Message from the Chair of the Board and the Executive Director

We cannot look back on the important progress we achieved with our research and development (R&D) partners in 2019 without acknowledging the unprecedented and rapidly evolving challenges we face today. As this report goes to print, the world is gripped by COVID-19 – one of the biggest pandemic catastrophes in living memory.

DNDi is working continuously to assess and, where possible, mitigate the impact of the pandemic on our R&D programmes and near-term ambitions. We are also leveraging our resources and experience as an instigating member of the COVID-19 Clinical Research Coalition, which seeks to fast-track research into tools for prevention and treatment that are adapted for use in resource-limited settings.

The health, safety, and well-being of patients in our clinical trials, our partners, and our team will remain our foremost concern in the face of this crisis. Many of our medical partners are already, or will soon be, on the front lines of the COVID-19 response. We stand in solidarity with our colleagues in these trying times.

Dr Marie-Paule Kieny, Chair of the Board of Directors and Dr Bernard Pécoul, Executive Director

HUMAN AFRICAN TRYPANOSOMIASIS (SLEEPING SICKNESS)

Added to the World Health Organization (WHO) Essential Medicines List in 2019, the first all-oral cure for sleeping sickness, fexinidazole, is now being donated by Sanofi to WHO for distribution in T.b. gambiense-endemic countries. DNDi is supporting pharmacovigilance and training to scale up access to this new treatment while advancing clinical development of acoziborole – a potentially game-changing, single-dose oral treatment that could provide an even better treatment option and facilitate sustained elimination of the disease.

VISCERAL LEISHMANIASIS (VL)

Short-term strategies to develop better treatment regimens using existing drugs progressed, with Phase Ib/II studies in Africa testing new regimens for VL and post-kala-azar dermal leishmaniasis (PKDL) and a Phase II study in South Asia testing a new regimen for PKDL. Results from HIV/VL Phase III studies in Ethiopia and India were presented to national and international authorities to inform review of HIV/VL treatment guidelines. In addition, multiple new chemical entities have progressed in pre-clinical and Phase I studies, marking significant progress towards DNDi’s long-term goal of developing an entirely new generation of all-oral drugs for VL.

CUTANEOUS LEISHMANIASIS (CL)

Preliminary results from a Phase II study in Latin America showed the combination of thermotherapy with a shorter course of oral miltefosine to be significantly better than thermotherapy alone for the treatment of uncomplicated CL in the Americas. Planning for first-in-human studies is underway for CpG-D35, a novel immunomodulator designed to promote the immune system’s response to the parasitic infection that causes CL.

CHAGAS DISEASE

Preliminary results of a Phase II study evaluating new therapeutic regimens of benznidazole showed that all treatment arms were effective and had good safety profiles. The two-week course of treatment with benznidazole alone was particularly promising. Based on these results, DNDi is planning to run an international, multisite confirmatory Phase III study.
**MYCETOMA**

In Sudan, the first-ever double-blind, randomized clinical trial for fungal mycetoma is ongoing and had enrolled 101 patients by January 2020. The primary objective of the study is to demonstrate the superiority of the new chemical entity fosravuconazole over the current standard treatment, itraconazole.

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**FILARIA – RIVER BLINDNESS**

With first-in-human studies for emodepside in healthy volunteers successfully completed, preparations are underway to run a Phase II clinical trial at two sites in Ghana. In the Democratic Republic of the Congo (DRC), training and trial site renovations are advancing ahead of a Phase II proof-of-concept study for TylAMac, which was shown to be safe and well tolerated in Phase I studies. And new efforts to identify novel treatments against ‘nematode’ worms have kicked off following the launch of a new multidisciplinary consortium: the Helminth Elimination Platform (HELP).

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**HIV**

DND’s pharmaceutical partner Cipla submitted the ‘4-in-1’ fixed-dose combination treatment for infants and young children with HIV to the US Food and Drug Administration (FDA) for tentative approval. The easy-to-administer, strawberry-flavoured treatment requires no refrigeration and is a great improvement over the current treatment option: a bitter-tasting syrup with high alcohol content. Cipla will price the 4-in-1 at under USD 1 a day for children weighing up to 14 kg.

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**HEPATITIS C**

Following excellent results from the first stage of a Phase II/III trial evaluating the ravidasvir/sofosbuvir combination, a second stage of the study in Malaysia and Thailand is testing the treatment in patients with hepatitis C genotypes 1a, 1b, 2, 3, and 6 to further establish the pan-genotypic profile of ravidasvir. Plans to submit for the conditional registration of ravidasvir with the Malaysian National Pharmaceutical Regulatory Authority are underway, with filing expected in mid-2020.

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**MAIN R&D PARTNERS**

From drug discovery and pre-clinical research to clinical trials and large-scale implementation studies, a diverse range of alliances and research collaborations with over 180 partners in more than 40 countries continues to enable DND’s work to address the major unmet treatment needs of the world’s poorest people.

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**SCIENTIFIC PUBLICATIONS**

In 2019, DND staff members authored or co-authored 45 peer-reviewed publications. Of these, 34 had at least one author from a partner institution in an endemic country, 19 had at least one endemic country author from one of DND’s regional offices, 23 had a female lead or co-lead author, and 43 were published in an open access journal, in keeping with DND’s commitment to open access.

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**A WORD OF THANKS**

Only a fraction of the world’s pharmaceutical R&D focuses on diseases affecting poor and vulnerable communities. DND is deeply grateful to its donors, whose support puts patients, not profits, at the heart of drug discovery and development.

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HUMAN AFRICAN TRYPANOSOMIASIS
(SLEEPING SICKNESS)

DNDi aims to deliver new oral treatments to cure sleeping sickness that are safe, affordable, effective and easy to use, and that support the sustainable elimination of the disease.

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New chemical entity
* Treatments delivered by DNDi

SCYX-1330682 & SCYX-1608210

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

DNDi continues to provide support and advice to researchers working on discovery of new candidates for human African trypanosomiasis (HAT) and maintains two back-up candidates from the oxaborole class to ensure future development options, if needed.

Acoziborole

Objective: Develop and register acoziborole as a new, single-dose, oral treatment

The delivery of fexinidazole [see right] has improved therapeutic options for people with sleeping sickness. But the development of an additional oral treatment, especially one that could be given as a single dose, could provide an even better treatment option and facilitate sustained elimination of the disease. In 2012, acoziborole became DNDi’s first new chemical entity resulting from DNDi’s own lead optimization programme to enter clinical development. Phase I trials were completed in 2015 and allowed the therapeutic dose to be determined, administered as a single dose of three tablets. A pivotal Phase II/III trial started in 2016 to study the safety and efficacy of this new chemical entity with potential as a treatment for stage-2 HAT caused by T.b. gambiense [g-HAT] that could also be safe and effective for stage 1 of the disease.

With enrolment of 208 patients in the trial completed in March 2019, the trial will conclude at the end of 2020 once 18-month post-treatment follow-up has been completed for all patients at clinical sites in the DRC and Guinea. In the interim, non-clinical studies to meet European Medicines Agency and US FDA requirements will be carried out.

Delivered

Fexinidazole (for T.b. gambiense)

In 2005, DNDi undertook an extensive compound mining exercise and identified fexinidazole, whose development had been shelved by Hoechst AG (now Sanofi) in the 1980s. After completing preclinical studies, DNDi partnered with Sanofi in 2009 for the development, manufacturing, and distribution of fexinidazole. Phase I studies started in 2009, and a Phase II/III clinical trial began in the DRC and the Central African Republic in 2012.

Fexinidazole received a positive scientific opinion by the European Medicines Agency’s Committee for Medicinal Products for Human Use in November 2018 and was registered in the DRC in December 2018. It is the first new chemical entity developed by DNDi.

In August 2019, the World Health Organization (WHO) revised its HAT treatment guidelines to include fexinidazole as the first-line treatment for T.b. gambiense sleeping sickness except in cases of advanced disease. Fexinidazole was added to the WHO Essential Medicines List for children and adults in June 2019.

Fexinidazole is now being donated by Sanofi to WHO for distribution to national sleeping sickness control programmes in disease-endemic countries. Distribution began in DRC in January 2020.

WHO began training of trainers in 2019, first in DRC, followed by trainings in the HAT-endemic countries of Central and West Africa. DNDi will continue in-country training in collaboration with the HAT Platform, targeting relevant staff from 250 hospitals and health centres in T.b. gambiense-endemic countries. DNDi is supporting roll-out of fexinidazole in DRC, Guinea, Central African Republic, Angola, and South Sudan to scale up access and pharmacovigilance.
Ongoing fexinidazole studies (including for *T. b. rhodesiense*)

DNDi’s investment in fexinidazole continues – with support for access and extension of the indication to *T. b. rhodesiense*. In 2016, DNDi initiated a Phase IIIb trial to obtain clinical data on special populations not included in previous trials, including pregnant and breast-feeding women, and people with poor nutritional status or chronic diseases. Patients were treated either in hospital or at home, thereby also providing information about treatment adherence and final effectiveness in ambulatory patients. Patient enrolment at clinical sites in the DRC and Guinea was completed in 2019; patient follow-up will conclude in February 2021.

In addition, a Phase II/III study began in October 2019 to assess fexinidazole to treat sleeping sickness caused by *T. b. rhodesiense*, the other more virulent subspecies of the parasite affecting humans, occurring primarily in Eastern and Southern Africa. The first patient was included in October 2019.

To provide clinical data to extend the indication to treat *rhodesiense* sleeping sickness with fexinidazole, we have joined with partners to form the HAT-r-ACC consortium with funding from the European & Developing Countries Clinical Trials Partnership. The consortium is working on a five-year project in Uganda and Malawi, which together account for 88% of *rhodesiense* sleeping sickness cases globally. The study aims to support WHO control and elimination efforts in Eastern Africa by providing evidence for the potential of a new and easier-to-administer oral drug.

Better treatments for *rhodesiense* sleeping sickness are urgently needed: the only treatment available for stage 2 *rhodesiense* sleeping sickness is melarsoprol, a toxic arsenic drug dating from the 1940s that kills up to 5% of patients treated with it. While the treatment option for stage 1, suramin, is less toxic, it is difficult to administer, requiring five intravenous injections given every seven days for a month. Without prompt diagnosis and treatment, sleeping sickness is usually fatal. *Rhodesiense* sleeping sickness progresses more rapidly than *gambiense* sleeping sickness, causing death within months if not treated.

Delivered

Nifurtimox-eflornithine combination therapy (NECT)

Before 2009, treatment for sleeping sickness based on eflornithine alone was extremely complex to distribute and administer. All too often, doctors would have no choice but to use melarsoprol, a highly toxic, arsenic-based drug that killed one in 20 patients.

In 2009, results from DNDi/MSF-sponsored clinical trials showed that NECT, a combined treatment of Bayer’s nifurtimox and Sanofi’s eflornithine, was safe and effective to cure sleeping sickness. NECT has significant practical benefits: treatment is simpler, shorter, and more cost-effective than using eflornithine alone. NECT was included on the WHO Essential Medicines List in 2009 and the Essential Medicines List for Children in 2013. Fexinidazole was included in WHO’s HAT treatment guidelines in August 2019, making NECT the second-line treatment for *T. b. gambiense* sleeping sickness, though it remains the recommended first-line treatment in cases of advanced disease. Endemic countries will continue to receive free supplies of the drug through WHO via drug donations.
**LEISHMANIASIS**

DNDi aims to make treatments safer, shorter, and more affordable and effective for all forms of leishmaniasis. In the short term, better treatment regimens are being developed using existing drugs. In the long term, the goal is to develop an entirely new generation of all-oral drugs.

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### Discovery

**Objective:** Deliver a robust portfolio of drug discovery hit and lead series for leishmaniasis

DNDi is searching for chemical compounds with activity against Leishmania parasites. High-throughput screening of diverse compound libraries from pharmaceutical companies, biotechs, and commercial vendors have been completed against *Leishmania donovani*, in collaboration with screening partners University of Dundee and Institut Pasteur Korea.

DNDi has identified a variety of novel hit series via the screening of new compound libraries to continuously feed the early discovery pipeline for visceral leishmaniasis (VL). Those new starting points originate from both natural product and synthetic compound collections, either accessed through partnerships, acquired via purchase, or obtained as in-kind contributions to DNDi.

### Translation

**Objective:** Through collaborative hit-to-lead projects, identify new leads with potential for further optimization

The process of hit-to-lead optimization is ongoing, with multiple series being progressed based on outputs of the screening programme. A variety of hit-to-lead mechanisms and exploration strategies are being used to progress towards in vivo proof-of-concept studies in pre-clinical efficacy models of leishmaniasis.

Through the NTD Drug Discovery Booster project, DNDi brings together pharmaceutical companies in a non-competitive search to speed up the process and cut the cost of finding new treatments for leishmaniasis. The project conducts multilateral, simultaneous searches of millions of compounds based on an active seed supplied by DNDi and uses computational approaches to refine the search iteratively. Since its creation in 2015, the Booster has launched 45 iterations around 22 seed compounds, with the result that 13 hit series have been released, of which six have progressed to in vivo proof-of-concept studies for Chagas disease and/or leishmaniasis. The Booster consortium is comprised of eight pharmaceutical companies: AbbVie, Astellas, AstraZeneca, Celgene (now part of Bristol-Myers Squibb), Eisai, Merck, Shionogi, and Takeda.

Discovery Booster screening activities were placed on temporary hold in early 2019 to focus efforts on transitioning existing hit series into lead optimization projects. Two hit series are currently under further investigation with Takeda, and work is underway to transition at least one of these series into lead optimization in 2020.

The frontrunning series that is the current focus of the Daiichi Sankyo hit-to-lead project has clear activity against the *T. cruzi* parasite, which causes Chagas disease. This series will therefore be progressed for Chagas disease.

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**IJP**

**Drugs and Drug Resistance**

*Novel oxaborole, nitroimidazole, and aminopyrazoles with activity against experimental cutaneous leishmaniasis*


February 2019
DNDi’s long-term goal in leishmaniasis is to radically transform patient therapy: from today’s complex, poorly adapted and tolerated treatments, to patient-friendly, simple oral therapies that are short-course, affordable, safe, and efficacious in both children and adults.

Together with partners at the Drug Discovery Unit (DDU) and Wellcome Trust Centre for Anti-Infectives Research at the University of Dundee, pharmaceutical companies GlaxoSmithKline (GSK), Pfizer, Takeda, and Celgene, and the product development partnership TB Alliance, with the support of the Global Health Innovative Technology (GHIT) Fund, DNDi has built an unprecedented portfolio of lead series, pre-clinical, and clinical candidates for leishmaniasis from different chemical classes with different mechanisms of action against Leishmania parasites.

In a novel consortium with these partners, DNDi is working to advance this unique portfolio, with the goal of progressing drug candidates through Phase I clinical development, and for the most promising clinical candidates to be selected for a Phase II clinical trial testing the safety and efficacy of a combination of two entirely new chemical entities.

By bringing together several projects at various stages, the consortium provides a strong basis for advancing towards oral leishmaniasis therapies, in priority for VL and potentially also for CL, and provides options to overcome attrition in drug development. Complementing the efforts of the consortium, DNDi and Novartis initiated a collaboration and licence agreement in early 2020 to jointly develop LXE408 – a first-in-class compound, discovered at Novartis with financial support from Wellcome Trust – as a potential new oral treatment for VL.

### Lead optimization projects:

- **CF series**: The chemical starting points for the CF series were identified through screening of the GSK kinetoplastid ‘box’, which identified a series of compounds of intermediate potency. Modulation of the core scaffold led to the CF-series compounds, which displayed promising levels of efficacy in mouse models of VL suitable for progression to lead optimization. Optimization of the CF series lead series has led to compounds displaying increased potency against the *L. infantum* and *L. donovani* parasite strains. In addition, the pharmacokinetic profile of the compounds has also been significantly improved. Further optimization is ongoing to select additional compounds for in vivo testing.

- **Leishmaniasis L205 series**: Lead compound DNDI-6174 showed great efficacy in vivo in both mouse and hamster models for VL, and the best overall safety and drug metabolism and pharmacokinetics profile. DNDI-6174 is moving forward into pre-clinical development; a number of potential back-up compounds have been synthesized and are being profiled.

- **Aminopyrazoles**: Further work on the back-ups from this series is currently on hold; however, new chemical spaces continue to be investigated through the Open Synthesis Network, a collaborative project that engages master’s and undergraduate students in research for neglected diseases.

- **DNDI-5421 and DNDI-5610**: Further work on the back-ups from the oxaborole series is currently on hold as efforts focus on the lead compound DNDI-6148, which progressed to a Phase I study in early 2020.

- **DNDI-0690**: Nitroimidazole derivatives hold great potential to address unmet needs in tuberculosis (TB) therapy. As well as developing a clinical candidate for TB, the TB Alliance instituted a back-up programme to maximize the potential of this class of antibacterial agents. Through a contractual agreement with TB Alliance, DNDi gained access to a library of around 70 nitroimidazoles which were then tested for potential anti-leishmanial activity. DNDI-0690 was nominated as a pre-clinical candidate in 2015, and in 2018 the decision was made to progress to a first-in-human Phase I single ascending dose in healthy volunteers. Results are expected in early 2020. A multiple ascending dose study is planned for 2020.

- **DNDI-6174**: Emerging from the leishmaniasis L205 lead optimization series after showing great efficacy in vivo in both mouse and hamster models for VL, DNDI-6174 was nominated as a pre-clinical candidate for VL in 2019. Planning is underway to start pre-clinical activities in 2020.

- **DNDI-6148**: DNDi’s screening of Anacor’s library of drug compounds from the oxaborole class, followed by focused medicinal chemistry efforts, led to the discovery of a number of analogues showing efficacy in animal models of sleeping sickness, Chagas, and leishmaniasis. While one of these compounds, acoziborole, is currently progressing in Phase II/III trials for sleeping sickness, an analogue, DNDI-6148, was shown in various in vitro and in vivo studies to be effective against Leishmania strains. The decision was made in 2018 to progress to a first-in-human Phase I single ascending dose in healthy volunteers. The clinical trial application for this study was approved in November 2019 and the first volunteer was enrolled in January 2020.

- **GSK3186899/DDD853651 and GSK3494245/DDD1305143**: In 2017, DNDi and GSK entered into an agreement for the pre-clinical development of two compounds for leishmaniasis developed by a collaboration between the GSK Global Health Unit and the DDU at the University of Dundee, with co-funding support from Wellcome. A Phase I single ascending dose study of GSK3186899/DDD853651 in healthy volunteers was completed in 2019; preparations for a Phase I single ascending dose study of GSK3494245/DDD1305143 are underway.

- **DNDI-5561**: Due to unfavourable safety results in pre-clinical studies, the decision was made to stop development of this compound in 2019.
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

People co-infected with HIV and VL rarely achieve sustainable control of the parasite and present multiple episodes of relapse. In 2011, MSF began using a compassionate regimen, combining liposomal amphotericin B (LAmB) with the oral drug miltefosine in Abdurafi Health Centre in North-West Ethiopia. To provide the necessary scientific evidence, DNDi ran a Phase III study, starting in 2014, testing both LAmB monotherapy as per current WHO and international recommendations, and a combination of LAmB infusion and miltefosine orally for 28 days in 58 HIV/VL patients in two sites in Ethiopia.

Results demonstrated the high efficacy of the combination therapy with a 67% cure rate when treatment lasted 28 days, increasing to an 88% cure rate when patients who were not cured received a second round of treatment to clear the parasite, with a full treatment lasting 58 days.

In addition, DNDi and the Rajendra Memorial Research Institute acted as technical partners in a Phase III study sponsored by MSF in India to evaluate the currently recommended LAmB therapy and a combination of LAmB and miltefosine for the treatment of VL in people co-infected with HIV. The last patient follow-up visit for the study was completed in May 2019 and the publication of study results is expected in 2020.

Both studies were presented to the national authorities in Ethiopia and India, and guidelines are under review at the national levels to consider adopting the new combination treatment. At the international level, a WHO Guideline Development Group is expected to evaluate HIV/VL treatment recommendations in 2020.

New treatments for PKDL

Objective: Determine the safety and efficacy of treatment regimens for people with PKDL in East Africa and South Asia, and understand the role of PKDL in VL transmission

PKDL is a non-lethal complication of VL which can develop months or years after VL treatment has been completed and can be severely disfiguring and stigmatizing, as the symptoms are characterized by a skin rash, often on the face. Better treatment options are needed, as existing treatments include options that are expensive and lengthy, with complex administration and potentially toxic effects.

A Phase II study to test both liposomal amphotericin B in combination with miltefosine, and paromomycin in combination with miltefosine began in Dooka, Sudan in 2018 and had enrolled 73 patients by January 2020. Results are expected by 2021.

In South Asia, patient enrolment at three sites in India Kala Azar Medical Research Centre and Rajendra Memorial Research Institute of Medical Sciences and Bangladesh (icddr,b) was completed in January 2019 for DNDi’s Phase II study to assess the safety and efficacy of liposomal amphotericin B monotherapy and a combination of liposomal amphotericin B and miltefosine. Results are expected by mid-2021 following completion of a 24-month follow-up period.

In addition, PKDL has long been thought to play an important role in transmission during outbreaks or during inter-epidemic periods, as PKDL lesions may be infective to sandflies. In Sudan, work continues at University of Gedaref to establish a sandfly colony in preparation for infectivity studies in PKDL and VL patients. A similar study completed in Bangladesh in 2018 confirmed that PKDL acts as a reservoir for ongoing leishmaniasis infection.
Miltefosine + paromomycin combination for East Africa

Objective: Compare the efficacy and safety of two combination regimens of miltefosine and paromomycin with the current standard treatment

Based on the good results of the miltefosine and paromomycin (MF+PM) combination in South Asia, and on the need for an alternative and safer treatment to replace SSG, a Phase III study was launched in 2018 to compare the combination regimen of MF+PM with the current standard VL treatment, SSG+PM.

By January 2020, a total of 350 patients, both children and adults, were enrolled in the study across seven sites in Ethiopia (Gondar and Abdurafi), Kenya (Kacheliba), Sudan (Dooka, Um el Kher, and Tabarak Allah), and Uganda (Amudat). Completion of patient enrolment is targeted for late 2020.

Delivered

SSG+PM for East Africa

Treatment options for VL in Africa had considerable limitations: liposomal amphotericin B was very costly and antimonials such as sodium stibogluconate had lengthy treatment times, difficult administration, emerging resistance, and poor tolerability that caused frequent side effects.

DNDi partnered with the Leishmaniases East Africa (LEAP) Platform in clinical trials that showed the combination of sodium stibogluconate and paramomycin (SSG+PM) was as safe and effective as the existing standard treatment. With SSG+PM, treatment is easier for patients and health centres, and it means more patients can be treated during outbreaks. Since 2010, SSG+PM has been recommended by WHO as first-line treatment for VL in East Africa, and PM has been registered in Kenya, Uganda, Sudan, and Ethiopia.

KalaCORE, the UK Aid-funded partnership that included DNDi and supported the control and elimination of VL in six countries, supported the implementation of SSG+PM in East Africa. Access has been considerably improved thanks to the strengthening of the national control programmes of Ethiopia, South Sudan, and Sudan, and regular supply and distribution of diagnostics and medicines.

DNDi continues to accompany the implementation of this treatment in East Africa.

New VL treatments in Latin America

New VL treatments for South Asia

In the early 2000s, treatments for VL in South Asia were difficult for patients to take or were growing ineffective. Resistance was increasing, and antimonials such as sodium stibogluconate had lengthy treatment times, difficult treatment administration, and poor tolerability. In 2010, WHO recommended using new short-course treatments for VL in South Asia based on excellent results in Phase III studies. However, more evidence was needed on their safety and effectiveness under field conditions.

DNDi convened a consortium of partners to identify the best combination therapies for South Asia. The consortium conducted a four-year-long implementation study in Bangladesh and India to assess the safety, efficacy, and patient adherence to three new treatment options including single-dose liposomal amphotericin B, paromomycin and miltefosine, and liposomal amphotericin B and miltefosine combinations.

The results showed that these treatments were safe and effective, with cure rates above 95%. They also shortened treatment length, reduced the risk of resistance, and reached patients closer to home, making it easier for patients to take the full treatment course.

The research provided key evidence for policy change by the Bangladeshi, Indian, and Nepali Ministries of Health, which made the following recommendations: single-dose liposomal amphotericin B as a first-option treatment for VL patients, and paromomycin and miltefosine as a second option.

DNDi continues to accompany the implementation of these new treatment options for VL in South Asia.
CUTANEOUS LEISHMANIASIS IN FOCUS

Current treatment for CL relies on drugs known as antimonials. Developed over 70 years ago, they are toxic, costly, require repeated painful injections, and are less effective in children under five years of age. Treatment with antimonials is also long – between 20 and 30 days – and not indicated for patients who are pregnant, have diabetes, or have heart, liver, or kidney problems.

To improve people’s hope of healing from this disfiguring and stigmatizing disease, DNDi seeks to develop short-duration, safe, effective, non-invasive, affordable, and field-friendly treatments for CL.

Objective: Demonstrate the suitability of an immunomodulator to stimulate the innate immune system to fight the parasitic infection responsible for CL

This project aims to produce, in partnership with GeneDesign, an immunomodulator to stimulate the innate immune system to fight Leishmania infection, as an adjunct to drug therapy.

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). Pre-clinical toxicology studies were initiated in 2019 and should be completed by mid-2020. Planning for first-in-human studies is underway pending final results.

New CL combination therapies

Objective: Explore whether existing approved treatment approaches for CL are more effective when used in combination

In uncomplicated CL cases (people with small lesions in number and size, not located on the face or on joints), thermotherapy – applying heat to the wound for a short duration – is the most practical and effective treatment option.

Preliminary results of a Phase II study completed in April 2019 show the combination of thermotherapy with a shorter course of oral miltefosine to be significantly better than thermotherapy alone for the treatment of uncomplicated CL in the Americas.

Planning is underway for a Phase III study to compare the non-inferiority of the combination against the current recommended treatments, sodium stibogluconate or miltefosine.
DNDi aims to deliver new, safer, more affordable and effective treatments for people affected by Chagas disease. DNDi is also focused on improving access to diagnosis and treatment using existing tools.

Screening

Objective: Deliver a robust portfolio of early hits and lead series to enable drug discovery for Chagas disease

To identify new hit series that could be progressed and become new drug candidates for Chagas disease, DNDi tests chemical compounds for activity against *Trypanosoma cruzi*. High-throughput screening of compounds from natural product and synthetic compound collections from partners or commercial suppliers have been conducted, and hits have been identified and are currently being progressed.

**Hit-to-lead**

DNDi has continued its efforts in screening chemically diverse libraries to replenish the discovery pipeline. Confirmed new hits are continuously feeding the hit-to-lead pipeline.

- In 2019, a new consortium was established in collaboration with University of Campinas and University of Sào Paulo in Brazil. Through a team of scientists working in a global network, the Research Partnership for Technological Innovation (PITE) aims to deliver a high-quality pre-clinical candidate compound that could become a new treatment for Chagas disease.
- Through the NTD Drug Discovery Booster project, DNDi brings together pharmaceutical companies in a non-competitive search to speed up the process and cut the cost of finding new treatments for Chagas disease. The project conducts multilateral, simultaneous searches of millions of compounds based on an active seed supplied by DNDi and uses computational approaches to refine the search iteratively.

Since its creation in 2015, the Booster has launched 45 iterations around 22 seed compounds, with the result that 13 hit series have been released, of which six have progressed to in vivo proof-of-concept studies for Chagas disease and/or leishmaniasis. The Booster consortium is comprised of eight pharmaceutical companies: AbbVie, Astellas, AstraZeneca, Celgene (now part of Bristol-Myers Squibb), Eisai, Merck, Shionogi, and Takeda.

Screening activities were placed on temporary hold in early 2019 to focus efforts on transitioning existing hit series into lead optimization projects. Two hit series are currently under further investigation with Takeda, and work is underway to transition additional series for potential lead optimization in 2020.

- DNDi partnered with Japanese pharmaceutical company Daiichi Sankyo in a hit-to-lead project that ended in September 2018. The project milestone was reached with the identification of a progressable Chagas lead series with proven in vivo efficacy.

**C205 Series**

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

DNDi has been working on this late-stage lead optimization series as part of a collaboration agreement made in 2018 with the DDU of Dundee University in Scotland and GSK Global Health Unit in Spain. With work on the series resulting in a drug candidate for leishmaniasis that will move into translational research, research for a candidate for Chagas from the C205 series is currently on hold.
**Biomarkers**

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

There is no single reliable test of cure that can be used to monitor treatment effectiveness in chronic Chagas disease patients in a timely manner. This lack of validated early markers of parasitological cure poses a significant hurdle for the development and regulatory approval of new drugs.

Current work focuses on raising awareness among Chagas stakeholders about the need for biomarkers, with particular emphasis on regulatory aspects and the biomarker development process. DNDi is also supporting the development of a prototype assay for newly identified biomarkers – Apo A1 and Fbn fragments issued from a collaboration with McGill University – together with InfYnity Biomarkers. The analysis of a multicentre study carried out by NHEPACHA, an Ibero-American network of researchers working on Chagas, is being finalized and will be published in 2020.

**New benznidazole regimens**

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

Current Chagas treatment is effective but has limitations: it lasts 60 days, and some 20% of patients stop treatment due to side effects, which include gastric intolerance, skin rashes, or neuromuscular problems. To explore whether these were related to dose or treatment duration, DNDi decided to test the efficacy of new regimens where exposure to benznidazole would be reduced, either due to shorter treatment, lower doses, or both. The objective of the BENDITA study (Benznidazole New Doses Improved Treatment & Therapeutic Associations) was to find regimens at least as effective as the standard treatment, with fewer side effects. This could improve patients’ adherence and make the treatment more acceptable to physicians.

A Phase II, randomized, placebo-controlled study was carried out in three sites in Bolivia between 2016 and 2018. It tested, against a placebo, six benznidazole treatments of differing lengths and dosages, both as a monotherapy and in combination with fosravuconazole. The aim was to improve efficacy, safety, and tolerability of treatment of adults with chronic indeterminate Chagas.

Preliminary Phase II trial results showed that all treatment arms were effective compared to placebo and the new regimens presented good safety profiles. The two-week course of treatment was particularly promising. While significantly shorter than the standard eight-week treatment, it showed 83% efficacy, and none of the patients assigned to this arm had to discontinue treatment due to side effects. The primary measure of efficacy for this study was sustained parasitological response at six-month follow-up with a final assessment at 12 months.

Based on these results, DNDi is planning to run an international, multisite confirmatory Phase III study and will continue to work with national programmes, partners, and health ministries of endemic countries to confirm results and, if results are good, encourage the necessary steps to adopt the new regimen.

<table>
<thead>
<tr>
<th>Analysis of parasitological response at 6-month follow-up and 12-month follow-up*</th>
<th>BZN 300 mg 6 wks</th>
<th>BZN 300 mg 4 wks</th>
<th>BZN 300 mg 2 wks</th>
<th>BZN 150 mg 4 wks/E1224 300 mg</th>
<th>BZN 150 mg 4 wks/E1224 300 mg (Weekly)</th>
<th>BZN 300 mg Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-months follow-up</td>
<td>89.3%</td>
<td>89.3%</td>
<td>82.8%</td>
<td>83.3%</td>
<td>85.2%</td>
<td>82.8%</td>
</tr>
<tr>
<td>12-months follow-up</td>
<td>82.8%</td>
<td>89.3%</td>
<td>79.3%</td>
<td>80.0%</td>
<td>85.2%</td>
<td>82.8%</td>
</tr>
<tr>
<td>Subject with treatment-related side effects leading to treatment discontinuation</td>
<td>6 (20.0%)</td>
<td>1 (3.3%)</td>
<td>0</td>
<td>1 (3.3%)</td>
<td>3 (10.0%)</td>
<td>4 (13.3%)</td>
</tr>
</tbody>
</table>

* Intention-to-treat analysis, meaning that all patients enrolled in the study and randomized to a treatment arm were included in the analysis, whether or not they started or completed treatment.
Fexinidazole

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

While fexinidazole was registered as a drug to treat sleeping sickness in 2018, DNDi is also exploring its potential as a new drug for Chagas disease.

This Phase II proof-of-concept study, carried out in five sites in Spain, evaluated different short-course regimens of fexinidazole for adults with chronic indeterminate Chagas. The follow-up phase of the study was completed in late 2019; results will be available in 2020.

Delivered

Two sources of paediatric benznidazole

Until 2011, benznidazole, the main drug of choice for treating Chagas disease, was only available in an adult-strength tablet. Infants and children were treated with divided or crushed adult tablets, which was complicated for caregivers and resulted in inconsistent dosing.

A first paediatric formulation was developed through a collaboration between DNDi and Laboratório Farmacêutico do Estado de Pernambuco (LAFEPE) of Brazil and was registered in 2011, in Brazil. A second paediatric benznidazole source was registered in Argentina in 2018, the result of a partnership between Fundación Mundo Sano, DNDi and Laboratorio Elea Phoenix to enable a stable supply and registration in additional disease-endemic countries.

Chagas Access Project

Objective: Demonstrate the feasibility of scaling up access to diagnosis and treatment in pilot projects that can then be replicated on a larger scale

In 2015, DNDi launched an initiative to increase access to diagnosis and treatment for Chagas disease in close collaboration with local, regional, and national partners through pilot projects in several endemic countries.

The approach was first implemented in Colombia in collaboration with the Ministry of Health and Social Protection, targeting a highly endemic area for Chagas disease. The new patient-centred approach involves training health care staff, simplifying and accelerating the procedure for diagnosis, and decentralizing treatment to ensure it is available closer to where patients live. After two years since the first pilot projects started, the number of people screened in the municipalities of Támara and Nunchía in Casanare state increased from 25 in 2017 to 400 in 2019. For those who had access to diagnostic testing, the wait time to receive their results was reduced on average from one year to less than one month. Approximately 20% of people who had access to diagnosis during the two-year period tested positive for the disease.

In 2019, the Chagas Treatment Access project continued to consolidate and expand its activities in the Latin American region, working with partners in Colombia, Guatemala, Brazil and, since late 2019, Mexico. In November 2019, DNDi and partners held a barriers seminar in the state of Veracruz, Mexico to identify the obstacles preventing people from receiving treatment. This is the first step in a four-stage methodology developed by DNDi to increase access to diagnosis and treatment for the disease, covering ‘the four Ds’: diagnosis, design, delivery, and demonstration of impact.
Mycetoma

DNDi aims to develop an effective, safe, affordable, and simpler curative treatment. There is currently no effective cure for fungal mycetoma.

<table>
<thead>
<tr>
<th>DISCOVERY</th>
<th>TRANSFORMATION</th>
<th>DEVELOPMENT</th>
<th>IMPLEMENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>Hit-to-lead</td>
<td>Lead optimization</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

New chemical entity

### MycetOS

**Objective:** Use an open-source approach to discover compounds that could lead to new treatments

The Mycetoma Open Source (MycetOS) project was launched in 2018 by the University of Sydney, Australia, Erasmus MC (Erasmus University Medical Center, Rotterdam, the Netherlands), and DNDi to use an ‘Open Pharma’ approach to discover compounds that could lead to new treatments for patients affected by fungal mycetoma (eumycetoma).

MycetOS progresses drug discovery efforts through community-driven, in-kind scientific contributions and a robust, fully transparent online presence. All ideas and results are published immediately in real time to an open-access database.

Results and the associated data form the starting point for the MycetOS community, which communicates on Twitter (@MycetOS) and uses a dedicated forum (subreddit) for transparent interactive discussion, and another platform (GitHub) for sharing data and key project files. In 2019, a list of targets for MycetOS was compiled and opportunities given to researchers at two institutions in DNDi’s Open Synthesis Network interested in working on them to identify new compounds with potential activity against mycetoma.

### Fosravuconazole

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

In 2017, the Mycetoma Research Centre (MRC), a WHO Collaborating Centre in Khartoum, Sudan, began enrolling patients in the first-ever double-blind, randomized clinical trial for eumycetoma (fungal mycetoma). The trial is studying the efficacy, in moderate-sized lesions over 12 months, of weekly treatment with fosravuconazole, versus the current standard of care, daily treatment with itraconazole.

Fosravuconazole, an orally bioavailable azole developed for onychomycosis by Eisai (Japan), could be an effective and affordable treatment for eumycetoma. Its pharmacokinetic properties are favourable, and its toxicity is low. Fosravuconazole is also being evaluated by DNDi for Chagas disease. Following slower than anticipated patient enrolment, a protocol review and amendment was conducted in 2018 to extend the inclusion criteria in relation to lesion size and site, as well as the age range of participants.

By January 2020, 101 patients of a targeted enrolment of 165 patients had been enrolled in the study. A Data and Safety Monitoring Board (DSMB) meeting was held in 2019 after the study reached the threshold for interim analysis (84 participants). The DSMB reviewed study data and decided to continue with all three treatment arms (200 mg vs 300 mg of fosravuconazole weekly vs daily itraconazole).

**Call for Action**

DNDi supported the Mycetoma Research Centre to organize the Sixth International Conference on Mycetoma in Khartoum, Sudan in February 2019 and joined other stakeholders in endorsing a ‘Call for Action’ to accelerate collaborative global efforts to address the plight of mycetoma patients, including by broadening access to existing diagnostics and medicines, and investing in research for better treatments and improved diagnostic tests that can be easily used in rural areas and in the primary health-care system.
**FILARIA – RIVER BLINDNESS**

**DNDi aims to deliver** a safe, effective, affordable, and field-adapted drug that can kill adult filarial worms (a ‘macrofilaricide’) and be used for prevention or individual treatment.

<table>
<thead>
<tr>
<th>DISCOVERY</th>
<th>TRANSITION</th>
<th>DEVELOPMENT</th>
<th>IMPLEMENTATION</th>
</tr>
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<tbody>
<tr>
<td>Screening</td>
<td>Hit-to-head</td>
<td>Lead optimization</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td>Macrofilaricide 3</td>
<td>Oxfendazole</td>
<td>Emodepside</td>
<td>TylAMac (ABBV-4083)</td>
</tr>
</tbody>
</table>

**Screening**

DNDi’s filarial disease programme has actively identified potential new drug candidates for onchocerciasis by evaluating registered drugs, as well as pre-clinical and clinical drug candidates. DNDi has also investigated diverse chemical compounds against filarial worms. Well-characterized libraries of compounds that had already been extensively optimized for other indications were provided to DNDi by several pharmaceutical companies for screening.

With a portfolio of four potential treatments for people with onchocerciasis, DNDi has now ended its active screening programme for filaria. Some 530 compounds have been screened in partnership with Salvensis, Merck Sharp & Dohme, University of North Carolina, AbbVie, and others.

In 2019, DNDi announced the launch of a large public-private partnership called the Helminth Elimination Platform (HELP). Led by the Swiss Tropical and Public Health Institute, the new multidisciplinary consortium is working to identify new treatments against ‘nematode’ worms, including onchocerciasis, lymphatic filariasis, hookworm, and whipworm.

**Oxfendazole**

**Objective:** Advance the clinical development of oxfendazole as an anti-parasitic macrofilaricidal treatment

Screening of drug libraries obtained from biotech and pharmaceutical companies, along with active screening of the literature, identified oxfendazole, a veterinary product used for deworming in animals, as a potential candidate macrofilaricidal agent for river blindness.

Oxfendazole is currently under development for the treatment of neurocysticercosis and trichuriasis. Based on very encouraging pre-clinical efficacy data, DNDi is exploring the possibility of repurposing oxfendazole as a macrofilaricidal treatment for filarial indications.

DNDi is moving ahead with a first-in-human Phase I trial and pharmaceutical development. With funding from the European Union’s Horizon 2020 research and innovation programme, HELP will conduct a Phase I trial and continue late pre-clinical activities for oxfendazole.

**Macrofilaricide 3**

**Objective:** Develop a macrofilaricide candidate for filarial diseases

DNDi and Celgene (now part of Bristol-Myers Squibb) have signed an agreement covering pre-clinical and Phase I for a potentially macrofilaricidal compound known as CC6166. Celgene will cover all pre-clinical, Phase 1, and chemistry, manufacturing, and control activities, while DNDi will provide expertise and know-how.

**Clinical Infectious Diseases**

**MAJOR ARTICLE**

Projected number of people with onchocerciasis–loiasis coinfection in Africa, 1995 to 2025

Vinkeles Melchers NVS, Coffeng LE, Boussinesq M, Pedrique B, Pion SDS, Tekle AH, Zouré HGM, Wanji S, Remme JH, Stolk WA. Clinical Infectious Diseases

July 2019
Emodepside

Objective: Advance the clinical development of emodepside as an anti-parasitic macrofilaricidal treatment

Originating from the Japanese pharmaceutical company Astellas, emodepside was developed and commercialized by Bayer Animal Health as a veterinary drug for parasitic worm infections in cats and dogs. DNDi has a collaboration agreement with Bayer AG to jointly develop emodepside for the treatment of onchocerciasis. Bayer provides the active ingredient emodepside to DNDi, and DNDi is responsible for the clinical development of emodepside and Bayer for the pre-clinical and pharmaceutical development, as well as for registration, manufacturing, and distribution of the drug.

First-in-human studies for emodepside in healthy volunteers have successfully been completed, both a single ascending dose study in 2017 and a multiple ascending dose study in 2018. Emodepside is orally bioavailable, and a tablet that could be commercialized has been developed. As a next step, DNDi is preparing to run a Phase II proof-of-concept clinical trial in Hohoe, Ghana, investigating the safety and efficacy of the drug in people living with onchocerciasis. DNDi is renovating the site and will identify an additional site in the country for this study.

Contributing to the evidence

Research from DNDi and Erasmus MC, University Medical Centre Rotterdam in the Netherlands published in 2018 showed that over four million people in West and Central Africa will be infected with onchocerciasis in 2025, in areas where loiasis, or ‘African eye worm’ is endemic. To generate key data on disease burden in areas where DNDi will be recruiting for clinical trials, DNDi is now supporting onchocerciasis prevalence surveys organized by the DRC’s national programme for NTDs.

TylAMac (ABBV-4083)

Objective: Advance the clinical development of TylAMac as a macrofilaricidal treatment that targets Wolbachia bacteria

The filaria causing river blindness are dependent on the worm-symbiont Wolbachia bacteria for growth, development, reproduction, and survival; elimination of the symbiont with antibiotic drugs therefore has the potential to lead to worm death, delivering a new and practical solution for treating and eliminating this deadly disease.

TylAMac, or ABBV-4083, is a derivative of tylosin, a veterinary antibiotic that targets Wolbachia, and was identified by a screening of anti-infective compounds led by AbbVie and the anti-Wolbachia consortium A-WOL at the Liverpool School of Tropical Medicine. 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. Toxicology studies were completed in 2017 and an oral formulation was developed. In December 2017, AbbVie began the first human trial of TylAMac to test the drug’s safety in healthy volunteers and assist in the selection of doses for future trials. This Phase I study took place at AbbVie’s Clinical Pharmacology Research Unit and was completed in 2018. The results support progression to Phase II. DNDi is now preparing for a Phase II proof-of-concept study in the DRC. A hospital in Masi-Manimba that has long been one of the principal clinical sites for DNDi’s sleeping sickness studies has already been selected as one site for the study. Entirely renovated by DNDi for sleeping sickness trials, the site is again being upgraded by DNDi, with staff trained to run trials for river blindness.
HIV

DNDi aims to help end the neglect of paediatric HIV by developing optimal child-friendly antiretroviral formulations for children living with HIV, with a special focus on infants and young children who are at the highest risk of dying without treatment.

**DISCOVERY**

<table>
<thead>
<tr>
<th>Screening</th>
<th>Hit-to-lead</th>
<th>Lead optimization</th>
<th>Pre-clinical</th>
<th>Phase I</th>
<th>Phase IIa/IIb/III</th>
<th>Registration</th>
<th>Treatment access</th>
</tr>
</thead>
</table>

**TRANSLATION**

- 5 FC (cryptococcal meningitis)
- 4-in-1 (ABC/3TC/LPV/r)

**DEVELOPMENT**

- Super-booster therapy for children with HIV/TB
- 2-in-1 LPV/r pellets and ABC/3TC or AZT/3TC

**IMPLEMENTATION**

- New chemical entity
- December 2019

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### '4-in-1' ABC/3TC/LPV/r

**Objective:** Develop and register a solid, taste-masked, heat-stable, first-line, fixed-dose formulation of the protease inhibitors lopinavir and ritonavir and the nucleoside reverse transcriptase inhibitors (NRTIs) lamivudine and abacavir

In October 2019, Cipla submitted the ‘4-in-1’ fixed-dose combination of abacavir, lamivudine, lopinavir, and ritonavir (ABC/3TC/LPV/r) to the US FDA for tentative approval. In December, Cipla announced that this strawberry-flavoured HIV treatment will be priced at under USD 1 a day for children weighing up to 14 kg. The 4-in-1 is a protease inhibitor-based regimen that comes in the form of granule-filled capsules. Developed for infants and young children weighing from 3 to 25 kg, parents and caretakers will be able to administer the drugs by opening the capsules and sprinkling the granules on soft food, water, or milk. The 4-in-1 does not require refrigeration and is a great improvement over the current option, a bitter-tasting syrup of LPV/r with high alcohol content that must be refrigerated.

DNDi is running a Phase I/II study called LOLIPOP to assess this 4-in-1 combination as an easy-to-use paediatric formulation. The LOLIPOP study began in 2019 in Uganda and will generate pharmacokinetic, safety, and acceptability data on the 4-in-1 in infants and young children living with HIV to provide evidence for worldwide scale-up.

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### '2-in-1' LPV/r pellets and ABC/3TC

**Objective:** Evaluate the effectiveness of lopinavir/ritonavir (LPV/r) pellets, given with the NRTIs abacavir and lamivudine (ABC/3TC), in an implementation study in infants and young children with HIV who cannot swallow pills

In 2015, following the tentative approval by the US FDA of the LPV/r 2-in-1 pellets developed by Cipla (India), DNDi launched the LIVING study in five sites in Kenya to provide early access to the new formulation. The pellets are taken orally and are a significant improvement over the high-alcohol, bitter-tasting, refrigerated syrups that were previously the only available LPV/r formulation for young children.

The study was expanded to Uganda in 2016 and Tanzania in 2017. As of December 2018, the LIVING study had enrolled 1,003 children across 12 sites in Kenya, Uganda, and Tanzania, and follow-up was completed for the Kenyan and Ugandan sites. In February 2018, interim results of the LIVING study were released, showing that 83% of the children were virologically suppressed at 48 weeks with the 2-in-1, compared to 55% at the beginning of the study. These results show that the 2-in-1 is effective and well tolerated by children.

DNDi is now actively preparing to build on the work on the 2-in-1 to facilitate transition and support access to the 4-in-1, once it is registered.

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### 5 FC for cryptococcal meningitis

**Objective:** Advance the development of sustained-release flucytosine to simplify inpatient and outpatient treatment of cryptococcal infections

Cryptococcal meningitis is a common, life-threatening opportunistic infection for people with advanced HIV, responsible for 11-15% of all HIV-related mortality. Flucytosine is a key component of WHO-recommended first-line treatment for HIV-related cryptococcal meningitis. However, standard formulations of the drug – delivered in four divided doses per day – are poorly adapted for use in under-staffed and overburdened hospitals in resource-limited settings.

This project aims to deliver a simpler, sustained-release formulation of flucytosine. Following the performance of pharmaceutical development studies and physiologically based pharmacokinetic modelling in 2019, preparations to initiate Phase I studies are now underway.
Super-booster therapy for paediatric HIV/TB

Objective: Support implementation of and access to a stand-alone pharmacokinetic ritonavir booster formulation, to be added to any protease inhibitor-based paediatric ARV regimen for the treatment of children co-infected with HIV and TB

Ritonavir (LPV/r), as the backbone of the regimen to treat TB in children, reduces the bioavailability of protease inhibitors such as lopinavir/ritonavir (LPV/r). This negative drug-drug interaction is a major challenge in treating children infected with both HIV and TB. As part of its development of protease inhibitor-based antiretroviral regimens for children, DNDi carried out a pharmacokinetic study in 96 infants and young children co-infected with HIV and TB at five sites in South Africa. The objective was to demonstrate the safety and effectiveness of ‘super-boosting’, which involves adding extra ritonavir to the LPV/r regimen in order to counter this drug-drug interaction.

The results were presented to the WHO Guidelines Review Committee and have strengthened the WHO recommendation to super-boost ritonavir in HIV/TB co-infected children on an LPV/r-based therapy. This study has been completed and final results were presented in 2017 and published in 2018, showing that super-boosting is safe and effective.

DNDi is now preparing to conduct a similar study to evaluate the 4-in-1 for treatment of young children co-infected with HIV and TB.
HEPATITIS C VIRUS (HCV)

**DNDi aims to deliver:**
- A safe, effective, and easy-to-use direct-acting antiviral regimen, to be used as an affordable combination paving the way for a public health approach to hepatitis C.
- Increased access to affordable treatments by supporting policy change and encouraging political will to treat hepatitis C.
- Innovative programmes to improve access to hepatitis C diagnosis and treatment in a variety of countries.

**DISCOVERY**
- **Screening**
- **Hit-to-lead**
- **Lead optimization**

**TRANSLATION**
- **Preclinical**
- **Phase I**
- **Phase IIa/Proof-of-concept**

**DEVELOPMENT**
- **Phase IIb/III**
- **Registration**
- **Treatment access**

**IMPLEMENTATION**
- **Ravidasvir + sofosbuvir**
- **Ravidasvir**

December 2019

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**Working together to find the missing millions**

Recent years have seen a revolution in medical innovation for hepatitis C, which can now be cured thanks to safe, simple, and effective treatment. But barely 7% of people living with the disease worldwide have benefited, notably because new drugs are too expensive to enable countries to implement a public health approach to this disease.

In July 2018, DNDi and diagnostic product development and delivery partnership FIND announced a partnership, in collaboration with the Ministry of Health in Malaysia, to generate evidence to support policy change and scale up HCV diagnosis and treatment.

As a part of the project, funded by Unitaid, simplified decentralized screening for HCV was initiated in Malaysia. People who screened positive and were subsequently confirmed to have HCV were linked to treatment either in government hospitals or, on a voluntary basis, as part of the DNDi clinical trial.

Ahead of World Hepatitis Day 2019, the Malaysian Ministry of Health, DNDi, and FIND launched the #MYmissingmillions campaign, to raise awareness of the importance of early HCV diagnosis and treatment. The partnership offered Malaysians, especially those considered to be at high risk, the opportunity to be screened at more than 100 hospitals, primary healthcare centres, and study sites located across the country’s 14 states, and to receive highly effective treatment, for free.

More than 11,000 patients were screened over the course of 2019, with over 400 people linked to HCV treatment in government hospitals and 23 as part of the DNDi clinical trial.
Ravidasvir + sofosbuvir

Objective: Conduct Phase II/III clinical trials to evaluate the efficacy of a ravidasvir + sofosbuvir combination and register ravidasvir as a new direct-acting antiviral

Ravidasvir (RDV) was developed by the US biopharmaceutical company Presidio and identified by DNDi. In 2016, Presidio, DNDi, and the Egyptian generics manufacturer Pharco signed a licence agreement to secure supplies of RDV and sofosbuvir (SOF).

In 2016, DNDi launched a Phase II/III study in Malaysia and Thailand to assess the efficacy, safety, tolerability, pharmacokinetics, and acceptability of 12- and 24-week regimens containing the drug candidate RDV, in combination with SOF, for people living with hepatitis C.

The trial was co-sponsored by the Malaysian Ministry of Health and co-financed by Médecins Sans Frontières (Doctors Without Borders, or MSF). A total of 301 patients were included in the first stage of the trial: 220 in Malaysia and 81 in Thailand. Patients were included regardless of HIV co-infection status, as were people with compensated liver disease with or without cirrhosis. Interim results published in April 2018 showed that 12 weeks after the end of treatment, 97% of the 301 patients 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 generate further data on the profile of RDV in multiple genotypes, the second stage of the trial was launched in December 2018 in Malaysia and in May 2019 in Thailand. Out of a target of 300 patients, 180 had been enrolled by January 2020. Additional trials are envisioned in other parts of the world.

Registration of RDV will be pursued in Malaysia with DNDi pharmaceutical partners Pharmaniaga in mid-2020, before registration in other middle-income countries, including Argentina, with industrial partners Elea Phoenix.

DNDi signed a technology transfer agreement with Pharco (Egypt) and Pharmaniaga in late 2017.

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### STORM-C-1 TRIAL

**SUSTAINED VIRAL RESPONSE FOLLOWING 12 WEEKS OF TREATMENT (SVR 12) - INTERIM RESULTS**

<table>
<thead>
<tr>
<th>Percentage of patients achieving sustained virological response at 12 weeks</th>
<th>Overall</th>
<th>Genotype</th>
<th>Cirrhosis</th>
<th>HIV co-infection</th>
<th>Prior HCV treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>97%</td>
<td>97%</td>
<td>100%</td>
<td>100%</td>
<td>97%</td>
</tr>
<tr>
<td>1a</td>
<td>78%</td>
<td>81%</td>
<td>Yes</td>
<td>No</td>
<td>95%</td>
</tr>
<tr>
<td>1b</td>
<td>213/270</td>
<td>90%</td>
<td>Yes</td>
<td>No</td>
<td>96%</td>
</tr>
<tr>
<td>2</td>
<td>204/210</td>
<td>97%</td>
<td>Yes</td>
<td>No</td>
<td>98%</td>
</tr>
<tr>
<td>3</td>
<td>196/201</td>
<td>99%</td>
<td>Yes</td>
<td>No</td>
<td>96%</td>
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<tr>
<td>6</td>
<td>153/158</td>
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<tr>
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<td>27</td>
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<td>No</td>
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<tr>
<td>2</td>
<td>2</td>
<td>100%</td>
<td>Yes</td>
<td>No</td>
<td>98%</td>
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<tr>
<td>291/300</td>
<td>97%</td>
<td>Yes</td>
<td>No</td>
<td>96%</td>
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</tr>
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2019 DNDi R&D Programmes in Review
**Sleeping sickness**

Accelera, Italy; Advinus Therapeutics Ltd., India; Aesica, UK; Amatisi Aquainte (formerly Bertin Pharma), France; Analytical Discovery GmbH, Germany; Anacor Pharmaceuticals (now Pfizer Inc.), USA; Aptuit, Italy; Asinex Corporation, USA; Avista Pharma (formerly SCYNEXIS), USA; Basilea Pharmaceutica AG, Switzerland; Biotrial, France; Bureau d’Etudes d’Ingénierie et d’Architecture (DINA) Sarl, Guinea; Banook Group, France; BIOTEC, Thailand; CBCO, DR Congo; Celgene Corporation, USA (now Bristol-Myers Squibb); Centiphrm, France; Chiron Corporation, USA (now Novartis); Cisapharm, France; Debiopharm SA, Switzerland; Dow AgroSciences LLC, USA; Drugabisil, France; Eurofins-Optomed, France; Evanston Northwestern Healthcare, USA; Evolva SA, Switzerland; Foundation for the National Institutes of Health, USA; Genzyme, USA; HAT Platform; HES-50 Valais Wallis, Switzerland; Institut de Recherche pour le Développement, France; Institut National de Recherche Biomédicale, DRC; Institute of Tropical Medicine Antwerp, Belgium; Joint Clinical Research Centre, Uganda; Laboratoire La Reference, Guinea; Laboratory of Microbiology, Parasitology and Hygiene, University of Antwerp, Belgium; Luxembourg Institute of Health, Luxembourg; Médecins Sans Frontières; Ministry of Health, Malawi; Murdoch University, Australia; National Control Programmes of the Democratic Republic of Congo, the Central African Republic, and of Guinea; Novartis, Switzerland and USA; Otsuka Pharmaceutical Co., Ltd., Japan; Pace University, USA; Pathzone, UK; Pfizer Inc., USA; Pharmadyn Inc., USA; Phinc, France; Quotient Sciences, UK; RCTs, France; Roche, Switzerland; Sanofi, France; SG5, Belgium; SFS, France; Swiss Tropical and Public Health Institute, Switzerland; Tehran University, Iran; Theradis Pharma, France; TIPharma, Netherlands; Trade Factors Overseas Ltd., UK; Uganda National Health Research Organisation, Uganda; Venn Life Sciences, Ireland; WHO-NTD (Neglected Tropical Diseases department).

**Leishmaniasis**

AbbVie, USA; Accelera, Italy; Academic Medical Center; the Netherlands; Addis Ababa University, Ethiopia; Advinus Therapeutics Ltd., India; Amatsi Aquainte (formerly Bertin Pharma), France; AMC Medical Research BV, the Netherlands; Amudat Hospital, Uganda; Anacor Pharmaceuticals (now Pfizer Inc.), USA; Analysis Ltd. RAK, Aputit, Italy; United Arab Emirates; Arba Minch Hospital, Ethiopia; Astellas Pharma Inc., Japan; AstraZeneca, Sweden and UK; Auckland University, New Zealand; Banook Group, France; BaseCon, Denmark; Basilea Pharmaceutica AG, Switzerland; Bayer, Germany; Bioascent, UK; Bioaster, France; Biologik, Kenya; Biologik, USA; BioDeliverySciences International Inc., USA; BIOTEC, Thailand; Brasilisa University, Brazil; Bristol-Myers Squibb, USA; Broad Institute of MIT and Harvard, USA; Celgene Corporation (now Bristol-Myers Squibb), USA; Centre for Drug Candidate Optimisation, Monash University, Australia; Centro de Inovação e Ensaios Pré-Clinicos (CIENP), Brazil; Centro Nacional de Pesquisa em Energia e Materiais (CNPEM), LN Bio, Brazil; Charles River Laboratories (WII Research), France and the Netherlands; Cornell University, USA; Crystallisle, Switzerland; Daiichi Sankyo Company, Limited, Japan; Daiichi Sankyo RD Novare Co., Ltd., Japan; Dermalaser, Bolivia; Dow AgroSciences LLC, USA; Drug Discovery Unit, University of Dundee, UK; El du Pont de Nemours, USA; Eisai Co., Ltd., Japan; Epicemich, Australia; Eurofins Cerep, France; Eurofins Panlabs Thailand, Thailand; Eurofins Panlabs, USA; Eurofins-Optimed, France; Evolva SA, Switzerland; Foundation for Innovative New Diagnostics, Switzerland; Fundação de Amparo a Pesquisa do Estado de São Paulo, Brazil; GeneDesign Inc., Japan; Genomics Institute of The Novartis Research Foundation, USA; Genzyme, USA; Gilead Sciences, USA; GlaxoSmithKline, Spain and UK; Gordion University Hospital, Ethiopia; Griffith Institute for Drug Discovery, Griffith University, Australia; Hospital São José do Doencas Infecciosas, Brazil; Humax Pharmaceutical, Colombia; Hypha Discovery Ltd., UK; Ikots, France; Indian Institute of Technology Gandhinagar, India; 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 Ciências Biomedicas, Universidade de São Paulo, Brazil; Instituto de Fisica, Universidade de São Paulo, Brazil; Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Peru; Instituto de Quimica, Universidade Estadual de Campinas, Brazil; Instituto de Salud Carlos III, Spain; International Centre for Diarrhoeal Disease Research, Bangladesh; Johnson & Johnson, USA; Intertek, UK; Kacheliba District Hospital, Kenya; Kala-Azar Medical Research Centre, India; Kenya Medical Research Institute, Kenya; Kimmel Center, USA; Kisanas Foundation 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; Mahidol Oxford Tropical Medicine Research Unit, Thailand; Mitsubishi Tanabe Pharma Corporation, Japan; Montes Claros State University, Brazil; Mott McDonald Ltd., UK; Nagasaki University, Japan; National Institute of Pathology, India; National Institutes of Health, USA; Netherlands Cancer Institute, the Netherlands; NKK Stichting het Nederland Kanker Instituut, the Netherlands; Northeastern University, USA; Northwick Park Institute for Medical Research, UK; Novartis, Switzerland and USA; Novartis Institutes for BioMedical Research, USA; Ohio State University, USA; Osaka University, Japan; Oswald Cruz Foundation (Fiocruz), Brazil; Otsuka Pharmaceutical Co. Ltd., Japan; Paediatric Hospital João Paulo II – FEMIG, Brazil; Pasteur Institute of Iran, Iran; Pentland Management Systems Ltd., UK; Pkpdesign Sas, France; Pfizer Inc., USA; Pharmadyn Inc., USA; Phi Pharma SA, Switzerland; Piaui Federal University, Brazil; Pierre FABre Laboratories, France; PolyTherics Ltd., UK; Programa de Estudio y Control de Enfermedades Tropicais, Universidade de Antioquia, Colombia; Programa Nacional de Leishmaniasis, Colombia; Quotient Sciences, UK; Rajendra Memorial Research Institute of Medical Sciences, India; René Rachou Research Center – Fiocruz-MG, Brazil; Research Foundation of the Netherlands Cancer Institute, the Netherlands; Sandeox, USA; Sanofi Merial, USA; Sanofi, France; Sanofi-Aventis, France; Sara Pharm, Romania; Scynexis, USA; Sequella Inc., USA; Serigie Federal University, Brazil; SG5, Belgium; Shionogi & Co., Ltd., Japan; Shobhaben Prataphari Patel School of Pharmacy & Technology Management, India; SK Hospital, Mymensingh, Bangladesh; State Health Society, Bihar, India; Swiss Tropical and Public Health Institute, Switzerland; Syngene, India; Takeda Pharmaceutical Company Limited, Japan; TB Alliance, USA; TCG Lifesciences, India; Thermosurgery Technologies Inc., USA; TIPharma, the Netherlands; UBC, Switzerland; Universidade Estadual do Rio de Janeiro, Brazil; University of Cape Town, South Africa; University of Gedaref, Sudan; University of Glasgow, UK; University of Gondar, Ethiopia; University of Oxford, UK; Upssala University, Sweden; 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.

**Chagas disease**

AbbVie, USA; Anacor Pharmaceuticals (now Pfizer Inc.), USA; Astellas Pharma Inc., Japan; AstraZeneca, Sweden and UK; Barcelona Centre for International Health Research, Spain; Barcelona Institute for Global Health (ISGlobal), Spain; Basilea Pharmaceutica AG, Switzerland; Bayer, Germany; Bioascent, UK; BioDeliverySciences International Inc., USA; Bioaster, France; Brazilian Biosciences National Laboratory, Brazil; Bristol-Myers Squibb, USA; Broad Institute of MIT and Harvard, USA; CEADES, Bolivia; Celgene Corporation (now Bristol-Myers Squibb), USA; Centre for Drug Candidate Optimisation, Monash University, Australia; Center of Excellence for Chagas Disease, USA; Centro de *Partners listed here include partners involved since the start of the project.

DNDi is deeply grateful to our R&D partners, whose commitment and collaboration have sustained our work since 2003*
Chagas y Patología Regional, Hospital Independencia, Argentina; Centro de Innovación y Ensayos Pró-Clinicos (CIENP), Brazil; Centro Nacional de Pesquisa em Energia e Materiais, LN Bio, Brazil; Chembridge Corporation, USA; Chiron Corporation, USA (now Novartis); Collective of Applied Studies and Social Development, Bolivia; Daichi Sankyo Company, Limited, Japan; Cornell University, USA; Daichi Sankyo RD Novare Co., Ltd., Japan; Dow AgroSciences LLC, USA; Drug Discovery Unit, University of Dundee, UK; El du Pont de Nemours, USA; Eisai Co., Ltd., Japan; Exelixis, USA; Epichem, Australia; Eurofins, France; Evanston Northwester Healthcare, USA; FP Clinical Pharma – Ethel Feleder, Argentina; Fundação de Amparo à Pesquisa do Estado de São Paulo, Brazil; Fundació Cardiogenfiàl, Institut de Cardiologia, Colombia; Fundacio Investigaciò Hospital General Valencia, Spain; Fundación Instituto de Investigaciones Biotecnológicas, Argentina; Hospital Universitario La Paz, Spain; GlaxoSmithKline, Spain and UK; Griffith Institute for Drug Discovery (GRIDII), Griffith University, Australia; Hospital Clínico de Barcelona, Spain; Hospital de Niños Ricardo Gutierrez, Argentina; Hospital General de l’Hôpitalet Concorci Sanitari Integral, Spain; Indian Institute of Technology, Gandhinagar, India; University of Oxford, UK; Infiny Biomarkers, France; Instituto de Física, Universidade de São Paulo, Brazil; Institut d’Investigació Biomedica de Bellvitge, Spain; Institute of Microbial Chemistry, Japan; Instituto Nacional de Parasitología Dr Fatala Cháben, Argentina; Institut Pasteur Korea, South Korea; Instituto de Efectividad Clínica y Sanidad (IECS), Argentina; Instituto de Quimica, Universidade Estadual de Campinas, Brazil; Insud Pharma, Argentina; International Development Research Centre, Canada; Janssen Research & Development LLC, USA; Johnson & Johnson, USA; Kitasato Institute for Life Sciences, Japan; International Development Research Center, Uruguay; Laboratório Elea Phoenix, Argentina; Laboratório Farmacêutico do Estado de Pernambuco, Brazil; 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; Ministry of Health, Colombia; Mitsubishi Tanabe Pharma Corporation, Japan; Mundo Sano Foundation, Argentina; Murdoch University, Australia; National Council of Scientific and Technological Research (INGEBI-CONICET), Argentina; NHEPACHA network; Northeastern University, USA; Northwick Park Institute for Medical Research, UK; Novartis, Switzerland and USA; Nucleus of Pharmaceutical and Cosmetics Development, Brazil; Pfizer Inc., USA; PhinC, France; Pierre Fabre Laboratories, France; Platform of Integral Care for Patients with Chagas Disease, Spain/Bolivia; Sandexis, UK; Sanofi, France; Sequella Inc., USA; Shionogi & Co., Ltd., Japan; Shubhendet Pratapbhai Patel School of Pharmacy & Technology Management, India; Swiss Tropical and Public Health Institute, Switzerland; Syn bios Health, LLC, USA; Takeda Pharmaceutical Company Limited, Japan; TB Alliance, USA; TCG Life Sciences, India; University Hospitals of Geneva, Switzerland; University of Cape Town, South Africa; University of Georgia Research Foundation, USA; University of Texas at El Paso, USA; Uppsala University, Sweden; Vall d’Hebron University Hospital, Spain; Venn Life Sciences, Ireland; Walter Reed Army Institute of Research, USA; Washington University in St Louis, USA; WHO-TDR [Special Programme for Research and Training in Tropical Diseases]; WuXi AppTech, China; Zoetis (formerly Pfizer Animal Health), USA.

**Filarial diseases**

AbbVie, USA; A-WOL, UK; Analytical Services International, UK; Bayer, Germany; Bonn University Hospital, Institute of Medical Microbiology, Immunology and Parasitology, Germany; Celgene Corporation [now Bristol-Myers Squibb], USA; Commissariat à l’énergie atomique et aux énergies alternatives, France; Datametrix AG, Switzerland; Erasmus Medical Center, the Netherlands; Hammersmith Medicines Research, UK; Imperial College, UK; Institut Bousson Bertrand, France; Institut National de Recherche Biomédicale, DR Congo; Institut de Recherche pour le Développement, France; Liverpool School of Tropical Medicine, UK; Mahidol University, Thailand; Margan Clinical Research Organisation, Ghana; MC Toxicology Consulting GmbH, Austria; Merck, USA; National Museum of Natural History, France; Niche Science and Technology, UK; Northwick Park Institute for Medical Research, UK; Programme national de lutte contre le Paludisme à Niégolè et Chimiothérapie Préventive, Côte d’Ivoire; Research Foundation for Tropical Diseases and the Environment, Cameroon; Salvensis, UK; University of North Carolina, USA; Swiss Tropical and Public Health Institute, Switzerland; The Task Force for Global Health, USA; University of Health and Allied Sciences, Ghana; University of Liverpool, UK; University of Oxford, UK; Washington University in St Louis, USA.

**HIV**

AMPATH, Kenya; 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; Cipla Ltd, India; Clinton Health Access Initiative, USA; Department of Health, South Africa; Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, South Africa; Elizabeth Glaser Pediatric AIDS Foundation, USA; Emplify Services and Research Unit, Rahima Moosa Mother and Child Hospital, South Africa; Enhancing Care Foundation, South Africa; epicentre, Uganda; Family AIDS Care and Education Services Project, Kenya; Gertrude’s Children’s Hospital, Kenya; i-Base, UK; ICAP, Columbia University, USA; Ifakara Health Institute, Tanzania; Institute of Tropical Medicine, Antwerp; International Community of Women Living with HIV, Kenya; Joint Clinical Research Centre, Uganda; Kenya Medical Research Institute, Kenya; Kenya Lady Health Workers Association, USA; Khoo Teck Puat Hospital, Singapore; LIDOS (Livelihoods and Development Strategies for the Integrated Control of HIV/AIDS and other linked non-communicable diseases), Tanzania; Ministry of Health, Kenya, Tanzania, Uganda, and Zimbabwe; Moi Teaching and Referral Hospital, Kenya; Moi University Kenya; Necker Institute, France; NERPHAK, Kenya; Nyumbani Le Toto Project, Children of God Relief Institute, Kenya; Perinatal HIV Research Unit, University of Witswatersrand, South Africa; Shandukani Research Centre, Wits Reproductive Health and HIV Institute, South Africa; St Lumumba Health Centre, Kenya; Stellenbosch University and Tygerberg Children’s Hospital, South Africa; Swiss Tropical and Public Health Institute, Switzerland; UNAIDS, The Global Parliamentarians Network to End Infectious Diseases; 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 Centre, Malaysia; Clinical Research Malaysia, Malaysia; Crystal Pharmatech, USA; Doppel Farmaceutici, Italy; HIV-NAT AIDS Research Centre, Thailand; Info Kinetics Sdn Bhd, Malaysia; Institute of Medical Research, Malaysia; Insud Pharma/Elea, Argentina; Kinapse Ltd, UK; Maharaj Nakorn Chiang Mai University, Thailand; Médecins Sans Frontières, Ukraine; Ministry of Health, Malaysia; Ministry of Health, Thailand; Ministry of Industry, Science and Technology, Thailand; Mundo Sano Foundation, Argentina; Nakornping Hospital, Thailand; National Science and Technology Development Agency, Thailand; Pharcopharmaceuticals Inc., Egypt; Pharmaniaga, Malaysia; Pharmetheus AB, Sweden; Presidio Pharmaceuticals, USA; Public Health Promotion Research and Training, Thailand; Toxipharm Laboratoire, France; University Hospitals of Geneva, Switzerland; Zhejiang Ausun Pharmaceutical Co., Ltd.
2019 Scientific publications

In 2019, DNDi staff members authored or co-authored 45 peer-reviewed publications. Of these, 34 had at least one author from a partner institution in an endemic country, 19 had at least one endemic country author from one of DNDi’s regional offices, 23 had a female lead or co-lead author, and 43 were published in an open access journal, in keeping with DNDi’s commitment to open access. DNDi authors are underlined in the listing below.

Leishmaniasis


Target Product Profile for a point-of-care diagnostic test for dermal leishmaniasis by Cruza I, Albertini A, Batistella M, Arana B, Picado A, Ruiz-Postigo JA, Ndungu UJM, Parasite Epidemiology and Control, January 2019


Biomarkers in post-kaala-azar dermal leishmaniasis by Zilstra EE. Frontiers in Cellular and Infection Microbiology, July 2019


Innovations for the elimination and control of visceral leishmaniasis by Selvapandian A, Croft SL, Rial S, Nakhashi HL, Ganguly NK. PLoS Neglected Tropical Diseases, September 2019


Chagas disease


Drug discovery for Chagas disease: Impact of different host cell lines on assay performance and hit compound selection by Franco CH, Alcântara LM, Chatellain E, Freitas-Junior L, Borso Moraes C. Tropical Medicine and Infectious Disease, May 2019


Drug discovery for Chagas disease: A viewpoint by Kratz JM. Acta Tropica, July 2019

Metabolomics, lipidomics, and proteomics profiling of mycoblasts infected with Trypanosoma cruzi after treatment with different drugs against Chagas disease by Henning K, Abi Ghanem J, Bunesque A, Moniche X, Bilaniu E, Ouattara AD, Lewis MD, Kelly JM, Brassard S, Ceuterghem C, Chatellain E, Béquet P. Metabolomics, August 2019


The unmet medical need for Trypanosoma cruzi-infected patients: Monitoring the disease status by Tresp M, Chatellain E. BBA – Molecular Basis of Disease, December 2019

23
Filaria – River blindness

Projected number of people with onchocerciasis-loiasis coinfection in Africa, 1995 to 2025 by Vinkeles Melchers NVS, Coffeng LE, Bruss oppos M, Pedr ign B, Plion SDS, Tiskle AH, Zour HGM, Wanji S, Ramma JH, Stolk WA. Clinical Infectious Diseases, July 2019

Mycetoma


Hepatitis C


HIV


Malaria*


Competing risk events in antimalarial drug trials in uncomplicated Plasmodium falciparum malaria: a WorldWide Antimalarial Resistance Network individual participant data meta analysis by WWARN Methodology Study Group – including Kiechel JR. Malaria Journal, July 2019

Focus on children

Hard to study, hard to treat: putting children at the centre of antibiotic research and development by Balasegaram M, Pécoul B, Gray G, Sharland M, Swaminathan S. The Lancet Infectious Diseases, June 2019

BMJ special supplement: Innovation for Neglected Diseases in South Asia

With its high disease burden and regional expertise in end-to-end solutions, ranging from drug discovery through to regulation, manufacture, and distribution, South Asia has an important role to play in combating neglected diseases. This special series highlights regional public health programme successes, and explores issues that still need supportive policy and research.

Series articles:

- Editorial introduction: Innovation is vital for elimination of neglected diseases in South Asia by Rijal S, Pécoul B, Bhargava B. BMJ, January 2019
- Elimination of lymphatic filariasis in South East Asia by Specht S, Suma TK, Pedr ign B, Hoerauf A. BMJ, January 2019
- The timing is right to end snakebite deaths in South Asia by Ralph R, Sharma SK, Faiz MA, Ribeiro J, Rijal S, Chappuis F, Kuch U. BMJ, January 2019
- Neonatal sepsis in South Asia: huge burden and spiralling antimicrobial resistance by Chaurasia S, Sivanandan S, Agarwal R, Ellis S, Sharland M, Sankar MJ. BMJ, January 2019

*Implementation of DNDi malaria programmes transferred to Medicines for Malaria Venture in 2015
DNDi has now delivered eight new treatments for neglected patients and aims to deliver another eight to ten, for a total of 16-18 new treatments by 2023. DNDi is deeply grateful for the support of all its donors, and for their commitment and collaboration since 2003. All contributions large and small have contributed towards the advancement of DNDi’s mission and goals. Listed below are supporters who have given a cumulative contribution of at least USD/EUR 10,000 since 2003.

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- Australian Trade and Investment Commission (Austrade), Australia
- Banco Nacional de Desenvolvimento Econômico e Social (BNDES), Brazil
- Department of Health and Social Care (DHSC), UK*
- Dutch Ministry of Foreign Affairs (DGIS), the Netherlands
- Dutch Ministry of Health, Welfare and Sport (VWS), the Netherlands*
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- Federal Office of Public Health (FOPH) Switzerland*
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- PANAFTOSA – Organização Pan-Americana da Saúde/Organização Mundial da Saúde (OPAS/OMS)
- Region of Tuscany, Italy
- Republic and Canton of Geneva, International Solidarity Service, 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*
- Spanish Agency for International Development Cooperation (AECID), Spain
- Swiss Agency for Development and Cooperation (SDC), Switzerland
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- UK aid, UK
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- World Health Organization – Special Programme for Research and Training in Tropical Diseases (WHO-TDR)

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- Carlos Slim Foundation through the Carlos Slim Health Award, Mexico
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- Clifford N. Burnstein & Sabra C. Turnbull, USA
- craigslist Charitable Fund, USA
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- Family of Richard Rockefeller, USA
- Fondation André & Cyprien, Switzerland
- Fondation Anne Maurer-Cecchini, Switzerland
- Fondation ARPE, Switzerland
- Fondation de bienfaisance du groupe Pictet, Switzerland
- Fondation Pro Victimis, Switzerland
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- Jeff Nelson and Betsabe Aristud-Carrillo, USA
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- Leopold Bachmann Foundation, Switzerland
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- P B and K Family Foundation, USA
- Peter Mensch, USA
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- Ronald L. Thatcher, USA
- Sandoz Family Foundation, Switzerland
- Sasakawa Peace Foundation, Japan
- Starr International Foundation, Switzerland
- Stavros Niarchos Foundation, USA
- Steve Rabin and Jonathan Winslow, USA
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- The Rockefeller Foundation (through the ‘Next Century Innovators Award’), USA
- The Stainman Family Foundation, USA
- Tully Family Foundation, USA
- UBS Optimus Foundation, Switzerland
- Wellcome, UK
- Zegar Family Fund, USA
- Anonymous individuals and organizations

In memory of Guy Mazué

Guy worked closely with DNDi from its founding in 2003 and even before, advising the working group that created DNDi. He was involved in much of DNDi’s toxicology work for many years, including on pre-clinical and clinical drug candidates for malaria, sleeping sickness, and leishmaniasis. Guy continued to work with DNDi as a consultant in his retirement, and most recently helped to successfully bring leishmaniasis drug candidates DNDI-0690 and DNDI-6148 to first-in-human clinical trials.

For a great many of us, Guy’s passing in early 2020 marked the loss of a devoted and generous adviser and friend. We are grateful for his contributions and extend our deepest condolences to his family.
Best science for the most neglected

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, mycetoma, paediatric HIV, and hepatitis C.

DNDi’s primary objective

Establish a robust R&D portfolio of new drug candidates that addresses patients’ treatment needs, deliver 16 to 18 new treatments by 2023 for targeted neglected diseases, and ensure equitable access to these treatments.

In doing this, DNDi has two further objectives

1. Use and strengthen capacities in disease-endemic countries via project implementation;

2. Raise awareness of the need to develop new drugs for neglected diseases, and advocate for increased public responsibility.