for 8.4% of R&D spending in 2017 compared to 3% in 2016 with an increase (+EUR 2.4 M) due to the growth of GARDP activities, including neonatal sepsis (+EUR 0.5 M), antimicrobial memory recovery and exploratory (+EUR 0.2 M), and sexually transmitted infections (+EUR 0.2 M).

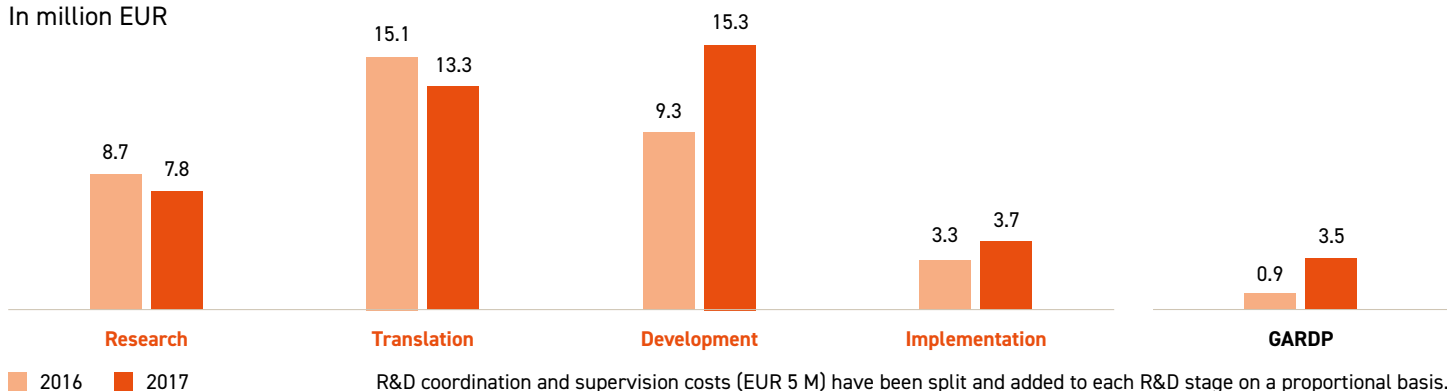
Expenditure by disease does not include R&D coordination and supervision. R&D coordination and supervision costs have not been here split and added to each disease.

## EXPENDITURE

Spending on development increased with 21 clinical studies ongoing, new projects entering clinical development (+EUR 6 M), and GARDP projects starting.

### R&D expenditure per stage of development

In million EUR



#### Research

- Discovery and research activities accounted for 18% of R&D expenditure in 2017 (down from 23% in 2016).
- There were savings in discovery activity (-EUR 0.6 M) thanks to innovative partnerships:
  - The NTD Drug Discovery Booster was fully operational in 2017 with 10 hit series identified and under further investigation, and eight participating companies (up from six in 2016);
  - The Open Synthesis Network, an open innovation initiative, expanded in 2017 to 13 participating universities with four more under discussion.
- Lead optimization activities decreased slightly (-EUR 0.3 M) despite the nomination of a new pre-clinical candidate in 2017:
  - Fees for services decreased in 2017 because the NTD Drug Discovery Booster provided higher-quality hit-to-lead series and lead series for optimization;
  - In-kind contributions from pharmaceutical partners increased, particularly with the Lead Optimization in Latin America (LOLA) consortium (supported by collaborative funding).

#### Translation

- Spending on translational projects accounted for 31% of R&D expenditure in 2017 to reach a total of EUR 13.3 M in 2017 (-EUR 1.8 M). The decrease in expenditure was due to one project moving to the development stage (acoziborole for HAT: -EUR 2.1 M) and two projects terminated end of 2016 (Anfoleish for CL and fexinidazole for VL: -EUR 2 M). This decrease was partially offset by three new projects that drove an increase in 2017 spending:
  - Emodepside: Phase I (single ascending dose) study completed in 2017 and multiple ascending dose and relative bioavailability studies started (+EUR 1.2 M).
  - Phase II proof-of-concept study ("BENDITA") of new benzimidazole regimens in combination with fosravuconazole (E1224): Recruitment was finalized in July 2017 (+EUR 0.6 M).

- New chemical entities (NCEs) for leishmaniasis: Major progress was made in advancing NCEs to pre-clinical and Phase I studies for both visceral and cutaneous leishmaniasis (+EUR 0.5 M).

#### Development

- Development activities accounted for 35% of R&D expenditure with an increase of EUR 6 M over 2016, by R&D stage, the most significant increase in 2017 spending, with four major projects ongoing:
  - VL: Preparation of Phase III combination trial testing miltefosine with paromomycin in East Africa (Kenya, Sudan, Ethiopia, Uganda) in both paediatric and adult patients (+EUR 1.6 M).
  - HCV: Phase III clinical trials to test a pan-genotypic treatment combining ravidasvir and sofosbuvir began in Malaysia in 2016 and Thailand in 2017 (co-sponsored by DNDi and the Ministry of Health). In late 2017, DNDi closed the database for the first stage of these trials (+EUR 0.9 M).
  - Mycetoma: Recruitment of patients started in 2017 for the proof-of-concept study of fosravuconazole in Sudan (+EUR 0.4 M).
  - Acoziborole Phase II/III trial: To increase patient recruitment, two new clinical trial sites were opened (Bandundu Regional and Roi Baudouin Hospitals) and active and passive detection of new HAT cases was scaled up (+EUR 3.1 M).

#### Implementation

- Implementation activities increased slightly in 2017 (+EUR 0.4 M) and represented 9% of R&D expenditure. Some implementation projects nearing completion saw decreased expenditure (-EUR 0.1 M) while the Phase IV LIVING study for paediatric HIV expenditure increased (+EUR 0.5 M), completing recruitment in Kenya and Uganda.

#### GARDP

- Expenditures are presented separately and include costs related to the exploration and initiation of the initiative's three programmes.



## R&amp;D project-related expenditure

Recognized in (expressed in EUR)	2017	2016
<b>IMPLEMENTATION PROJECT</b>		
ASAQ Fixed-dose Artesunate - Amodiaquine (Malaria)	34,390	180,457
ASMQ Fixed-dose Artesunate - Mefloquine (Malaria)	13,989	34,175
NECT Nifurtimox - Eflornithine co-administration for stage 2 (HAT)	-	7,554
New VL treatments in Asia	401,884	340,465
Chagas disease - access	471,047	424,087
HIV-LIVING Study	2,178,810	1,701,790
Superboosting ritonavir for TB/HIV co-infected children	140,377	209,472
<b>TOTAL IMPLEMENTATION PROJECTS</b>	<b>3,240,497</b>	<b>2,898,001</b>
<b>DEVELOPMENT PROJECTS (PHASE IIB/III, REGISTRATION)</b>		
Fexinidazole (HAT)	5,270,280	5,392,577
Acoziborole (HAT) <i>(Development phase as of Nov 2016)</i>	2,886,610	-
New visceral leishmaniasis treatments in Latin America	145,100	94,726
New visceral leishmaniasis treatments in Africa	1,623,205	209,094
HIV/visceral leishmaniasis co-infection	309,021	594,485
Post Kala-Azar Dermal Leishmaniasis	524,684	341,054
Hepatitis C	1,721,537	890,530
Mycetoma	920,196	566,903
<b>TOTAL DEVELOPMENT PROJECTS</b>	<b>13,400,633</b>	<b>8,089,369</b>
<b>TRANSLATION PROJECTS (PRE-CLINICAL, PHASE I, PHASE IIA/PROOF-OF-CONCEPT)</b>		
Fexinidazole (Chagas)	785,537	292,977
Acoziborole (ex SCYX-7158) (HAT) <i>(Development phase as of Nov 2016)</i>	-	2,086,459
Combination Fexinidazole/Miltefosine (VL)	-	1,563,690
Anfoleish (CL)	-	255,492
CL Combination	505,339	418,665
CpG-D35 (CL)	547,225	721,524
New Combination including New Benz Regimen (Chagas)	2,227,190	1,599,290
Biomarkers (Chagas)	329,503	886,045
Paediatric HIV ("4 in 1" LPV/r based fixed-dosed combination)	950,779	990,532
Leishmaniasis candidates: DNDI-0690 + DNDI-6148 + GSK compounds	2,304,746	1,764,553
Emodepside Macrofilaricide and Coordination (Filaria)	2,708,971	1,458,439
Oxfendazole Macrofilaricide (Filaria)	74,853	23,702
TylAMac/ABBV-4083 Macrofilaricide (Filaria)	1,076,830	1,097,214
<b>TOTAL TRANSLATION PROJECTS</b>	<b>11,510,972</b>	<b>13,158,583</b>
<b>RESEARCH PROJECTS (SCREENING, HIT-TO-LEAD, LEAD OPTIMIZATION)</b>		
Lead Optimization Consortia	4,768,916	4,933,020
Screening Resources & Reference Screening Centres	1,321,962	1,697,768
Screening Filaria	920,801	949,444
<b>TOTAL RESEARCH PROJECTS</b>	<b>7,011,679</b>	<b>7,580,231</b>
<b>PROJECT-RELATED VARIABLE EXPENDITURE</b>		
GARDP	3,242,228	887,256
Exploratory Activity	91,918	28,598
R&D Coordination & Supervision	5,001,608	4,691,590
<b>TOTAL PROJECT-RELATED EXPENDITURE</b>	<b>43,499,534</b>	<b>37,333,628</b>

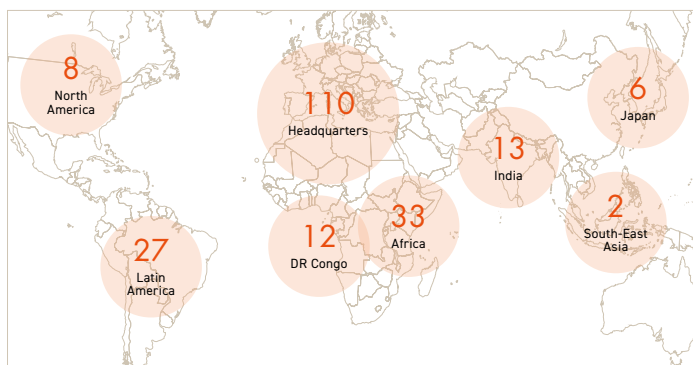
Extracted from DNDI's '2017 Financial and Performance Report' audited by Deloitte. The full report is available on DNDI's website at: [www.dndi.org/key-financial-figures](http://www.dndi.org/key-financial-figures)

## HUMAN RESOURCES

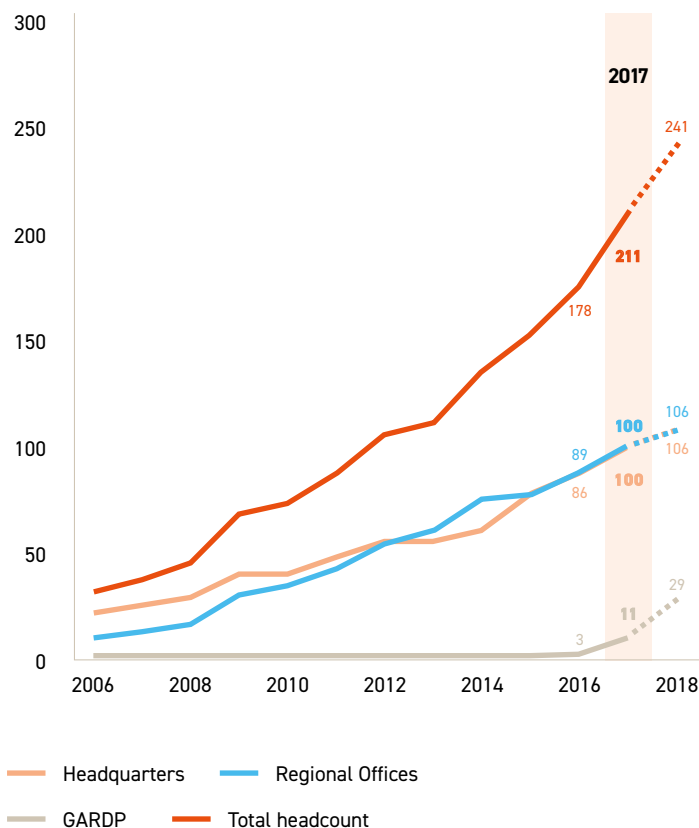
**HR expenses increased by 26% to support the incubation of GARDP and further development of the DNDi R&D portfolio.**

- To meet the needs of DNDi's growth and the demands of the external environment, and as part of the incubation of GARDP, teams were strengthened and new expertise added in 2017. DNDi recruited an additional 33 positions, representing an increase of 19% over 2016 staffing levels.
- The increase in HR expenses (+EUR 4.4 M) included:
  - Recruitment and effective start of 33 new positions (+EUR 2.1 M) in 2017;
  - New positions recruited in 2016 (23 new positions) that received a full year's salary in 2017 (+EUR 1.5 M);
  - Annual incremental salary increase (~+1%), promotions, inflation rate applicable in some countries, provision for holidays not taken, training costs, and executive recruiter (+EUR 0.8 M).
- The split between DNDi's headquarters and regional offices remained balanced in 2017 (52%/48%), with 110 core staff and consultants working in headquarters and 101 working in regional offices.
- Eight core staff were recruited to support the development of GARDP, located primarily at the DNDi headquarters office.
- Ten new core positions were recruited to support R&D in 2017. This was driven by the need to support diseases recently added to the portfolio and to support R&D coordination to address compliance requirements from regulatory authorities, external stakeholders, partners, and donors. New core positions included: R&D portfolio and planning leader, pharmacovigilance manager, and project coordinators.
- Nine new core positions were dedicated to support functions (four in DR Congo, one in Japan, one in Brazil, and three in Switzerland). Initially these positions were contracted on a short-term basis as associate staff, but with the growth of the organization they have been stabilized and moved to core positions, including: assistant accountant, logisticians, business analysis officer, and HR officers.
- Six new core staff and consultants joined the External Affairs team (two in regional offices and four at headquarters): Policy & advocacy advisors, senior corporate and scientific communications manager, external relations managers, and digital content officer.
- Considering all employees' start and end dates, as well as the percentage of time worked for each position in DNDi, the 2017 total core staff and consultant count at the end of 2017 was 189 full-time equivalent (FTE) staff. This represents an increase of 21% over 2016.

### Distribution of DNDi staff & consultants around the world



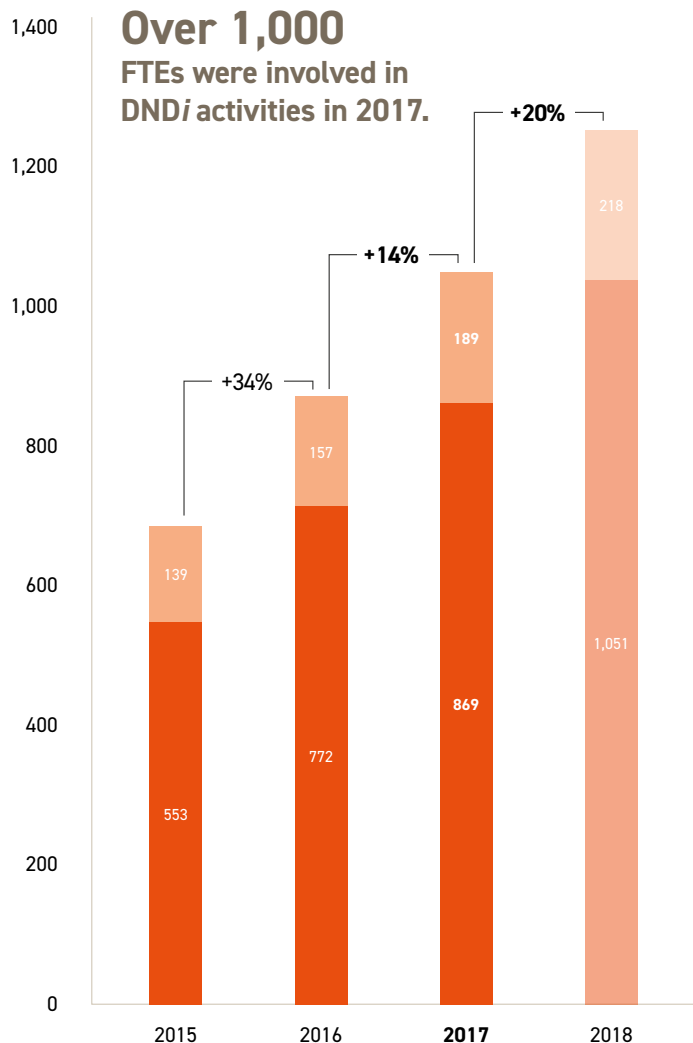
### Human resources evolution at DNDi Number of core staff & consultants Includes DNDi and GARDP staff



## Every DNDi FTE generates four FTEs through subcontracted research activities.

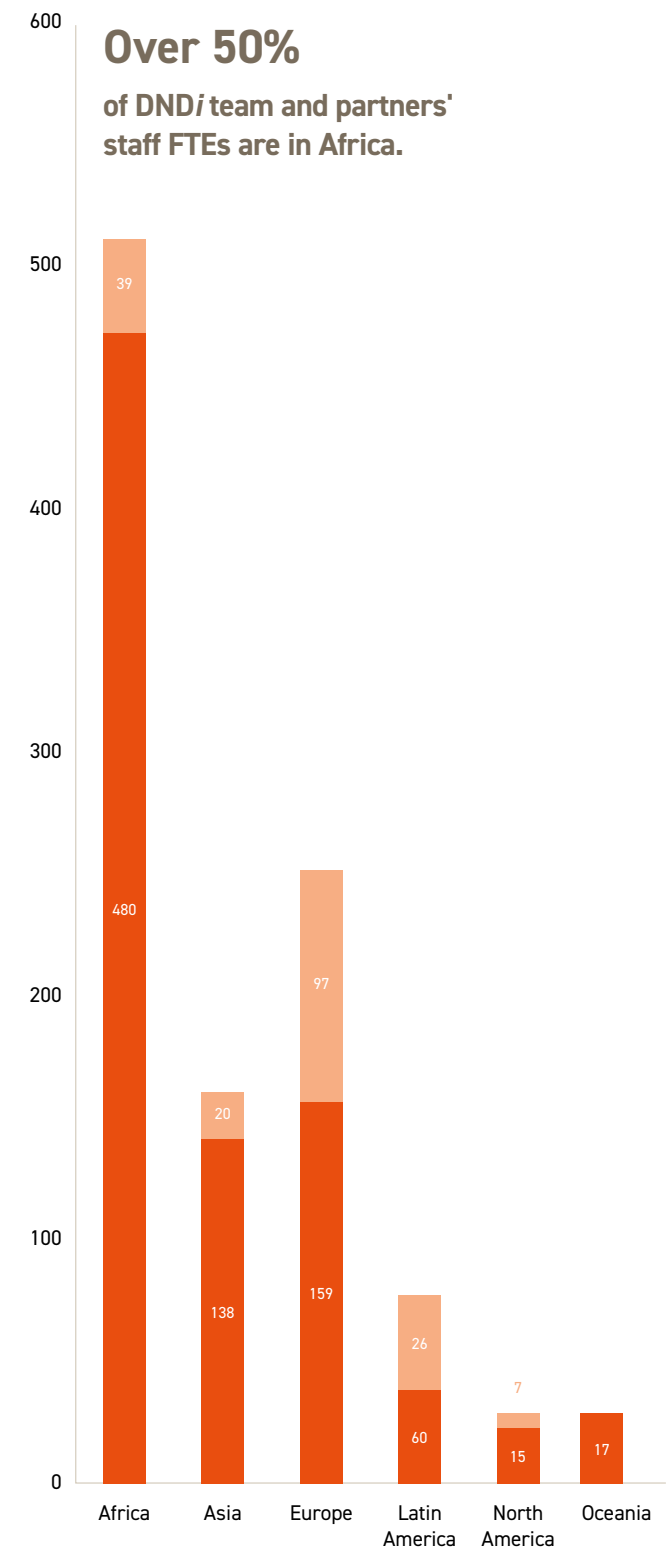
- As a virtual R&D organization, DNDi subcontracts its research activities to partners. The number of FTEs created in partner organizations and working on DNDi activities has been tracked in recent years, showing a consistent trend of four to five FTEs in partner organizations for every DNDi FTE.
- In 2017, this trend was maintained, with 869 FTEs in partner organizations and staff associates for 189 FTEs at DNDi.
- The forecast for 2018 based on an analysis of contracts gives 1,051 FTEs in partner organizations and staff associates for 218 FTEs at DNDi.

### Ratio of DNDi to partner staff in FTE



■ DNDi team (core staff + core consultants)  
■ Staff from partners, subcontractors and staff associates

### Geographical distribution of FTE staff in 2017



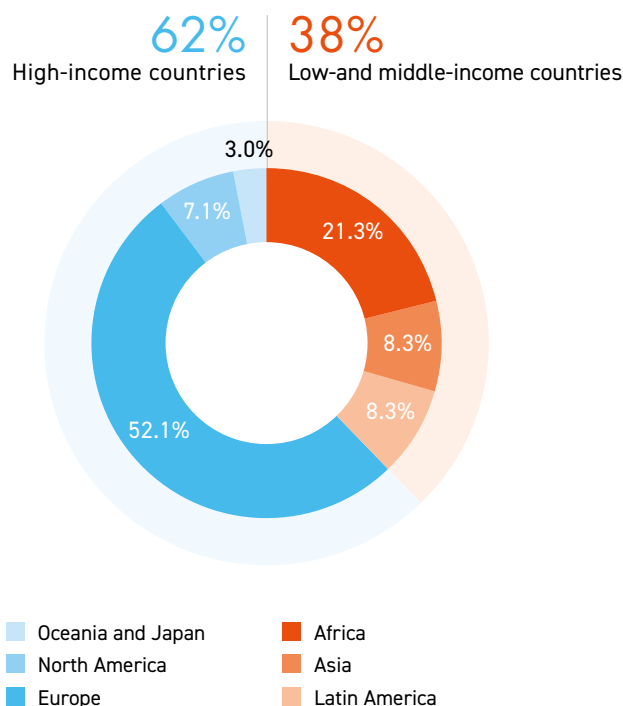
■ DNDi team (core staff + core consultants)  
■ Staff from partners, subcontractors and staff associates

## PARTNERSHIPS AND SUBCONTRACTORS

### Number of partners and subcontractors similar to 2016

- In 2017, the number of partners and service providers with whom DNDi had business relations valued at over EUR 5,000 remained relatively stable (169 in 2017, up slightly from 167 in 2016). Note that these figures do not include some of DNDi's important partnerships where these contain no financial component.
- Partnerships and service providers increased in Europe at 52% of partnerships in 2017 compared to 47% in 2016. This reflects the expansion of GARDP and the leishmaniasis portfolio focus on chemistry, manufacturing, and control (CMC), and pharmaceutical development and pre-clinical activities.
- The ratio of low- and middle-income country partners to high-income country partners is relatively stable, at 38% versus 62%.

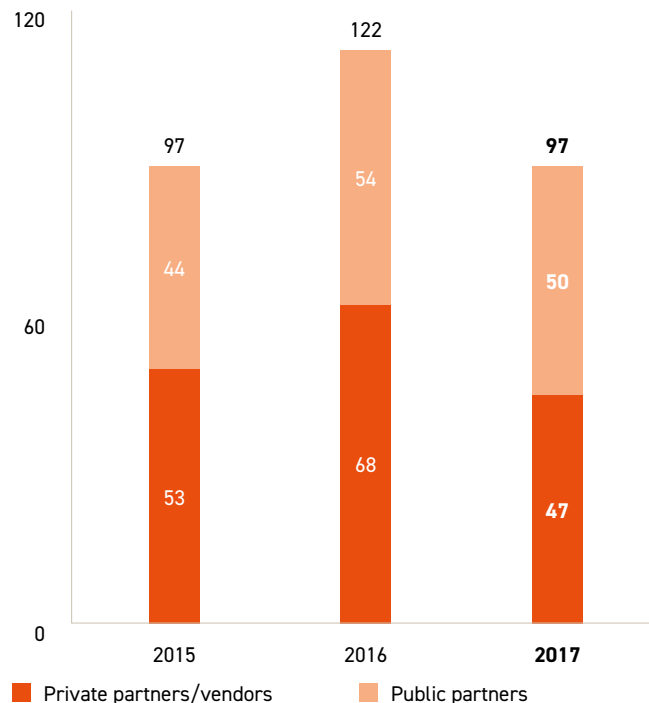
### 2017 partners & service providers



### Contracting remained balanced between private and public sector partners.

- In 2017, a total of 97 new R&D contracts were signed. Note that the figures exclude confidentiality agreements and work orders but include contract extensions/amendments as 'new' contracts.
- Organizations from the public institutional sector (including research institutes, public hospitals, academic groups, universities, product development partnerships, and other not-for-profit organizations) accounted for 50 (52%) contracts signed in 2017, with private sector organizations (including pharmaceutical and biotechnology companies, and contract research organizations) accounting for 47 (48%). The overall ratio of public to private contracts has remained stable over the past three years.

### Number of R&D contracts signed per year



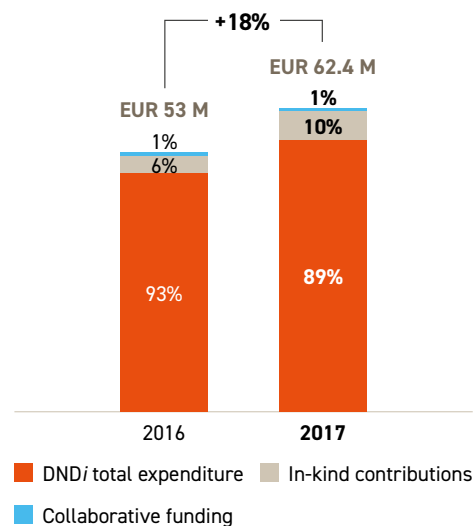


## LEVERAGING PARTNERS' RESOURCES

### Collaborative funding and in-kind contributions

- To present a comprehensive picture of its activities, DNDi accounts for collaborative funding from partners and attributes an estimated value to the generous in-kind contributions of its partners, be they private companies, academic groups, or individuals.
- Collaborative funding in 2017 was valued at EUR 0.8 M, a 37% increase (+EUR 0.2 M) due to the contributions of Thailand and Malaysia for hepatitis C clinical trial implementation, valued at EUR 0.5 M in 2016.
- In 2017, in-kind contributions were valued at EUR 6 M, representing an increase of 64% (+EUR 2.3 M) over 2016, when total in-kind contributions were valued at EUR 3.1 M. This increase is mainly due to the contribution of partners to develop a pre-clinical candidate for filarial disease.
- Cumulative in-kind contributions over the last eleven years amount to EUR 40 M, reflecting DNDi's continued investment in building strong partnerships. This represents more than 11% of the total expenditure for the same period.

### Total DNDi valued activity

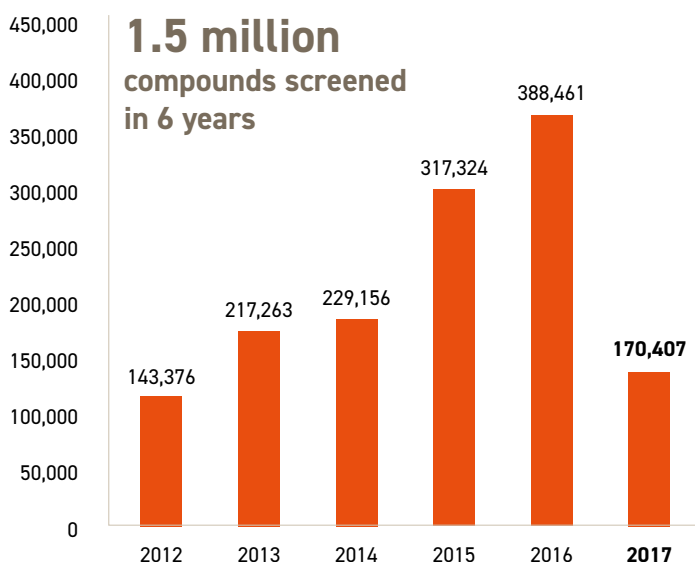


### Access to compound libraries

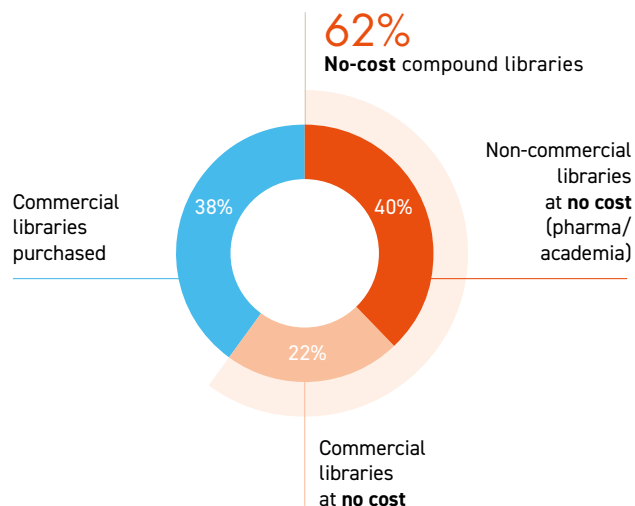
- Over 170,000 compounds were screened in VL and Chagas assays in 2017. The smaller number of compounds assessed over this period compared to 2016 (388,461) was largely due to a heavy focus on hit confirmation and profiling of active compounds previously identified from primary screening of commercial collections. This work has mainly been completed in collaboration with the University of Dundee for hit confirmation, as well as with other screening partners for hit profiling.

- The screening capacity of partner Institut Pasteur Korea was primarily dedicated to the support of the NTD Booster and Daiichi Sankyo hit-to-lead (H2L) programmes. Those projects are based on thorough screening evaluations of compounds supplied by DNDi's pharmaceutical partners (around 9,000 for the NTD Booster and 1,500 for Daiichi Sankyo H2L).
- Overall, the total number of completed screens delivered by screening partners in 2017 was similar to 2016.

### Number of compounds screened per year



Since 2012, more than 900,000 compounds have been provided to DNDi at no cost from academic and commercial libraries.

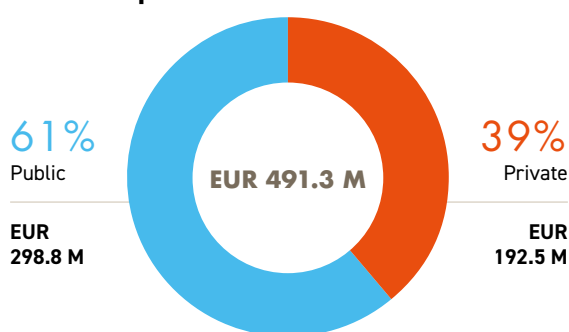


## CONTRIBUTIONS

### Balanced and diversified funding was maintained in 2017

- DNDi seeks diversified sources of funding from public and private sources, which were further diversified in 2017 with the addition of five new donors:
  - Three public: Grand Duchy of Luxembourg for GARDP; Dutch Ministry of Health, Welfare and Sport (VWS) for GARDP; and International Development Research Centre (IDRC), Canada;
  - One private: Médecins Sans Frontières - Transformational Investment Capacity (MSF-TIC), for the STORM-C hepatitis C project;
  - One collaborative source of funding from an endemic country: National Science and Technology Development Agency (NSTDA), a member of the Ministry of Science and Technology of Thailand (for the STORM-C hepatitis C project).
- The HAT Campaign, a fundraising initiative launched by DNDi North America, more than doubled private funds raised in North America for HAT projects and core funding (USD 0.5 M) compared to 2016 (USD 0.2 M). These donations were mostly from private donors and family fund foundations, including (but not limited to): Charina Endowment Fund, USA; craigslist Charitable Fund, USA; P B & K Family Foundation, USA; The Broder Family Foundation, USA; The Robin O'Brien Fund, USA; and Zegar Family Fund, USA.
- DNDi policy is to ensure that no single donor contributes more than 25% to the Business Plan. However, with renewal of the UK government grant and its increase by more than 40% in 2017, this donor represented 28% of total income in 2017. We anticipate that this will drop again in 2018-2019 with the renewal of several key grants.
- DNDi also seeks to ensure that the majority of its budget is covered by public funds as an expression of public leadership. In 2017, with secured funds until 2021, public funding accounted for 61% (55% in 2016) and private support for 39% (45% in 2015). Most of DNDi's public donors have been renewed in the last two years, while commitments from major private donors will be at the renewal stage in 2019-2020.
- 90% (EUR 75.2 M) of the EUR 83.4 M in new funding granted in 2017 was granted by public institutions: UK government; GHIT, Japan; EDCTP, EU; WHO-TDR; Norad, Norway; FOPH, Switzerland; SDC, Switzerland; MoH<sup>1</sup>, The Netherlands; Grand Duchy of Luxembourg; SAMRC, South Africa; Federal MoH<sup>1</sup>, Germany.

### Public vs private contributors 2003-2021



#### PRIVATE CONTRIBUTIONS

**EUR 192.5 M**

<b>20.7%</b>	Bill & Melinda Gates Foundation	EUR 101.6 M
<b>15.1%</b>	Médecins Sans Frontières	EUR 74.2 M
<b>3.4%</b>	Various private donors: Wellcome Trust, Medicor, others	EUR 16.7 M

#### PUBLIC INSTITUTIONAL CONTRIBUTIONS

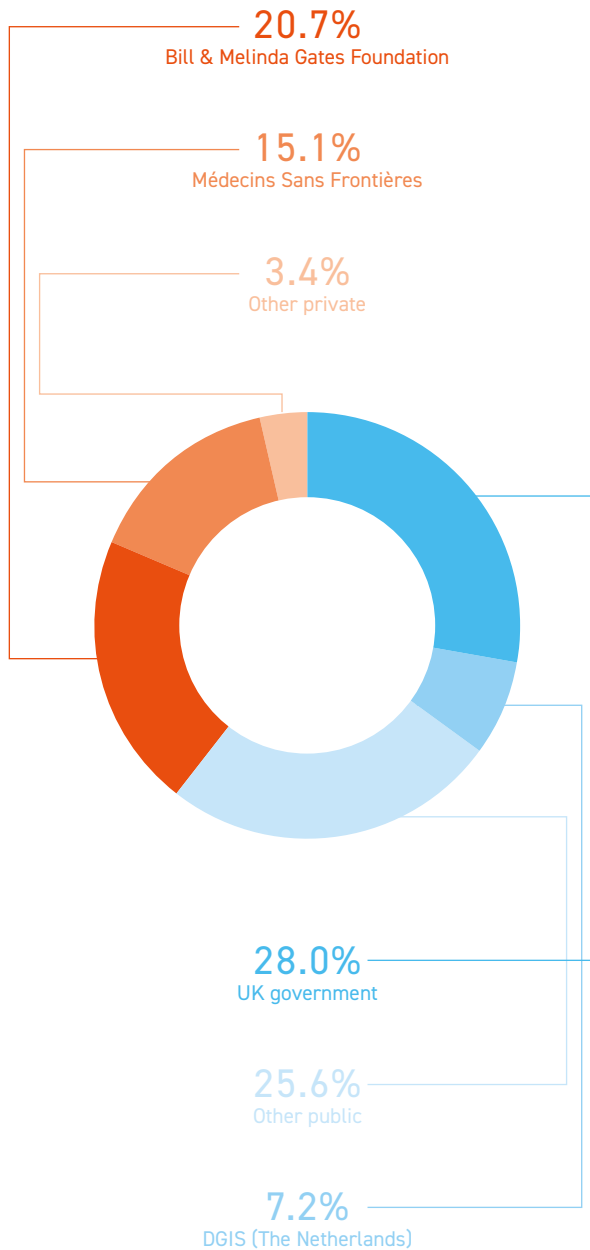
**EUR 298.8 M**

<b>28%</b>	UK government	EUR 137.7 M
<b>7.2%</b>	The Netherlands (DGIS and MoH <sup>1,2</sup> )	EUR 35.5 M
<b>4.6%</b>	Germany (BMBF through KfW, GtZ, and MoH <sup>1,2</sup> )	EUR 22.7 M
<b>4.3%</b>	Switzerland [SDC, Canton of Geneva, and FOPH <sup>2</sup> ]	EUR 21 M
<b>3.3%</b>	France (AFD)	EUR 16.3 M
<b>2.8%</b>	Japan (GHIT Fund)	EUR 13.9 M
<b>2.6%</b>	Unitaid	EUR 12.5 M
<b>2.4%</b>	Spain (AECID)	EUR 12.0 M
<b>2.1%</b>	US Government NIH/NIAID/USAID	EUR 10.1 M
<b>2%</b>	European Union (FP5, FP6, FP7, EDCTP)	EUR 10 M
<b>1.5%</b>	Others	EUR 7.1 M

<sup>1</sup> MoH: Ministry of Health

<sup>2</sup> for GARDP

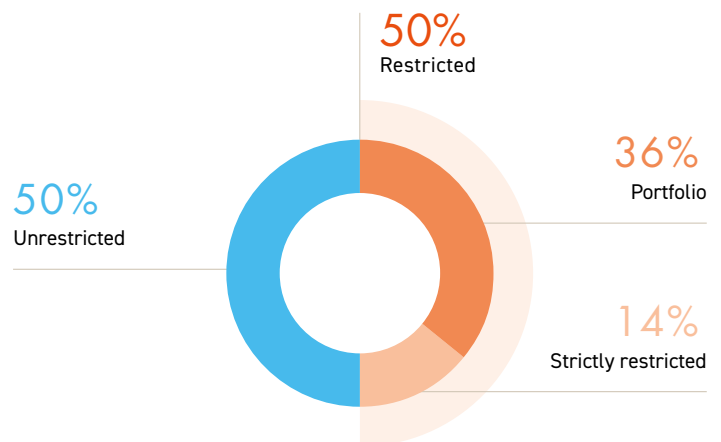
**From 2003-2021, four funders accounted for 71% of funds committed to DNDi.**



## Continued shift toward unrestricted funding

- Over the last six years, DNDi has maintained a balance between restricted and unrestricted grants. Unrestricted funding allows the organization to respond quickly to research opportunities and to end projects that do not meet targets.
- Looking at cumulative funding from 2003 to 2021, restricted funding accounted for 50% of total funds raised (36% allocated to portfolio funding - allowing for some flexibility within a range of diseases - and 14% restricted to specific R&D projects), and unrestricted funding for 50%.
- The share of portfolio grants progressively increased until 2016 (from 18% in 2011 to 38% in 2016). In 2017, it decreased due to the significant increase in unrestricted funding, which rose by EUR 68.4 M (+38%).

**A total of EUR 491.3 M\* was raised by the end of 2017.**



*\*Funds committed to GARDP (EUR 10.7 M) are included in the total amount raised by year-end 2017*

# INCOME

## Cumulative donations committed to DNDi and/or received by 2017

DONORS	Currency	Total commitment in currency	Total commitment in EUR	As per statement of operations 2017 in EUR	To be used after 2017 in EUR
UK Government <sup>(1)</sup>	GBP	112,364,550	134,258,381	16,896,822	37,993,446
Bill & Melinda Gates Foundation <sup>(2)</sup>	USD	125,580,434	101,604,227	11,792,654	20,743,676
Médecins Sans Frontières <sup>(3)</sup>	EUR	73,653,142	73,653,142	4,410,573	11,415,192
Dutch Government DGIS <sup>(4)</sup>	EUR	32,975,000	32,975,000	3,700,000	8,300,000
German Government BMBF through KfW <sup>(5)</sup>	EUR	20,101,381	20,101,381	2,300,000	6,500,000
Swiss Government SDC <sup>(6)</sup>	CHF	21,520,000	18,271,000	2,073,953	284,340
French Government MEAE / AFD <sup>(7)</sup>	EUR	16,255,006	16,255,006	1,234,149	606,593
GHIT Fund, Japan <sup>(8)</sup>	USD/JPY	1,777,537,856	13,907,659	2,682,374	5,170,986
Unitaid <sup>(9)</sup>	USD	14,470,189	12,515,559	3,151,176	3,210,341
Spanish Government AECID	EUR	12,000,000	12,000,000	-	-
US Government NIH/NIAID/USAID	USD	12,196,791	10,091,589	873,011	6,327,342
European Union, FP5, FP6, FP7, EDCTP <sup>(10)</sup>	EUR	9,973,885	9,973,885	127,561	5,433,223
Wellcome Trust, UK	EUR/USD	5,579,614	4,913,759	-	-
Medicor Foundation, Liechtenstein	EUR/USD	4,250,000	3,627,821	300,000	300,000
Various other donors (Fondation ARPE, Brian Mercer Charitable Trust, Rockefeller Brothers Fund, Sandoz Family Foundation, Sasakawa Peace Foundation, Region of Tuscany, North American foundations and private donors, and anonymous individuals and foundations) and royalties <sup>(11)</sup>	EUR/GBP	3,405,894	3,300,977	532,782	135,360
WHO-TDR <sup>(12)</sup>	EUR/USD	2,675,000	2,624,159	400,493	-
Norwegian Government Norad	NOK	22,000,000	2,469,551	479,328	-
Associação Bem-Te-Vi Diversidade, Brazil	BRL	8,200,000	2,268,699	401,101	430,052
Canton of Geneva, Switzerland	CHF	2,580,000	1,972,513	159,026	128,370
UBS Optimus Foundation, Switzerland	CHF	2,000,000	1,441,755	-	37,575
The Starr International Foundation, Switzerland	USD	875,000	709,088	217,686	-
The Global Fund	EUR	532,809	532,809	-	-
Brazil Government MoH and Finep	BRL	1,384,212	409,611	-	-
BBVA Foundation, Spain	EUR	400,000	400,000	-	-
KalaCORE	GBP	213,900	256,228	58,022	80,854
UK Government DFID for GARDP <sup>(1)</sup>	GBP	3,075,000	3,485,279	1,539,519	1,859,887
German Government MoH for GARDP <sup>(13)</sup>	EUR	2,600,000	2,600,000	1,419,905	722,636
Dutch Government MoH for GARDP <sup>(14)</sup>	EUR	2,500,000	2,500,000	463,570	2,037,430
Swiss Government FOPH for GARDP	CHF	860,000	761,569	274,766	303,974
South African Medical Research Council for GARDP	ZAR	10,000,000	699,316	139,875	559,441
MSF for GARDP <sup>(15)</sup>	EUR	600,000	600,000	324,975	-
Grand Duchy of Luxembourg for GARDP	EUR	100,000	100,000	100,000	-
<b>TOTAL DONATIONS (EUR)</b>			<b>491,279,963</b>	<b>56,053,320</b>	<b>117,580,718</b>

Extracted from DNDi's '2017 Financial and Performance report' audited by Deloitte. The full report is available on DNDi's website at: [www.dndi.org/key-financial-figures](http://www.dndi.org/key-financial-figures)



## BALANCE SHEET

At 31 December 2017 with 2016 comparative figures

(Expressed in EUR)	NOTES	2017	2016
<b>CURRENT ASSETS:</b>			
<b>Cash and cash equivalents</b>			
Cash and banks at headquarters		18,453,459	21,338,896
Cash and banks at regional and affiliate offices		1,146,406	1,310,387
Time deposits		4,059,227	3,408,386
<b>Total cash and cash equivalents</b>	12	<b>23,659,092</b>	<b>26,057,668</b>
<b>Stocks of drugs</b>	3	<b>429,318</b>	<b>287,735</b>
<b>Current accounts and receivables:</b>			
Advances to staff and regional offices		35,100	45,370
Receivables from public institutional donors		5,531,012	1,487,890
Other receivables		956,269	597,053
Prepaid expenses		985,496	684,552
<b>Total current accounts &amp; receivables</b>		<b>7,507,877</b>	<b>2,814,866</b>
<b>TOTAL CURRENT ASSETS</b>		<b>31,596,287</b>	<b>29,160,269</b>
<b>NON-CURRENT ASSETS:</b>			
Tangible fixed assets, net	4	261,413	324,369
Bank guarantee deposits	12	340,019	242,091
<b>TOTAL NON-CURRENT ASSETS</b>		<b>601,432</b>	<b>566,460</b>
<b>TOTAL CURRENT &amp; NON-CURRENT ASSETS</b>		<b>32,197,718</b>	<b>29,726,729</b>
<b>CURRENT LIABILITIES:</b>			
Payables		5,569,320	6,648,043
Accrued expenses		3,396,091	1,718,804
Deferred income	7	11,964,155	10,248,121
Provisions	5	492,632	452,166
<b>Total current liabilities</b>		<b>21,422,198</b>	<b>19,067,134</b>
<b>ORGANIZATIONAL CAPITAL:</b>			
Paid-in capital		32,510	32,510
Restricted operating funds		0	0
Unrestricted operating funds		10,743,010	10,627,084
<b>Total organizational capital</b>		<b>10,775,520</b>	<b>10,659,595</b>
<b>TOTAL CURRENT LIABILITIES &amp; ORGANIZATIONAL CAPITAL</b>		<b>32,197,718</b>	<b>29,726,729</b>

Extracted from DND's '2017 Financial and Performance report' audited by Deloitte. The full report is available on DND's website at: [www.dndi.org/key-financial-figures](http://www.dndi.org/key-financial-figures)

# STATEMENT OF OPERATIONS

At 31 December 2017 with 2016 comparative figures

(Expressed in EUR)	NOTES	2017	2016
<b>INCOME</b>			
<b>Public institutional funding:</b>			
Governments & public international organizations unrestricted		20,231,337	14,608,068
Governments & public international organizations restricted		17,842,213	16,536,879
<b>Total public institutional funding</b>		<b>38,073,550</b>	<b>31,144,948</b>
<b>Private resources:</b>			
Private foundations, corporate and individuals, unrestricted		553,949	161,135
Private foundations, corporate and individuals, restricted		12,690,274	13,387,722
<b>Total private resources</b>		<b>13,244,223</b>	<b>13,548,857</b>
<b>Resources from founders:</b>			
Médecins Sans Frontières, unrestricted		4,324,974	4,275,025
Médecins Sans Frontières, restricted		410,574	15,556
<b>Total resources from founding partners</b>		<b>4,735,548</b>	<b>4,290,581</b>
<b>Sundry income &amp; reimbursements</b>		<b>46,685</b>	<b>54,878</b>
<b>TOTAL INCOME</b>	7	<b>56,100,006</b>	<b>49,039,263</b>
<b>SOCIAL MISSION EXPENDITURE</b>			
<b>Research &amp; development expenditure:</b>	8		
Research & development coordination and supervision		5,001,608	4,691,590
Other diseases projects (malaria and exploratory)	2 (o)	140,297	243,230
Lead optimization & portfolio building		6,090,878	6,630,788
Human African trypanosomiasis projects		8,156,889	7,486,589
Leishmaniasis projects		6,361,203	6,303,749
Chagas disease projects		3,813,277	3,202,400
Filarial disease projects		4,781,455	3,528,799
Mycetoma projects		920,196	566,903
Paediatric HIV projects		3,269,966	2,901,795
Hepatitis C projects		1,721,537	890,530
Global Antibiotic Research & Development Partnership (GARDP)	1 (d)	3,242,228	887,256
<b>Total research &amp; development expenditure</b>		<b>43,499,534</b>	<b>37,333,628</b>
<b>Strengthening capacities expenditure</b>	9	<b>3,070,693</b>	<b>3,177,076</b>
<b>Advocacy expenditure</b>	10	<b>2,576,624</b>	<b>2,500,878</b>
<b>TOTAL SOCIAL MISSION EXPENDITURE</b>		<b>49,146,850</b>	<b>43,011,582</b>
<b>NON-SOCIAL MISSION EXPENDITURE</b>			
Fundraising	10	2,112,651	1,912,520
General and administration	10	4,316,867	3,848,785
<b>TOTAL NON-SOCIAL MISSION EXPENDITURE</b>		<b>6,429,519</b>	<b>5,761,305</b>
<b>TOTAL EXPENDITURE</b>		<b>55,576,369</b>	<b>48,772,887</b>
Operating surplus		523,636	266,375
<b>OTHER EXPENSES</b>			
Financial loss, net		(21,404)	(9,436)
Exchange loss, net		(386,307)	(235,374)
<b>TOTAL OTHER EXPENSES</b>		<b>(407,711)</b>	<b>(244,810)</b>
Net surplus for the year prior to allocations		115,925	21,566
Release from restricted operating funds		0	53,364
Allocation to unrestricted operating funds		(115,925)	(74,930)
<b>NET SURPLUS FOR THE YEAR AFTER ALLOCATIONS</b>		<b>-</b>	<b>-</b>

Extracted from DND's '2017 Financial and Performance Report' audited by Deloitte. The full report is available on DND's website at: [www.dndi.org/key-financial-figures](http://www.dndi.org/key-financial-figures)

# **Governance & a word of thanks**

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# GOVERNANCE

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### Barbara Kessler

formerly with Novartis, Switzerland

Statutory auditors: Deloitte

### Bernard Pécoul

DNDi, Switzerland

### Marie-Paule Kieny

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### Marcel Tanner

Chair of DNDi Board of Directors (until July 2017), Switzerland

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\*Former DNDi Board or SAC member

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Manica Balasegaram, GARDP Director

Graeme Bilbe, Research & Development Director

Thomas Saugnac, Operations Director

### Headquarters

François Bompert, Paediatric HIV/HCV Programmes Director (since January 2018)\*

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Robert Don, Discovery & Pre-Clinical Director (until March 2017)

Jana Jauffret, Human Resources & Organization Director

Charles Mowbray, Discovery Director (since April 2017)

Jean-Pierre Paccaud, GARDP Business Development & Strategy Director

Serge Sagodira, Business Development and Legal Director

Nathalie Strub-Wourgaft, Medical Director

Laurence Vielfaure, Finance and Planning Director

\* Also members of the Executive team since January 2018

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Rachel Cohen, Executive Director, DNDi North America (affiliate office)

Suman Rijal, Director, DNDi India

Joël Keravec, Director, DNDi Latin America

Monique Wasunna, Director, DNDi Africa

Chirac Bulanga Milemba, Head of DNDi Project Office, Democratic Republic of the Congo

Daisuke Imoto, Head of Office, DNDi Japan

Jean-Michel Piedagnel, Head of Office, DNDi South East Asia

Carol Ruffell, Head of Office, DNDi South Africa (since Nov. 2017)

## DNDi TEAM WORLDWIDE

You can find more information on all DNDi staff, including programme, regional, and functional leaders, on DNDi's website: <https://www.dndi.org/about-dndi/our-people/leadership>.

# A WORD OF THANKS

DNDi would like to thank all its donors worldwide for their loyal commitment and collaboration since 2003. To date, DNDi has delivered seven new treatments and aims to bring 16-18 treatments to patients living with neglected diseases by 2023. DNDi is grateful for the support received from all donors who contributed toward the advancement of its mission and goals. Listed are supporters who have given a cumulative contribution of more than USD or EUR 10,000, as well as collaborative funding partners.

## PUBLIC INSTITUTIONAL SUPPORT

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- **Australian Trade and Investment Commission (Austrade)**, Australia
- **Banco Nacional de Desenvolvimento Econômico e Social (BNDES)**, Brazil
- **Dutch Ministry of Foreign Affairs (DGIS)**, The Netherlands
- **Dutch Ministry of Health, Welfare and Sport (VWS)**, The Netherlands (GARDP)
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- **Federal Ministry of Education and Research (BMBF) through KfW**, Germany
- **Federal Ministry of Health**, Germany (GARDP)
- **Federal Office of Public Health (FOPH)**, Switzerland (GARDP)
- **French Development Agency (AFD)**, France
- **Fundação Oswaldo Cruz (Fiocruz)**, Brazil
- **German International Cooperation (GIZ)** on behalf of the Government of the Federal Republic of Germany, Germany
- **Global Health Innovative Technology Fund (GHIT Fund)**, Japan
- **Grand Duchy of Luxembourg**, Luxembourg (GARDP)
- **International Development Research Centre (IDRC)**, Canada
- **Ministry of European and Foreign Affairs (MEAE)**, France
- **Ministry of Health**, Brazil
- **Ministry of Health**, Malaysia
- **National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID)**, USA
- **National Science and Technology Development Agency (NSTDA), Ministry of Science and Technology**, Thailand
- **Norwegian Agency for Development Cooperation (Norad), Norwegian Ministry of Foreign Affairs**, Norway
- **Region of Tuscany**, Italy
- **Republic and Canton of Geneva, International Solidarity Office**, Switzerland
- **Ruta-N, City of Medellin**, Colombia
- **Science and Technology Innovation Agency (Finep)**, Brazil, through the Regional and National Finep Awards for Innovation in Social Technology
- **South African Medical Research Council (SAMRC)**, South Africa (GARDP)
- **Spanish Agency for International Development Cooperation (AECID)**, Spain
- **Swiss Agency for Development and Cooperation (SDC)**, Switzerland
- **The Global Fund to Fight AIDS, Tuberculosis and Malaria**
- **UK aid**, UK (DNDi and GARDP)
- **Unitaid**
- **US Agency for International Development (USAID)**, USA
- **US Agency for International Development (USAID), via the 4th Sector Health Project implemented by Abt Associates, Inc.**, USA
- **World Health Organization - Special Programme for Research and Training in Tropical Diseases (WHO-TDR)**

## PRIVATE SUPPORT

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- **Associação Bem-Te-Vi Diversidade**, Brazil
- **BBVA Foundation (through the ‘Frontiers of Knowledge Award in Development Cooperation’)**, Spain
- **Bennett Shapiro and Fredericka Foster**, USA
- **Bill & Melinda Gates Foundation**, USA
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- **Harlan and Sally Weisman**, USA
- **Jeff Nelson**, USA
- **Leopold Bachmann Foundation**, Switzerland
- **Dr. Margaret Golden**, USA
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- **Medicor Foundation**, Liechtenstein
- **Meena and Liaquat Ahamed**, USA
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- **Rockefeller Brothers Fund**, USA
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- **The Rockefeller Foundation (through the ‘Next Century Innovators Award’)**, USA
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- **UBS Optimus Foundation**, Switzerland
- **Wellcome Trust**, UK
- **Zegar Family Fund**, USA
- **Anonymous individuals and organizations**

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The Drugs for Neglected Diseases *initiative* (DNDi) is a collaborative, patient-needs driven, not-for-profit research and development (R&D) organization that develops safe, effective, and affordable treatments for the millions of people across the world affected by neglected diseases, notably human African trypanosomiasis (sleeping sickness), leishmaniasis, Chagas disease, filarial infections, paediatric HIV, mycetoma, and hepatitis C.

In 2016, in collaboration with the World Health Organization, DNDi launched the Global Antibiotic Research & Development Partnership, a not-for-profit research and development organization that addresses global public health needs by developing and delivering new or improved antibiotic treatments while endeavouring to ensure sustainable access.

#### **DNDi's primary objective:**

> Deliver 16 to 18 new treatments by 2023 for targeted neglected diseases, ensure equitable access to these treatments, and establish a robust R&D portfolio of new drug candidates that addresses patients' treatment needs

#### **In doing this, DNDi has two further objectives:**

> Use and strengthen capacities in disease-endemic countries via project implementation

> Raise awareness about the need to develop new drugs for neglected diseases and advocate for increased public responsibility

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