



Partnerships
to Bridge
Innovation and
Access

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 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 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 patients suffering from the most neglected communicable diseases. Acting in the public interest, DND*i* will bridge 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.

DND*i*'s primary focus will be the development of drugs for the most neglected diseases, such as sleeping sickness, leishmaniasis, and Chagas disease; and it will also consider engaging R&D projects on other neglected diseases. DND*i* will address unmet needs by taking on projects that others are unable or unwilling to pursue and, as means permit, will consider development of diagnostics and/or vaccines.

In pursuing these goals, DND*i* will manage R&D networks built on South-South and North-South collaborations. While using the existing support capacities in countries where the diseases are endemic, DND*i* will help to build additional capacity in a sustainable manner through technology transfer in the field of drug research and development for neglected diseases.

DND*i*

Drugs for Neglected Diseases *initiative*

The Drugs for Neglected Diseases *initiative* (DNDi) is a patient-needs driven, not-for-profit research and development (R&D) organization that develops safe, effective, and affordable medicines for neglected diseases that afflict millions of the world's poorest people.

DNDi focuses on developing new treatments for the most neglected patients suffering from diseases such as sleeping sickness (or Human African Trypanosomiasis), leishmaniasis, Chagas disease, malaria, specific filarial diseases, and paediatric HIV.

The initiative's primary objective is to deliver 11 to 13 new treatments by 2018 and to establish a strong R&D portfolio for these diseases.

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REPORT**

MESSAGE FROM THE CHAIR OF THE BOARD AND THE EXECUTIVE DIRECTOR



Dr Bernard Pécoul
Executive Director



Prof. Marcel Tanner
Chair of the Board
of Directors

The year 2014 was forever marked by the Ebola crisis in West Africa. With more than 10,000 people who died because of a lack of suitable treatments and vaccines, how can we, as clinicians, scientists, and drug developers, accept such a fatality when we know that the science that could have mitigated the impact of the disease outbreak exists?

A strikingly unprecedented year for global public health, 2014 saw many seemingly unrelated global health issues and hitherto divergent voices converge on one and the same conclusion: there is a pressing need to prioritize, anticipate, innovate, research, and develop appropriate health tools for neglected patients. But the global response, as we have seen from the hard-hitting health crises such as antimicrobial resistance, hepatitis C, Ebola, and many other neglected diseases, hinges on several pillars that have not always been seen in a consistent and coherent way.

Public leadership is beginning to seem geared for the challenge of ensuring research and development (R&D) meets the needs of populations and, importantly, no matter what the income classification of the country is. On the agendas of important

political fora – including the World Health Assembly, G7, G20, African Union, BRICS, and United Nations Sustainable Development Goals – we might infer a growing consensus that public leadership is mandatory to define health priorities and establish a political environment that fosters innovation, including new incentives and financing mechanisms, but this remains to be proven. After a decade of high-level discussion and debate, with new experiments and initiatives for innovation for neglected diseases, might it be time to seriously table a new global fund and mechanism for R&D? We all recall the creation of the Global Fund against AIDS, tuberculosis and malaria, which resulted from, but also created the conditions for mobilization to tackle the ‘big three’. Today, a similar mechanism is needed, such as a global pooled fund, to complement the insufficient, albeit steadily increasing, financial flow of funding from public donors and philanthropists to support innovation for neglected patients, where market incentives are lacking.

In a way we have never seen before, these issues are now amplified through public opinion, mainstream media, and high-level political agendas and while the momentum is there, we need further action and decisions to create an irreversible trend.

Paving the way to an increasingly nimble and responsive organization

As these issues raged on in 2014, DNDi was intensely involved in the process of developing its Business Plan for 2015 to 2023. As part of this process, the organization, its Regional Offices, and other key stakeholders took part in an extensive consultation exercise to ensure the organization remains attuned to current and emerging patient needs, and that the business model incarnates the responsiveness required to do so. A structured consultation took place with a broad range and large number of stakeholders worldwide to actively explore patient needs and opportunities, which were

then synthesized into strategic options, to be developed and presented to the DNDi Board of Directors in 2014 and adopted in 2015.

This process also builds directly upon the lessons learned after over a decade of experience, successes, and challenges of the organization. These lessons rendered several key foundations on which the organization is built: a patients' needs-driven approach; the commitment to share knowledge and an access-oriented Intellectual Property (IP) policy; the fostering of innovative partnerships; and the diversification of funding sources to ensure scientific independence. It is clear that some important aspects of the organization will be reinforced as DNDi moves forward, including the role of the Regional Offices, engagement in patient access to treatments, and the strengthening of innovative partnerships with public and private actors.

Having built a robust portfolio with a mix of new chemical entities and improved treatments with existing drugs for the most neglected diseases over the past decade, DNDi has learned a great deal from experimental business models. These lessons, together with a recent analysis of the R&D landscape, will enable DNDi to consider new pathways towards a more nimble and responsive engagement in global health R&D.

A 'dynamic portfolio' approach

DNDi will now put into practice a 'dynamic portfolio', enabling the organization to maintain its core focus on the most neglected diseases, while providing flexibility to extend its disease scope to address current and future unmet, and/or urgent patient needs. This implies employing the most appropriate model of intervention, which ranges from long-term full R&D engagement, to short-term project-based engagement, to several forms of support including sharing of knowledge and information, driving the set-up of innovative platforms, or utilizing the organization's expertise to contribute to new initiatives that are taken on by others.

With this new 'dynamic portfolio' approach, new disease areas such as hepatitis C and mycetoma are slated for uptake in the portfolio with different approaches, and initiatives such as antimicrobial resistance are being analysed for feasibility and eventual 'incubation' for further uptake elsewhere.

The dynamic portfolio also implies completing projects when they have reached fruition. This is the case for the two malaria projects DNDi took on at its inception. In 2014, the transition of these projects to the Medicines for Malaria Venture (MMV) was prepared in a strategic move to consolidate the largest ever malaria portfolio at MMV, and thus concert efforts to make the best use of the WHO-recommended artemisinin-based combination treatments (ACTs) worldwide.

Innovative partnerships and new alliances

This is but one example of the fruitful partnerships that DNDi endeavours to undertake to ensure the greatest benefit to patients. It is also in this spirit that new alliances were formed during the year, including a new model of multilateral drug screening, the NTD Drug Booster, and new alliances aimed at removing barriers to patient access to treatments such as the launch of the Paediatric HIV Treatment Initiative, as well as the continued activities of the Global Chagas Disease Coalition. Very important milestones were achieved in several clinical trials through the hard work and diligence of all of our partners, and in many cases under difficult field conditions, for example the successful completion of patient recruitment, on time and on target, for the fexinidazole pivotal study for sleeping sickness in the Democratic Republic of the Congo.

As DNDi gains experience, we endeavour to be constructive and honest in rendering the lessons learned from conducting R&D for neglected patients – from drug discovery to implementation – and this with models that we hope can provide insight into alternative R&D pathways, including for access. However, the work of DNDi would be able to provide a more effective response if it were part of a more appropriate R&D framework at global, regional, and national levels. As expressed in a recent publication by a group of global public health leaders, we call for a 'Biomedical Research and Development Fund and Mechanism to Meet Pressing Global Health Needs' in order to be part of a true and lasting change for millions of neglected patients.



Dr Bernard Pécoul



Prof. Marcel Tanner



Organization & Strategy

Increased Engagement in Global and Regional Strategic Alliances

A partnership-based model by nature, DNDi has endeavoured to continually build and explore innovative ways of working with public and private entities in all aspects of the organization's work. Covering several disease areas throughout the R&D pipeline – from screening for molecules to ensuring patients' needs are met – and with regional rooting across the globe, DNDi would simply not exist without the trust and engagement of a wide range of partners. The year 2014 saw both inroads being made into unprecedented multilateral partnerships and to key new partners stepping up to the plate for new projects with DNDi.

Regional engagement to address endemic country needs

In 2014, DNDi Latin America entered into a strategic alliance with Ruta-N (see p.60), a corporation set up by the City of Medellin in **Colombia** to build sustainable science, technology, and innovation in the region. The collaboration between DNDi and Ruta-N involves local pharmaceutical partners, such as Humax Pharma, and scientific and academic institutions such as the Study and Control Programme for Tropical Diseases (PECET) of the University of Antioquia, **Colombia**. Ruta-N and DNDi will collaborate on evaluating alternative topical and oral

*DNDi
Latin
America*

therapies for cutaneous leishmaniasis (CL). The programme will also endeavour to map other urgent public health needs.

In **Brazil**, DNDi was part of a move to progress new interest in drug discovery with the São Paulo Research Foundation (FAPESP), notably through a key gathering of scientists called 'Frontiers of Science', where DNDi aimed to expand collaborations – such as that currently with the Brazilian State University of Campinas, or UNICAMP – within its Lead Optimization Latin America programme.

Also in **Brazil**, recognition of the collaboration with the Brazilian public pharmaceutical company Farmanguinhos/Fiocruz, and other partners, was given to DNDi Latin America for the innovative model employed in the development of ASMQ fixed-dose combination for malaria: the 'Award for Innovation in Social Technology', was granted by Brazil's innovation and science body FINEP (see p. 43).

Coalitions to address patient access to treatments

As DNDi does not have the capacity to act as an implementer, working closely with partners is a critical success factor. Building coalitions is an important part of ensuring that beyond specific projects, key groups join forces and align behind a common vision. In order to help remove barriers to patient access to treatments, the Consortium for the Control and Elimination of Visceral Leishmaniasis (VL), known as KalaCORE, geared up for its launch with DNDi, the London School of Hygiene and Tropical Medicine, Médecins Sans Frontières and Mott MacDonald. The consortium was appointed by the Department for International Development (DFID) to tackle VL in South Asia and East Africa. Specifically for Latin America, a group of key researchers was brought together in the new RedeLeish network to address research gaps for leishmaniasis in the region (see p. 50). Another new initiative was launched in the field of paediatric HIV, the Paediatric HIV Treatment Initiative (PHTI), set up to ensure that intellectual property, research and development, and procurement of child-adapted ARVs are accelerated to meet pressing patient needs (see p. 58). The Global Chagas Disease Coalition met in 2014 to ensure a consolidated push for diagnosis and treatment (see p.13).



Launch event for the Paediatric HIV Treatment Initiative (PHTI)

New pharmaceutical partnerships

The DNDi filarial programme achieved an important milestone in 2014, as a result of intense collaboration, with a landmark agreement signed with Bayer HealthCare for the development of emodepside as a new macrofilaricide for onchocerciasis. The lessons learned from a decade of business development with the pharmaceutical industry formed part of the innovation of this partnership accord, which was a true win-win scenario in which DNDi 'de-risked' the development of this drug, allowing the company to engage its expertise and know-how in new ways for an entirely new health tool and approach to filarial disease treatment programmes (see p. 42). DNDi's partnership with Celgene was reinforced and expanded through a research and collaboration agreement to identify and optimize new drug candidates for NTDs.

In **Japan**, the commitment of the Japanese government and private industry, through the new Global Health Innovation Technology Fund (GHIT), a relatively new funding mechanism for neglected disease R&D, reinforced the DNDi-Eisai collaboration in the field of Chagas disease R&D for improved treatments through a new grant. GHIT and DNDi also entered into discussions for entirely new prospects in the field of neglected tropical disease R&D, notably in the lead up to the NTD Drug Discovery Booster project (see pages 17, 57), in which several companies would agree to work together to accelerate drug discovery for leishmaniasis and Chagas disease through ground-breaking multilateral collaboration through DNDi.

*DNDi
Japan*

DNDi BOARD MEMBERS



Marcel Tanner
Chair; Swiss Tropical and Public Health Institute (Swiss TPH)



Els Torreele
Secretary; Open Society Foundations, USA



Derrick Wong
Treasurer; non-profit management consultant, France



Jorge Bermudez
Oswaldo Cruz Foundation (Fiocruz), Brazil



Christian Bréchet
Institut Pasteur, France



Abul Faiz
Patient representative; Sir Salimullah Medical College, Bangladesh



Noor Hisham Abdullah
Ministry of Health, Malaysia



Joanne Liu
Médecins Sans Frontières (MSF)



Bennett Shapiro
Pure Tech Ventures, formerly with Merck & Co, USA



Paulina Tindana
Patient representative; Navrongo Health Research Centre, Ghana (until 2014)



John Reeder (Permanent Observer)
Special Programme for Research and Training in Tropical Diseases (WHO-TDR), Switzerland

- **Position currently vacant**
Kenya Medical Research Institute (KEMRI)

- **Position currently vacant**
Indian Council of Medical Research (ICMR)

DNDi SCIENTIFIC ADVISORY COMMITTEE MEMBERS

Pierre-Etienne Bost, Chair; formerly with Institut Pasteur, France

Kirana Bhatt, University of Nairobi, Kenya

François Chappuis, Médecins Sans Frontières & Geneva University Hospitals, Switzerland (until Oct. 2014)

J. Carl Craft, formerly with Medicines for Malaria Venture (MMV), Switzerland

Simon Croft, London School of Hygiene and Tropical Medicine, UK

Lisa Frigati, Tygerberg Hospital, South Africa

C.M. Gupta, Central Drug Research Institute, India

Paul Herrling, Novartis International AG, Switzerland

Dale Kempf, AbbVie, USA

Kiyoshi Kita, Graduate School of Medicine, University of Tokyo, Japan

Nines Lima, Médecins Sans Frontières, Spain (SAC member since Dec. 2014)

Ana Rabello, Oswaldo Cruz Foundation (Fiocruz), Brazil

Murad Shahnaz, Institute for Medical Research, Malaysia

SHIV Dayal Seth, Indian Council of Medical Research (ICMR), India

Nilanthi de Silva, University of Kelaniya, Sri Lanka

Faustino Torrico, Universidad Mayor de San Simon, Cochabamba, Bolivia

Mervyn Turner, formerly with Merck Research Laboratories, USA

Muriel Vray, Institut Pasteur, France

Krisantha Weerasuriya, World Health Organization (WHO), Geneva

John Westwick, Imperial College, London University, UK (as of Dec. 2013)

Nick White, Mahidol University, Bangkok, Thailand

FRIENDS OF DNDi

Paulo Buss, specialist in Pediatrics and Public Health, and former President, Oswaldo Cruz Foundation (Fiocruz), Brazil

Yves Champey, former Chair, DNDi Board of Directors and founder, ITEEC, France

Abdallah Daar, Professor, Public Health Sciences and Surgery, University of Toronto, Canada, and Chair, Advisory Board, UN University International Institute for Global Health

Samih T. Darwazah, Founder and Chairman, Hikma Pharmaceuticals, Jordan

Philippe Desjeux, specialist in Leishmaniasis, former Senior Program Officer for Disease Control, iOWH, and Leishmaniasis Research Coordinator, TDR/WHO, France

Ahmed El Hassan, Emeritus Professor, Institute of Endemic Diseases, University of Khartoum, Sudan

Rowan Gillies, former President, MSF International Council, Australia

Lalit Kant, Deputy Director, Immunization, Bill & Melinda Gates Foundation, and former representative, Board, Indian Council of Medical Research (ICMR), India

Stephen Lewis, Chair, Board of the Stephen Lewis Foundation, and former Minister of Foreign Affairs of Canada, former United Nations Special Envoy for HIV/AIDS in Africa, Canada

Sheba K. Meymandi, Director, the Center of Excellence for Chagas Disease at Olive View-UCLA Medical Center, USA

Piero Olliaro, Head, Intervention and implementation research, WHO/TDR, Switzerland

Ricardo Preve, Film Director, Ricardo Preve Films LLC, Argentina

Morten Rostrup, former international President, Médecins Sans Frontières, Norway

Eloan dos Santos, former Executive Director, Farmanguinhos, Brazil

José Gomes Temporão, former Minister of Health, Brazil

Rafael Vila San Juan, Director, ISGlobal's Think Thank, Institute for Global Health of Barcelona, Spain

Dyann Wirth, Chair, Department of Immunology and Infectious Diseases, Harvard School of Public Health, USA

Yongyuth Yuthavong, former Minister of Science and Technology, Thailand

Nirmal Ganguly, Former SAC, Indian Council of Medical Research, and Advisor/Professor Science & Technology Institute, New Delhi

Carlos Morel, Former Board Member, DNDi, Director of the Centre for Technological Development in Health (CDTS) and Senior Researcher, Oswaldo Cruz Foundation (FIOCRUZ)

Ismail Merican, Former Board Member, DNDi, Pro Chancellor & Chairman MAHSA University, Malaysia

Unni Karunakara, Former DNDi Advisor, Former President MSF International

Jorge Velasquez, Special Advisor for Health & development, South Center, Geneva

Carlos Nery Costa, Professor of Federal University of Piaui, Former President of Brazilian Society of Tropical Medicine

Nila Neredia, General Coordinator of Latin American Association of Social Medicine

Mirta Roses Periago, Senior Advisor in Global Health Latin American & Caribbean Global Fund Board. Supporter of Chagas Coalition.

Reinaldo Guimaraes, Director of Brazilian Association of ABIFINA. Former Secretary of State.

REGIONAL OFFICE BOARDS

DNDi North America Board of Directors

Bennett Shapiro, Chair; Pure Tech Ventures, formerly with Merck & Co, USA

Darin Portnoy, Secretary; Montefiore Medical Center and Family Health Center, USA

Joelle Tanguy, Treasurer; International Federation of Red Cross and Red Crescent Societies, Switzerland

Shing Chang, former R&D Director, DNDi, and consultant, global health-related drug discovery and development, USA

Suerie Moon, Harvard School of Public Health and Harvard Kennedy School of Government, USA

James Orbinski, Centre for International Governance Innovation, Wilfrid Laurier University, Canada (until July 2014)

Bernard Pécoul, Drugs for Neglected Diseases *initiative* (DNDi), Switzerland

DNDi Latin America Board, Executive Members

Michel Lotrowska, Chair; Brazil

Vacant, Vice-president

Tyler Fainstat, Secretary; Médecins Sans Frontières (MSF), Brazil (until Sept. 2013)

Tatiana Zanotti, Secretary; Médecins Sans Frontières (MSF), Brazil (as of Oct. 2013)

• Fiscal Council

Nelson Faria de Oliveira, Lawyer

Marcus Manduca, PricewaterhouseCoopers

• Advisory board

Carlos Morel, Center for Technological Development in Health (CDTS/Fiocruz), Brazil (until Sept. 2013)

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Jorge Antônio Zepeda Bermudez, Production and Health Innovation, Fiocruz (as of Oct. 2013)

DNDi Japan Board of Directors

Haruki Yamada, Chair; Tokyo University of Pharmacy and Life Sciences

Koshin Nakahira, Nakahira Certified Tax Accounting Office, Japan (until March 2014)

Bernard Pécoul, Drugs for Neglected Diseases *initiative* (DNDi), Switzerland

Fumiko Hirabayashi, Drugs for Neglected Diseases *initiative* (DNDi), Japan

Laurence Vielhaure, Drugs for Neglected Diseases *initiative* (DNDi), Switzerland (as of April 2014)

DNDi LEADERSHIP

Executive Team

Bernard Pécoul, Executive Director*

Jean-François Alesandrini, Fundraising, Communication & Advocacy Director*

Graeme Bilbe, Research & Development Director*

Thomas Saugnac, Operations Director*

Geneva

Robert Don, Discovery & Pre-clinical Director*

Jean-Pierre Paccaud, Business Development Director*

Nathalie Strub Wourgaft, Medical Director*

Laurence Vielhaure, Finance & Planning Director*

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Rachel Cohen, Regional Executive Director, DNDi North America*

Suman Rijal (As of July 2014), Director, India Regional Office*

Bhawna Sharma, (Until Sept. 2014), Director, Research and Development Operations, India

Eric Stobbaerts, Director, DNDi Latin America*

Monique Wasunna, Director, Africa Regional office*

Fumiko Hirabayashi, Head of Liaison office, DNDi Japan

Visweswaran Navaratnam, Head of Liaison office, DNDi South-East Asia

* Member of the Strategic committee

DNDi Team Worldwide

GENEVA

Jorge Alvar, Fabiana Alves, Byron Arana, Clélia Bardonneau, Séverine Blesson, Raphael Bonacchi, Phouthasone Bouppha, Stéphanie Brailard, Patricia Caldwell, Thi-Hanh Cao, Gwenaëlle Carn, Pascal Carpentier, Eric Chatelain, Christine Crettenand, Brigitte Crotty, Graciela Diap, Violaine Dallenbach, Sophie Delhomme, Julia Fahrman, Anna Fitzgerald, Caroline Gaere Gardaz, Marion Genoulaz, Emilie Gutierrez, Alexandra Heumber, Nina Holzhauer, Jean-Robert Ioset, Michele Joannis, Dominique Junod Moser, Wendy Keller, Jean-Rene Kiechel, Fiona Knox, Marc Lallemand, Gabrielle Landry-Chappuis, Delphine Launay, Janice Lee, Sandrine Lo Iacono, Christophine Marty-Moreau, Janine Millier, Béatrice Mouton, Charles Mowbray, Nataliya Omelchuk, Claudia Pena Rossi, Sophie Raffle, Sylvie Renaudin, Isabela Ribeiro, Stephen Robinson, Ivan Scandale, Rebecca Schmitt, François Simon, Olena Sushchenko, Antoine Tarral, Donia Tourki, Olaf Valverde, Susan Wells

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Emi Nakamura

MALAYSIA

Richard George

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USA

Jennifer Duran, Richard Feiner, Robert Grembowitz, Ilan Moss, Oliver Yun



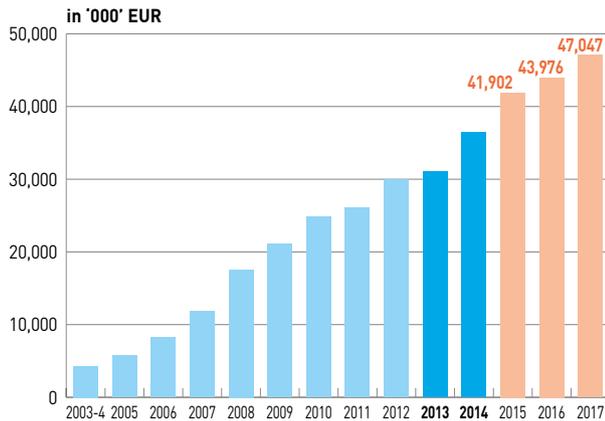
2014 KEY FINANCIAL PERFORMANCE INDICATORS

MAJOR GROWTH IN DEVELOPMENT AND TRANSLATION PROJECTS

Significant increase in R&D expenditure

DNDi expenditure totals EUR 217 million since its inception in 2003. In 2014, expenditure amounted to EUR 36.4million, +17% (+EUR 5.4M) as compared to 2013. This increase is principally due to fexinidazole projects expenditure that increased meaningfully in 2014 (+EUR 2.6 for HAT, +EUR 0.9 for VL and +EUR 1.1 M for Chagas Disease); and also to catch-up 2013 expenditure since the contingency plan implemented in 2013 incurred a relative stability between 2012 and 2013 (+4%). The operating gain of EUR 0.158 million is partly canceled because of exchange rate loss (EUR 0.103).

STATEMENT OF ACTIVITIES 2003-2014

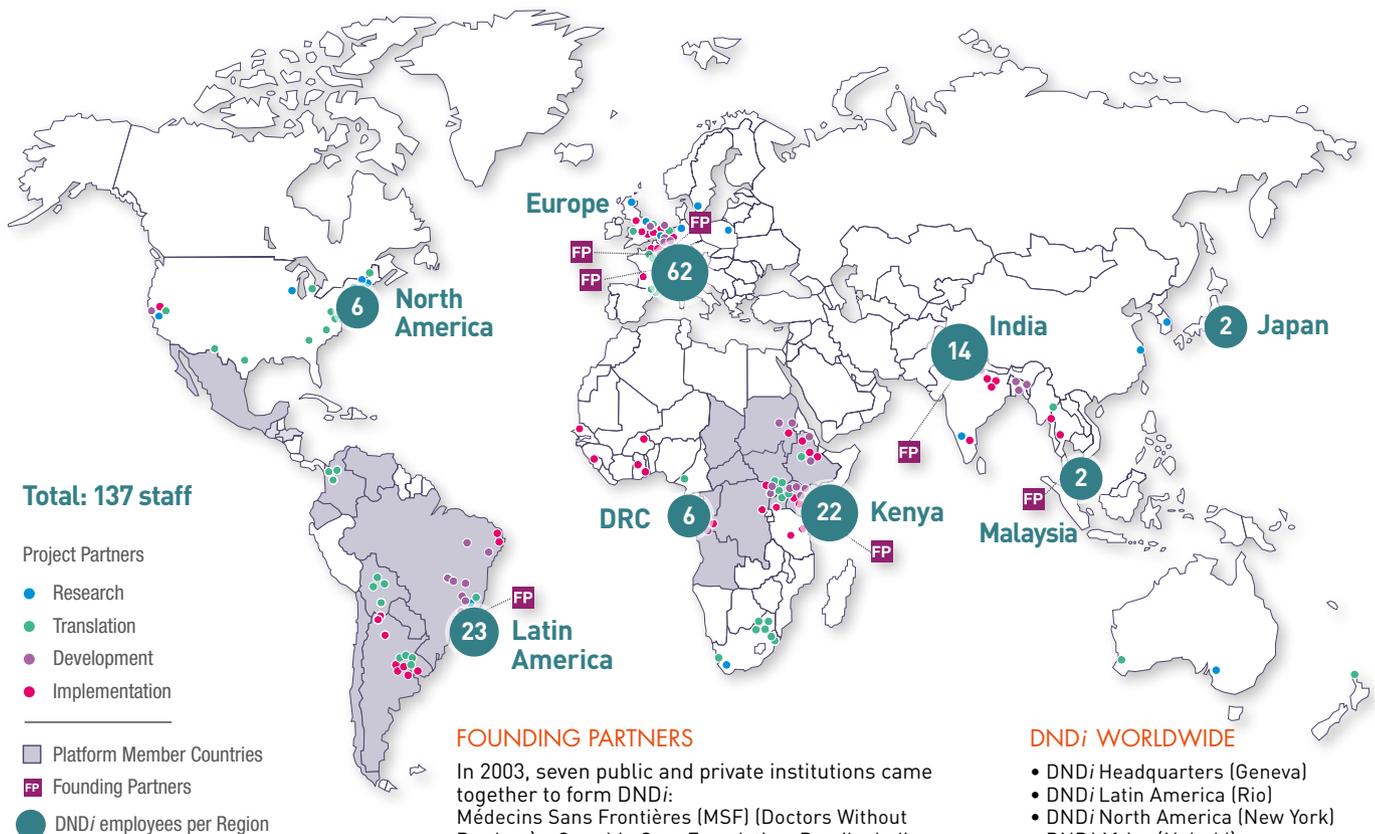
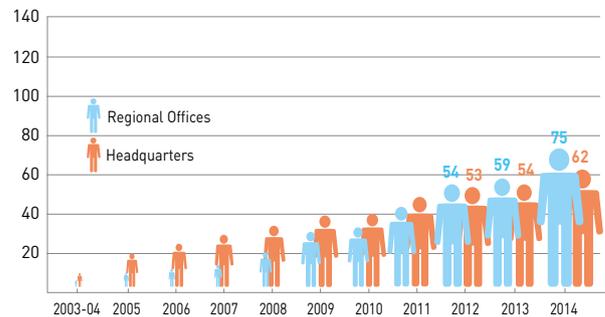


137 people worldwide, with almost all positions created in 2014 based in regional offices

In 2014, DNDi recruited an additional 24 people (in 2013 recruited six people) this represents an increase of 21%, mainly in regional offices (ROs): 16 people in Nairobi, New Delhi, Kinshasa, New York, and Rio de Janeiro (+27%) and eight people at Headquarters in Geneva (+15%). This trend, underway since 2012, reached a substantial level in 2014: RO staff (55%) is higher than headquarters staff (45%), in accordance with the business plan 2011-2018.

As of 2014 we calculate the exact amount of FTE working at DNDi (taking into account the start date, the end date and the percentage of time for each person working in DNDi). We reach a total of 117.42 FTE with 137 people working at DNDi.

HUMAN RESOURCES EVOLUTION 2004-2014



Total: 137 staff

Project Partners

- Research
- Translation
- Development
- Implementation

■ Platform Member Countries

■ Founding Partners

● DNDi employees per Region

FOUNDING PARTNERS

In 2003, seven public and private institutions came together to form DNDi: Médecins Sans Frontières (MSF) (Doctors Without Borders) • Oswaldo Cruz Foundation, Brazil • Indian Council for Medical Research, India • Kenya Medical Research Institute, Kenya • Ministry of Health, Malaysia • Institut Pasteur, France • The Special Programme for Research and Training in Tropical Diseases (WHO-TDR)

DNDi WORLDWIDE

- DNDi Headquarters (Geneva)
- DNDi Latin America (Rio)
- DNDi North America (New York)
- DNDi Africa (Nairobi)
- DNDi India (Delhi)
- DNDi Malaysia (Penang)
- DNDi Japan (Tokyo)
- DNDi in DRC (Kinshasa)



2014 KEY FINANCIAL PERFORMANCE INDICATORS

On track with Business Plan targets

2014 SOCIAL MISSION BREAKDOWN: 87.4% OF EXPENDITURE



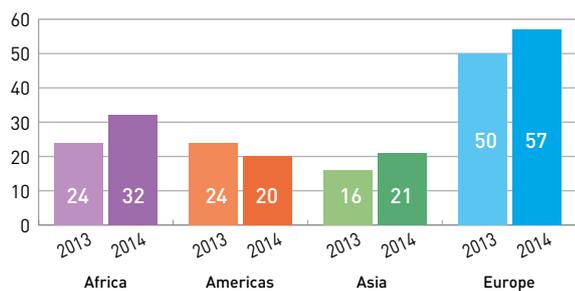
In 2014, DNDi's non-social mission ratio decreased from 13.5% in 2013 to 12.4% in 2014 because the growth of non-social mission expenditures was maintained at 8% (+EUR 0.3 M) compared to social mission expenditures that increased in the same time by 19% (+EUR 5.1 M).

The R&D ratio increased in 2014 (from 74.9% in 2013 to 76% in 2014) because of human African trypanosomiasis projects (an increase of 35%) and filaria projects (an increase of 70%).

In addition, activities of the platforms (other social mission: capacity strengthening) increased by 49% (+EUR 06 M) in 2014 because of major scientific events involving the platforms: a special scientific day during the LEAP platform, the HAT platform organized a symposium in Kinshasa and the Chagas disease platform participated in the International Congress of Parasitology (ICOPA meeting). This increase in regional activities resulted in a decrease in the communication activities at headquarters (-12%).

Stable increase in partnerships to support the growth of R&D activities

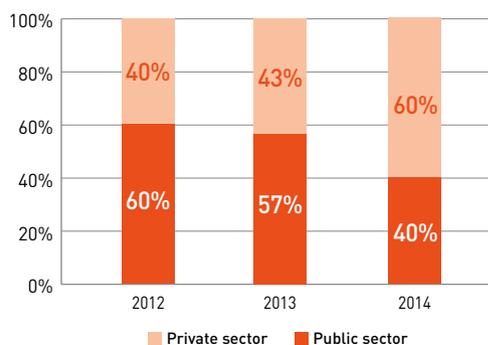
MAIN R&D PARTNERS & SERVICE PROVIDERS PER CONTINENT, with financial compensation over EUR 5,000



In 2014, the number of partners and service providers DNDi had business relations valuing over EUR 5,000 with increased by 14% (130 in 2014 as compared to 114 in 2013). The main increase was in Africa (+33%; with eight additional partners & service providers), reflecting the growth of the HAT activities in 2014 in DRC with additional clinical trial sites and in Asia (+31% with five new service providers) driven by the India implementation study (Bihar State support, partners for logistical support). In Europe, the increase of 14% is due to project progression related to our filarial activities and preparations for new VL combinations.

Number of partners and service providers: The private sector ratio is increasing significantly

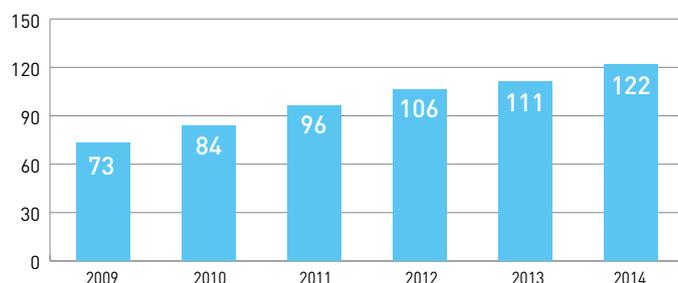
EVOLUTION OF NUMBER OF PARTNERS AND SERVICES PROVIDERS with financial compensation over EUR 5,000



Comparison of the public institutional sector (research institutes, public hospitals, academic groups, universities, PDPs, and other not-for-profit organizations) with the private sector (pharmaceutical and biotechnology companies and contract research organizations).

Steady growth in number of partnerships

NUMBER OF CONTRACTS SIGNED ANNUALLY*, **



*Except confidentiality agreements
 **Some new contracts may be extensions

Evolution of contracts finalized annually follows a trend similar to that of R&D partners & service providers with a financial compensation of over EUR 5,000. There is a regular annual increase between 5% and 15%, with 5% in 2013 and 10% in 2014. The 2014 table shows 74 new private partnerships versus 48 new public partnerships (which includes funding agreements).



R&D Model & Portfolio

Paving the Way to Improve R&D Outcomes for Neglected Diseases

Drug discovery and development is inherently challenging, and failure (or attrition) – while often providing a key source of knowledge for next steps – is inevitable. Given the high attrition rates in the R&D process, keeping a steady flow of backups to feed into the pipeline is of paramount importance. The early phase of research therefore requires not only access to large libraries of compounds to screen from, but also the knowledge, data, and expertise that go with them.

Experimenting new R&D pathways

In 2012, at the launch of the London Declaration, DNDi called for a move beyond the silos of bilateral agreements with pharmaceutical partners and

sought more 'out-of-the-box' mechanisms of working in new, multilateral ways. In order to accelerate the early phases of research, and to multiply effectiveness while potentially reducing cost, DNDi began to engineer a Drug Discovery Booster that would allow for cross-company screening. Unthinkable years ago, the partnership model of drug discovery is ripe for experimentation in innovation when the benefits for all can outweigh the risks.

In just over a decade, DNDi has developed partnerships with many major pharmaceutical and biotechnology companies that range from bilateral screening of selections of libraries, to the beginnings of multilateral screening projects. In addition, agreements can be targeted to a specific drug that has already

shown great promise for a particular disease, such as the agreement concluded last year with Bayer HealthCare for the development of emodepside as a potential oral macrofilaricide for onchocerciasis. Further down the pipeline, solid manufacturing and distribution partners are key to ensuring that when a drug passes through the threshold of attrition, and proves safe and effective in patients, access to the treatment is guaranteed.

R&D for policy change and access

The year 2014 saw some important results that show the extent to which evidence from clinical research can feed directly into policy decisions of ministries of health, and can help to ensure that regulatory approval is not hindered by lack of evidence. For example, SSG&PM pharmacovigilance study results in Africa were key for inclusion of the leishmaniasis treatment in **Ethiopia's** essential drug list, which is part of the regulatory requirements to ensure procurement and treatment access in this high-burden country. India awaited results of a pilot study for visceral leishmaniasis treatments in order to adapt its national guidelines, thus aligning with the WHO-

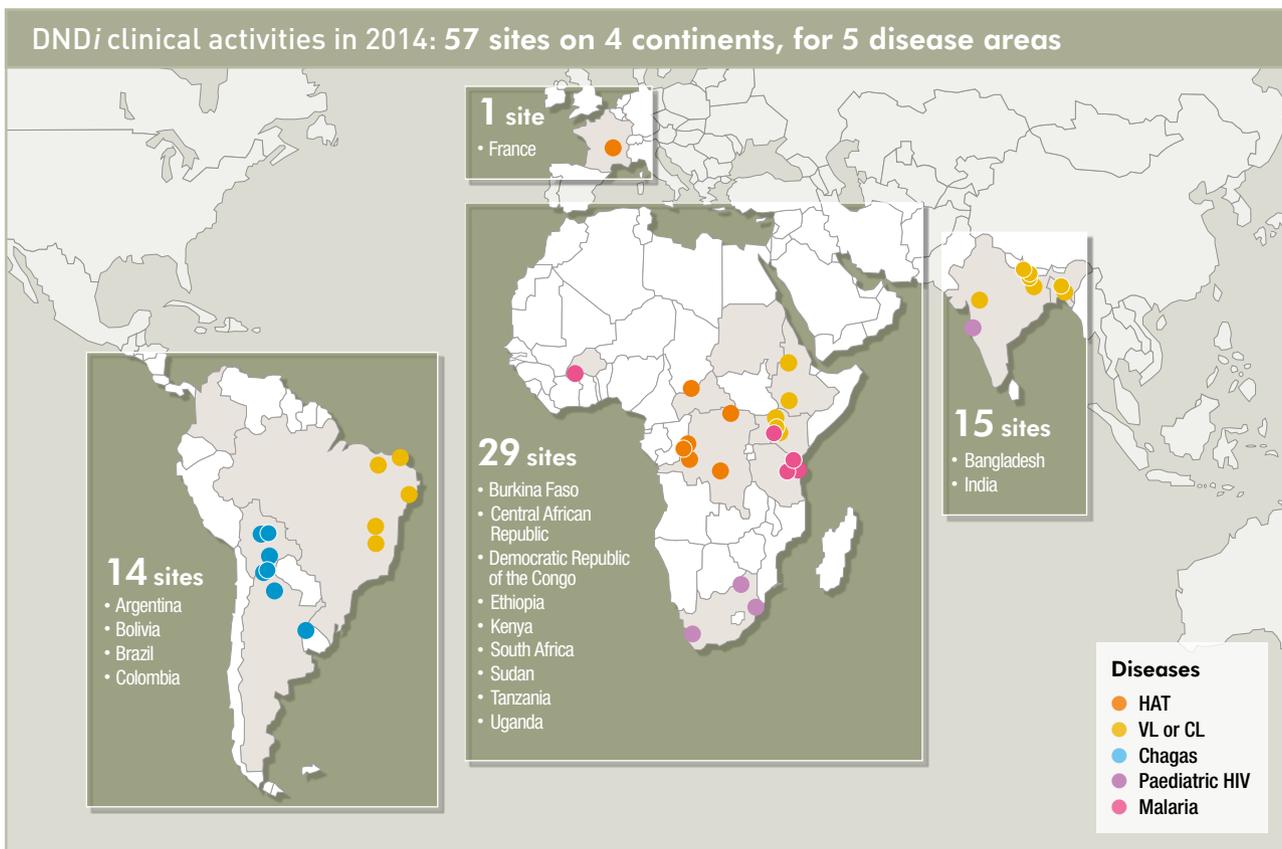
recommended treatments being tested in the trial. In addition, a comparable drug trial was completed in **Bangladesh**, with a view to similar policy changes, as was also the case in **Nepal**. These trials in Asia share the important outcome of replacing the use of miltefosine as a monotherapy. These examples show the extent to which national guidelines require in-country clinical testing of treatments, which then allow governments to take important policy decisions that affect their populations.

In the field of Chagas disease, support was given to prepare a deployment strategy in **Argentina, Brazil, Bolivia, Mexico, Colombia**, and the **USA**, in collaboration with the Pan-American Health Organization/WHO and national control programmes, through the work of the Global Chagas Disease Coalition, aimed at analysing and acquiring accurate numbers of cases to improve demand forecasting for treatments. Projects such as these can pave the way to greater access to existing treatments when appropriate, but also ensure that when new essential medicines reach fruition through clinical trials, they respond as quickly as possible to urgent public health needs.

DNDi Africa

DNDi India

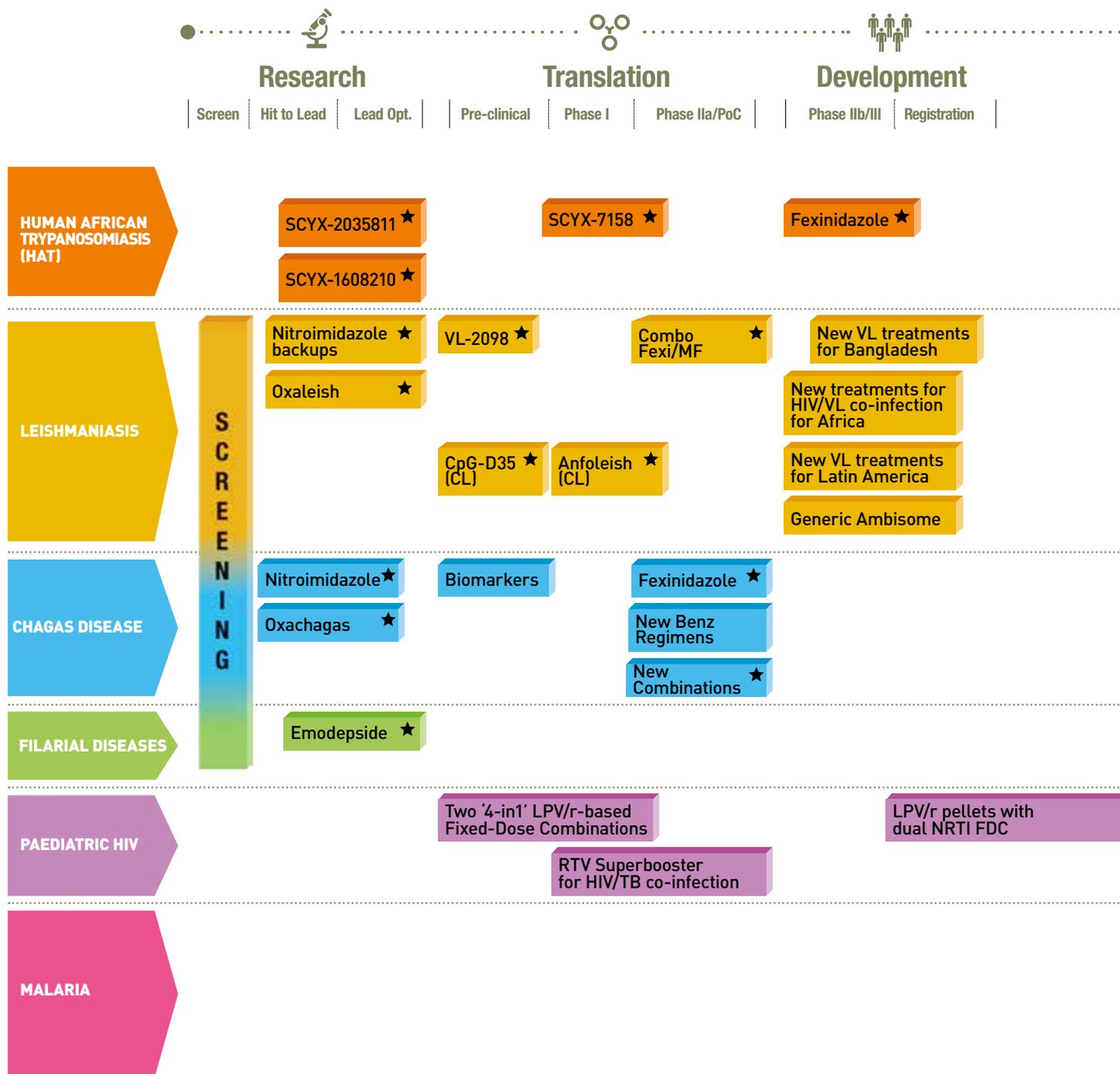
DNDi Latin America



Building a robust portfolio

Projects are divided into five categories:

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



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

- **New treatments developed from compounds with known antimicrobial/antiparasitic activities** aiming to maintain or improve efficacy and tolerability.
- **Compound repurposing for new indications of existing treatments in other diseases** (therapeutic switching).
- **Combinations or new formulations of existing drugs that are better adapted to field conditions and patient needs** (paediatric dosage forms, long-acting forms, new route of administration, fixed-dose combinations, co-packaging, or co-administration).
- **Geographical extension of existing treatments**, including completion of regulatory dossiers in new countries.



Implementation

Access

NECT
Nifurtimox-Eflornithine
Combination Therapy

SSG&PM
Sodium Stibogluconate
& Paromomycin
Combination Therapy
for VL in Africa

**New VL treatments
for India**

Benznidazole
Paediatric
dosage form

ASAQ FDC
Artesunate Amodiaquine
Fixed-Dose Combination

ASMQ FDC
Artesunate-Mefloquine
Fixed-Dose Combination

Key R&D milestones in 2014

HUMAN AFRICAN TRYPANOSOMIASIS (HAT)

- Oxaborole SCYX-7158 phase I trial nearing completion
- Fexinidazole: 359 patients recruited into a pivotal trial by end of year and two complimentary studies initiated: one for early second stage/first stage HAT in adults, and another for children aged 6 to 14 years

LEISHMANIASIS

- Pharmacovigilance results confirmed safety and high efficacy of SSG&PM to treat VL in East Africa
- Trials with combination treatments and AmBisome monotherapy confirmed safety and efficacy for kala-azar in Bangladesh (Phase III), with interim results from the pilot implementation study used by the Indian government to revise VL treatment policy
- Two nitroimidazole pre-clinical candidate drugs identified for VL
- VL-2098 safety studies completed
- CpG-D35 nominated as a pre-clinical candidate for CL

CHAGAS DISEASE

- Fexinidazole proof-of-concept trial initiated
- E1224/benznidazole interaction study undertaken
- A nitroimidazole series identified for optimization in Chagas disease

FILARIAL DISEASES

- Agreement signed with Bayer to develop emodepside as new oral treatment for onchocerciasis

PAEDIATRIC HIV

- Over 20 solid formulations of taste-masked LPV/r were tested in animal models
- Recruitment into RTV superbooster pharmacokinetics trial nearing completion

MALARIA

- Multicentre study in African children found ASMQ FDC to be as safe and efficacious as artemether-lumefantrine FDC
- Large scale field-monitoring trial with ASAQ FDC almost complete in partnership with MMV and Sanofi (results expected in 2015) and DNDi malaria projects formally handed over to MMV (in 2015)

Discovery

DNDi has a pragmatic approach to early stage drug discovery in order to maximize success from screening campaigns and minimize the attrition rate in subsequent hit-to-lead and lead optimization programmes, whilst working within the confines of limited resources.

Optimizing the number of 'hit' compounds

Screening against *Leishmania* parasites is particularly challenging and gives rise to very low hit rates, no doubt due in some part to the intracellular nature of the parasite. Core diversity libraries offer the best opportunities for maximizing the number of hits obtained. Screening for Chagas and visceral leishmaniasis (VL)

against these and other pharmaceutical or commercial libraries – including natural products, collections made up of particular classes, or of compounds with specific properties – generates 'hit' compounds for further evaluation and optimization. The Swiss Tropical and Public Health Institute (Swiss TPH) and the University of Antwerp (LMPH) serve as reference screening centres to ensure that screening methodologies are comparable, and that assays performed at different sites and with different groups meet the same standards.

Compound mining of well-annotated chemical compound libraries aims to identify new active starting points for VL, Chagas, and filariasis, for which data on chemistry, early pre-clinical profiling, druggability, and possibly even targets

Transmission



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



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



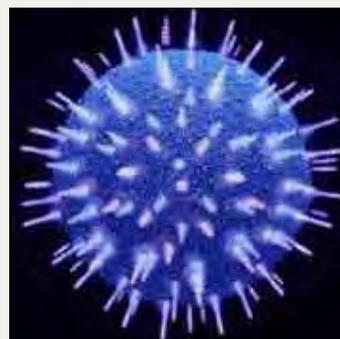
Leishmaniasis is a diverse and complex disease caused by more than 20 species of the kinetoplastid protozoan parasite. *Leishmania* parasites can be transmitted to humans by some 30 species of phlebotomine sandflies.



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



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



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

and modes of action are already available. Promising compound classes are identified by sampling a subset of representative compounds and testing for antiprotozoal activity. Classes successfully identified, and which form part of the DNDi's lead optimization programme, include oxaboroles (Anacor Pharmaceuticals), nitroimidazoles (TB Alliance and other compound sources), and aminopyrazoles (Pfizer), with numerous series from different companies in hit-to-lead research. Re-purposing of pre-clinical and clinical candidates – active compounds which have been previously developed for different therapeutic indications, and for which there may be a significant amount of pre-clinical or even clinical data available – has resulted in the successful development of fexinidazole, a nitroimidazole currently undergoing clinical development.

DNDi
Latin
America

Working with lead optimization consortia, and most recently within the DNDi Lead Optimization Latin America (LOLA) programme, DNDi aims is to advance new chemical classes identified through its screening programmes, and to develop backups in case of failure of more advanced compounds. Optimization efforts focus on, amongst others, improving antiparasitic activity, increasing tolerability and safety, and enhancing compound absorption and distribution in the body whilst mitigating breakdown and excretion.

Adopting a multilateral approach

With a view to rapidly expanding promising hits/hit series against *L. donovani* (leishmaniasis parasite) and *T. cruzi* (Chagas disease parasite), DNDi is moving from a bilateral to a multilateral approach with drug companies, and was in negotiation with a number of companies throughout 2014 with the aim of building a global consortium for its Neglected Tropical Disease (NTD) Drug Discovery Booster experiment. This will provide series with well-developed structure activity relationships (SAR) ready for immediate *in vivo* proof-of-concept studies or, where necessary, focused medicinal chemistry optimization to provide improved tools ready for *in vivo* studies.

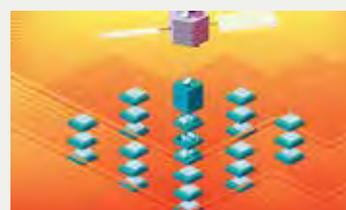
Snap shots of the NTD drug discovery booster experiment*



Today DNDi is identifying promising new compounds to develop effective drugs, by searching through segments of their partners' vast compound libraries, and testing them against infected cells.



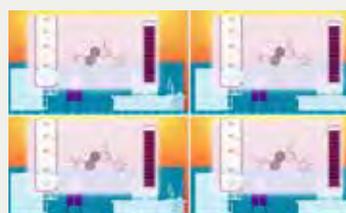
But working in this bilateral way, with limited capabilities and limited access means only a small amount of compounds are screened. Imagine this process being multilateral rather than bilateral.



The Drug Discovery Booster is an experiment in innovation and collaboration, between several pharmaceutical companies working together through DNDi, as a consortium, to achieve faster, cheaper, more efficient process.



As before, the same 'hit' is sent to each consortium member as the seed for growing into a collection of related molecules: a chemical series. But now there are several libraries, with each member looking simultaneously for similar yet potentially better structures than that of the seed.



Not only is the consortium cutting the time, but the quality of the hit and the series to which it belongs, is greater, due to the increased amount of information that went into its creation.



If it works, we hope it reveals another avenue to creating the drugs of tomorrow, today, by reducing the time and cost of development, and accelerating patient access to new life-saving drugs.

* To see the full animated film about the NTD drug discovery booster experiment please visit www.dndi.org/drugdiscoverybooster

Screening

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

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

2014 OBJECTIVES: Access and screen compound collections from pharmaceutical and commercial sources for kinetoplastids; secure a high-quality screening capacity; focus high throughput screening on identification of novel hit series for VL and Chagas

High-throughput screening (HTS) of core diversity libraries from several pharmaceutical companies (Sanofi, Takeda, Eisai, Merck, AbbVie) was completed against *Leishmania donovani* and *Trypanosoma cruzi* in 2014, in collaboration with screening partners (University of Dundee and Institut Pasteur Korea). Several new starting points are currently being followed up in hit profiling, annotation, and hit-to-lead programmes. A high-throughput screening assay which uses cidal axenic *L. donovani* was previously developed by the University of Dundee and is now part of DNDi's routine VL screening cascade there, enabling the screening of very large collections (more than 50,000 compounds).

Over 170,000 compounds screened in assays against leishmaniasis and Chagas disease in 2014

Several VL active series were identified from GlaxoSmithKline's global compound library screen and progressed through a hit-to-lead programme by DNDi during 2014 in collaboration with the University of Dundee. Furthermore, a screening collaboration agreement with the university signed in December 2014 aims to screen approximately 500,000 compounds against VL.

PARTNERS: AbbVie, USA; Anacor, USA; Astellas, Japan; AstraZeneca, Sweden; Bayer, Germany; Bioascent, UK; Bristol-Myers Squibb, USA; Celgene, USA; Centro Nacional de Pesquisa em Energia e Materiais (CNPEM) LN Bio, Brazil; Drug Discovery Unit (DDU) at the University of Dundee, UK; E.I. du Pont de Nemours, USA; Eisai Co. Ltd, Japan; GlaxoSmithKline, Tres Cantos, Spain; Institut Pasteur Korea (IPK), South Korea; Johnson & Johnson, USA; Laboratory of Microbiology, Parasitology, and Hygiene (LMPH), University of Antwerp, Belgium; London School of Hygiene & Tropical Medicine (LSHTM), UK; Medicines for Malaria Venture (MMV), Switzerland; Merck (MSD), USA; Microbial Chemistry Research Foundation, Japan; Northwick Park Institute for Medical Research, UK; Pfizer, USA; Pfizer Animal Health, USA; Sanofi, France; Sanofi Merial, USA; Special Programme for Research and Training in Tropical Diseases (WHO-TDR); Takeda, Japan; TB Alliance, USA; Swiss Tropical and Public Health Institute (Swiss TPH), Switzerland

Screening of repurposing libraries for filarial diseases

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

2014 OBJECTIVE: Identify one or two pre-clinical candidates

With the limited throughput of phenotypic screening against filarial nematodes, screening large chemical libraries is not possible and DNDi has negotiated access to smaller focused chemical series that are more likely to give rise to drug candidates. These include indications sets (compounds that have progressed to pre-clinical or clinical research but failed to reach the market), well-annotated sets of compounds (e.g. bioavailable sets or compounds which have been through lead optimization), chemical series from veterinary anti-infective research programs, or orthologous sets (compounds directed against human targets with similar gene sequences to the parasites). Over 7,000 compounds were screened *in vitro* (*Onchocerca*) and *in vivo* (*Litomosoides* model) in 2014, including from bioavailability sets (such as AbbVie, GlaxoSmithKline, Sanofi), and other libraries with specific properties or indications (for example NIH, MMV): approximately 100 compounds have shown activity. Those with appropriate pharmacokinetic profiles are being screened in rodent models of onchocerciasis and lymphatic filariasis. Drug repurposing is high risk, but with the potential to be highly rewarding if successful; and although most compounds will probably not be suitable as macrofilaricidal drugs, they will be a rich resource for developing new clinical candidates.

In addition to compounds that kill the adult worm, DNDi is also investigating compounds that target the endosymbiotic *Wolbachia* bacterium. A number of promising drug candidates for both targets are under review.

PARTNERS: Northwick Park Institute for Medical Research, UK; University Hospital of Bonn, Germany; AbbVie, USA; Sanofi Merial, USA; GlaxoSmithKline, UK; Novartis AH, Switzerland; Johnson & Johnson, USA; National Museum of Natural History Paris (MNHN), France; Medicines for Malaria Venture, Switzerland; National Institute of Health, USA; Merck Sharp & Dohme, USA

Over 7,000 compounds screened in 2014



Lead Optimization

OVERALL AIM: Establish a robust portfolio of drug discovery quality lead series for the three kinetoplastid diseases

2014 OBJECTIVES:

- Leishmaniasis – progress two new chemical classes into lead optimization
- Chagas disease – develop new tools (*in vitro/in vivo*) to improve translation to humans

With new chemical entities currently undergoing clinical development for human African trypanosomiasis (HAT), since 2012 the focus of screening and lead optimization efforts has been on identifying compounds to develop for VL and Chagas disease.

Many advances have been made during 2014. The first *in vivo* proof of concept for a new chemical class (VL series 12 – aminopyrazoles) from Pfizer was achieved in the early curative model of VL. A full lead optimization programme is now underway. Several compounds demonstrated excellent activity *in vivo*. Two advanced lead oxaboroles, DNDi-2166148 and DNDi-2310789, were identified and will be scaled up to enable exploratory toxicology studies, which could enable selection of one as an optimized lead for VL.

A programme is ongoing to identify nitroimidazole backups in case VL-2098 (see p.27) does not successfully complete pre-clinical testing. Over 200 analogues have been pre-

pared so far, and two backup compounds originating from different core structures have been selected and are being further profiled for *in vivo* efficacy and safety. Multiple hits from screening with several pharmaceutical partners or from other sources were progressed into hit confirmation and expansion studies. Several series have moved into the hit-to-lead stage for both Chagas disease and VL.

A number of pharmacokinetic and pharmacodynamic studies have been conducted in animal models of VL using existing and experimental drugs to build improved PK/PD models and ameliorate the translation of new drugs from discovery into clinical studies. In addition, a new screening cascade for Chagas disease has been implemented: the insight gained into the PK/PD relationship of compounds from additional *in vitro* assays coupled with a new *in vivo* model will enable compounds to be moved forward with more confidence.

PARTNERS: Centre for Drug Candidate Optimisation (CDCO)/ Monash University, Australia; Epichem, Australia; Griffith University (Eskitis), Australia; iThemba, South Africa; LMPH, University of Antwerp, Belgium; LSHTM, UK; Novartis Institute for Tropical Diseases (NITD), Singapore; Pfizer, USA; Sandexis, UK; WuXi AppTech, China; Pace University, USA; LNBio, Campinas, Brazil; University of Campinas, Brazil; TCG Life Sciences, Kolkata, India; AbbVie, USA



HAT in Democratic Republic of the Congo (DRC)

DNDi mobile teams arrive by boat and car, to a remote village in the region of Bandundu in DRC. Firstly the mobile teams explain the screening procedure to the local population. Then blood tests are carried out by a member of the mobile team. The blood samples are examined to determine the presence of trypanosomes which is responsible for HAT. From these results patients are identified who need follow up treatment.

DEVELOPING ORAL TREATMENTS FOR USE AT VILLAGE LEVEL

Sleeping sickness, or HAT, was on the verge of elimination in the 1960s, but relaxed surveillance, civil unrest, lack of investment and competing health priorities, combined with population displacement and poverty, led to a rise in the number of cases. The number of detected cases peaked in 1998, but efforts since then by the WHO, National Control Programmes, NGOs and other partners have improved detection, treatment, and control of the disease, resulting in significant decreases. HAT elimination as a public health problem (less than 1 case per 10,000 inhabitants in at least 90% of endemic foci) is targeted by the WHO for 2020. Part of this success is due to the introduction of nifurtimox-eflornithine combination therapy (NECT) in 2009, developed by DNDi, MSF, and partners, which is now the first-line treatment for the advanced stage of HAT in all endemic countries and is included in the WHO Essential Medicines List for adults and children. But there is no room for complacency.

Advancing towards oral treatments

While extremely successful, NECT is only effective against gambiense HAT, and still requires a lumbar puncture test to confirm the disease stage, and intravenous drug administration in hospital by skilled medical practitioners. There is also a desperate need for a less toxic treatment for rhodesiense HAT than the current melarsoprol. Furthermore, determination of the stage of the disease, necessary to decide which treatment should be used, is currently ascertained by microscopic examination of cerebrospinal fluid obtained by a painful lumbar puncture. Fexinidazole, in Phase III clinical development, is intended to be the first

fully oral treatment for HAT covering both stages of the disease and without the requirement of a risky lumbar puncture: as such it would represent a fundamental change in the management of the disease. It is expected that SCYX-7158 be administered as a one-dose-only treatment and may become part of a less specialized programme, integrated into other health activities, to be used as a village-focused treatment. The combination of a safe and effective oral treatment for both parasite sub-species and disease stages, together with a simplified diagnostic tool, would transform the health system approach to the disease, taking diagnosis and treatment out of the hospital and into the village.

Recruiting patients in neglected areas

In the meantime, the clinical trials conducted by DNDi and partners are, in themselves, contributing to improved patient care and access to treatment, by supporting the mobile teams who go out into the remote villages where patients live in order to screen, determine the stage, and ensure patients are referred for treatment. In 2014, DNDi treated in its trials 8.5% of all patients worldwide, and supported almost 25% of all populations screened by the mobile teams in the Democratic Republic of the Congo. While taking place in very remote areas, patient recruitment for the fexinidazole pivotal Phase II/III study was completed on time and at the highest international standards of drug trials, which is no small feat. It is vitally important that financing of mobile healthcare is sustained until the tools and expertise required to carry out these activities at the primary healthcare level become available.

21 million people living in areas at medium to high risk (above one case per 10,000 population)

36 countries in sub-Saharan Africa are endemic to the Tse-tse fly, but DRC reported 89% of all cases in 2013 Chad and South Sudan detected over 100 cases in 2013 each

3,796 cases reported in 2014

Disease is caused by *Trypanosoma brucei gambiense* (98%) and *T. b. rhodesiense* (2%) and occurs in two stages: the early stage 1 has non-specific symptoms and is often undiagnosed without active HAT surveillance, and the advanced stage 2, where the parasite crosses the blood-brain barrier, causing serious sleep cycle disruptions, paralysis, progressive mental deterioration and, without effective treatment, may lead to death. A lumbar puncture is needed to differentiate between stages to choose the appropriate treatment.

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

TREATMENT OF STAGE 1 HAT

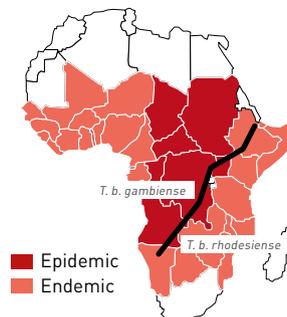
Pentamidine (1940) and **suramin** (1920s), require injections and are ineffective for stage 2.

TREATMENT OF STAGE 2 HAT

NECT – nifurtimox-eflornithine combination therapy (2009): a simplified therapy option for stage 2 *T. b. gambiense* HAT, requires 14 injections of eflornithine over 7 days together with 10 days of oral treatment with nifurtimox. Requires hospital administration.

Melarsoprol (1949): the only drug available for stage 2 *T. b. rhodesiense*, a toxic arsenic derivative that causes pain and fatal encephalopathy in up to 5% of patients who receive it.

Eflornithine (1981): today rarely used alone, requires an extended stay in hospital during administration (56 intravenous infusions taking two hours each to administer, over 14 days, four times per day).



WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?

At its inception, DNDi's **short-term strategy** was to make better use of existing treatments by combining drugs already in use. In September 2009, DNDi and partners **launched the first new treatment for sleeping sickness** in 25 years: nifurtimox and eflornithine combination therapy (NECT). NECT is included on the WHO Essential Medicines Lists (EML) for adults (since 2009) and children (since 2013), and all countries with endemic *T. b. gambiense* are now using NECT as first-line treatment for stage 2 HAT.

As a medium-term strategy, DNDi initiated a compound mining effort to identify existing chemical compounds with potential against kinetoplastid diseases, resulting in the rediscovery of fexinidazole, currently undergoing evaluation in a **pivotal Phase II/III study** in stage 2 HAT, with two complementary studies examining efficacy and safety in adults with stage

1 and early stage 2 HAT, and in children aged 6-14 years. Sanofi is the industrial partner.

In order to build a strong pipeline for long-term drug discovery, DNDi established a HAT Lead Optimization Consortium resulting in identification of the oxaborole **SCYX-7158**, which successfully progressed through pre-clinical development. **Phase I clinical** development is due for completion in 2015. Other backup compounds were evaluated by the consortium and remain available for further development if necessary.

In addition, DNDi supports the **HAT Platform** (see p. 52) that was launched in Kinshasa, Democratic Republic of the Congo (DRC) in 2005. The HAT Platform is a clinical research and access-supporting network that brings together key players in the fight against sleeping sickness in endemic countries and those involved in HAT from the

international research arena.

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

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

- **An oral, safe, effective treatment to be used for both stage two and stage one HAT**



SCYX-2035811

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

2014 OBJECTIVE: Project on hold

PROJECT START: June 2011

The nitroimidazole backup programme for HAT identified SCYX-2035811 as a suitable candidate for further exploration, and although initial results in animal models had shown excellent activity, further studies showed the doses tested to give insufficient cure. Given the progress of fexinidazole (Phase II/III) and SCYX-7158 (Phase I), further development was put on hold in 2013, and the project has now been stopped.

PARTNERS: TB Alliance, USA; University of Auckland, New Zealand; SCYNEXIS Inc., USA; Pace University, USA; Wuxi AppTech, China



SCYX-1608210

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

2014 OBJECTIVE: Project on hold

PROJECT START: April 2007

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

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



SCYX-7158

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

2014 OBJECTIVES:

- Complete reproxicology and plan additional pre-clinical studies
- Complete SCYX-7158 Phase I programme

The oxaborole SCYX-7158, originally provided by Anacor Pharmaceuticals, was found to be active against *T. brucei* at the University of California San Francisco; was further investigated by a consortium consisting of DNDi, Anacor, SCYNEXIS, Pace University, and Swiss TPH; and was selected as a promising pre-clinical candidate for HAT in late 2009. In pre-clinical studies, SCYX-7158 was shown to be safe and efficacious in treating stage 2 of the disease, as it is able to cross the blood-brain barrier. A tablet formulation demonstrated comparable pharmacokinetics to capsules used in a Phase I study and is therefore suitable for further clinical studies.

A reproductive toxicity package was completed in 2014, showing that the drug did not induce any abnormalities. In March 2012, SCYX-7158 became DNDi's first new chemical entity resulting from lead optimization efforts to enter clinical development. Due to the longer than expected half-life in humans, additional animal studies were performed, which supported continued testing with single ascending doses of treatments in healthy volunteers. Safety profiling above the expected therapeutic dose was ongoing at the end of 2014 with no identified cause for concern. Recruitment for a patient trial will begin in the DRC in 2016.

PARTNERS: Anacor Pharmaceuticals Inc., USA; SCYNEXIS Inc., USA; Penn Pharma, UK; BaseCon, Denmark; Optimed, France; PhinC Development, France; Cardiabase, France; SGS Cephaç, France; Patheon, UK; Accelera S.r.l., Italy



DEVELOPMENT



Fexinidazole

OVERALL OBJECTIVE: Develop and register fexinidazole as a new drug for the treatment of stage 2 HAT caused by *T. b. gambiense*, ideally also for stage 1 HAT and *T. b. rhodesiense*

2014 OBJECTIVES:

- Complete recruitment in pivotal study
- Initiate recruitment for study in adults with early stage two / stage one HAT
- Initiate recruitment for study in children between 6 and 14 years of age

PROJECT START: 2007

359 patients enrolled thus completing recruitment at **10** sites

The result of successful compound-mining efforts pursued by DNDi in 2005, fexinidazole entered clinical development in September 2009 and is now being co-developed with Sanofi: DNDi is undertaking clinical and pharmaceutical development whilst Sanofi is responsible for the industrial development and production. Preparations for product registration are underway.

A pivotal Phase II/III study, initiated in October 2012, aims to evaluate the safety and efficacy of fexinidazole compared to NECT, initially at eight sites in Democratic Republic of the Congo (DRC) and Central African Republic (CAR). Patient inclusion was halted in December 2013 in CAR due to conflict and security concerns in the country, and at one site in DRC due to a lack of new cases, although these sites remained open. A replacement site was opened in 2014 in DRC and, by the end of the year, the full cohort of 359 patients had been recruited. All trial safety data are regularly reviewed by the Data Safety and Management Board: serious adverse events for other indications were reviewed and no new risks identified. A strategy to accelerate the availability of fexinidazole was submitted to the regulators. Two complementary studies were initiated in May 2014 one for early stage 2 and stage 1 adult HAT patients, and another for children with HAT aged 6 to 14 years.

PARTNERS: BaseCon, Denmark; Bertin Pharma, France; Venn Life Sciences (previously Cardinal Systems), France; Cardiabase, France; Médecins Sans Frontières, and other HAT Platform members; Phinc Development, France; National Control Programmes of the Democratic Republic of Congo and the Central African Republic; RCTs, France; Sanofi, France; Swiss Tropical and Public Health Institute (Swiss TPH); SGS, France; Theradis Pharma, France

IMPLEMENTATION



NECT – Nifurtimox-Eflornithine Combination Therapy

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

2014 OBJECTIVE: Finalize NECT field study report and complete the project

PROJECT START: May 2004

630 patients enrolled thus completing recruitment

NECT, a co-administration of intravenous eflornithine and oral nifurtimox, was developed by Epicentre, MSF, DNDi, Swiss TPH, and the national HAT control programmes of the Republic of the Congo and DRC. It quickly became the first-line treatment for the neurological, or late, stage of the *T. b. gambiense* form of sleeping sickness, as it is simpler to administer and less expensive than eflornithine alone, making it more adapted to field conditions. DNDi and partners conducted the 'NECT-Field' study between 2009 and 2012, to document the safety, effectiveness, and ease-of-use of NECT in real-life conditions. Included in the 630 patients enrolled were children and pregnant or breast-feeding women. The final study report has now been received, the results will be submitted for publication in 2015 and the project has reached completion.

NECT was included on the WHO Essential Medicines List in 2009, and extended to the Essential Medicines List for children in April 2013. With the recommendation of NECT as first-line treatment in Nigeria in 2014, it is now available in all endemic countries, all of which receive free supplies from WHO via drug donations by Sanofi and Bayer.

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





Cutaneous Leishmaniasis, Colombia

About a year ago, Serafin believed he was about to die, 'I counted 98 ulcers in total at a certain point, the worst was the one on my forehead, very deep, I could no longer hide it and could not find work anymore' he recounts. In his village, the waiting period for the medicine was about two months, so Mr Moreno decided to spend the little money he had, leave his wife and children, and sought out treatment in Medellin, 180 kilometres away. Although the treatment was harsh with very difficult side effects, Serafin persevered.

TAILORED APPROACHES TO REGIONAL DIFFERENCES

Leishmaniasis is one of the most neglected diseases and is strongly associated with poverty and malnutrition. It is a truly global problem, endemic in over 100 countries and prone to outbreaks, with multiple *Leishmania* species spread by over 30 species of the sandfly and responsible for causing the disease. The number of people affected by the cutaneous form varies from 700,000 to 1,300,000 people annually. Visceral leishmaniasis (VL) is deadly if untreated, and there are an estimated 200,000 to 400,000 cases per year, mostly in children. Despite drawbacks in terms of their ease of administration and in some cases their sustainable supply, the current treatments are working well in Asia, but these same treatments are not as effective in patients in East Africa or Latin America. Even within Africa, there are regional differences in treatment response. The role as disease reservoirs of asymptomatic carriers and those affected by post-kala azar dermal leishmaniasis (PKDL) also needs to be better documented. Of increasing concern is that VL co-infection with HIV is causing the disease to spread into previously unaffected areas of southern Europe, Ethiopia, and India.

To address these complex disease scenarios, DNDi has put in place a three-fold strategy for R&D:

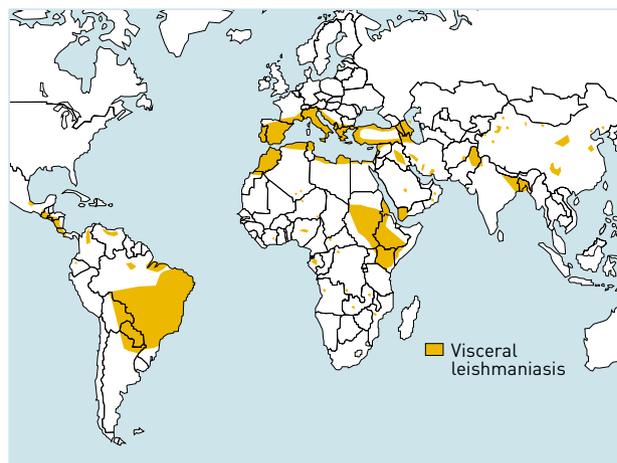
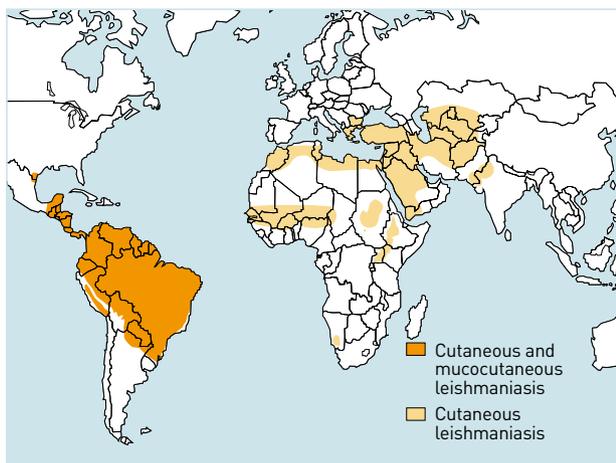
- The first part of the strategy comprises the improvement of patient access to existing treatments in each affected region. For example, the SSG&PM combination as a 17-day regimen is recommended by the WHO as first-line treatment for VL in Eastern Africa. The combination was assessed in real-life conditions in 3,000 patients, over half of whom were children. Results in 2014 confirmed the high safety and efficacy of the combination treatment.
- The second part of the strategy targets the improvement of treatment for specific disease scenarios, including HIV-VL co-infection notably in Africa, PKDL, and VL in Brazil.
- The third part of the strategy is to address the challenge of accelerating the translation of new chemical entities to clinical trials. In order to support sustained elimination of the disease new drugs that are oral-only combinations will be needed, which is why DNDi will continue to invest heavily in drug discovery activities.

In Bangladesh and India, where elimination is targeted by 2020, the WHO-recommended treatments were evaluated in both hospitals and primary healthcare centres to provide evidence to support national policy changes, notably to move away from miltefosine monotherapy to avoid developing resistance. Based on available interim data, the Indian government revised the VL treatment policy in September 2014, so that liposomal Amphotericin B (AmBisome®) alone is the first treatment option, with miltefosine/paromomycin in combination as the second option, a policy also reflected in Bangladesh and Nepal. Policy change and elimination efforts were supported politically at the regional level through a Memorandum of Understanding signed by Asian countries in 2005 and renewed in 2014. Patient access to treatment is part of a larger DFID-supported consortium for the Control and Elimination of Visceral Leishmaniasis, called the KalaCORE, launched in early 2015.

350 million people
at risk in
98 countries

0.7 - 1.3 million
cases of **CL** annually

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



CURRENT TREATMENTS AND THEIR LIMITATIONS

Existing drugs have serious drawbacks in terms of safety, resistance, stability, and cost. They have low tolerability, long treatment duration, and are difficult to administer.

- **Pentavalent antimonials:** (sodium stibogluconate – SSG – and meglumine antimoniate): used for VL and CL for over 60 years. Acquired resistance in areas of high prevalence and high transmission. Serious cardiotoxicity leading to death is well documented. In monotherapy, they require a 30-day parenteral treatment for VL. Registered in South East Asia, Latin America, and some Mediterranean and African countries.
- **Amphotericin B deoxycholate:** only an alternative treatment for VL in areas with high rates of unresponsiveness to antimonials where no other options are available. Need for hospitalization, constant renal monitoring of patients, 28-day duration of treatment, and infusion-related adverse events are notable drawbacks. Amphotericin B displays dose-limiting toxicity. Registered in South Asian countries and some countries in Africa and Latin America.
- **AmBisome®:** a liposomal formulation of amphotericin B, which is much safer and highly efficacious. A single infusion of 10mg/kg has shown a 96.4% cure rate in Asia. However, high cost and the need for a cold chain limit widespread use. Registered for VL in India, USA, and Europe and used as a second-line drug for the treatment of PKDL in East Africa at higher doses than in India and for VL in Brazil. It is also used to treat PKDL cases in Sudan. A donation to WHO facilitates free distribution of AmBisome® to the three countries involved in the elimination strategy in South Asia for primary VL patients, and as a rescue treatment for African VL. It is not properly evaluated for cutaneous leishmaniasis (CL).
- **Miltefosine:** oral drug registered for use in India for VL, but is expensive and requires 28-day treatment. Major limitations include low compliance, risk of resistance, and contraindication in pregnancy and mandatory contraception for women of child-bearing age for the duration of therapy and three months beyond. A recent study in Asia indicated an emerging lack of efficacy in monotherapy in the region, probably associated with drug underexposure in children. For CL, currently approved for lesions caused by three *Leishmania* species. Miltefosine is not registered in many endemic countries and consequently not available.
- **Paromomycin (PM):** a low-cost parenteral formulation for VL that requires three weeks of painful intramuscular administration is also highly efficacious in Asia but is associated with some degree of renal and ototoxicity with limited efficacy as monotherapy in East Africa.



WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?

■ VISCERAL LEISHMANIASIS

DNDi's **short-term approach** for VL was to develop new treatments by combining existing drugs and/or shortening treatment duration in order to increase tolerability, reduce burden on health systems, and offer greater affordability, whilst also preventing or delaying emergence of resistance. Another objective is the geographical extension of existing drugs in other countries and regions. In 2010, DNDi and LEAP partners **delivered the SSG&PM combination therapy for East Africa**, now recommended as first-line treatment for VL in the region. SSG&PM has been included in the national guidelines of Sudan, South Sudan, Ethiopia, and Kenya. PM is registered in Uganda (2011) and Kenya (2013), and is in the process of registration in Sudan and Ethiopia. In India, a Phase III trial demonstrated the efficacy of combination therapies of already-registered drugs (see p. 30). In 2014, the government of **India** recommended use of single-dose AmBisome® as a first option and paromomycin/miltefosine combination as the second option for treatment instead of using miltefosine as monotherapy. DNDi has collaborated with the National Control Programmes of India and Bangladesh, MSF, the Bihar State Health Society, and the Indian Council for Medical Research to assess the effectiveness and safety of these new treatments at the primary healthcare level and facilitate their introduction. In **Latin America**, DNDi is

■ CUTANEOUS LEISHMANIASIS

For CL, DNDi's objective is to develop short, safe, efficacious, affordable, and field-adapted treatments, at least for lesions caused by *L. tropica* and *L. braziliensis*. As a **short-term** strategy, DNDi is developing a topical treatment based on amphotericin B, and aims to improve treatment strategies using currently available treatment modalities in combination. In the **medium to long term**, DNDi aims to develop an oral drug and an immune-modulator for use in combination with chemotherapy. This novel approach aims to initially eliminate parasites with

participating in a study sponsored by the Brazilian Innovation Agency (FINEP) to evaluate the safety and efficacy of Glucantime®, AmBisome®, and amphotericin B as monotherapies, and of AmBisome®/Glucantime® combination to treat VL patients. The national control programme has extended the use of AmBisome® as second-line treatment based on the interim safety data from this trial.

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

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

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

chemotherapy, followed by enhancement of the patient's immune response with an immune-stimulating agent.

A new topical or oral treatment for CL would ideally be **efficacious against all species**, show at least **95% efficacy**, be **easy to use, short course** (14-28 days), compatible for **combination therapy**, produce **minimal scarring**, be **safe** in pregnant and breastfeeding women, **affordable** and **adapted to tropical climates**.

In addition, DNDi supports the **Leishmaniasis East Africa Platform** (LEAP) (see p. 51). A new VL treatment for adults and children based on a new chemical entity would ideally be **efficacious against all species of Leishmania in all regions** as well as **against resistant strains**, have at least **95% efficacy**, be **short course** (once a day for 10 days oral; or 3 shots over 10 days), **easy to use**, compatible for **combination therapy**, **safe** in pregnant and breastfeeding women and for immunocompetent/immunosuppressed patients, **affordable**, and **adapted to tropical climates**.



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

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

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

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

RESEARCH



Nitroimidazole series

OVERALL OBJECTIVE: Select a backup candidate to move forward in case VL-2098 fails in preclinical toxicology studies or clinical trials

2014 OBJECTIVE: Complete profiling of nitroimidazole back-ups to VL-2098 and then put on hold

PROJECT START: July 2010

In 2010, the Global Alliance for Tuberculosis Drug Development (TB Alliance) and DNDi entered into a first-ever royalty-free license agreement between two not-for-profit drug developers, with the TB Alliance granting rights to DNDi to develop a class of potential anti-TB compounds showing promise for other neglected diseases, such as VL. Within TB Alliance's nitroimidazole library, VL-2098 was identified as a candidate with potent efficacy against VL (see opposite), and a focused programme is ongoing to identify a backup pre-clinical candidate in case VL-2098 does not successfully complete pre-clinical or clinical testing.

Two potential backups belonging to two sub-series of nitroimidazooxazines (DNDi-0690 from the 7-substituted sub-series; DNDi-8219 from the PA-824 subseries) have been selected for further profiling, as they showed good efficacy *in vivo*, better solubility, and lower hERG potential. Pre-CMC activities to support comparative exploratory toxicity study with VL-2098 were initiated and are on track.

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



Oxaleish series

OVERALL AND 2014 OBJECTIVE: Select an oxaborole for pre-clinical evaluation

PROJECT START: 2009

DNDi and Anacor have been working together over the last few years to identify oxaborole compounds, initially for the HAT programme, and this has expanded to include both leishmaniasis and Chagas disease. DNDi-2035804

had shown excellent reductions in parasitemia in an animal model of VL using *L. infantum*. However, the compound failed in exploratory toxicology testing and has now been replaced with other lead compounds.

PARTNERS: Anacor Pharmaceuticals, USA; LMPH, University of Antwerp, Belgium; WuXi AppTech, China; Sandexis, UK; LSHTM, UK

TRANSLATION



VL-2098

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

2014 OBJECTIVE: Complete reproductive toxicology pre-clinical safety and toxicology studies and manufacture GMP (Good Manufacturing Practice) API (Active Pharmaceutical Ingredient)

PROJECT START: July 2010

From the initially selected 70 nitroimidazoles belonging to four chemical sub-classes, VL-2098 was identified as a very potent and safe molecule and was selected for in-depth evaluation of its efficacy, pharmacokinetic, and early safety profile on the basis of these preliminary results. This compound is potent against *L. donovani in vitro* and shows efficacy in acute and chronic VL animal models after oral dosing. Toxicology and pharmacokinetic studies were completed in 2014 and a batch of high purity active pharmaceutical ingredient (API) successfully manufactured.

Results performed in three animal species indicated a link between dose, length of treatment, and testicular toxicity. Further studies of longer duration will be undertaken in the animal model most sensitive to the therapeutic window in order to determine the safety margin, and a decision on whether to move the candidate forward will be taken in 2015.

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

CpG-D35 (CL)

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

2014 OBJECTIVE: Advance the development of CpG-D35

PROJECT START: June 2014

DNDi initially undertook a survey to identify potential treatments for CL, evaluating available evidence for potential efficacy and drug availability. The U.S. Food and Drug Administration (FDA) had previously undertaken the development and optimization of CpG-D35 and found it to be efficacious in an animal model, and was willing for DNDi to continue its development. The project aims to combine the use of antimicrobials with a novel innate immune modulator that activates the immune cells embedded in the skin and so boosts parasite clearance.

The development of CpG-D35 as an adjunct to chemotherapy for cutaneous leishmaniasis and post kala-azar dermal leishmaniasis (PKDL) has been selected as one of the WHO's CEWG Health R&D Demonstration projects (see p.56), undertaken with the US FDA and the University of Osaka.

The project has four phases: 1) production and characterization of GMP-grade CpG-D35; 2) pre-clinical studies in two species to assess potential toxicities; 3) proof-of-concept clinical trials for CpG-D35 and the combination of CpG-D35 with antimonials establishing safety profile and optimal dose; and 4) establishing efficacy across *L. major* species. The project will demonstrate 'delinkage' of R&D costs and product price through equitable or humanitarian licensing in an agreement to be signed with the FDA which, as part of its mission, has no interest in recovering the agency's investments in R&D.

CpG-D35 is easy to produce at a reasonably low price and was nominated as a pre-clinical candidate in 2014.

PARTNERS: University of Osaka, Japan; US FDA, USA



Anfoleish (CL)

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

2014 OBJECTIVE: Continue exploratory trial to evaluate safety, PK, and efficacy of Anfoleish for the treatment of uncomplicated CL in the New World.

PROJECT START: September 2011

22 patients recruited at 2 sites

The rationale for development of a topical formulation of amphotericin B was to provide a treatment to be applied locally at the CL lesion, showing high anti-parasitic effect, but without the systemic toxicity associated with amphotericin B. Anfoleish, a cream containing 3% amphotericin B, was selected by DNDi for clinical development after completion of pre-clinical assessments. A Phase Ib/II open-label, randomized, non-comparative, two-arm exploratory study is being conducted in Colombia. The first subject was enrolled on 1 February 2014 and it is expected that the initial step (30 patients) will be completed in April 2015. If no safety concerns are identified, 50 additional patients will be included. Initial efficacy will be determined on all 80 patients by measuring the percentage of subjects with initial clinical cure at day 90.

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

PARTNERS: PECET (Program for the Study and Control of Tropical Diseases), Universidad de Antioquia Medellin, Colombia; Humax Pharma, Colombia

Combo Fexi/MF

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

2014 OBJECTIVE: Continue Phase II proof-of-concept fexinidazole study in Sudan

PROJECT START: September 2012

14 patients recruited at 1 site

Fexinidazole has shown potent activity against *L. donovani* *in vitro* and *in vivo* in a VL mouse model, assessed in studies in healthy volunteers and shown to be safe when given as a single dose or as repeated dosing after 14 days. The Phase II proof-of-concept study with fexinidazole for the treatment of primary VL patients in Sudan aimed to estimate the efficacy of fexinidazole in adult primary VL patients, and to establish safety and the pharmacokinetic/pharmacodynamic (PK/PD) profile. The doses selected for the study were identical to those of the Phase II/III HAT trial. Enrolment began in November 2013 and ended in May 2014, with a total of 164 patients screened and 14 enrolled in the study. Efficacy was not conclusive for the majority of patients although an initial parasite clearance was observed. The study was interrupted and new regimens including fexinidazole are under investigation

An expert safety review of the Phase I data concluded that it would be safe to increase the dose. Safety results from trials in HAT and Chagas disease, expected in 2015, will be taken into account before undertaking any further trials.

Miltefosine is the only other oral drug currently available and will be evaluated in combination with fexinidazole in East Africa. A previous study carried out in Africa indicated miltefosine underdosing in children compared to adults, and that dose adjustment is required. A pharmacokinetic and safety study of miltefosine in children was submitted to ethics committees in Uganda and Kenya. Results should be available at the same time as the PoC fexinidazole trial results.

PARTNERS: Kenya Medical Research Institute (KEMRI), Kenya; Institute of Endemic Diseases (IEND), University of Khartoum, Sudan; MSF; Leishmaniasis East Africa Platform (LEAP); BaseCon, Denmark; Utrecht University, The Netherlands; Koninklijk Instituut voor de Tropen, The Netherlands



DEVELOPMENT



New VL treatments – Bangladesh

OVERALL OBJECTIVE: Provide evidence for adoption of combination treatment as second line option in national policy

2014 OBJECTIVES: Provide evidence for policy change to include combinations and complete six-month patient follow-up of Phase III study

PROJECT START: July 2010

The Phase III trial conducted by DNDi and its partners in India demonstrated the efficacy of combination therapies based on AmBisome®, miltefosine, and paromomycin. In Bangladesh, this two-step Phase III study (first in hospital settings, then in primary healthcare centres) in 602 patients uses the same combination therapies. Six-month follow-up was completed in April 2014 and sites closed in June. Results, presented in Dhaka in October 2014, showed all tested treatments demonstrated excellent cure rates and were well tolerated by patients, in support of policy change in the country. The Clinical Study Report was finalized by the end of the year.

PARTNERS: Ministry of Health and Family Welfare, Bangladesh; GVK Biosciences, Bangladesh; Pvt Ltd, India and Bangladesh

HIV/VL for Africa

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

2014 OBJECTIVE: Initiate HIV/VL co-infection study in Ethiopia and conduct three interim analyses

PROJECT START: September 2011

20 patients recruited at 2 sites

This study aims to evaluate the efficacy of a combination regimen of AmBisome® with miltefosine, and of AmBisome® (at a higher dose) monotherapy in Ethiopian patients co-infected with VL and HIV. A secondary objective is to assess relapse-free survival one year after initial cure (after initial cure at day 28 or at day 56 after extended treatment). Viral load and CD4 count will be measured in all patients, and the pharmacokinetics of antiretrovirals, AmBisome®, and miltefosine, as well as immune function markers, will be examined in a subset of patients.

In anthroponotic transmission areas, the WHO recommends secondary prophylaxis with drugs not given in treating primary VL cases, to avoid resistance development. A second, follow-up study, sponsored by the Institute of Tropical Medicine-Antwerp, Belgium, will assess the use of pentamidine as secondary prophylaxis for HIV/VL co-infected patients.

Importation problems encountered with AmBisome®, after a drug recall issued by Gilead, caused a temporary halt to the trial in 2013. These studies are taking place at Gondar and Abdurafi in Ethiopia. Enrolment was initiated in August

2014 and 20 patients had been enrolled by the end of the year, 10 of whom were included in the sub-studies. The arm with AmBisome® alone has been dropped due to lack of efficacy, leaving AmBisome®/miltefosine as the only choice in the study.

PARTNERS (AFRICOLEISH): LSHTM, UK; Institute of Tropical Medicine-Antwerp, Belgium; MSF, The Netherlands; Addis Ababa University, Ethiopia; Gondar University, Ethiopia; LEAP; Slotervaart Hospital, The Netherlands Cancer Institute, The Netherlands; Utrecht University, The Netherlands



New VL treatments – Latin America

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

2014 OBJECTIVE: Finalize patient recruitment in Phase IV trial

PROJECT START: February 2011

378 patients recruited at 5 sites

Approximately 90% of VL cases in Latin America occur in Brazil, and most of them are children. In 2013, Brazil reported 3,253 new cases with a fatality rate of 6.7%. DNDi is supporting the implementation of a Phase IV clinical trial, sponsored by the Brazilian Ministry of Health, to assess treatments for VL. In 2014, patient recruitment was stopped following DSMB recommendations based on the interim analysis of 50% of the recruited patients. The five trial sites concluded six months follow-up of the 378 patients enrolled in the study and final study analysis will be available in 2015. Evidence provided by this project will guide policies on the treatment of VL caused by *L. infantum* in Brazil. The Ministry of Health already changed treatment recommendations in 2013, expanding the use of AmBisome® as a second-line treatment, based on interim safety data provided by the trial.

PARTNERS: Rene Rachou Research Institution – Fiocruz-MG, Brazil; Paediatric Hospital Joao Paulo II – FHEMIG, Brazil; Brasilia University, Brazil; Montes Claros State University, Brazil; Piau Federal University, Brazil; Sergipe Federal University, Brazil; Leishmaniasis Control Programme/Ministry of Health, Brazil; Universidade Estadual do Rio de Janeiro, Brazil; Hospital Sao José de Doencas Infecciosas, Brazil



Generic AmBisome

OVERALL OBJECTIVE: Have pre-qualified generic AmBisome® by 2017

2014 OBJECTIVE: Project on hold

PROJECT START: November 2013

AmBisome®, an effective but expensive treatment for VL, is still under patent protection in the US until 2016 but no longer in Europe. Several producers in India and elsewhere are in the process of developing generic versions of AmBisome®; however, a thorough analysis on the composition of new products, their physico-chemical characteristics, quality-assurance, and GMP production is needed to assess whether these products have the qualifications to characterize a potential generic version of AmBisome®. At present, WHO has not set any standards for the regulatory evaluation of liposomal drugs and there is a lack of regulatory guidance in stringently regulated countries. A second producer of quality-assured, liposomal amphotericin B would ensure treatment availability for the next decade, particularly given Gilead's past problems (batch recall in 2013), and hopefully competition would lead to lower prices.

With the prospect of an alternative FDA-approved generic AmBisome® being available shortly, together with falling numbers of patients in Asia whose needs are adequately covered by a Gilead donation programme through the WHO, this project has been put on indefinite hold.

PARTNER: MSF



SSG&PM

OVERALL OBJECTIVE: Development of short-course (combination) treatments from current drugs, registration of products, and facilitation of access through policy change

2014 OBJECTIVE: Complete SSG&PM pharmacovigilance study and complete registration for SSG&PM in East Africa

PROJECT START: November 2004

In 2010, DNDi and LEAP successfully showed that the combination of SSG and PM (17 days) was as efficacious as SSG monotherapy (30 days); this shorter course lessens the burden on patients and health systems, and is more cost effective. Since then, DNDi and LEAP have worked with local ministries of health to ensure recommendation and uptake of the new treatment following its recommendation as first-line therapy for VL patients in Eastern Africa by WHO. SSG&PM implementation has begun in the region, and the treatment is included in the national VL guidelines of Sudan, Kenya, and Ethiopia. SSG&PM treatment is part of the national programme in South Sudan and was rolled out in public health structures and MSF centres during the recent massive outbreak.

A large pharmacovigilance study with MSF and Ministry of Health sites in Ethiopia, Sudan, Kenya, and Uganda to monitor safety and efficacy of SSG&PM was undertaken between 2011 and 2013, recruiting 3,000 patients. Study results obtained in 2014 showed a 95% cure rate. The results were presented in September at the LEAP conference in Ethiopia and disseminated to stakeholders.

PARTNERS: Kenya Medical Research Institute (KEMRI); IEND, University of Khartoum, Sudan; University of Makerere, Uganda; Addis Ababa University, Ethiopia; Gondar University, Ethiopia; LSHTM, UK; Ministries of Health of Ethiopia, Sudan, Kenya, and Uganda; MSF; i+ solutions, The Netherlands; LEAP

New VL treatments for India

OVERALL OBJECTIVE: To develop one to two new (combination) treatments and support recommendations from the authorities in the main endemic countries

2014 OBJECTIVE: Progress significantly in the implementation study and completion of patient follow up from the pilot phase

PROJECT START: December 2006

1761 patients
recruited
at **12** sites

The Phase III trial conducted by DNDi and its partners in 2010 demonstrated the efficacy of combination therapies based on AmBisome®, miltefosine, and paromomycin, and an additional study showed the efficacy of single-dose AmBisome® given as an intravenous infusion. To facilitate the introduction of these new treatments for VL in South Asia, DNDi is carrying out effectiveness studies, including a pilot project in the Bihar State of India implementing combination therapies at the primary healthcare level, and single-dose AmBisome® at the hospital level. The project is monitoring pharmacovigilance as well as treatment effectiveness of the different treatment options when used outside a clinical trial by the public sector. The study began in 2012 in two districts in India. A total of 919 patients were enrolled during the pilot phase. In 2014, the study entered into the implementation phase, which aims to treat 6,000 more patients. The trial was expected to end in 2015 and results made available.

In August 2014, the Indian National Roadmap for Kala-Azar Elimination recommended use of single dose AmBisome® (shown to be 96.7% efficacious in the implementation study) as a first option treatment for the treatment of VL patients in high endemicity areas, with paromomycin and miltefosine as a second option in areas of lower endemicity. This represents an important policy change in removing the use of miltefosine monotherapy. Following a Technical Advisory Committee meeting, it was agreed that the implementation study would stop recruiting. However, DNDi will continue the 12-month follow up of patients who were included in the study.

PARTNERS: Indian Medical Research Council (ICMR); Rajendra Memorial Research Institute of Medical Sciences (RMRI), India; Kala-Azar Medical Research Centre, India; State Health Society, Bihar (BSHS), India; National Vector Borne Disease Control Programme (NVBDCP), India; MSF





Chagas, Bolivia

A young mother, Maria, was diagnosed with Chagas disease three years ago. Her baby was born with Chagas and both started treatment. Exams from the baby showed that treatment with benznidazole was a success. He is now free of Chagas disease. Treatment in children has an efficacy rate above 90% and children have a much better tolerability than adults. In 2010, DNDi and partners delivered a paediatric formulation of benznidazole, making treatment easier for children.

INCREASING ACCESS TO ADAPTED TREATMENTS

Chagas disease is transmitted predominantly through contact with the faeces of infected triatomine bugs, deposited on the skin during a blood meal. These insects typically hide in crevices of poorly-constructed homes in rural or suburban areas. Blood, organ transplant, and congenital transmission also occurs, and cases of oral transmission through ingestion of food infected by bugs have recently been documented.

The distribution and impact of the disease varies from country to country. In Bolivia, it is likely that the majority of the population is affected by Chagas disease: prevalence estimates vary between 40-70% of the adult population, and are difficult to assess more accurately without sero-epidemiological surveys, given the frequently asymptomatic nature of the chronic form of the disease. In Brazil, only 2% of the population is infected, although given that the population exceeds 200 million people, the actual numbers affected are huge.

Maximizing the impact of diagnosis and treatment

Until recently Chagas disease was confined to the Americas, principally Latin America, but over the years it has spread to North America and Europe due to population flows. Today, one of the most important areas of work in Chagas disease is access to medicines and diagnosis. The majority of patients with Chagas disease are asymptomatic and just a very small fraction of those affected are being detected and treated. The numbers are staggering, with estimates of less than 1% of Chagas disease patients receiving treatment with either

benznidazole or nifurtimox. A number of factors are involved, but there is a clear need for concerted multi-disciplinary action to change the current situation. Despite growing evidence of drug efficacy and the different operational approaches employed, no medical or operational consensus has been reached in many endemic countries. It is necessary and imperative to ensure registration of existing drugs against Chagas disease in all endemic countries. In order to evaluate which deployment models have the greatest local impact, DNDi and partners will initiate a series of pilot projects in strategic countries which aim to assess the impact of scaling up diagnosis and treatment, with integration into local health systems. Different delivery models will be evaluated and defined with local stakeholders, from governments to academia and civil society, and are expected to be sustainable and replicable in similar contexts.

DNDi, as part of the Global Chagas Coalition and with other partners, advocates strongly for increased diagnosis and access to treatment across all age groups, but notably infants, young children and non-pregnant women of child-bearing age. Recent data indicate that treating the latter prevents transmission of Chagas disease during pregnancy, and is therefore an important disease control strategy.

There is also a need for international registries to support surveillance of diagnosis and treatment of chronic cases, pharmacovigilance, and long-term follow-up for a better understanding of Chagas epidemiology and distribution, as well as to identify major gaps in existing data.

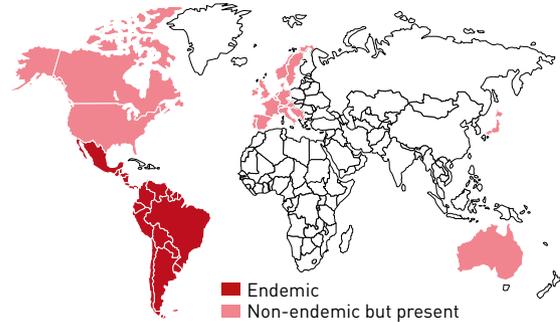
70 million people
at risk in the region

Endemic in
21 countries
in Latin America

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

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

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



WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

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

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?

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

As a **medium-term** strategy, DNDi has been assessing known families of compounds such as the new azole antifungal drug, E1224, for activity against *T. cruzi* in adult chronic patients. Results from a proof-of-concept trial showed E1224 monotherapy to have some short-term effect on parasite clearance but with insufficient long-term efficacy, and the current regimen of benznidazole to

be efficacious in the long term, but with side effects. Alternative benznidazole regimens, including reduced dosing and duration of treatment in monotherapy and combination treatment with E1224 are being explored. Fexinidazole, also in development for HAT and VL, is also being evaluated. Additionally, DNDi continues to search for potential biomarkers of treatment response to enhance clinical trial capabilities for evaluation of new compounds.

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

In addition, DNDi supports clinical research capabilities and access through the Chagas Clinical Research Platform (see p. 53), which was launched in 2009.

Ideally, a new treatment would be for **both acute and chronic** phases of the

disease, useful against most parasite species in all regions, with a better **safety** profile than existing drugs, non-inferior **efficacy** to benznidazole, **easy-to-use** (oral, once-a-day for less than 30 days, requiring no hospitalization and little or no monitoring), **affordable, and adapted** to tropical climates.

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

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



Nitroimidazole

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

2014 OBJECTIVE: Select at least one back-up compound from VL programme to test *in vivo*

PROJECT START: April 2012

An opportunistic approach has been undertaken to assess compounds issuing from the VL-2098 back-up programme (nitroimidazooxazine series) showing activity against *T. cruzi* *in vitro*, evaluating the most promising candidates in *in vivo* models of Chagas disease. Two VL lead back-ups belonging to different sub-series (7-substituted nitroimidazooxazines and PA-824 analogues) are active and have been selected for further assessment against Chagas disease in the new bioluminescence *in vivo* model at LSHTM.

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

Oxachagas

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

2014 OBJECTIVE: Profile and assess the oxaborole class

PROJECT START: May 2011



DNDi is pursuing several oxaborole series optimization projects for kinetoplastid diseases, including Chagas disease. Following significant (between five and ten times) improvement in *in vitro* potency against *T. cruzi*, three oxaborole

candidates were tested in a mouse model of Chagas disease at Murdoch University in 2013. These compounds produced similar reductions in parasitemia and increases in mouse survival to that observed with benznidazole, but did not produce a complete, or sterile, cure. Further profiling of oxaborole candidates is planned in new mouse models once validated, which are under development to include clinical insights into compound profiling resulting from the analysis of data from the E1224 proof-of-concept trial (see page 35). Lead optimization of the oxaborole series for Chagas disease is now being managed by a new partnership between Anacor and the University of Georgia, which will work closely with the DNDi lead optimization project for leishmaniasis for this class in order to maximize cross-fertilization of ideas and leads.

PARTNERS: Anacor Pharmaceuticals, USA; WuXi AppTech, China; Sandexis, UK; LMPH, Belgium; LSHTM, UK



Biomarkers

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

2014 OBJECTIVES: Progress Non-Human Primate Study through dosing period and 12 month assessments; conclude PCR work and data review; follow-up validation studies on selected markers

PROJECT START: 2010

The lack of clear and early biological markers that can indicate parasitological outcome following treatment and, ultimately, definitive cure is a major problem in drug development for Chagas disease. To date, the only measurable outcomes are clinical benefit and seroconversion, but the latter can take several decades.

The initial focus has been on optimizing blood sampling procedures and validation of DNA quantification through polymerase chain reaction (PCR). The TRAENA and BENEFIT projects, two placebo-controlled clinical studies of benznidazole in adult patients with chronic Chagas disease, offer the opportunity to correlate serological response and PCR outcomes with long follow-up after treatment. In the longer-term, DNDi is working towards identifying new biological markers including those identified through proteomic platforms, lytic antibodies, T-cell assays, multiplex serodiagnostic assays and gene expression profiling. Continued follow-up evaluation of lytic antibodies and PCR is underway, together with an analysis of the landscape of known biological markers.

A project with the University Hospitals of Geneva and McGill University to assess the use of proteomic signatures in serum samples of nifurtimox-treated Chagas patients identified biological markers of potential for early assessment of therapeutic response, and preliminary results from children treated with benznidazole have now been obtained.

DNDi is collaborating with the University of Georgia and the Texas Biomedical Research Institute in a Wellcome Trust funded, non-human primate study in naturally infected animals with chronic Chagas disease, to further determine PCR and other markers as sensitive tools to consistently differentiate parasitological cure from treatment failure. The dosing period of this study has now been concluded and a 12-month follow-up assessment is to be completed in August 2015. DNDi is a member of the NHEPACHA network of investigators created for the long-term cohort evaluation of potential biomarkers.

PARTNERS: Médecins Sans Frontières (MSF); Universidad Mayor de San Simon, Bolivia; Universidad Autónoma Juan Misael Saracho, Bolivia; Barcelona Centre for International Health Research (GRESIB), Spain; Dr Mario Fatała Chaben National Institute of Parasitology (INP), Argentina; University of Georgia, USA; Texas Biomedical Research Institute, USA; University of Texas at El Paso, USA; National Council of Scientific and Technological Research (INGEBI-CONICET), Argentina; McGill University, Canada; University Hospitals of Geneva, Switzerland; NHEPACHA network; Universidad San Martín, Buenos Aires

Fexinidazole

OVERALL OBJECTIVE: Evaluate fexinidazole for treatment of chronic Chagas disease

2014 OBJECTIVE: Initiate proof-of-concept evaluation of fexinidazole

PROJECT START: December 2013

**47 patients
in 2 sites**

Nifurtimox and benznidazole are currently the only treatments available for Chagas disease, but concerns about their safety and tolerability mean that alternative treatments, or treatment regimens, are necessary, especially for adult patients. Pre-clinical results with fexinidazole showed that the safety profile and activity in acute and chronic animal models of disease support its clinical evaluation in patients. In July 2014, the Phase II PoC trial started in Bolivia, to determine whether at least one of six dosing regimens of fexinidazole administered orally at either 1200mg/day or 1800mg/day over two, four, or eight weeks (longer period of administration than that of HAT Phase II/III study) are efficacious and safe compared to placebo in clearing *T. cruzi* parasitemia in adult patients with chronic Chagas disease. After recruiting 47 participants by October 2014, some safety and tolerability issues were noticed. DNDi, the investigator teams and the data safety committee reviewed all data and agreed to conclude the trial without inclusion of additional participants. The safety review did not identify the same frequency or severity of adverse events for other fexinidazole indications.

PARTNERS: Platform of Integral Care for Patients with Chagas Disease, Tarija and Cochabamba (Bolivia); Molecular Biology Laboratory (BioMol) - Universidad Mayor de San Simón, Cochabamba, Bolivia; Universidad Mayor de San Simón, Cochabamba, Bolivia; Universidad Autónoma Juan Misael Saracho, Bolivia; Collective of Applied Studies and Social Development (CEADES), Bolivia; Centre de Recerca en Salut Internacional de Barcelona (CRESIB), Spain; National Council of Scientific and Technological Research (INGEBI/CONICET), Argentina; PhinC, France; JSS Medical Research, Canada; Cardiabase, France; CREAPHARMA, France

New benznidazole regimens

OVERALL OBJECTIVE: Develop a new benznidazole monotherapy regimen for chronic Chagas disease

2014 OBJECTIVE: Initiate proof-of-concept evaluation of alternative treatment regimens of benznidazole (short course)

PROJECT START: December 2013

The E1224 proof-of-concept trial carried out in 2013 showed that E1224 had good safety and was effective at clearing the parasite, but efficacy was not sustained. Benznidazole, the standard treatment for Chagas, had sustained efficacy until 12 months post-therapy, but was associated with side effects that resulted in treatment discontinuation. An expert meeting in 2014 reviewed the available data in support of the evaluation of benznidazole-sparing (shorter duration courses and lower dosing) regimens for Chagas disease. Proof-of-concept evaluation of new treatment regimens of benznidazole in monotherapy or in combination with E1224, for the treatment of adult patients with chronic Chagas disease, will be initiated in 2015, to determine if the safety and tolerability issues of benznidazole can be managed by reduced doses and treatment duration.

PARTNERS: Eisai Co. Ltd, Japan; Platform of Integral Care for Patients with Chagas Disease, Spain/Bolivia; Universidad Mayor de San Simón, Bolivia; Universidad Autónoma Juan Misael Saracho, Bolivia; Collective of Applied Studies and Social Development (CEADES), Bolivia; NUDFAC – Nucleus of Pharmaceutical and Cosmetics Development, Brazil; Centre de Recerca en Salut Internacional de Barcelona (CRESIB), Spain; National Council of Scientific and Technological Research (INGEBI-CONICET), Argentina; Instituto Nacional de Epidemiología Dr Fatala Cháben, Argentina

New combinations

OVERALL OBJECTIVE: Development of a new benznidazole and E1224 combination treatment regimen for chronic Chagas disease

2014 OBJECTIVES: Evaluate drug-drug interaction of E1224 and benznidazole in combination

PROJECT START: December 2013

Within the context of the partnership between DNDi and Eisai Co. Ltd for the development of E1224, a Phase I drug-drug interaction study was performed in 2014, to assess the safety and pharmacokinetics interaction of E1224 and benznidazole administered first separately and then in combination in healthy human volunteers. The study was undertaken in a Phase I clinical unit in Buenos Aires, Argentina. Twenty-eight healthy human volunteers were recruited and the trial concluded with no major clinically relevant safety or tolerability issues identified.

PARTNERS: Eisai Co. Ltd, Japan; Platform of Integral Care for Patients with Chagas Disease, Spain/Bolivia; Universidad Mayor de San Simón, Bolivia; Universidad Autónoma Juan Misael Saracho, Bolivia; Collective of Applied Studies and Social Development (CEADES), Bolivia; Nucleus of Pharmaceutical and Cosmetics Development (NUDFAC), Brazil; Centre de Recerca en Salut Internacional de Barcelona (CRESIB), Spain; National Council of Scientific and Technological Research (INGEBI/CONICET), Argentina; LAT Research, Argentina; FP Clinical Pharma - Ethel Feleder, Argentina; Fundación Mundo Sano and ELEA, Argentina; PhinC, France





Paediatric dosage form of benznidazole

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

2014 OBJECTIVES: Ensure paediatric benznidazole availability in Latin American Chagas-endemic countries and secure a second source of treatment

PROJECT START: May 2011

In July 2008, DNDi and LAFEPE entered a joint development programme that led to the determination and production of the most appropriate paediatric dosage formulation, strength, and dosing regimen of benznidazole. A population pharmacokinetic study involving 81 children aged 0 to 12 years with Chagas disease was conducted and showed complete parasitic clearance in all children after treatment and that those assessed 12 months later were still clear of *T. cruzi* parasites. The study also showed that children have lower blood levels of benznidazole than previously documented in adults, suggesting a reduction of adult dosing regimens may be possible. The paediatric formulation, adapted for babies and children up to two years of age, was registered in Brazil (2011). In July 2013, the treatment was included on the WHO Essential Medicines

List for children. In November 2013, the Mundo Sano Foundation and DNDi signed a collaboration agreement to deliver a second source of the treatment in partnership with ELEA (producers of Abarax®). ELEA produced pilot and scale-up batches in 2014, and stability testing is underway. Submission for regulatory approval is planned initially in Argentina in 2015, and will proceed in all countries where Abarax® is currently registered.

Through this project, DNDi has also stepped up efforts to support the scale up of treatment with benznidazole for adult patients with Chagas disease.

PARTNERS: Laboratório Farmacêutico do Estado de Pernambuco (LAFEPE), Brazil; Hospital de Niños Ricardo Gutierrez, Argentina; Instituto Nacional de Parasitología Dr M Fatała Chabén, Argentina; Hospital de Niños de Jujuy, Argentina; Ministerio de Salud, Provincia de Jujuy, Argentina; Hospital Público Materno Infantil – Salta, Argentina; Centro de Chagas y Patología Regional, Hospital Independencia, Santiago del Estero, Argentina; CONICET/INGEBI, Argentina; Centro Nacional de Diagnóstico e Investigación de Endemo-epidemias (CeNDIE), Ministry of Health, Argentina; University of Liverpool, UK; NUDFAC, Brazil; Administración Nacional de Laboratorios e Institutos de Salud (ANLIS), Argentina; Mundo Sano Foundation, Argentina; Laboratorio ELEA, Argentina





Paediatric HIV, Nairobi

Simon is 21 months old, and HIV positive. His mother Gloria struggles every day to administer the treatment in a syrup form while he cries and tries to get away because of its terrible taste. Gloria lost her regular job when she was diagnosed with HIV, and as a consequence has no money for a refrigerator or electricity with which to keep Simon's medicine cool. She therefore resorts to storing the syrup in a bucket containing water and sand, but, as it cannot be kept at room temperature for more than six weeks, she must leave her family every month to go refill his medicine and take him for a check-up at the health clinic. DNDi is working to develop a four-in-one formulation suitable for babies and small infants that will be easier to administer.

REMOVING THE BARRIERS TO TREATMENT ACCESS

It is a harsh reality that over 3.2 million children under the age of 15 are currently infected with HIV, mostly in sub-Saharan Africa. The virus is transmitted during pregnancy, childbirth, or breast-feeding. The WHO recommends that the HIV status of pregnant women be known as soon as possible in order to start antiretroviral therapy and so prevent transmission. However many mothers do not know their HIV status and therefore do not receive the treatments that would preserve their own health and avoid transmission to their child. In 2013, 190,000 children died from the disease.

Most of these children were under the age of two – deaths which could have been avoided if diagnosis had been made in the first weeks of infection and treatment started immediately. Unfortunately, only 15% of infants exposed to HIV are tested in the first two months of life. Thanks to international efforts in preventing mother to child transmission, the number of infants newly infected with HIV is now declining, but the need for paediatric treatment will continue to increase until at least 2020.

Furthermore, the vast majority of infants and young children lack access to treatment, without which half of them die before their second birthday and 80% before reaching the age of five. Only a very limited number of drugs have been approved for use in infants and young children, and antiretroviral therapies are not well adapted to tropical environments or easy for caregivers to administer.

In May 2014, UNITAID, DNDi, and the Medicines Patent Pool (MPP) launched a partnership, now also including the Clinton Healthcare Access Initiative (CHAI), to expedite the development and delivery of new antiretroviral formulations, with a focus on overcoming the barriers to developing and delivering specific formulations and combinations appropriate for children (see p.58). In December of the same year, in agreement with AbbVie, lopinavir and ritonavir were placed into the MPP, thus removing any intellectual property barriers to the development of treatments containing these drugs, including those which are currently under development by DNDi and Cipla Ltd.

3.2 million children
under the age of 15 living with HIV/AIDS,
more than 91% in sub-Saharan Africa

190,000 children
under 15 years of age died of AIDS-related illness
in 2013 globally

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

The 2013 WHO guidelines recommend early diagnosis, and immediate treatment of HIV-positive infants and children under the age of five, regardless of CD4 count; infants under the age of three should be treated with an antiretroviral treatment (ART) combination that includes protease inhibitors regardless of whether they have been exposed to ARVs for the prevention of mother-to-child transmission (PMTCT). The combination of a **boosted protease inhibitor (PI) with two nucleoside reverse transcriptase inhibitors (NRTIs)** is considered by the WHO as the most effective first-line therapy for infants and children.

However, this combination therapy is not being widely used. According to a WHO survey performed in 45 countries, in 2010 only 12.2% of children with HIV were receiving a first-line treatment containing a PI (mostly lopinavir/ritonavir, LPV/r), 97% of whom were in South Africa. The only available PI for young children, LPV/r does not come in a child-friendly formulation: the oral solution formulation is unpalatable, contains 42% alcohol, and is not adapted to resource-poor settings due to major logistical constraints: it requires refrigeration, has a short shelf-life when exposed to heat, is expensive, and difficult to store and transport.

In some places, the levels of co-infection of TB and HIV in infants and children are high. Drug-drug interactions between PIs in particular and rifampicin, one of the drugs used to treat TB, greatly diminish the blood levels of PIs and hinder the efficacy of the antiretroviral (ARV) treatment. In order to counteract this interaction, extra ritonavir needs to be added to the standard proportion of LPV/r. This is called 'superboosting', and requires the development of an infant-friendly formulation of ritonavir. The currently available ritonavir formulation suffers the same limitations as the current formulation of LPV/r with regard to taste, high alcohol content, and logistical constraints imposed by its short shelf-life.

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?

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

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

Develop and register two solid first-line 4-in-1 LPV/r-based fixed-dose combinations (FDCs) with two NRTIs. All components of the combination will be developed in the form of taste-masked granules, stable with no need for refrigeration, presented in a single unit with appropriate strengths to accommodate weight band dosing.

Develop and register a heat stable stand-alone ritonavir booster formulation that is well taste-masked and can be added to any PI-based paediatric ARV regimen and can be used to counteract the negative drug-drug interactions between PIs and rifampicin-containing TB treatments.

Before these formulations are made available however, as a **short-term strategy**, DNDi will start testing the use of PI-based treatment with existing LPV/r-based solid formulations before the availability of the 4-in-1 FDC, in order to provide better treatment for infants today and promote in-country adoption. The heat-stable pellets are already a great improvement, however the bitter taste remains and is a barrier to use in treating this chronic disease. DNDi participated in the CHAPAS-2 trial that compared LPV/r sprinkles (hereafter referred to as pellets) to the LPV/r liquid formulation. These pellets will be used in combination with NRTI dispersible tablets in implementation studies (LIVING Study).

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

In addition, in order to address the needs of HIV/TB co-infected children, DNDi is developing a formulation of ritonavir for superboosting LPV/r at

a 1:1 ratio. As a short-term strategy, DNDi is conducting a study to establish the pharmacokinetics, efficacy and safety of superboosted LPV/r in children in South Africa with the existing ritonavir solution.

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

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

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

TRANSLATION



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

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

2014 OBJECTIVE: Develop a taste-masked and bioavailable paediatric formulation

PROJECT START: 2012

27 formulations tested in 2014 Pharmacokinetic modelling was carried out and results, for LPV/r, ABC, 3TC, and AZT, shared with WHO paediatric experts. The proposed dosing for the two 4-in-1 LPV/r based FDCs and RTV booster were incorporated into Annex 7 of the 2013 WHO's new *Consolidated Guidelines on The Use of Antiretroviral Drugs for Treating and Preventing HIV Infection*, under 'urgently needed ARV drugs for children recommended by the Paediatric ARV Working Group', and published in 2014.

The first test formulation of LPV/r 40/10 mg taste-friendly granules to be mixed with the NRTI components of the FDCs was found not to be bio-equivalent to originator liquid formulations. Reformulation of LPV/r and RTV granules is challenging and these formulations require further optimization; the Chapas-2 extension study in children has been put on hold. Since the start of the project 39 formulations of LPV/r and nine formulations of Ritonavir have been tested in animal models, 27 of which in 2014, taking into account the data already generated. The most promising formulations will be evaluated in healthy human volunteers in 2015.

PARTNERS: Cipla Ltd., India; UNITAID; National Department of Health, South Africa; Centre for Disease Control and Prevention (CDC)/President's Emergency Plan for AIDS Relief (PEPFAR), USA; Médecins Sans Frontières; Medical Research Council, UK; Necker Institute, Paris; various academic partners in South Africa and Kenya; AbbVie, USA; WuXi, China

'Superboosting' – TB/HIV

OVERALL OBJECTIVE: To develop a stand-alone pharmacokinetic enhancer/booster formulation to be added to any PI-based paediatric ARV regimen

2014 OBJECTIVE: Ongoing recruitment for the RTV superboosting (PK) study in South Africa

PROJECT START: 2012

82 patients recruited at 5 sites Rifampicin is commonly used to treat tuberculosis (TB) in children. However, rifampicin reduces the bioavailability of protease inhibitors (PIs) in treatments used to combat HIV infection. A stand-alone ritonavir booster formulation is being developed that can be added to any PI-based paediatric ARV regimen, in order to counteract the

negative drug interactions between PIs and rifampicin-containing TB treatment.

A pharmacokinetic (PK) study is being carried out in infants and young children co-infected with TB and HIV at five sites in South Africa to supplement existing information and evaluate the effect of the 'super-boosting' strategy. The study will evaluate the effect of lopinavir/ritonavir in a 1:1 ratio on the PK of lopinavir in children concomitantly receiving rifampicin as treatment for TB. Recruitment began in January 2013 and is expected to end in 2015. By the end of 2014, 82 patients had been included.

PARTNERS: Stellenbosch University and Tygerberg Children's Hospital, South Africa; Perinatal HIV Research Unit, South Africa; Shandukani Research Centre, South Africa; Empilweni Services and Research Unit, Rahima Moosa Mother and Child Hospital, South Africa; Enhancing Care Foundation, South Africa; Department of Health and Department of Science and Technology, South Africa

DEVELOPMENT



LPV/r pellets with dual NRTI FDC

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

2014 OBJECTIVE: Initiate implementation studies

PROJECT START: 2014

Cipla Ltd., India, has developed LPV/r pellets (mini-'melt' tablet formulation), stored in 40/10 mg capsules, which can be opened and administered orally to small children, allowing the drug to be mixed with food and offering the advantage, over the current liquid formulation of these drugs, of being alcohol-free. These pellets do not require a cold chain and are less costly in terms of weight of product for transport; however, their poor taste is still a barrier.

This project comprises large-scale implementation studies to provide supportive clinical data on the feasibility, efficacy, safety, and PK of LPV-based therapies in routine treatment settings in order to facilitate registration in the countries concerned. Originally scheduled to begin in 2014, the study was delayed pending regulatory approval but this was obtained by the end of 2014 and the LIVING study will start in Kenya and Uganda in 2015 using the first generation of LPV/r pellets, expanding to additional countries soon after.

PARTNERS: Cipla Ltd., India; UNITAID; National Department of Health, South Africa; Kenya Partners: University of Nairobi; KEMRI Walter Reed Project; St Lumumba Health Centre, Kisumu; Mbagathi District Hospital; KEMRI Wellcome Trust; Gertrudes Children's Hospital; Moi Teaching and Referral Hospital; Kenyan Ministry of Health; Joint Clinical Research Centre (JCRC) in Uganda; Baylor International Pediatric AIDS Initiative; Epicentre, Uganda; Elizabeth Glaser Paediatric AIDS Foundation (EGPAF) in Tanzania



Filarial disease, Ghana

A medical team visits a village in Kumasi, Ghana, to assess the needs of patients with lymphatic filariasis (elephantiasis).

DEVELOPING NEW TREATMENTS FOR DEBILITATING INFECTIONS

DNDi aims to develop improved treatments for the millions of people worldwide that suffer from filarial diseases: **lymphatic filariasis** (elephantiasis) and **onchocerciasis** (river blindness). Although current treatments for these debilitating and stigmatizing illnesses help to prevent infection, health tools that rapidly cure patients are lacking.

What are filarial diseases?

Filarial diseases are caused by parasitic worms of the helminth family. While rarely fatal, these diseases affect millions of people and inflict immense hardship. Onchocerciasis is the world's second leading infectious cause of blindness and has a host of other symptoms, including skin discoloration and intense itching. The disease is contracted through the bite of an infected female blackfly. *Lymphatic filariasis* is the second cause of chronic disability worldwide and is transmitted to humans by mosquitoes. It may lead to lymphoedema (massive swelling, principally of the legs and genitals), elephantiasis (the late disfiguring stage), and hydrocele (fluid accumulation in the testes). Together, these two diseases are responsible for considerable financial and social burden on people already living in deep poverty.

Addressing R&D gaps in existing treatments

Large-scale programmes for the control of filarial diseases have been in place for over twenty years, based on the mass drug administration (MDA) of medicines donated by the pharmaceutical industry. These programmes have been successful in reducing transmission but significant R&D gaps remain. MDA programmes use microfilaricidal drugs that kill juvenile worms (microfilariae) but leave adult worms (macrofilariae) alive in the body for up to 15 years. Therefore, MDA needs to

be repeated for a number of years until the adult worms naturally die out. Evidence also shows that current treatments for filarial diseases can cause neurological damage or even death for those also infected with *Loa loa* by causing sudden, massive death of juvenile *Loa loa* worms.

A safe, short-course drug that can kill adult filarial worms is therefore needed. This macrofilaricidal drug could be an essential tool for health workers in rural areas and also greatly shorten the length of MDA programmes, thus contributing to the WHO goals of eliminating lymphatic filariasis (defined as 70% of countries free of disease and 30% engaged in post-surveillance activities) and controlling onchocerciasis by 2020. New treatments are also essential for areas where *Loa loa* and other filarial diseases are co-endemic, to enable the safe treatment of co-infected patients.

DNDi aims to register a new drug as a short course, oral macrofilaricide with potential application to treat both onchocerciasis and lymphatic filariasis, and has a two-fold strategy in place. As part of its medium term strategy DNDi will focus on repurposing candidates used for other indications in the pharmaceutical and the animal health industries, such as emodepside, a potent drug used in veterinary medicine, which will be developed for patient use with Bayer HealthCare. The second strategy is based on partnering with other discovery initiatives on developing compounds identified from DNDi's screening campaign. In 2014, DNDi began putting in place a clinical research platform for filarial diseases by expanding its existing network of partners and other platforms (see p. 50).

Without R&D for better treatments, filarial diseases will continue to exact a terrible burden on the most neglected patients.

37 million people infected with onchocerciasis

worldwide, with 99% cases in 31 African countries, and 169 million at risk

Over 120 million people infected with lymphatic filariasis globally,

with about 40 million disfigured or incapacitated; more than 1.4 billion people in 73 countries at risk of infection

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

Current treatments for onchocerciasis and lymphatic filariasis are based on repeated mass drug administration (MDA) of antiparasitic drugs through programmes directed by the WHO. WHO recommends MDA for onchocerciasis at least once yearly for 10-15 years, and for lymphatic filariasis once yearly for at least five years. The drugs used in MDA programmes are **ivermectin** for onchocerciasis; and for lymphatic filariasis, **albendazole** plus either **ivermectin** in areas where onchocerciasis is also endemic (*i.e.* African countries), or **diethylcarbamazine** (DEC) in areas where onchocerciasis is not co-endemic (*i.e.* non-African countries).

By killing microfilariae, and inducing a temporary sterilization of adult worms, MDA drugs can prevent vector-borne transmission for several months, until the adult worms produce more microfilariae larvae. However, because adult worms continue to live in the body, they eventually produce new microfilariae, often before the next MDA, thus requiring repeated MDAs for several years to decades until the adult worms die naturally.

Ivermectin is safe and has been used widely as a monotherapy in MDA programmes for onchocerciasis, killing the microfilarial stage of the parasite. However, in lymphatic filariasis and onchocerciasis patients co-infected with *Loa loa*, the sudden death of large numbers of *Loa loa* microfilariae following treatment can lead to serious adverse events, such as encephalopathy, possibly resulting in permanent brain damage and death. Furthermore, reports of a suboptimal response to ivermectin by *O. volvulus* may be a sign of developing resistance.



WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?

DNDi's strategy is to develop a new compound with macrofilaricide activity for use as a safe and field-adapted macrofilaricidal drug for patient case management and possibly later MDA if needed. As a **medium-term strategy**, DNDi is assessing emodepside, a potent antihelminthic drug used in combination with praziquantel to treat parasitic worms in cats and dogs, as a clinical candidate to treat humans.

As a **long-term strategy**, DNDi is assessing additional opportunities through an active screening programme of drug compounds emanating from animal health/pharmaceutical companies and academic institutions, with the goal of selecting one or two candidates to move into clinical development.

Ideally a new treatment for adults and children will be a macrofilaricide (efficacious against the adult form of worms), oral, short-course treatment, well tolerated, affordable, and adapted to tropical climates.

Emodepside

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

2014 OBJECTIVE: Sign agreement with Bayer HealthCare

PROJECT START: March 2013

Emodepside is a semi-synthetic product (originated by Astellas and out-licensed to Bayer Animal Health for animal use); its precursor is synthesized by a fungus living in the leaves of *Camellia japonica*. It is a potent antihelminthic drug used in combination with praziquantel (Profender®) and in combination with toltrazuril (Procox®) for the treatment of parasitic worms in cats and dogs. Originating from the Japanese pharmaceutical company Astellas, the compound has been developed by Bayer Animal Health for animal health uses and commercialized as an anthelmintic veterinary drug for cats and dogs in combination with praziquantel (Profender™) and in combination with toltrazuril (Procox™). Following its successful animal use, the compound has been found in relevant animal models of the human diseases to be effective in killing the adult worm in pre-clinical studies, a unique feature permitting to envisage a shorter therapeutic intervention to treat infected patients. Emodepside shows outstanding activity against filarial parasites. In 2014, DNDi signed an agreement with Bayer HealthCare to develop emodepside for treatment of patients with onchocerciasis. DNDi will be responsible for the pre-clinical and clinical development of emodepside and Bayer for the pharmaceutical development, manufacturing, registration, and supply of the drug. The agreement ensures that emodepside, if successful in subsequent phases of drug development, would be available at the lowest sustainable price to ensure affordability and access in 31 African disease-endemic countries. The rights to use technology or data generated within the collaboration allow each party to pursue the project with third partners in case of withdrawal of the other party, thus securing the development and accessibility of emodepside for the benefit of patients. DNDi is also exploring other potential drug candidates.

PARTNER: Bayer HealthCare, Germany





MALARIA

ASAQ AND ASMQ, TWO INNOVATIVE APPROACHES

Among the very first projects undertaken by DNDi was the development of two artemisinin-combination therapies (ACTs) to treat malaria, based on recommendations made by the WHO in 2001.

The FACT (Fixed-Dose Combination Therapy) consortium was formed in 2002 to develop combinations of artesunate (AS) with amodiaquine (AQ) or mefloquine (MQ). Having fixed dose combinations (FDCs) of drugs would lead to simplified administration and increased compliance, the aim being to develop field-adapted formulations that would be easy to administer to all age/weight categories of patients, particularly to infants and young children, whilst also able to withstand the heat and humidity of tropical climates.

In 2007, ASAQ FDC became the first treatment to be launched by DNDi, having been developed by a number of partners across almost the full development range, from formulation work through to post-registration studies. The development of ASAQ FDC required innovation in four ways: through the establishment of an innovative partnership with a major pharmaceutical company, Sanofi, including agreement to develop ASAQ FDC as a non-patented product at the price of one US dollar per treatment; an innovative approach to developing this product with public and private partners; an innovative implementation strategy, which began with manufacturing the product at Sanofi's facility in Morocco and its registration in African countries; and an innovative Risk

Management Plan with Sanofi and MMV, the first of its kind to be submitted to the WHO, and the first to be entirely undertaken in Africa.

The ASMQ FDC, launched in 2008, was developed in collaboration with Farmanguinhos/Fiocruz, a Brazilian public pharmaceutical company, and for which DNDi received the Funding Authority for Studies and Projects (FINEP) award for Innovation in Social Technology in November 2014. A South-South technology transfer agreement to Cipla Ltd in India ensures a second supplier of the treatment, principally for the Asian market but also for Africa. Recent results from the multi-centre trial carried out in Africa showed ASMQ FDC is as safe and efficacious as artemether-lumefantrine – Africa's most widely adopted treatment – in children under five years of age.

Malaria projects handed over to MMV

The successful development of these two antimalarials, although not always easy, provided good lessons learned and experience to DNDi's team and partners in building an alternative model for R&D.

In May 2015 the malaria projects were formally handed over to the Medicines for Malaria Venture (MMV), long term partners of DNDi, who have successfully built the largest portfolio of antimalarials ever seen in the history of the disease, ensuring the future implementation of these two treatments.



ASAQ Winthrop

OVERALL OBJECTIVES: Develop and make available an affordable, field-adapted FDC of AS and AQ, which is easy to administer to all age/weight categories, particularly to infants and children

2014 OBJECTIVES: Contribute to disseminate ASAQ broadly and participate in large-scale data assessments (see WWARN); support the technology transfer of ASAQ manufacture to Zenufa in Tanzania

PROJECT START: January 2002

400 million ASAQ treatments distributed by Sanofi and generic companies in 35 countries by end of 2014

ASAQ Winthrop, the fixed-dose combination (FDC) of artesunate (AS) and amodiaquine (AQ), was the first treatment made available by DNDi in 2007 through an innovative partnership with Sanofi. ASAQ Winthrop was pre-qualified

by WHO in October 2008 and included on the WHO Essential Medicines List (EML) in 2011. First registered in Morocco, where it is manufactured, ASAQ is now registered in 31 African countries, as well as in India, Bangladesh, Colombia, and Ecuador.



There were significant challenges to overcome: the development of a stable bilayer formulation of the two drugs, together with the dual-aluminium blister packaging designed to withstand the rigors of a tropical environment; as a result it is the only ACT FDC with a three-year shelf-life currently available. ASAQ Winthrop obtained WHO authorization in 2010, for a three-year shelf life, giving the product the longest shelf life of any pre-qualified FDC artemisinin-based treatment available for malaria. Registration, manufacture and distribution of this stable formulation was undertaken with Sanofi, the industrial partner, who were already providing co-blistered Coarsucam™ to Africa at the time, and who committed to making the generic ASAQ Winthrop® available at less than one US dollar per adult treatment for the public market. Its low price and prequalified status, allowing purchases by procurement agencies, led to price decreases not only of ASAQ but also other ACTs, and having an affordable

drug on the market led to increased patient access to high quality treatments.

In partnership with Sanofi, MMV and National Malaria Control Programmes, high-quality data on ASAQ effectiveness and safety in 'real-life' conditions is being collected, as part of a Risk Management Plan (RMP). The largest study, undertaken by Sanofi and MMV with support from DNDi, has been ongoing in 15,000 patients in Côte d'Ivoire, and results are expected in 2015.

DNDi and partners are also working on the transfer of technology to a second manufacturer in Africa, Zenufa, based in Tanzania (see p. 49).

By the end of 2014, 400 million treatments had been distributed, by Sanofi and generic companies.

PARTNERS: Sanofi, France; MMV, Switzerland; AEDES, Belgium; Zenufa, Tanzania; National Centre for Research and Training on Malaria, Burkina Faso; Universiti Sains Malaysia; Oxford University, UK; Institute of Research for Development (IRD), Senegal; Université de Bordeaux Faculté de Pharmacie, France; Mahidol University, Thailand; Bertin Pharma, France; Médecins Sans Frontières; Epicentre, France; WHO-TDR; Kenya Medical Research Institute (KEMRI), Kenya; Indian Council of Medical Research (ICMR), India; National Malaria Control Programme, Ministry of Health, Burundi; Ministry of Health, Sierra Leone; Ministry of Health, Ghana; Komfo Anokye Teaching Hospital (KATH), Ghana

ASMQ FDC

*DNDi
Latin
America*

OVERALL OBJECTIVE: Develop and make available worldwide an affordable fixed-dose combination of AS and MQ which would be easy to administer, particularly to infants and children, targeted initially for use in Asia and Latin America

2014 OBJECTIVES: Increase the number of countries where ASMQ FDC is approved; conclude the study performed in children in Africa

PROJECT START: January 2002

over 830,000 treatments distributed by end of 2014

The ASMQ fixed-dose combination treatment (ASMQ FDC) was developed by the FACT consortium created by DNDi and TDR in 2002.

Within FACT, the Brazilian government-owned pharmaceutical company, Farmanguinhos/Fiocruz, was the first manufacturer of ASMQ FDC. Through a South-South technology transfer, ASMQ FDC production was transferred to the Indian pharmaceutical company Cipla in 2010 to ensure availability in India and Asia at affordable, pre-agreed prices. Both Farmanguinhos and principally Cipla supplied treatments in response to a large request from Venezuela in 2013 (over 382,000 treatments). ASMQ FDC is now registered in Brazil (2008), India (2011), Malaysia and Myanmar (2012), Tanzania (2013), Vietnam, Niger and Burkina Faso (2014), Thailand and Cambodia (2015). The Cipla ASMQ FDC product was prequalified by the WHO in 2012 and was included in the WHO Essential Medicines Lists for adults and children in April 2013,

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in line with current treatment guidelines. Farmanguinhos/Fiocruz was admitted into the PAHO Strategic Fund in April 2013, allowing procurement by South American national control programmes. In 2014 Farmanguinhos was requested to obtain WHO prequalification in order to remain in the Fund. The pre-qualification file is being generated and submission is planned for 2015.

Additional clinical studies are ongoing that will provide information of ASMQ FDC use in children, adults, and pregnant women in Africa. According to WHO recommendations, AS+MQ could be considered for use in some countries in Africa. DNDi sponsored a key multicentre Phase IIIB study in Tanzania, Burkina Faso, and Kenya to assess the efficacy, safety, and pharmacokinetics

of ASMQ FDC compared to artemether-lumefantrine in children below the age of five with uncomplicated *P. falciparum* malaria. The study found ASMQ FDC to be as safe and efficacious as Artemether-Lumefantrine (AL) FDC – Africa's most widely adopted treatment – results which were presented at ASTMH in November 2014. The pharmacokinetic data collected confirmed there was no need to change the dosing in children. The report is being finalized and publications are planned for 2015.

By the end of 2014, 832,000 ASMQ treatments were distributed.

PARTNERS: Farmanguinhos, Brazil; Cipla Ltd., India; Shoklo Malaria Research Unit, Thailand; Universiti Sains, Malaysia; Oxford University, UK; WHO-TDR; Indian Council of Medical Research (ICMR), India; Epicentre, France; Centre Hospitalier Universitaire Vaudois (CHUV), Switzerland; National Institute of Medical Research (NIMR), Tanzania; Kenya Medical Research Institute (KEMRI), Kenya; Centre National de Recherche et de Formation sur le Paludisme (CNRFP), Burkina Faso; Medicines for Malaria Venture (MMV), Switzerland; Ifakara Health Institute, Tanzania; Worldwide Antimalarial Resistance Network (WWARN)

After more than a decade, DNDi hands over its malaria programme to MMV

In May 2015, DNDi and MMV signed a landmark project transfer agreement and convened a high-level event exploring 15 years of progress in the fight against malaria. The event was hosted to mark the handover of DNDi's malaria activities to MMV, according to DNDi's 2011-2018 Business Plan objectives.

The two fixed-dose artemisinin combination therapies (ACTs) developed by DNDi and partners, artesunate-amodiaquine (ASAQ) and artesunate-mefloquine (ASMQ), will be henceforth managed by MMV.

The event was chaired by Prof. Marcel Tanner, Chairman of the DNDi Board and Director of the Swiss Tropical and Public Health Institute, and opened with a keynote speech from Dr Pedro Alonso, Director of the WHO Global Malaria Programme. A panel discussion included the Minister of Health of Côte d'Ivoire, as well as high-level representatives from Ethiopia, Roll Back Malaria, Asia Pacific Leaders Malaria Alliance, UNITAID, Cipla, Sanofi, and Novartis.

Before passing over a commemorative rugby ball to Dr David Reddy, CEO of MMV, to symbolize the handover, Dr Bernard Pécoul, Executive Director of DNDi, applauded his team for their work in launching the two ACTs, stating that 'these projects have proved how essential a nimble partnership model is to success, and how crucial the engagement and dedication of numerous public and private partners, and individuals, is to reaching a common goal'. Dr Reddy replied declaring that 'the goal is to ensure these medicines reach as many vulnerable people as possible and save lives'.



From left to right: Representative of Health Ministry, Ethiopia – Dr Ben Rolfe, Executive Secretary, APLMA – Dr James Banda, Senior Advisor RBM – Brigadier General (Dr) G Gwinji, Permanent Secretary for Health and Child Welfare, Republic of Zimbabwe – H. E. Dr Raymonde Goudou Coffie, Minister of Health and HIV/AIDS Programme, Côte d'Ivoire.



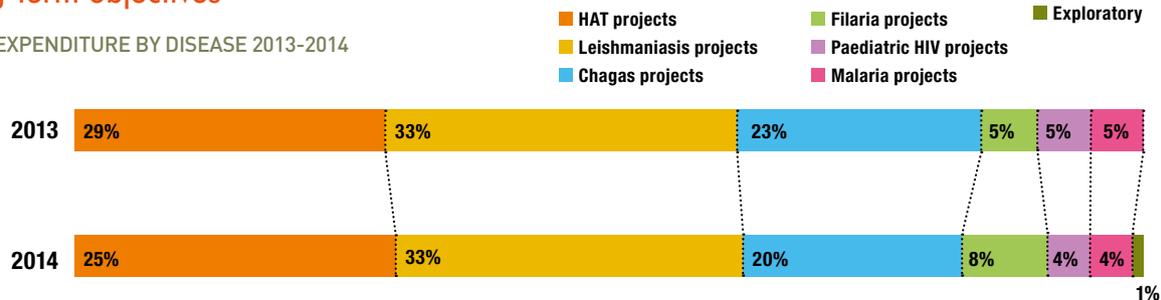
Dr David Reddy, CEO, MMV and Dr Bernard Pécoul, Executive Director, DNDi at the malaria handover event.



2014 KEY FINANCIAL PERFORMANCE INDICATORS

EUR 27.6 million to achieve key milestones while maintaining a robust pipeline to support long-term objectives

R&D EXPENDITURE BY DISEASE 2013-2014



Overall R&D expenditures (EUR 27.6 M) increased by 19% (EUR 4.4 M) compared to 2013.

Percentage breakdown highlights of 2014 R&D expenditures per disease (screening and lead optimization expenditures are split and allocated toward disease expenditures):

- HAT:** With a total of EUR 7.1 M, HAT investments increased (+EUR 1.3 M) due to the growth in clinical activities for fexinidazole in 2014 (+EUR 2.6 M), with the opening of one new clinical trial site (reaching a total of 10 operating sites) in DRC that helped to recruit 359 patients for our fexinidazole phase II/III clinical study. Two new complementary cohort trials, one for stage 1 and early stage 2 in adults included 110 patients, and another with children between 6 and 14 years of age included 56, for a total of 525 patients included in the three trials. The SCYX-7158 project continued the phase I study (total 128 patients enrolled by end of 2014) incurring a decrease of EUR 0.7 M in expenditures. Work on publication for the NECT study was ongoing in 2014 (- EUR 0.1 M). Screening and lead optimization efforts were entirely redirected towards leishmaniasis and Chagas disease (- EUR 0.5 M).

- Leishmaniasis:** This disease represents the most substantial R&D expenditure (33%) in 2014. The overall expenditures increased by EUR 1.3 M in 2014 (EUR 8 M in 2014 compared to EUR 6.7 M in 2013). New activities such as PKDL for VL with an infectivity study and CpG-D35 with manufacture non-GMP API for CL (+EUR 0.2 M) started in 2014: The HIV co-infection for VL study (+EUR 0.4M) progressed with a total of 18 patients recruited. The toxicology package for VL-2098 was completed (+EUR 0.5 M). Screening and lead optimization work focused more intently on VL, leading to an increase from 43% in 2012 to 50% in 2013 and 63% in 2014 (+ EUR 0.2 M).

- Chagas disease:** Projects remained stable in 2014 (+EUR 0.2 M), with EUR 5 M (20%) of R&D expenditures. The preparation of a new combination study for benznidazole new regimen, including a drug-drug interaction study started at the end of 2014 (+ EUR 0.3 M). The phase II fexinidazole for Chagas study was completed in 2014, incurring an increase of EUR 1.1 M. The E1224 phase II study was completed in Q1 2014 (-EUR 1.2 M).

- Portfolio expansion:** The three disease areas represent 12% compared to 10.5% in 2013. This increase (+EUR 0.7 M, +34%) is the most significant of the DNDi portfolio.

- Paediatric HIV:** Project expenditure remains stable in 2014. One new activity started in 2014: preparation of the implementation study for a 4-in-1 product (+EUR 0.1 M). The clinical 'super boosting' study (ritonavir for super boosting LPV/r) in South Africa (-EUR 0.3 M), and the formulation development of the 4-in-1 with Cipla Ltd as an industrial partner (+EUR 0.2 M) are ongoing.

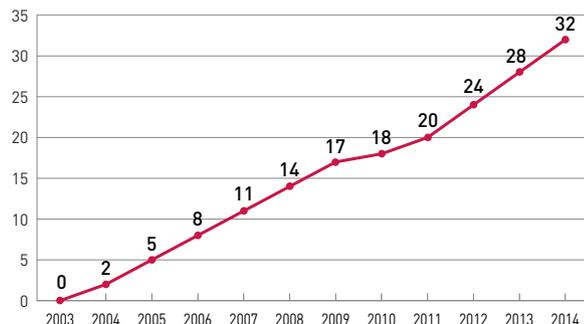
- Filaria:** Project expenditures increased by 70% (+EUR 0.7M). Three activities are ongoing: The preclinical activities increased with a new preclinical candidate (+EUR 0.1 M) and the flubendazole project that has been terminated (+EUR 0.4 M). The screening work is ongoing and maintained at the same level as in 2013. Preparation of clinical activities was set up in 2014 (+EUR 0.2 M)

- Malaria:** Despite the nearly completed handover to MMV, two activities are still on going in 2014 with the same level of expenditures as in 2013.

Regular increase of partnerships with research companies

CUMULATIVE NUMBER OF NEW PARTNERSHIPS ESTABLISHED WITH RESEARCH COMPANIES

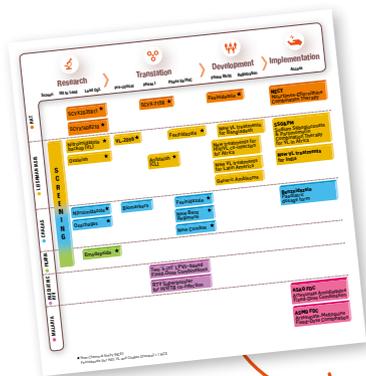
Number of partnership agreements signed per year



By the end of 2014, 32 partnership agreements had been signed between DNDi and research companies (pharmaceutical and biotech companies), including access to compound libraries, pre-clinical activities, and industrial development (+14%).



2014 KEY FINANCIAL PERFORMANCE INDICATORS



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

R&D EXPENDITURE PER R&D STAGE



Overall R&D expenditure increased by 19% between 2013 and 2014 to reach a total of EUR 27.6 Mio.

The most important fluctuation relates to growth of development projects (+39%), and the progress of translational projects (pre-clinical; phase I; phase IIa/proof of concept: + 21%). The R&D coordination & supervision costs (EUR 3.1 M) are included proportionally in the R&D expenditure per stage of new exploratory (+EUR 0.2 M).

• **Implementation:** Projects costs decreased by 13% (-EUR 0.3 M) in 2014 compared to 2013.

With six projects in implementation (the first one entered in 2007), two projects were terminated:

NECT finalized the final report for the field study (- EUR 0.1 M) and SSG & paramomycin combination therapy for VL in Africa ended (- EUR 0.2 M).

• **Development:** The progression of fexinidazole for HAT phase IIb/III clinical study (+EUR 2.6 M) with 10 operational sites in DRC and the respect of ambitious timelines is the major achievement for 2014.

The VL co-infection HIV (+EUR 0.4 M) study started the recruitment of patients in 2014.

The new VL treatment in Africa was stopped in 2014 and replaced by a combination fexinidazole /miltefosine study that is in preparation and allocated against the translation phase (- EUR 1 M).

• **Translation:** Expenditures increased between 2013 and 2014 (+EUR 1.7 M) because new projects entered this stage in 2014:

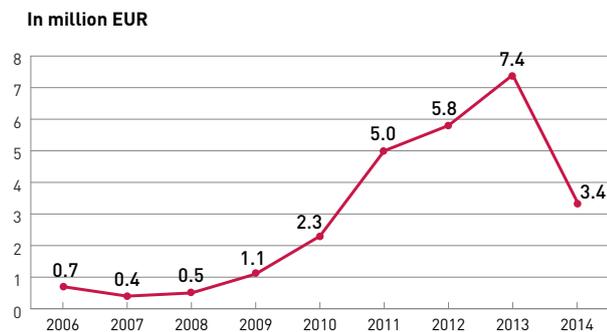
- Progress of two new fexinidazole projects: one for VL and one for Chagas disease (+EUR 2 M).
- Start of a new CpG-D35 project for CL (+EUR 0.2 M).
- Preparation of a combination study for a new benznidazole regimen for Chagas disease (combination of E1224 and benznidazole: +EUR 0.3 M).
- Pre-clinical package for VL2098 almost completed (+EUR 0.4 M)
- Completion of flubendazole project and a new candidate for filarial project entering into pre-clinical stage (+EUR 0.7 M).
- The E1224 phase II study for Chagas disease terminated in 2014 (-EUR 1.2 M).
- The SCYX-7158 expenditure decreased in 2014 compared to 2013 (-EUR 0.7 M).

• **Research:** Screening and lead optimization activities increased (+EUR 0.7 M) due to the purchase of compounds libraries (+EUR 0.3 M) and an increase of four FTE with partners involved with the lead optimization consortium (+ EUR 0.4 M).

• **Exploratory:** In relation to the new business plan that will be presented in 2015, exploratory activities were implemented for HCV, mycetoma, and anti-infective (+ EUR 0.2 M).

Leveraging partners' resources

IN-KIND CONTRIBUTIONS 2006-2014



NUMBER OF COMPOUNDS SCREENED



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

The cumulated in-kind contribution over nine years amounts to EUR 26.4 M, reflecting DNDi's investment in building strong partnerships. The 49% decrease in 2014 compared to 2013 (- EUR 4 M) is largely due to the fact that the flubendazole macrofilaricide project is phasing out and the in-kind contribution from the partner decreased by EUR 3.1 M (from EUR 4.1 M in 2013 to 1 M in 2014). More than 50% of the contribution relates to pharmaceutical and formulation development (reformulation for humans and new chemical entities (NCEs)). The Sanofi contribution towards the Fexinidazole projects is an important and strategic contribution, but it is not recognized financially due to the DNDi In-Kind Donation policy.

DNDi has access to pharmaceutical libraries that will allow the development of innovative medicines with NCEs. The pharmaceutical companies provide compound libraries for screening and lead optimization at no cost. It is complicated for companies to value such contributions given the number of internal and external collaborators involved in this important effort and the existence of many indirect and intangible contributions. To illustrate this contribution, the total number of compounds screened in 2012, 2013 and 2014 was consolidated and compared; it showed a 22% decrease (-47,263 compounds) that was compensated with the access to 1.8M data/hits resulting from the screening of the global GSK compound collection.



Strengthening Existing Capacities

‘Walking the Talk’ for Sustainable Capacity in Disease-Endemic Countries

Since DNDi’s creation, the role of neglected disease endemic countries in responding to their public health needs has been a central concern both in the innovative models DNDi has utilized in its functioning and in its advocacy activities. Research capacity in developing countries can be at risk of being directed towards the needs of populations in developed countries,⁽¹⁾ so not only must the capacity be built and maintained,

local leadership is also required to ensure that the research is serving the needs of the countries themselves. This is part of a larger need for increased public leadership, which also comprises regulatory and health systems strengthening.

To ensure that DNDi ‘walks its talk’, three areas of work are specifically addressed in the regions as part of the reinforcement of the role of DNDi Regional

Offices: technology transfer notably to increase suppliers and ensure supply of treatments through local production, data management capacity, clinical trial capacity strengthening, as well as two new initiatives that began to take shape in 2014 for leishmaniasis in Latin America and filariasis in Africa.

Ensuring alternative sources of ASAQ FDC antimalarial – technology transfer to Zenufa

DNDi took up a technology transfer project for the manufacture of ASAQ to a second partner, after Sanofi, in malaria-endemic countries of Africa in 2009. With the support of the pharmaceutical expert group, Office Technique d'Etude et de Coopération Internationale (OTECI), some 100 manufacturing sites in several African countries were reviewed and Zenufa in **Tanzania** was selected. Zenufa had the advantage of its presence in the **Democratic Republic of the Congo (DRC)**, a country highly plagued by malaria and where ASAQ is the recommended treatment.

A technology transfer contract with Zenufa was signed in March 2011. Zenufa required support from DNDi for technology transfer with a special emphasis on Good Manufacturing Practice (GMP). The partners for the technology transfer were Bertin Pharma (Bordeaux), who had previously partnered with DNDi for the initial ASAQ pharmaceutical development up to the industrial scale-up phase, and AEDES, responsible for the operational and financial management of the project, with support from OTECI. Sanofi also supported the project using its experience of having its ASAQ manufacturing site in **Morocco**. In October 2014, the Tanzanian Food and Drug Administration granted Zenufa Good Manufacturing (GMP) status, and registration batches were manufactured for which registration as well as WHO pre-qualification dossiers are expected to be filed in 2015.

*DNDi
Africa*

Data management centre in Africa – aiming for quality excellence

The DNDi Africa Regional Office has been running its own clinical trial Data Centre since 2004. The centre is part and parcel of a clinical trial management group based in the DNDi Africa office and is

responsible for data management and analysis to facilitate activities carried out by DNDi and LEAP in Africa. The centre has evolved its capacity to produce data based on international standards, *i.e.* International Conference on Harmonization (ICH) and Good Clinical Practice (GCP), by using GCP-compliant open source solutions, such as OpenClinica (www.openclinica.com), together with in-house built software for query management to deliver quality data in the region. In 2014, the Data Centre was engaged in a broader process of quality management, which aims at ISO9001 certification in the near future.

Clinical trial capacity

RedeLeish network to build expertise for leishmaniasis in Latin America

In order to bring together a collaborative network for the promotion and exchange of information on treatment and diagnosis, and to boost clinical research for leishmaniasis in Latin America, the Network of Investigators and Collaborators was formed in 2013. Initially mainly in **Brazil**, the network began to extend to researchers and experts from other Latin American countries, notably at a key gathering of some 60 regional experts from seven Latin American countries, hosted in Rio de Janeiro in September 2014.

*DNDi
Latin
America*



(1) Furtado T, Franzen S, van Loggerenberg F, Carn G, Grahek S, McBride M, et al. (2014) Strengthening Neglected Tropical Disease Research through Enhancing Research-Site Capacity: An Evaluation of a Novel Web Application to Facilitate Research Collaborations. *PLoS Negl Trop Dis* 8(11): e3225. doi:10.1371/journal.pntd.0003225



Supported by DNDi, the RedeLeish specific objectives are to bring together leishmaniasis experts in Latin America to increase collaboration and maximize existing resources and expertise in areas where serious gaps exist. The network also aims to strengthen institutional capacity for clinical research and to identify priority needs in the development of research projects whilst contributing to the implementation of strategic policies and research priorities. Finally, the network will promote the harmonization of clinical trial methodologies and design in the region.

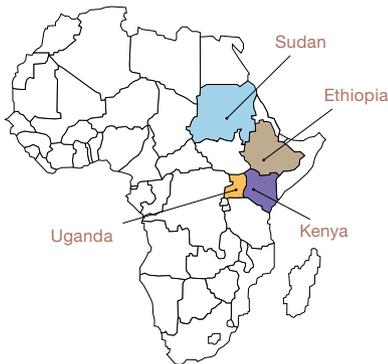


Filariasis platform to define future patient needs

In 2014, the filariasis programme aimed at fine-tuning the target product profile for a macrofilaricide as well as determining future patient needs and evolution of the disease epidemiology. Several expert meetings were held, notably with clinical trial investigators from the Democratic Republic of the Congo. In addition, these meetings aimed at refining the clinical development plans for onchocerciasis and lymphatic filariasis. The Joint Action Forum of APOC in Addis Ababa was attended, and the plans for a new DNDi filariasis clinical research platform, to be based on an in-depth stakeholder analysis, began to take shape. The platform structure will be based on the models of other DNDi disease-specific platforms in Africa, notably LEAP and the HAT Platform.



LEISHMANIASIS EAST AFRICA PLATFORM (LEAP)



Founded: 2003 in Khartoum, Sudan

Over 60 individual members,
representing over 20 institutions



The LEAP platform aims to strengthen clinical research capacity, which is lacking in part due to the remoteness and geographical spread of the patients, most of whom live in the most impoverished regions of Africa. The platform is also a base for ongoing educational cooperation between the countries in the East African region and standardization of procedures and practices in the region, within the scope of local regulations. LEAP evaluates, validates, and registers new treatments that address regional needs for visceral leishmaniasis.

Treatment and access

A roundtable discussion on Access to SSG&PM in Eastern Africa was held during the first LEAP Scientific Conference in Ethiopia. Pharmacovigilance (PV) Steering Committee meetings to disseminate results of the PV study to stakeholders from Ethiopia and Sudan were held in Ethiopia. Participants included representatives from Ministries of Health, Drug Regulatory Authorities including EFMHACA, WHO, and LEAP members.

Capacity building

Good Clinical and Laboratory Practices (GCLP) training in Gondar, Ethiopia, was delivered to **36 laboratory technicians** in accordance with the GCLP principles. The HIV/VL LEAP 0511 protocol training and GCLP refresher was carried out in Ethiopia. The Randox International Quality Assessment Scheme RIQAS training was conducted for laboratory technicians to improve their understanding of the RIQAS process. The 20th Principal Investigators (PI) meeting was held in Nairobi (Kenya) to evaluate progress made by LEAP over the last ten years and to plan for the next decade. The 20th and 21st LEAP meetings

were held in Kampala (Uganda) and Bahir Dar (Ethiopia).

Clinical trials

Recruitment into the HIV/VL study to evaluate the efficacy of AmBisome® +miltefosine combination and of a higher-dose AmBisome® monotherapy in Ethiopian patients with HIV/VL co-infection

commenced in 2014. The study is being conducted in Gondar and at the MSF Abudurafi site.

Communications

The second and third editions of the LEAP Newsletter were published in April and September 2014.



PARTNERS: Kenya Medical Research Institute (KEMRI), Kenya; Institute of Endemic Diseases (IEND), University of Khartoum, Sudan; MSF; Leishmaniasis East Africa Platform (LEAP); BaseCon, Denmark; Utrecht University, The Netherlands; Koninklijk Instituut voor de Tropen, The Netherlands

2014 HIGHLIGHTS

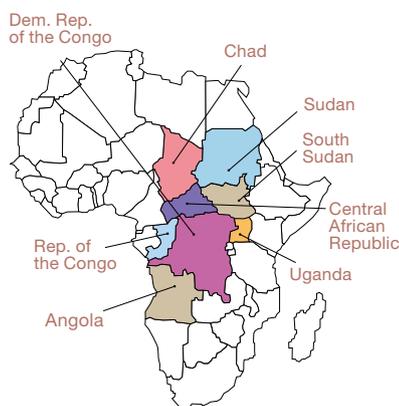
- **LEAP 'Scientific Conference'**, held in Ethiopia, with over 130 participants from some 14 countries, provided updates from LEAP activities and engaged a broad range of African researchers in VL and other neglected disease areas
- **Results from SSG&PM pharmacovigilance study** presented

NUMBER OF SITES IN 2014: 7

In 2014, the LEAP Platform was operational at several clinical trial sites: Gondar and Arba Minch (Ethiopia), Kimalle and Kacheliba (Kenya), Amudat (Uganda), Doka and Kassab (Sudan).

PEOPLE TRAINED IN 2014: 275

HUMAN AFRICAN TRYPANOSOMIASIS (HAT) PLATFORM



Founded: 2005 in Kinshasa, Democratic Republic of the Congo
Over 120 individual members, representing over 20 institutions

The HAT platform builds and strengthens treatment methodologies and clinical trial capacity in sleeping sickness-endemic countries, so that new treatments for this fatal disease can be rapidly and effectively evaluated, registered, and made available to patients. After the success of the Nifurtimox-Eflornithine Combination Therapy (NECT), included in the WHO List of Essential Medicines for the treatment of stage 2 HAT for adults and children, and its widespread uptake, the primary goals of the HAT Platform are to develop appropriate clinical trial methodologies for entirely new treatments tested for sleeping sickness, overcome system challenges related to administrative and regulatory requirements, build new and enhance existing clinical trial capacity (human resources, infrastructure, equipment), and share information and strengthen ties among endemic countries.

Treatment and access

In 2014, with the addition of Nigeria, NECT became first-line treatment for stage 2 sleeping sickness in all *T.b. gambiense*-affected countries, including for children.

Clinical trials

Fexinidazole: By the end of 2014, ten clinical trial sites had included 359 patients in fexinidazole Phase II/III clinical study in DRC and CAR. The two new complementary cohort trials, one for stage 1 and early stage 2 in adults, included 110 patients, and another with children between 6 and 14 years of age included 56 patients. A total of 525 patients have been included in the three trials thus far.

Capacity strengthening

The HAT Platform and EANETT co-organized an international scientific conference on HAT in September.

A training on Trypanosomiasis management was co-organized between the national sleeping sickness control programme of Chad and the HAT Platform in May in Bodo (Chad) with the support of DRC national control programme experts and the participation of **22 doctors and nurses**. The Platform supported and participated in the 6th International Course on Trypanosomiasis, organized by the association 'Les Trypanautes' with the support of WHO and DNDi. The Platform was also involved in the preparation for the investigators' meeting for the fexinidazole trials in Kinshasa for 30 participants.

Communications

Two HAT Platform Newsletters were published in July and December 2014.



Dr Augustin Kadima Ebeja, HAT Platform Coordinator, moved to a new position with the World Health Organization in November 2014. Dr Ebeja spent

eight years of his life building the HAT platform, working tirelessly to inspire his colleagues in HAT endemic countries to 'keep up the good fight' against the disease and to maintain the important capacity for clinical trials. We wish to thank Dr Ebeja for his immense service to DNDi and to HAT patients. We are also happy he is still working in the field of neglected diseases with the WHO in the DRC as their NTD focal point.

PARTNERS: 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 the Congo, Republic of Congo, South Sudan, Sudan, Uganda; Drugs for Neglected Diseases *initiative* (DNDi), Switzerland; Swiss Tropical and Public Health Institute (Swiss TPH), Switzerland; Institute of Tropical Medicine-Antwerp, Belgium; Institut National de Recherche Biomédicale (INRB), DRC; University of Makerere, Uganda; Kenya Agricultural Research Institute – Trypanosomiasis Research Centre (KARI-TRC), Kenya; Tropical Medicine Research Institute (TMRI), Sudan; Institut Pasteur Bangui, CAR; Médecins Sans Frontières (MSF); Foundation for Innovative New Diag-

nostics (FIND), Switzerland; Eastern Africa Network for Trypanosomiasis (EANETT); Centre interdisciplinaire de Bioéthique pour l'Afrique Francophone (CIBAF); WHO Department of Neglected Tropical Diseases as observer. Two new members joined in 2014: The National Sleeping Sickness Control Programme of Guinea and the INZI Project of the University of Edinburgh.

2014 HIGHLIGHTS

- **Opening of one additional trial site** for fexinidazole study recruitment (increase from 9 to 10)
- **Three ongoing trials** to study fexinidazole in both stages of the disease and in children
- **3rd HAT Platform-EANETT conference** in September, in Kinshasa, with 160 participants

NUMBER OF SITES IN 2014: Ten (eight sites actively including patients, with the remaining two doing follow up visits only). In 2014, the HAT platform was operational at ten sites for the fexinidazole study: Four sites were opened in the Democratic Republic of the Congo in 2012 (Bandundu, Vanga, Masi Manimba, and Dipumba), four sites were opened in 2013 (Dingila, Mushie, Katanda, and Isangi), and one in 2014 (Bagata). The latter site was opened to compensate for two issues: the 2013 trial interruption at the site in Batangafo, Central African Republic, and the steep reduction of cases in Dingila in DRC, which led to the trial stop there in January 2014. Follow-up of already-included patients is carried out at both sites.

PEOPLE TRAINED IN 2014: 235

CHAGAS CLINICAL RESEARCH PLATFORM (CCRP)



Countries highlighted on the map represent Chagas disease-endemic Latin American countries with platform members. Other CCRP members' countries not indicated on this map are listed below.

Founded: 2009 in Uberaba, Brazil

Over 80 institutions represented from 22 countries, bringing together over 250 people



To support its R&D activities on Chagas disease, DNDi launched the Chagas Clinical Research Platform (CCRP) in 2009. The platform brings together partners, experts, and stakeholders to provide support for the evaluation and development of new treatments for Chagas disease. The CCRP aims to facilitate clinical research, provide a forum for technical discussions, develop a critical mass of expertise, and strengthen institutional research capacities. In addition, it identifies and reviews research priorities and needs, works towards standardization of trial methodology to assess drug efficacy for treating *T. cruzi* infection, and reviews alternatives for using currently approved drugs (new schemes, doses, combination) and special scenarios (resistance).

Training, treatment, and access

In 2014, several meetings and trainings took place in regard to technical discussions and strengthening capacities for research on new treatments and on implementation of Chagas treatments including:

- Experts' meeting about New Treatment Regimens of Benznidazole, Geneva (Switzerland)
- Experts' Meeting (NHEPACHA Network) Barcelona (Spain)
- Lessons Learned in Clinical Trials and Animal models of Chagas disease, Mexico City (Mexico)
- Congenital Chagas Management, Mexico City (Mexico)

In 2014, the platform had a greater involvement in patient access to treatment

issues as a result of a survey conducted among members of the platform and various decision makers. Subsequently, the CCRP was present at all of the Regional Initiatives meetings, convened by PAHO and the National Programmes, where access issues were discussed including: The Andean Countries Initiative (IPA), Bogota (Colombia) with participants from Colombia, Ecuador, Peru. The Amazonian Countries Initiative, Rio Branco (Brazil). This meeting was parallel to the Congress of Tropical Medicine in Brazil (MedTrop), and the Southern Cone Countries Initiative, Arequipa (Peru), where the main countries recognized the lack of access to treatment and committed to investing more in R&D.

The CCRP also strongly supports the benznidazole registration process in

Mexico and is now encouraging its procurement by state programmes. Surveys were also conducted in order to assess the use of the *Demand Forecasting* tool. An update of the tool was produced and the CCRP is encouraging its proper use by national programmes.

Clinical trials

In 2014, two studies were supported by members of the CCRP: fexinidazole and benznidazole drug-drug interaction in Argentina (see p. 35) and the fexinidazole study in Bolivia (see p. 35).

Communications

The CCRP Web Forum continued to grow. This online workspace, created in 2011, highlights project milestones, provides clinical trial updates, links up CCRP members, and promotes events.

PARTNERS: Pan American Health Organization (PAHO); Department for the Control of Neglected Tropical Diseases, (WHO); Ministries of Health and National Control Programmes of high-burden endemic countries (Argentina, Bolivia, Brazil, Mexico, Paraguay, Honduras); Médecins Sans Frontières; International Federation of People Affected by Chagas Disease (FINDECHAGAS) 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 (CONICET); Fundación Mundo Sano, ELEA

BRAZIL: Instituto Oswaldo Cruz; Instituto de Pesquisa Evandro Chagas–Fiocruz; Centro de Pesquisas René Rachou–Fiocruz; LAFEPPE

BOLIVIA: Universidad Mayor de San Simón; Platform of Integral Care for Patients with Chagas Disease; CEADES

SPAIN: ISGlobal and Barcelona Centre for International Health Research (CRESIB); Hospital Clinic Barcelona; Instituto de Parasitología y Biomedicina López Neyra; Consejo Superior de Investigaciones Científicas; Instituto Catalán de la Salud

MEXICO: Instituto Carlos Slim de la Salud; Instituto Nacional de Salud Pública

COLOMBIA: CIMPAT; CIDEIM; PECET; Chagas Network

SWITZERLAND: Geneva University Hospitals

FRANCE: Institut de Recherche pour le Développement

USA: Merck; Sabin Vaccine Institute

JAPAN: Eisai Co. Ltd

GERMANY: Bayer HealthCare

UNITED KINGDOM: The Global Health Network

OTHER: Researchers from Universities of Colombia, Venezuela, Bolivia, USA, Canada, Brazil, and Paraguay

2014 HIGHLIGHTS

- **Creation of a Scientific Advisory Committee**, which contributed to defining the agenda of the Technical Sessions as well determining the future editorial lines of the CCRP newsletter

- **Annual Chagas Clinical Research Platform Meeting**, a satellite event of XIII ICOPA (International Congress of Parasitology) in Mexico, was held in August, and attended by over 120 participants representing national programmes, patient associations, research centres, clinical care centres, NGOs, and pharmaceutical companies

NUMBER OF SITES IN 2014: Three (one in Argentina – drug-drug interaction of E1224 and benznidazole combination; and two in Bolivia – fexinidazole)

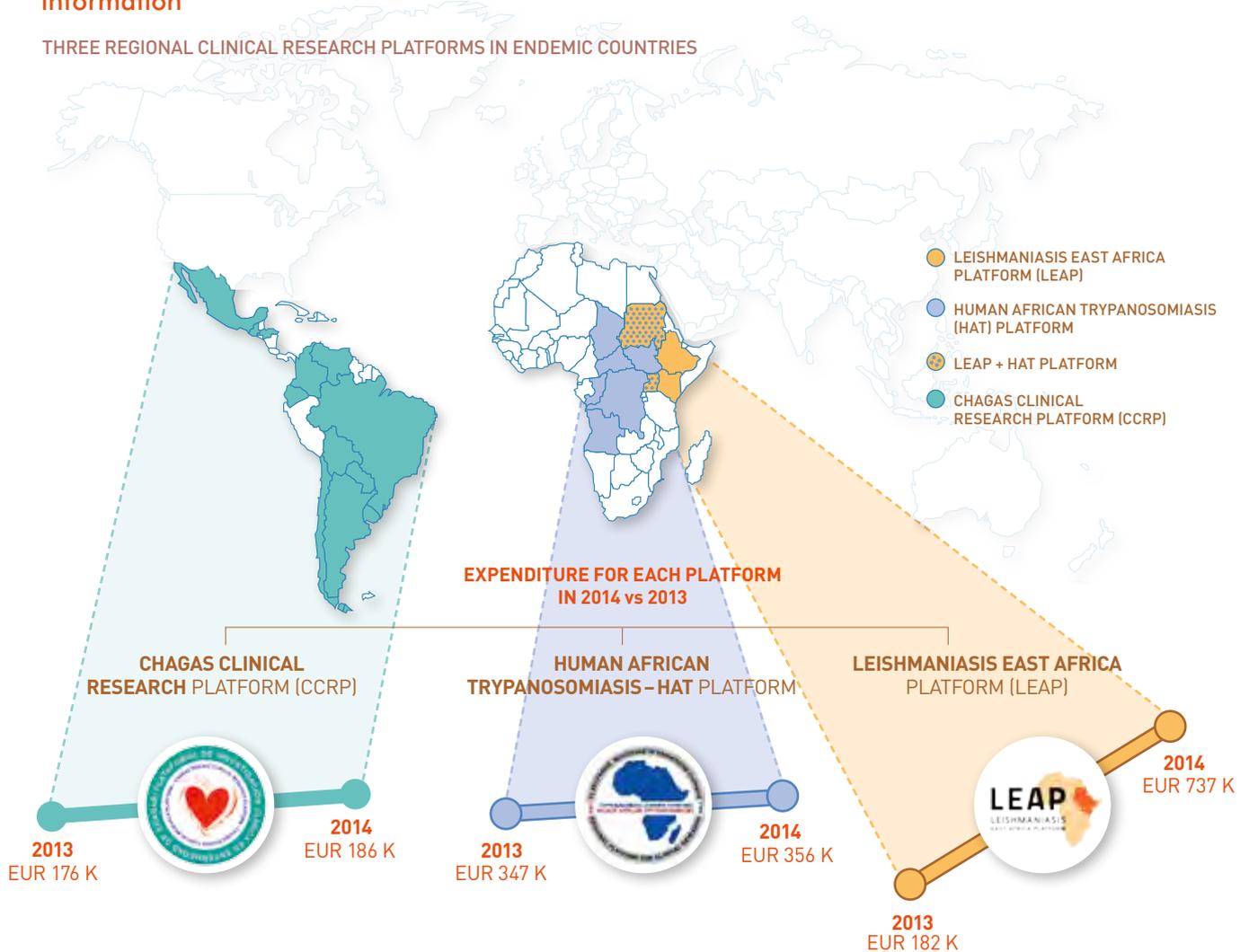
PEOPLE TRAINED IN 2014: 226



2014 KEY FINANCIAL PERFORMANCE INDICATORS

Significant increase of investment in regional disease-specific networks to build capacity, conduct clinical research in endemic countries, facilitate treatment access and disseminate information

THREE REGIONAL CLINICAL RESEARCH PLATFORMS IN ENDEMIC COUNTRIES



The overall Chagas (CCRCP) and HAT platform budgets remain stable between 2013 and 2014 (respectively EUR 0.2 M and EUR 0.35 M per year per platform). The Leishmaniasis (LEAP) platform costs were multiplied by four (+ EUR 0.6 M) due to the fact that some clinical trial sites have been maintained (mainly the team) even though they were not involved in R&D activities. The costs of these sites (Kimalael and Kacheliba clinical trial sites of Kemri in Kenya, Amudat Hospital with Makerere University in Uganda; Arba Minch Hospital in Ethiopia) were removed from R&D expenditures and allocated toward the strengthening capacities budget. Patients treated outside clinical trials in 2014 in the seven VL clinical trial sites reached 1,533.



2014 KEY FINANCIAL PERFORMANCE INDICATORS

Evolution of clinical sites

PLATFORMS FACILITATED CLINICAL RESEARCH IN RESOURCE-POOR AND RURAL SETTINGS

CHAGAS CLINICAL RESEARCH PLATFORM

In 2014, the platform was operational in two sites for Fexinidazole (Bolivia) and one site in Argentina for the Drug-Drug interaction with Benznidazole.

3 Clinical sites in 2014

HAT PLATFORM

In 2014, the HAT platform was operational in ten sites for the fexinidazole study: four sites were opened in DRC in 2012 (Bandundu, Vanga, Masi Manimba, and Dipumba) and five sites were opened in 2013: Dingila, Mushie, Katanda, and Isangi. A tenth site was opened in October 2014 to compensate for an inclusion stop in Batangafo in CAR where recruitment was suspended in December 2013 due to insecurity, and Dingila in DRC where the steep reduction of cases led to the stop in January 2014, while maintaining follow-up of already-included patients.

10 Clinical sites in 2014

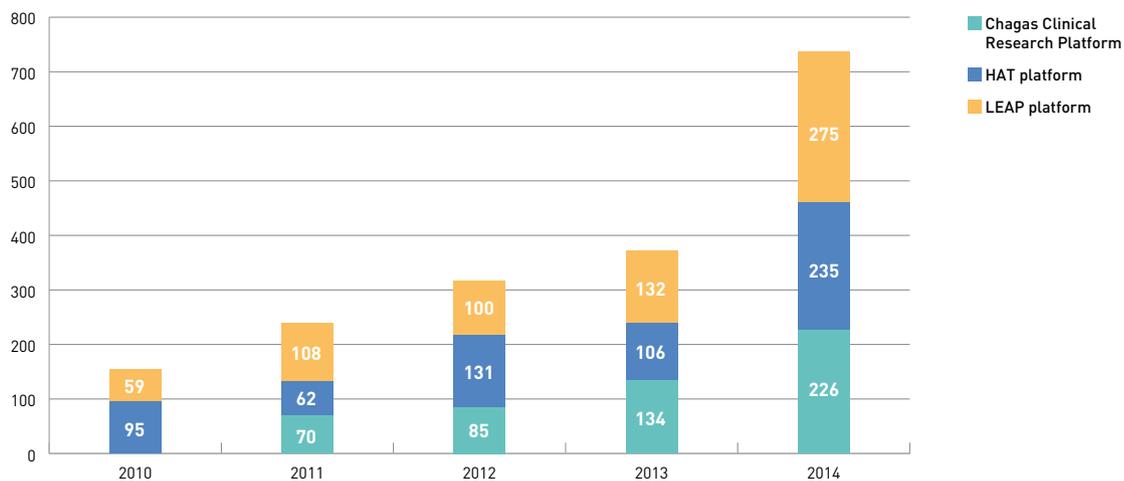
LEISHMANIASIS EAST AFRICA PLATFORM (LEAP)

In 2013, the LEAP platform was operational in seven DNDi clinical trial sites (the same as 2012 and 2014): Kassab and Doka (Sudan), Amudat (Uganda), Kimaltel and Kacheliba (Kenya), and Arba Minch and Gondar (Ethiopia).

7 Clinical sites in 2014

Developing research capacities in endemic regions

PEOPLE TRAINED BETWEEN 2013 AND 2014 ALMOST DOUBLED (+98%)





Advocacy, Communications & Fundraising

After the Ebola crisis, the need for greater mobilization

In the wake of the Ebola crisis, global opinion has shifted and voices have converged on the need for greater mobilization by governments and global health stakeholders to secure the political and financial commitments required to address public health priorities in a sustainable way, with public leadership at the helm. A recurring theme throughout all these global health concerns is the dearth of innovation for new health tools – for example diagnostics, drugs, and vaccines – to respond to clearly-identified and well-documented patient needs.

The current R&D landscape has several distinctive shortcomings: R&D priorities do not adequately address patients' needs and do not sufficiently emanate from

low- and middle-income countries; medical innovation is not linked to equitable access; and market-based incentives aligned with the intellectual property system generally fail to address the health needs of poor people.

WHO/CEWG process toward new incentive mechanisms for R&D

It is with a view to addressing these shortcomings that the WHO-mandated Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG) process selected several 'demonstration projects' that aim to employ collaborative approaches, including open knowledge approaches to R&D; promote the de-linkage of the cost of R&D

from product price; propose and foster financing mechanisms including innovative, sustainable, and pooled funding; and provide evidence in support of long-term, sustainable solutions to financing and coordination of R&D for neglected diseases.

One of the demonstration projects, the DNDi 'Leishmaniasis Global R&D and Access Initiative' aims to fill certain critical R&D gaps and provide health tools in support of the WHO control and elimination goals for visceral leishmaniasis (VL). The *initiative's* objective is to demonstrate that health R&D can be incentivized and optimized through innovative mechanisms, such as the NTD Drug Discovery Booster (see p. 17). Ultimately, these demonstration projects will examine the possibility of financing R&D, notably through pooled funding, increasing knowledge and decreasing the risk of failure, raising the resources needed while capitalizing on existing resources, and developing affordable health tools while applying the principle of de-linkage.

The follow up to the CEWG process received strong support and there was a consensus on the establishment of a pooled fund for R&D programmes, with concrete funding commitments. DNDi published a paper in 2014 entitled 'Considerations for the New International Fund for R&D', which examined the potential parameters of such an R&D fund to meet the public health needs of developing countries.

While there are encouraging signs of improvement, there is still a need to ensure that a framework is put into place to enable an adequate global response to the current crises in innovation and access, notably with the following key principles:

- Patient needs-driven priority setting;
- De-linkage of the cost of R&D from the price of products delivered;
- Integration of global health R&D monitoring, coordination, and financing;
- Creation of a more enabling regulatory environment to expedite approval of essential medicines; and
- Setting up of sustainable financing mechanisms, including through a global health pooled fund for long-term innovation.

A push to reform the US Priority Review Voucher programme

DNDi has long advocated for new incentive mechanisms to stimulate R&D for neglected patients. One such mechanism, the US Food and Drug Administration (FDA) Priority Review Voucher (PRV), holds promise, but requires reform in order to represent a true 'win-win' for both companies and neglected patients. Created in 2007, the PRV programme awards a voucher to companies that receive FDA approval for a drug against one of a list of neglected diseases, unfortunately not including Chagas disease. PRVs can be used to fast track a drug application of the company's choice or can be sold to other companies.

In July 2014, DNDi North America, MSF USA, and the TB Alliance wrote a joint letter to the US Congress expressing concern about the design of the PRV and recommending a number of ways to improve it. Among them: PRVs must be granted only in return for new investments in R&D, patient access must be guaranteed, and PRVs granted must meet real public health needs. MSF and DNDi also spelt out their concerns in a joint blog in PLOS Speaking of Medicine,⁽¹⁾ in which they advocated for changes to the design of the PRV to ensure it both stimulates new R&D and guarantees affordable access to the medicines for which it is granted.

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(1) <http://blogs.plos.org/speakingofmedicine/2015/01/20/fda-voucher-leishmaniasis-treatment-can-patients-companies-win/>

Launch of the Paediatric HIV Treatment Initiative (PHTI) in 2014

To scale-up treatment for children with HIV, DNDi, UNITAID, the Medicines Patent Pool (MPP), and the Clinton Health Access Initiative launched the Paediatric HIV Treatment Initiative (PHTI). The PHTI focuses on overcoming the barriers to developing and delivering specific paediatric formulations and combinations appropriate for children, by working to accelerate development of priority paediatric ARVs within the next three years. The *initiative* does this through working with drug manufacturers to develop and supply ARVs, and aims to increase access by facilitating regulatory approval, adoption, and rapid uptake in hard-hit countries as soon as drugs are available. A launch event took place on the eve of the 67th World Health Assembly, in the presence

of ministers of health from over fifteen countries, including Brazil, Chile, Mauritius, and South Africa; industry and global public health leaders; as well as senior representatives from the HIV/AIDS community.



'Of the 3.3 million children with HIV in the world, there is a great burden in South Africa. Current treatment options are insufficient and there is little to no incentive for drug development. The most commonly used regimens used today for children with HIV have toxicity and formulation concerns. New adapted treatments are an emergency, and a dream that must be made reality.'

H.E. Aaron Motsoaledi, South African Minister of Health

ICOPA XIII, Mexico City: test and treat Chagas disease patients

In August 2014, over 1,300 participants from 81 countries gathered for the first time in a Latin American country for the 13th International Congress of Parasitology (ICOPA). DNDi participated in nine symposia and satellite meetings, and Dr Bernard Pécoul, DNDi Executive Director, delivered a plenary presentation on 'R&D for Neglected Patients: Evolution over a Decade and Future Perspectives on Access & Innovation' in which he addressed the significant changes in the neglected disease R&D approach in recent years, examined progress made in Chagas disease, and surveyed the remaining gaps and challenges for innovation and access.

During the congress, the **Global Chagas Disease Coalition** hosted an event for key Chagas disease stakeholders, entitled 'Let's Raise Our Voice'. The gathering was aimed at mobilizing the Chagas community to urgently address the need to test and treat Chagas disease patients and rapidly improve the current treatment rate, which is only one percent. The event gathered 200 participants from governments, civil society, the healthcare sector, research groups, and patients to discuss simple actions, such as following WHO treatment recommendations for both acute and chronic phases of Chagas disease, and raising awareness of the disease within primary healthcare to boost patient access to diagnosis and treatment.



Selected scientific articles and press coverage

Drug discovery for human African trypanosomiasis: Identification of novel scaffolds by the newly developed HTS SYBR Green assay for *Trypanosoma brucei* by Faria J, Moraes CB, Song R, Pascoalino BS, Lee N, Siqueira-Neto JL, Cruz DJM, Parkinson T, Ioset JR, Cordeiro-da-Silva A, Freitas-Junior LH. *Journal of Biomolecular Screening* 2014, doi:10.1177/1087057114556236.

Lopinavir/ritonavir plus lamivudine and abacavir or zidovudine dose ratios for paediatric fixed-dose combinations by Bouazza N, Foissac F, Fauchet F, Burger D, Kiechel JR, Treluyer JM, Capparelli EV, Lallemand M, Urien S. *Antiviral Therapy* 2014, doi:10.3851/IMP2876.

Chagas disease drug discovery: Toward a new era by Chatelain E. *Journal of Biomolecular Screening* 2014, doi: 10.1177/1087057114550585.

Visceral leishmaniasis and HIV coinfection in the Mediterranean region by Monge-Maillo B, Norman FF, Cruz I, Alvar J, López-Vélez R. *PLOS NTDs* 2014, doi:10.1371/journal.pntd.0003021.

The role of modern drug discovery in the fight against neglected and tropical diseases by Burrows JN, Elliott RL, Kaneko T, Mowbray CE, Waterson D. *Medicinal Chemistry Communication* 2014, doi:10.1039/C4MD00011K

The pharmacokinetics and acceptability of lopinavir/ritonavir minitab sprinkles, tablets and syrups in African HIV-infected children by Musiime V, Fillekes Q, Kekitiinwa A, Kendall L, Keishanyu R, Namuddu R, Young N, Opilo W, Lallemand M, Walker AS, Burger D, Gibb DM. *JAIDS Journal of Acquired Immune Deficiency Syndromes* 2014, doi: 10.1097/QAI.000000000000013.

Determination of an optimal dosing regimen for fexinidazole, a novel oral drug for the treatment of human African trypanosomiasis: first-in-human studies by Tarral A, Blesson S, Valverde Mordt O, Torrelee E, Sassella D, Bray MA, Hovsepian L, Evène E, Gualano V, Felices M, Strub-Wourgaft N. *Clinical Pharmacokinetics* 2014, doi:10.1007/s40262-014-0136-3.

Safety and efficacy of single dose versus multiple doses of AmBisome® for treatment of visceral leishmaniasis in eastern Africa: A randomised trial by Khalil EAG, Weldegebreal T, Younis BM, Omollo R, Musa AM, Hailu W, Abuzaid A, Dorlo TPC, Hurissa Z, Yifru S, Haleke W, Smith PG, Ellis S, Balasegaram M, EL-Hassan AH, Schoone GJ, Wasunna M, Kimutai R, Edwards T, Hailu A. *PLOS Neglected Tropical Diseases* 2014, 8⁽¹⁾: e2613. doi:10.1371.

Plasmodium falciparum clearance in clinical studies of artesunate-amodiaquine and comparator treatments in sub-Saharan Africa, 1999–2009 by Zwang J, Dorsey G, Mårtensson A, d'Alessandro U, Ndiaye JL, Karema C, Djimde A, Brasseur P, Sirima SB, Olliaro P. *Malaria Journal* 2014, doi:10.1186/1475-2875-13-114.

Fixed dose artesunate amodiaquine - a phase IIb, randomized comparative trial with non-fixed artesunate amodiaquine by Ogutu B, Juma E, Obonyo C, Jullien V, Carn G, Vaillant M, Taylor WRJ, Kiechel JR. *Malaria Journal* 2014, doi:10.1186/1475-2875-13-498.



'How virtual R&D is leading to treatments for neglected diseases'
JUNE 2014

EL MUNDO
'Firman alianza para estudio de enfermedades olvidadas'
26 NOVEMBER 2014

EL FINANCIERO
'Mal de Chagas, el asesino silencioso de América Latina'
24 APRIL 2014

The East African
HIV/AIDS complicates fight against kala azar
21 OCTOBER 2014

FINANCIAL TIMES
'Diagnostic tools as essential as drugs in the fight to control disease'
9 OCTOBER 2014

The New York Times
'In Africa, broader ethical considerations are common'
1 DECEMBER 2014

Science Africa
NEW MALARIA DRUG
7 NOVEMBER 2014

EL HUFFINGTON POST
'Chagas Disease: A 2014 World Cup Yellow Card'
22 MAY 2014

FOLHA DE S. PAULO
'Diretor de ONG que trata de doenças negligenciadas critica falta de doações à pesquisa científica'
8 MARCH 2014

Le Monde
'UN MÉDICAMENT "MADE FOR AFRICA"
2 OCTOBER 2014

(1) <http://blogs.plos.org/speakingofmedicine/2015/01/20/fda-voucher-leishmaniasis-treatment-can-patients-companies-win/>

Nearly EUR 65 million additional funding secured in 2014

The year 2014 marked a cornerstone for DNDi's regional offices in their involvement in raising new funds.

DNDi North America received its first major public grant of USD 10 million provided by USAID. With this first-ever grant for R&D for neglected tropical diseases from USAID, DNDi will target the development of new oral drugs for onchocerciasis and lymphatic filariasis.

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DNDi Latin America signed an unprecedented agreement with the public organization Ruta-N for the development of innovative health tools targeting leishmaniasis, with a shared investment of USD 647,500 over a period of two years in **Colombia**. In **Brazil**, a partnership with the Brazilian Development Bank (BNDES) was agreed and a special 'Award for Innovation in Social Technology' of EUR 67,000 was granted to DNDi Latin America by the public Science and Technology Innovation Agency (FINEP). Private donors also continued to provide large donations for activities in the region.

*DNDi
Latin
America*

DNDi **Japan** continued to strengthen its involvement in fundraising activities in the country with the provision of a second grant of EUR 2.8 from the Global Health Innovative Technology Fund (GHIT) to develop new oral treatments for Chagas disease in partnership with Eisai.

*DNDi
Japan*

Another critical advancement was the provision of a new form of support from the Bill and Melinda Gates Foundation. Until this year, the Foundation financially supported earmarked projects, but with USD 60 million in 'portfolio funding', investments can be now used across three disease areas. Greater R&D flexibility and leveraging vital funding from other engaged donors are notable benefits. The Foundation also allocated a supplemental investment of USD 4.3 for fexinidazole for sleeping sickness and awarded DNDi an 'Innovative Fund Award' of USD 1 million. In addition, a number of donors reiterated their commitments to DNDi such as DFID (UK) with a supplemental grant of GBP 3 million. Private foundations such as ARPE and Starr International also continued to support DNDi.

DNDi has raised EUR 353 million since its inception in 2003, with 51% from public institutional donors.

Key contributions received in 2014

Bill & Melinda Gates Foundation / USA

USD 60 million (2015 – 2019)

Building upon the long-term partnership between DNDi and the Bill and Melinda Gates Foundation that began with a first grant in 2007, the Foundation granted USD 60 million through a new form of support called 'portfolio funding' that allows DNDi to use the grant across three disease areas (sleeping sickness, visceral leishmaniasis, and filarial diseases).

USD 1 million (Innovative Fund Award, 2014 – 2015)

The Foundation awarded DNDi a special grant of USD 1 million over a period of two years. This 'Innovative Fund' was awarded to six product development partnerships to commend their efforts to date and to stimulate exploration and innovation to identify, develop, and deliver new health tools.

USD 4.3 million for HAT

The Foundation provided a supplemental grant of USD 4.3 million to support the fexinidazole project for sleeping sickness, bringing the total of this grant to USD 19.4 million.

United States Agency for International Development (USAID) / USA

USD 10 million (2014 – 2019)

USAID awarded USD 10 million to DNDi to develop new treatments for onchocerciasis and lymphatic filariasis over five years. This is the first-ever USAID grant for R&D for neglected tropical diseases. The Bill and Melinda Gates Foundation is providing the mandatory matching of this project, included in the portfolio funding listed above.

Department for International Development (DFID) / UK

GBP 3 million (2014)

DFID provided DNDi with supplemental funding of GBP 3 million for the year 2014 to be used as core funding (excluding paediatric HIV activities). DFID's total contribution to DNDi has reached GBP 64.4 million since 2006.

Global Health Innovative Technology Fund (GHIT) / JAPAN

EUR 2.8 million (2014 – 2015)

The Japan-driven Global Health Innovative Technology Fund (GHIT), which celebrated its one-year anniversary in 2014, awarded a second grant of EUR 2.8 million to DNDi to support a Phase II, proof-of-concept study of the E1224-benzimidazole combination over a two-year period, in collaboration with the Japanese pharmaceutical company Eisai.

Ruta-N / City of Medellin / COLOMBIA

USD 317,500 (2015 – 2016)

Ruta-N and DNDi Latin America signed an unprecedented agreement for the development of health innovation with a shared investment of USD 647,500 for a period of two years in Latin America. The collaboration begins with a programme dedicated to leishmaniasis. Ruta-N is based in Medellin, Department of Antioquia, Colombia, and focuses on knowledge as a primary source for R&D.

Science and Technology Innovation Agency (FINEP) / BRAZIL

Brazilian Real 67,000 (2015)

DNDi Latin America received the FINEP Award for Innovation in Social Technology in recognition of its innovative R&D model that delivered a new antimalarial drug (ASMQ FDC) developed in Brazil.

IN MEMORIAM



On 13 June 2014, Dr Richard Rockefeller – a family physician who was instrumental to the creation of DNDi in 2003, as part of his long-standing commitment to Médecins Sans Frontières (MSF) – died tragically in a plane crash. DNDi deeply admired Richard and his dedication to the alleviation of human suffering, including his strong support for urgently needed R&D for neglected patients. He was a wonderful friend and advocate and is terribly missed. In December 2014, the Rockefeller Brothers Fund provided DNDi a one-time, one-year, general operating grant of USD 25,000 via the Staff Grantmaking Program to honour Dr Richard Rockefeller.

2014 KEY FINANCIAL PERFORMANCE INDICATORS

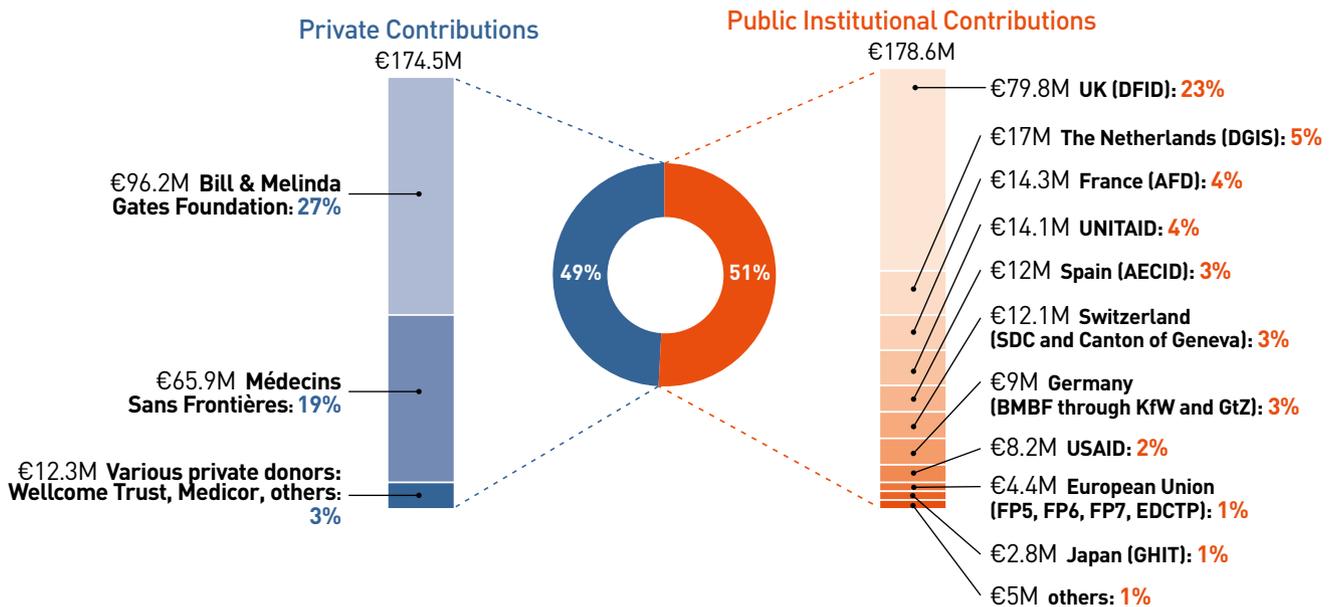
Maintaining balanced and diversified funding is essential to DNDi's vision and independence

To develop its activities and meet its objectives, DNDi seeks diversified sources of funding from public and private sources, which include financial contributions from governments, public institutions, private individuals, foundations, founding partners, and innovative funding mechanisms. The diversification of donors increased in 2014 with four new donors. DNDi welcomed: USAID, Ruta' N, FINEP, and the Rockefeller Brother Foundation. Among these new donors, two are from endemic countries.

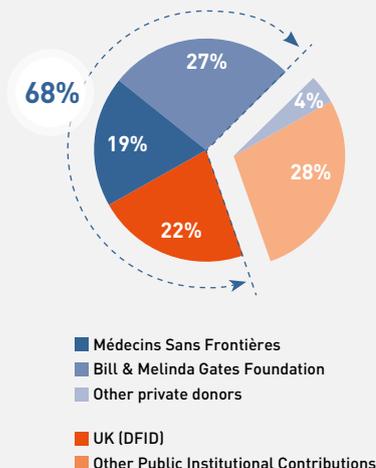
Concerted efforts were made to ensure that no one donor contributes more than approximately 25% toward DNDi's business plan and, that at maturity half of DNDi's budget is covered by public funds and half by private funds.

In 2013, public funding (projected to 2018) was at 57%, with 43% private support. In 2014 with secured funds until 2019, the split is much more balanced with public funding at 51% and 49% for private support. This is mainly due to the fact that one of the major private donors (Bill & Melinda Gates Foundation) renewed its long-term commitment until 2019 with broader portfolio support, which amounts to EUR 49.2 M (14% of total income committed).

PLATFORMS FACILITATED CLINICAL RESEARCH IN RESOURCE-POOR AND RURAL SETTINGS



THREE MAIN FUNDERS BETWEEN 2003-2019 CUMULATE 68% OF THE FUNDS COMMITTED TO DNDi



A successful shift toward unrestricted funding

Over the last five years, DNDi managed to maintain a balance between restricted and unrestricted grants. While the ratio is relatively balanced, this requires substantial effort. Unrestricted funding has been part of DNDi's success to date as it allows the organization to respond quickly to research opportunities and also terminate projects that do not meet targeted goals set forth in the business plan. In 2014 DNDi received significant portfolio funding from the Bill & Melinda Gates Foundation which allows a certain degree of risk mitigation within restricted grants because this is supporting three diseases and various projects within each diseases. Portfolio grants were estimated at 18% in 2011, 22% in 2012, 29% in 2013 and 33% of the 2014 total income.

CUMULATED 2003-2019: EUR 353 MILLION



A photograph of a woman with short dark hair, smiling warmly at the camera. She is wearing a dark brown t-shirt. In her arms, she holds a young child with short dark hair, wearing a red top and a blue and white beaded necklace. The background is a blurred outdoor setting with green grass and a white vehicle. A dark purple rectangular box is overlaid on the left side of the image, containing the text 'Financial Report' in white.

Financial Report

2014 Financial statements and audit report

BALANCE SHEET

AT 31 DECEMBER 2014 (with 2013 comparative figures)

<i>(Expressed in EUR)</i>	Notes	2014	2013
CURRENT ASSETS			
Cash and cash equivalents:			
Cash and banks at head office		13,138,390	8,425,396
Cash and banks at regional offices and affiliate		775,596	517,220
Time deposits		18,885,961	13,067,160
Total cash and cash equivalents		32,799,947	22,009,776
Stocks of drugs	3	173,164	189,414
Current accounts and receivables:			
Advances to officers and liaison offices		88,625	73,199
Receivables from public institutional donors		1,434,538	252,127
Other receivables		880,820	1,370,591
Prepaid expenses		595,381	429,298
Total current accounts and receivables		2,999,364	2,125,216
TOTAL CURRENT ASSETS		35,972,475	24,324,406
NON-CURRENT ASSETS			
Tangible fixed assets, net	4	69,806	48,379
Bank guarantee deposits	2.k.	89,483	74,160
Total non-current assets		159,289	122,538
TOTAL		36,131,764	24,446,944
CURRENT LIABILITIES			
Payables		2,433,459	2,339,695
Accrued expenses		1,991,183	1,314,291
Deferred income	7	20,955,657	10,203,966
Provisions	5	233,442	136,558
Total current liabilities		25,613,741	13,994,511
CAPITAL OF THE ORGANIZATION			
Paid-in capital		32,510	32,510
Restricted operating funds	6	114,547	159,846
Unrestricted operating funds		10,370,966	10,260,077
Total capital of the organization		10,518,023	10,452,433
TOTAL		36,131,764	24,446,944

STATEMENT OF OPERATIONS

FOR THE YEAR ENDED 31 DECEMBER 2014 (with 2013 comparative figures)

(Expressed in EUR)

	Notes	2014	2013
INCOME			
Public institutional funding:			
Govern. & public int. organiz. unrestricted		13,460,530	5,600,067
Govern. & public int. organiz. restricted		10,396,427	12,212,969
Total public institutional funding		23,856,957	17,813,036
Private resources:			
Private foundations, corp. and individuals, unrestricted		215,634	507,286
Private foundations, corp. and individuals, restricted		8,383,666	7,726,668
Royalties on drug sales	6	5,762	15,270
Total private resources		8,605,062	8,249,224
Resources from founders:			
Médecins Sans Frontières, unrestricted		4,000,000	4,556,230
Médecins Sans Frontières, restricted		19,102	392,500
Total resources from Founding Partners		4,019,102	4,948,730
Other income:			
Sundry income & reimbursements		74,352	230,666
Other income net		74,352	230,666
TOTAL INCOME	7	36,555,473	31,241,656
SOCIAL MISSION EXPENDITURE			
Research & development expenditure:			
Research & development coordination and supervision	8	3,109,458	2,656,917
Human African trypanosomiasis projects		7,137,019	5,300,867
Leishmaniasis projects		4,398,588	3,929,291
Chagas disease projects		2,803,540	2,627,175
Other diseases projects (malaria, filarial, HIV)		3,983,750	3,229,498
Lead optimization & Portfolio building		6,213,755	5,463,001
Total research & development expenditure		27,646,111	23,206,749
Strengthening capacities	9	2,574,948	1,731,925
Advocacy expenses	10	1,653,489	1,875,887
TOTAL SOCIAL MISSION EXPENDITURE		31,874,548	26,814,561
NON-SOCIAL MISSION EXPENDITURE			
Fundraising	10	1,579,783	1,518,054
General and administration	10	2,942,777	2,677,889
Total non-social mission expenditure		4,522,560	4,195,943
TOTAL EXPENDITURE		36,397,108	31,010,504
Operating surplus / (loss)		158,365	231,152
OTHER INCOME (EXPENSES)			
Financial income, net		10,290	31,170
Exchange gain (loss), net		(103,066)	(147,070)
TOTAL OTHER INCOME (EXPENSES), NET		(92,776)	115,900
Net surplus for the year prior to allocations		65,589	115,252
Release from restricted operating funds	6.a-6.b.	45,299	21,182
Allocation to unrestricted operating funds		(110,888)	(136,434)
NET SURPLUS FOR THE YEAR AFTER ALLOCATIONS		-	-

FUNDS FLOW STATEMENT

FOR THE YEAR ENDED 31 DECEMBER 2014 (with 2013 comparative figures)

(Expressed in EUR)

	2014	2013
FUNDS FLOW FROM OPERATIONS		
Net surplus for the year, unrestricted	110,888	136,434
Usage for the year, restricted	-45,299	-21,182
Depreciation of fixed assets	53,368	85,304
(Increase) decrease in provisions	96,884	-90,345
Increase (decrease) in stocks	16,250	-25,241
Increase (decrease) in advances	-15,426	23,194
Increase (decrease) in receivables from public institutional donors and private donors	-1,182,411	1,184,017
(Increase) decrease in other receivables	489,771	75,155
(Increase) decrease in prepaid expenses	-166,082	-249,481
Increase (decrease) in payables	93,764	723,910
Increase (decrease) in accrued expenses	676,892	158,701
Increase (decrease) in deferred income	10,751,691	2,054,811
Funds flow from operations	10,880,289	4,055,278
FUNDS FLOW FROM INVESTING ACTIVITIES		
(Increase) decrease of investments in tangible fixed assets	-74,795	-82,698
(Increase) decrease in bank guarantee deposits	-15,324	-44,685
Funds flow from investing activities	-90,119	-127,382
FUNDS FLOW FROM FINANCING ACTIVITIES		
Cash increase (decrease)	10,790,171	3,927,896
Cash and cash equivalents – beginning of year	22,009,776	18,081,878
Cash and cash equivalents – end of year	32,799,947	22,009,774

STATEMENT OF CHANGES IN CAPITAL

FOR THE YEAR ENDED 31 DECEMBER 2014 (with 2013 comparative figures)

Internally generated funds

(Expressed in EUR)

	Opening balance	Allocation	Internal fund transfers	Closing balance
FUNDS FLOW FROM OPERATIONS				
Paid-in capital	32,510	-	-	32,510
Surplus for the year	-	65,589	(65,589)	-
Restricted operating funds	159,846	-	(45,299)	114,547
Unrestricted operating funds	10,260,077	-	110,888	10,370,966
Capital of the organization	10,452,434	65,589	-	10,518,023

NOTES TO THE FINANCIAL STATEMENT

FOR THE YEAR ENDED 31 DECEMBER 2014

1 GENERAL INFORMATION

a) Legal aspects

The Drugs for Neglected Diseases *initiative* (DNDi) is a Swiss foundation registered in Geneva under statutes dated 17 July 2003 as a not-for-profit legal entity, with its headquarters in Geneva. DNDi is monitored by the Swiss Federal Supervisory Board for Foundations, and has been granted 'other international organization' status in 2011. DNDi is compliant with Swiss law and with Swiss GAAP FER.

DNDi aims to, as per the Charter:

a) Stimulate and support research and development of drugs, as well as vaccines and diagnostics for neglected diseases;

b) Seek equitable access and development of new drugs, to encourage the production of known effective drugs, diagnostic methods and/or vaccines for neglected diseases;

c) Adapt new treatments for neglected diseases, to meet patients' needs, as well as to meet the requirements of delivery and production capacity in developing countries;

d) Raise awareness of the need to research and develop drugs for neglected diseases.

DNDi is Governed by the Board of Directors, with the Scientific Advisory Committee, Audit Committee, and Executive Board Committee providing key scientific and management guidance for decision making, the DNDi Executive Team implements the R&D strategy, manages the global portfolio, allocates resources, raises funds and advocates.

DNDi Executive Team is led by the Executive Director and includes the R&D Director, the Operations Director and the Fundraising, Advocacy and Communication Director.

The Strategic Committee, in addition to the Executive Team members, includes the Finance and Planning Director, Business Development Director, Medical Director, Discovery & Pre-Clinical Director, and Directors of Regional Offices.

b) Income tax

An agreement was signed with the Swiss Federal Council under provisions of the promulgated Swiss Host State Act, to grant DNDi certain privileges effective as of 1 January 2011 for an indeterminate period. The principal advantages for DNDi as a Swiss foundation with Other International Organization status are:

- Exoneration from all indirect federal, cantonal and communal taxes
- Exoneration from VAT on all goods and services acquired for the sole use of the foundation within Switzerland and abroad
- Unrestricted access to work permits for non-Swiss, non EU nationals

DNDi is exonerated from income tax from the Swiss federal income tax and from the Geneva cantonal and communal taxes for a ten-year period granted in September 2008 until 2018.

c) Situation of Regional Offices (RO)

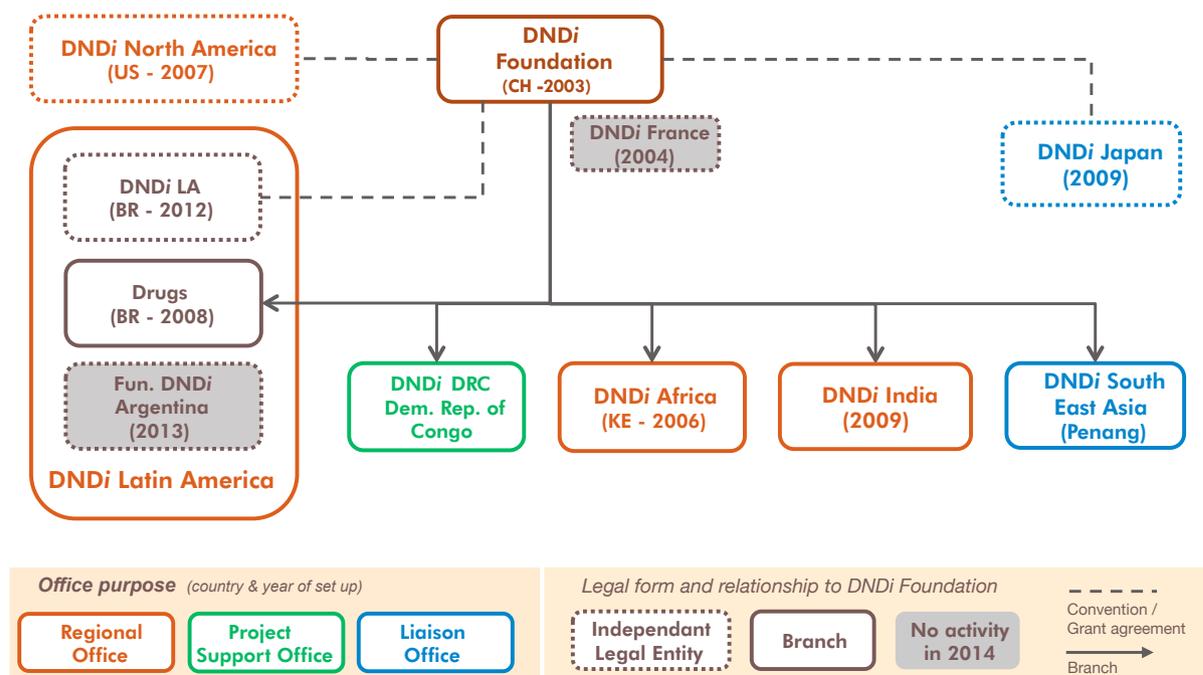
DNDi has seven Regional Offices that help identify patients' needs, support Heads of Disease Programmes, identify and support regional partners, and undertake regional advocacy work for DNDi. Their strategic role is defined in the Business Plan of DNDi. Their operational contributions are defined in the context of the Yearly Action Plan and budget approved by the Board of Directors of DNDi.

From an operational perspective the RO can be characterized as a Regional office, a Liaison Office or a Project Support Office depending on the purpose of its mission.

From a legal standpoint, DNDi can establish the RO as a branch of the DNDi Foundation or as an independent legal entity, depending on needs, local regulations, and requirements. Establishment of a DNDi RO outside Switzerland requires the authorization of the Board of Directors. Such ROs are set up according to the DNDi vision and mission, and model (in particular as a Not for Profit organization). DNDi is compliant with all local laws and regulations, where it operates, including financial regulations.

RO accounting is fully incorporated into DNDi accounts, following the method of full integration (i.e. all income and expenditures are incorporated in the DNDi financial statements).

The following chart gives an overview of the relationship established between DNDi Geneva and offices:



As of December 2014, DNDi has established branches in Kenya (2006), in Brazil (2008), in India (2009) and in Penang, Malaysia. Additionally, DNDi has one Project Support Office in the Democratic Republic of Congo (DNDi DRC; 2006).

In June 2009, the Board approved the creation of a liaison office in Japan, under the form of a 'specified non-profit organization', a legal entity registered with the city of Tokyo. DNDi Japan was established in November 2009.

Drugs for Neglected Diseases *initiative* North America, Inc., a Delaware not-for-profit corporation exempt from U.S. Federal income taxation pursuant to Section 501(c) (3) of the U.S. Internal revenue Code (DNDi NA), was established in February 2007. This affiliate is based in New York City, New York, USA, and operates under the Direction of the DNDi NA Board of Directors.

In June 2009, the Board approved the creation of a new legal entity in Brazil, in addition to the branch in the form of an 'Organização da Sociedade Civil de Interesse Público', DNDi Latin America. The process was completed in October 2012. Since 2012 accounts were audited by an external auditor and by Deloitte Touche Tohmatsu as from 2014 accounts.

In addition to its RO DNDi has setup two other entities, these entities did not have any activity in 2014:

1. In 2013, a legal entity was set-up in Argentina in response to regional fundraising needs.
2. In September 2004 a legal entity was set up in France in the form of a not-for-profit association for administrative purposes.

2 SIGNIFICANT ACCOUNTING POLICIES

a) Statement of compliance

The financial statements have been prepared in accordance with Swiss GAAP FER. They include:

- a) Balance sheet
- b) Statement of operations (activity based method)
- c) Funds flow statement
- d) Statement of changes in capital
- e) Notes, and
- f) Performance Report.

These financial statements present all activities of the Foundation. A list of in-kind income and expenditures is disclosed in Note 13.

b) Basis of preparation

The financial statements have been prepared on a historical cost basis. The principal accounting policies are set forth below.

c) Social mission expenditure

Social mission expenditures represent expenses made according to the purposes defined in Article 5 of the DNDi statutes. They are defined in the present general notes under point 1.a) Legal aspects. Research & development, strengthening existing capacities, and advocacy are the three chapters that comprise 'social mission expenditure'.

d) Functional currency

The Board of DNDi has determined that the assets, liabilities, and operations should be measured using EUR as the functional currency. The environment in which the entity primarily generates and expends cash determines this decision. All amounts presented in the financial statements are stated in EUR, except when specified otherwise.

e) Foreign currency translation

Transactions in currencies other than the entity's measurement and reporting currency (EUR) are converted at the average monthly rates of exchange. Year-end balances in other currencies are converted at the prevailing rates of exchange at the balance sheet date. Resulting exchange differences are recognized in the statement of operations.

The following are the principal rates of exchange used at the end of the year to revalue the balance sheet items to EUR for reporting purposes:

	2014	2013
USD	0.8226	0.7256
CHF	0.8315	0.8157
GBP	1.2804	1.1996
100 CDF	0.0915	0.0816
100 INR	1.2971	1.1746
100 KES	0.9146	0.8401
100 JPY	0.6875	0.6908
100 BRL	31.0965	30.7257

f) Income

Restricted public and private institutional donations based on annual or multiyear agreements are recorded, over the life of the agreement, as and when the milestones set out in the agreement are achieved.

Unrestricted public and private institutional donations based on annual or multiyear agreements are recorded on an accruals basis over the life of the agreement. A reconciliation between donations committed to DNDi and income recognized in the statement of operation is shown in table 7.a. Other donations are recorded on a cash basis.

g) Funding committed to projects

After Board approval of the annual action plan and budget comprising the approved projects to be funded by DNDi, contracts are drawn up and signed by two Directors, including the Executive Director, the R&D Director, the Discovery & Pre-clinical Director, and/or the Medical Director for important and complex agreements and contracts above EUR 50,000, as detailed in the agreement signature Policy. Thereafter, funds are allocated to the partner(s) in charge of the project.

Partners' Expenditures are recorded:

a) According to a financial report presenting expenditures incurred during the year on an accrual basis;

b) If financial reports are unavailable as per the deadline of the March 15 of the following year, an estimated amount is calculated on a prorata temporis basis, based on the time between the contract signing date and December 31. This estimated amount is considered as an accrued expense following Swiss GAAP FER to be regularized in the following year. The unpaid portion remaining at year-end is included under current liabilities.

h) Expenditures incurred for projects and activities

The annual action plan and budget as well as the revised budgets are approved by the Board.

They include funding for projects subcontracted to partners (See point g) and current expenditures required (mainly via Vendors) to achieve the objectives of the year. All expenditures incurred on behalf of a project or for any activity of DNDi are recorded on an accrual basis.

i) Credit risk, market risk and liquidity risk cash-flow management

DNDi's liquid assets are maintained in cash, low-risk short-term deposits or capital guaranteed investments. At the balance sheet dates, there are no significant concentrations of credit risk. Any form of speculation is prohibited.

The main financial risk for DNDi is the volatility of foreign exchange rates that can affect the value of its holding in various currencies (USD, EUR, GBP and CHF). DNDi is exposed to currency risk on donations received, projects expenditure and general and administrative expenses that are denominated in a currency other than the functional currency (EUR). These transactions are mainly denominated in EUR, CHF, USD, GBP, BRL, KES, INR, JPY and AUD. DNDi ensures that its net exposure is kept to an acceptable level by buying or selling foreign currencies at spot rates when necessary to address short-term imbalances. In addition the diversity of fundraising currencies represents a 'natural hedging' mechanism (income in BRL, USD, CHF, GBP, EUR).

j) Tangible fixed assets

Tangible fixed assets are stated at cost in Euro less accumulated depreciation. Depreciation is charged to the statement of operations on a straight-line basis over the estimated useful lives of the tangible fixed asset items.

The rates of depreciation used are based on the following estimated useful lives:

Office fittings and equipment	20%
IT equipment	33%

k) Bank guarantee deposits

Guarantees are presented as non-current assets. To date, DNDi has six guarantees representing six deposits related to office rental in Tokyo, New Delhi, and Geneva (office and parking) and deposits for a travel agent and petrol in Kinshasa. In addition, a letter of guarantee pertaining to the Geneva premises is still valid.

It is recoverable, subject to prevailing contract terms, upon vacating the premises.

	Currency	Amount in Currency	Amount in EUR
Guarantees office Geneva	CHF	56,186	46,719
Guaranty office Tokyo	JPY	770,000	5,290
Guaranty office New-Delhi	INR	630,000	8,171
Guaranty office Kinshasa	USD	18,000	14,806
Guaranty travel agency and Petrol Kinshasa	USD	6,500	5,347
Guaranty Nairobi credit cards	KES	1,000,000	9,150
Total guarantees			89,483

l) Provisions

A provision is recognized on the balance sheet when the organization has a legal or constructive obligation as a result of a past event, and it is probable that an outflow of economic benefits will be required to settle the obligation.

Provisions are measured at the management's best estimates of the expenditure required to settle that obligation at the balance sheet date.

m) Capital of the organization

The founding capital (paid-in capital) of EUR 32,510 (CHF 50,000) referenced in the statutes was received from the founding members of DNDi, including the Indian Council of Medical Research, the Institut Pasteur, the Kenya Medical Research Institute, and the International Office of Médecins Sans Frontières. The capital is fully paid in.

n) Restricted and unrestricted reserves

Restricted and unrestricted reserves represent the excess of income over expenditure since the inception of DNDi. Restricted reserves are available to DNDi for future operations and project funding costs as its evolving research and development project pipeline dictates. Unrestricted reserves will be utilized for expenditures of DNDi as incurred.

o) In-kind donations

Gifts-in-kind are not recorded but disclosed in the notes to the financial statements and valued at fair market values according to the following principles: Goods transferred to a DNDi project or services rendered to DNDi must be free, excluding the involvement of a monetary transfer.

They must be:

- Clearly identifiable and part of DNDi's projects and activities as defined by DNDi's action plans and budgets;
- Recognizable as a visible contribution to DNDi's projects and activities and in line with DNDi's mission and objectives.
- Partners' voluntary involvement in joint projects and activities, in particular if the partner does not aim to achieve DNDi's project objectives, are not considered as gifts-in-kind.
- For goods or services paid at prices below market prices, the difference between real payment and current market price is not considered as a gift-in-kind.
- Fair market value is defined as the price DNDi would have paid to utilize the goods or service. Fair market value can be suggested by partners. However, DNDi will be careful not to overestimate such valuations in compliance with Swiss GAAP FER 3 basic principles of materiality and prudence.
- Gifts-in-kind estimated at EUR 5,000 and above are taken into account. Exceptions can be made by DNDi when it serves the purpose of providing consistency and completeness of a project's accounts.

3 STOCKS OF DRUGS

In 2014, DNDi purchased vials of SSG, AmBisome®, paromomycin, and caps of miltefosine 10mg and 50mg at an estimated value of EUR 372,939 from various partners (MSF Logistique, MSF supply, Gilead), for use in the on-going clinical VL trials: SSG&PM combination pharmacovigilance study, HIV/VL co-infection study,

fexinidazole study, VL implementation study in India. Stocks of SSG, AmBisome®, miltefosine, and paromomycin at an estimated value of EUR 173,164 are stored at clinical trial sites in Ethiopia, Kenya, Sudan, Uganda and India.

2013	Quantity Vials			Quantity Caps		Total in EUR
	Countries / drugs	SSG (1)	AmBisome® (2)	Paromomycin	Miltefosine 50mg	
India		4,154	5,600	22,331	20,513	106,600
Bangladesh		237	1,910	1,102	952	7,281
Ethiopia	995	1,381	5,065	7,378	1,120	39,862
Kenya	1,249	420	6,126	-	-	20,749
Sudan	425	139	4,150	-	-	9,071
Uganda	300	250	250	-	-	5,850
Total vials/caps	2,969	6,581	23,101	30,811	22,585	189,414
Total in EUR	20,783	92,134	23,101	30,811	22,585	189,414

2014	Quantity Vials			Quantity Caps		Total in EUR
	Countries / drugs	SSG (1)	AmBisome® (2)	Paromomycin	Miltefosine 50mg	
India		2,895	13,050	15,894	38,022	107,496
Ethiopia	500	1,839	3,000	2,300	-	34,546
Kenya	1,070	128	4,060	-	-	13,342
Sudan	1,000	160	930	-	-	10,170
Uganda	650	140	1,100	-	-	7,610
Total vials/caps	3,220	5,162.00	22,140	18,194	38,022	173,164
Total in EUR	22,540	72,268	22,140	18,194	38,022	173,164

SSG cost per vial = EUR 7; AmBisome® cost per vial = USD 18 (EUR 14); Paromomycin & Miltefosine are valued at EUR 1 per unit

4 TANGIBLE FIXED ASSETS, NET

<i>(Expressed in EUR)</i>	Computer Equipment	Office fittings & Installations	Office Equipment	Total
Net carrying amounts 1.1.2013	44,200	6,784	1	50,985
Gross values of cost				
Beginning of the period 1.1.2013	354,845	161,839	162,302	678,986
Additions	66,946	5,528	10,224	82,698
Disposals				-
End of the period 31.12.2013	421,791	167,367	172,526	761,684
Accumulated amortization				
Beginning of the period 1.1.2013	(310,645)	(155,055)	(162,301)	(628,001)
Change of the year	(64,293)	(10,788)	(14,639)	(89,720)
Non systematic amortization ⁽¹⁾			4,415	4,415
End of the period 31.12.2013	(374,938)	(165,843)	(172,525)	(713,306)
Net carrying amounts 31.12.2013	46,854	1,524	1	48,379
Net carrying amounts 1.1.2014	46,854	1,524	1	48,379
Gross values of cost				
Beginning of the period 1.1.2014	421,791	167,367	172,526	761,684
Additions	53,275	5,037	16,483	74,795
Disposals				-
End of the period 31.12.2014	475,066	172,404	189,009	836,479
Accumulated amortization				
Beginning of the period 1.1.2014	(374,938)	(165,843)	(172,525)	(713,306)
Change of the year	(47,539)	(2,531)	(3,298)	(53,368)
End of the period 31.12.2014	(422,477)	(168,374)	(175,823)	(766,674)
Net carrying amounts 31.12.2014	52,589	4,030	13,186	69,806

1. Notably correction for impact of foreign exchange rates EUR/CHF on valuation of office furniture in CHF in 2013. As from 2014 we value all tangible fixed assets in EUR.

5 PROVISIONS

<i>(Expressed in EUR)</i>	Provision for taxes (Social taxes)	Provision for HR expenses (holidays not taken)	Provision for running expenses (other)	Provision for pension plan (DRC team)	Total
Carrying period as per 1.1.2013	113,024	111,003	2,877		226,904
Creation		136,558			136,558
Utilization		(108,270)			(108,270)
Reversal	(113,024)	(2,733)	(2,877)		(118,634)
Carrying period as per 31.12.2013	0	136,558	0	0	136,558
Carrying period as per 1.1.2014	-	136,558	-	-	136,558
Creation	15,386	213,945		4,111	233,442
Utilization		(136,558)			(136,558)
Reversal					0
Carrying period as per 31.12.2014	15,386	213,945	0	4,111	233,442

6 RESTRICTED OPERATING FUNDS

Restricted Funds	Increased	Utilization	Net utilization
Royalties	5,762	(69,456)	(63,694)
Donor Advance	18,395		18,395
Total	24,158	(69,456)	(45,299)

a) Royalties

In December 2004, DNDi signed an agreement with Sanofi, a pharmaceutical company, pertaining to the implementation of co-formulation treatments artesunate + amodiaquine (ASAQ) against malaria, developed originally by DNDi together with Sanofi. Article VI of the contract states that 3% royalties resulting from net sales of this drug, whose brand name is Coarsucam®, to the private sector in developing countries are to be paid to DNDi.

DNDi has decided to allocate this money to supporting pharmacovigilance projects or activities such as the implementation of

the ASAQ and ASMQ treatment in developing countries notably in Africa or ASMQ clinical trial in Africa.

The 3% royalties on the 2013 sales of Coarsucam® amounting to EUR 5,762 have been allocated entirely to the Malaria (ASAQ and ASMQ) projects.

The total costs of this project in 2014 amount to EUR 69,456. The balance of EUR 63,694 was taken from the 'Restricted operating fund', which is used for collaborative projects for observational studies and other access-related expenses in Africa and in Asia for ASAQ and ASMQ treatment. After the 2014 utilization, the total amount of the restricted fund incurred by the payment of the royalties amounts to EUR 96,152 as per 31 December 2014.

b) Restricted operating funds

In December 2014 the Drugs for Neglected Diseases *initiative* North America raised a grant from the Rockefeller Brother foundation of USD 25,000. Out of this grant USD 2,083 has been allocated against 2014 accounts and the balance of the grant has increased the restricted funds (USD 22,916 = EUR 18,396).

7 INCOME

a) Deferred income

The total deferred income increased by EUR 10,751,691 in 2014 compared to 2013, mainly because a donor grant advance related to a new five year grant signed in 2014 (2015 -2019). The payment schedule of the grant plan is for a 15 month advance payment. The 30th Oct. 2014 DNDi received USD 16,092,044 valued at EUR 13,237,315 as advance payment of this grant to be used as from the year 2015.

b) Cumulative donations committed to DNDi and/or received by 2014 (in EUR)

DONORS	Currency	Total Commitment in currencies ⁽⁵⁾	Total Commitment in EUR ⁽⁵⁾	As per Statement of Operations 2014 in EUR	To be used after 2014 in EUR
Bill & Melinda Gates Foundation	USD	126,635,417	96,232,693	6,803,379	51,471,617
UK Government DFID ⁽¹⁾	GBP	64,389,550	79,830,841	11,812,204	24,967,800
Médecins Sans Frontières	EUR	65,933,920	65,933,920	4,019,102	16,136,300
Dutch Government DGIS	EUR	16,975,000	16,975,000	4,000,000	0
French Government MAEE/AFD ⁽²⁾	EUR	14,255,000	14,255,000	1,597,244	2,202,143
UNITAID	USD	17,335,304	14,110,883	970,347	12,533,283
Spanish Government AECID	EUR	12,000,000	12,000,000	-	-
Swiss Government SDC ⁽³⁾	CHF	13,020,000	10,546,098	1,648,325	3,326,000
USA Government NIH/NIAID/USAID	USD	12,488,363	10,307,445	29,122	8,682,887
German Government ⁽⁴⁾	EUR	9,000,000	9,000,000	2,000,000	1,598,561
European Union, FP5, FP6, FP7, EDCTP	EUR	4,413,102	4,413,102	857,493	1,879,319
Wellcome Trust UK	EUR/USD	4,999,801	4,306,810	915,217	402,528
Medicor Foundation	EUR/USD	3,219,424	3,027,821	220,000	480,000
GHIT	USD/JPY	384,247,986	2,766,756	126,142	2,640,614
Norwegian Government NORAD	NOK	15,000,000	1,728,000	567,666	567,636
Canton of Geneva	CHF	2,100,000	1,530,451	137,657	138,584
UBS Optimus Foundation	CHF	2,000,000	1,408,410	87,914	332,763
Various other donors (ARPE Foundation, Foundation NA, individual NA, royalties, Stover, Brian Mercer Charitable Trust, Rockefeller Brother Found.)	EUR/GBP	693,288	1,059,989	211,707	56,808
Family Moreau	BRL	2,000,000	655,729	326,699	-
Sasakawa Peace Foundation, Tuscany Region, and others	EUR	611,396	611,396	-	-
Global Fund (AMFm)	EUR	532,809	532,809	-	-
BBVA	EUR	400,000	400,000	-	-
Starr International Foundation	USD	500,000	374,899	77,973	-
Brazil Government MoH and FINEP	BRL	1,195,000	377,333	110,757	235,039
Ruta n Medellin	EUR	317,500	261,176	-	261,176
Sandoz Family Foundation & anonymous donation	CHF	701,229	308,700	-	-
Rockefeller Foundation & Carlos Slim Foundation	USD	200,000	147,550	36,525	-
TOTAL DONATIONS (EUR)			353,102,810	36,555,473	127,913,059

(1) The UK Government, DFID, funded DNDi with 6 grants. A first unrestricted grant of GBP 6.5 million in 2006 for the period 2006-2008; a second unrestricted grant of GBP 18 million in 2009 for the period 2009-2013; a third restricted grant of GBP 1,381,529 in 2010 for the period 2010-2011; a fourth restricted grant of GBP 2 million in 2011 for 2011; a fifth restricted grant of GBP 3.5 million in 2012 for the period 2011-2013; and a sixth unrestricted grant of GBP 33 million for the period 2013-2018.

(2) The French Government, Ministry of Foreign and European Affairs, funded DNDi with 5 portfolio grants. From the MAEE: EUR 5.955 million in April 2007 for the period 2007-2010; from the MAEE: EUR 1.3 million in December 2009 for the period 2009-2011; from the AFD: EUR 1.5 million in June 2006 for the period 2006-2008; from the AFD: EUR 0.5 million in December 2009 for the period 2009-2010; and from the AFD: EUR 5 million in November 2012 for the period 2012-2017.

(3) The Swiss Government, SDC, funded DNDi with 4 grants. A first restricted grant of CHF 0.12 million in 2008 for the period 2008-2009; a second unrestricted grant of CHF 4 million in 2010 for the period 2010-2012; a third restricted grant of CHF 0.9 million in 2012 for period November 2012 to November 2013; and a fourth unrestricted grant of CHF 8 million in 2013 for the period 2013 to 2016.

(4) The German Government funded DNDi with 2 portfolio grants. From the GtZ: EUR 1 million for the period 2008-2009; and from the BMBF through KfW: EUR 8 million in November 2011 for the period 2011-2015.

(5) Exchange rates used for 'Total Commitment in EUR' and 'As per Statement of Operations 2014' are real exchange rates following the DNDi exchange rate policy. Exchange rates used for 'To be used after 2014' appear in EUR at the USD/EUR, CHF/EUR, and GBP/EUR exchange rates as per 31.12.2014 (see note 2). 'Total Donations' therefore yield an approximate value as exchange rates will vary over time.

c) Funding per project (restricted and unrestricted)

Operational Income (Grand TOTAL = 36,555,473) [Expressed in EUR]

	UK Government DFID ⁽¹⁾ (Unrestricted)	Dutch Government DGIS (Restricted)	German Government KfW-BMBF (Restricted)	Switzerland SDC (Unrestricted) ⁽⁴⁾	French Government AFD (Restricted) ⁽²⁾	European Union EDCTP/EU FP7 (Restricted)	UNITAID (Restricted)	Norwegian Government (Restricted)
Implementation & Development	FACT (ASAQ & ASMQ fixed-dose) for Malaria	490,139			439,426	47,732		
	Nifurtimox + Eflornithine co-administration (NECT) for stage 2 for HAT	19,337			37,923			
	New VL treatments (Asia, SSG & Paromo, Latin America; co infection HIV/ VL)	113,011	90,954		121,381	314,441		
	Fexinidazole for HAT	1,040,898	461,712		645,300			267,966
	Benznidazole Paediatric dosage form for Chagas		48,231					
Translation	Nitroimidazole VL-2098 (& back-up) for VL	317,763	216,770	273,939				
	Macrocyclics for Filariasis (Flubendazole, Emodepside)							
	Combination Fexinidazole/Miltefosine for VL	312,388	216,455	42,834	111,571	273,341		
	Fexinidazole for Chagas	585,700		239,296	110,435			
	Oxaborole SCYX-7158 for HAT (Preclinical until 2011)	295,026	210,333	398,717	100,976			228,690
	Azoles E1224 & Biomarkers for Chagas	121,873						
	New Combination for Chagas	76,854	66,380	21,684				
	New Benz Regimen for Chagas	39,586						
	Anfoleish for CL (Exploratory until 2011)	251,391						
	CpG-D35 (CL) + PKDL	167,187						
Research	Paediatric HIV: PI sprinkles CHAPAS-2 & super boosting TB/HIV (Preclinical until 2011)				245,392		736,576	
	Lead Optimization Consortia (for VL, Chagas, and HAT), including Fenarimol series and Nitroimidazole & Oxaborole back-ups	2,366,188	1,373,939	230,477	223,584			
	Discovery & Exploratory Kinoplastids	686,580	110,659	300,977	56,025			
Exploratory	Filariasis Screening	209,688		19,910				
	HCV, Mycetoma, Anti-infective	35,970						
	R&D Coordination, Supervision costs	1,111,385	583,700	150,142	384,534		73,479	
	HAT, LEAP, Filariasis & Chagas Platforms	304,953	256,351	141,110	16,410	108,865	101,402	31,475
	Other Strengthening Capacity activities	697,113			91,138			
	Advocacy	849,983			259,023		44,713	
	Fundraising	602,378	73,824	43,222	33,549	25,734	26,100	38,273
	General Management	1,116,813	290,692	137,691	101,776	119,470	94,476	77,306
	Net surplus allocated to unrestricted funds					13,057		
Net surplus allocated to restricted funds								
TOTAL Income (36,555,473)								
+ other income (-92,775)	11,812,204	4,000,000	2,000,000	1,648,325	1,597,244	857,493	970,347	567,666

7. b) Funding per project

(1) UK Government, DFID: 1) an unrestricted grant of GBP 6.5 M [EUR 8,013,293] an exceptional unrestricted grant of GBP 3,000,000 [EUR 3,798,911 covering the period from Oct to Dec 2014 only]. **(2)** European Union, 1) EDCTP: multiyear restricted grant of EUR 52,796 from Jan to Apr 2014 for FACT project; 2) European Union, FP7: restricted multiyear grant started with an amount of EUR 804,997 for the New VL Treatment in Africa project. **(3)** GHIT: 2013/2014 restricted grant of USD 158,722 [EUR 126,142] for early discovery project. **(4)** Brazilian MoH: multiyear restricted grant for activities in Brazil BRL 343,388 [EUR 110,757] for 2014 **(5)** US Government, USAID: multiyear restricted grant of USD 36,540 [EUR 29,122] covering the period from Oct to Dec 2014 for Filariasis diseases. **(6)** B&M Gates Foundation, includes five restricted grants: 1) Grant for the fexinidazole for HAT project which ended in Oct 2014 amended in July 2014 with a supplemental grant covering the entire year 2014 amounting EUR 3,310,581; 2) EUR 1,055,226 for new VL Treatments in Asia project; 3) EUR 1,200,070 for flubendazole macrocyclics for the filarial programme with an extension until Mar 2015; 4) EUR 1,009,830 for the NTD screening programme with an extension until Mar 2015, 685,571 in 2014 and 5) EUR 227,672 for an innovative fund starting as from May 2014.

Switzerland Canton of Geneva (Restricted)	GHIT (Restricted)	MOH Brazil (Restricted)	USAID (Restricted) ⁽³⁾	Bill & Melinda Gates Foundation (Restricted) ⁽⁷⁾	Médecins Sans Frontières (Restricted/ Unrestricted) ⁽⁸⁾	Wellcome Trust (Restricted) ⁽⁹⁾	Medicor Foundation (Restricted)	UBS OPTIMUS (Restricted)	Foundations & Other (Restricted/ Unrestricted) ⁽¹⁰⁾	Financial income (Net) =	Utilization of restricted reserves	TOTAL Expenditure = 36,397,108
					19,347				23,951		63,694	1,084,289
												57,259
				865,070	111,829		31,023		92,520			1,740,230
60,745				2,752,817	613,709							5,843,148
	38,762								56,797			143,790
												808,472,42
				996,914	497							997,411
					184,022		107,283		4,704			1,252,599
					257,103				20,135			1,212,669
					2,869							1,236,612
	2,718				95,243	915,217			43,123			1,178,174
					17,040				31,190			213,148
					16,174							55,760
	34,030				53,609				11,688			350,718
					49,064							216,251
					16,279			79,879				1,078,126
	34,964				437,991							4,667,142
	126,142				78,962							1,359,345
				582,059					12,268			823,924
				151,298								187,268
				487,950	318,266							3,109,458
60,723			17,467	10,644	169,935		38,319		79,981			1,337,635
					420,927		23,895		34,559			1,267,631
				35,905	412,825				51,040			1,653,489
12,963			7,017	298,906	388,894				10,179			1,579,783
3,227			4,638	621,815	319,617		19,479	8,035	6,953			2,942,777
	283				34,900				155,422	(92,776)		110,888
									18,395		(63,694)	-45,299
137,657	126,142	110,757	29,122	6,803,379	4,019,102	915,217	220,000	87,914	652,904	(92,776)		36,462,698

[7] MSF: 1) a multiyear unrestricted grant of EUR4,000,000 2) EUR19,102 for the payment for services of the data management center based in Nairobi from May 2014 until Dec 2014.

[8] ARPE Foundation [EUR 18,189]; Rockefeller Foundation [EUR 36,524]; Starr Foundation [EUR 77,973]; Family Moreau [EUR 326,699]; Brian Mercer Charitable Trust [EUR 12,268]; Various individual donations [EUR 66,060], of which EUR 62,195 came from North America and EUR 3,865 from Europe; Foundations and corporations based in North America [EUR 34,013 and EUR 1,063] of which EUR 18,469 have been allocated in the restricted operating fund to be used in 2015.

Royalties from Sanofi for EUR 5,762 earmarked for FACT activities (see note 6). The restricted operating fund has been partially used [EUR 69,694] to fund and support the total expenditure attached to this project [EUR 69,456].

In addition, DNDi in Geneva has collected various reimbursements and participation of partners throughout the year for a total of EUR 65,384 plus exceptional incomes for the year for a total of EUR 8,968.

8 EXPENDITURE

a) R&D projects related expenditure

Recognized in <i>(Expressed in EUR)</i>	2014	2013
IMPLEMENTATION PROJECT		
ASAQ Fixed-dose Artesunate - Amodiaquine (Malaria) ⁽¹¹⁾	386,214	244,894
ASMQ Fixed-dose Artesunate - Mefloquine (Malaria) ⁽²⁾	698,075	826,145
NECT Nifurtimox - Eflornithine co-administration for stage 2 (HAT) ⁽³⁾	57,259	138,645
SSG & Paromomycin Combination Therapy for VL in Africa ⁽⁴⁾	96,869	315,411
New VL treatments in Asia ⁽⁵⁾	659,246	701,945
Paediatric Benznidazole (Chagas) ⁽⁶⁾	143,790	110,949
TOTAL IMPLEMENTATION PROJECTS	2,041,453	2,337,989
DEVELOPMENT PROJECTS (PHASE IIB/III; REGISTRATION)		
Fexinidazole for (HAT) ⁽⁷⁾	5,843,148	3,229,681
New VL treatments for Bangladesh ⁽⁵⁾	205,824	261,223
New VL treatments in Africa; project is now included in Combination Fexinidazole/Miltefosine (VL)	-	1,011,050
New VL treatments in Latin America	110,517	104,590
Coinfection HIV / Visceral Leishmaniasis ⁽⁸⁾	698,094	304,568
TOTAL DEVELOPMENT PROJECTS	6,857,581	4,911,112
TRANSLATION PROJECTS (PRE-CLINICAL; PHASE I; PHASE IIA/POC)		
Fexinidazole for Chagas ⁽¹¹⁾	1,212,669	134,417
Oxaborole SCYX-7158 (HAT) ⁽⁹⁾	1,236,612	1,932,540
Combination Fexinidazole/Miltefosine (VL) ⁽⁴⁾	1,252,599	385,029
Anfoleish (CL) ⁽¹⁰⁾	350,718	489,759
CpG-D35 (CL) ⁽¹⁰⁾ + PKDL ⁽¹⁰⁾	216,251	
Azoles E1224 (Chagas) ⁽¹¹⁾	46,892	1,172,426
New Combination including New Benz Regimen (Chagas) ⁽¹¹⁾	268,908	
Biomarkers (Chagas) ⁽¹¹⁾	1,131,282	1,084,027
Paediatric HIV ('4 in 1' LPV/r based fixed-dosed combination) & Superboosting TB/HIV ⁽¹²⁾	1,078,126	1,086,495
Nitroimidazole (VL-2098) ⁽¹³⁾	808,472	355,717
K777 for Chagas	-	125,356
Flubendazole Macrofiliaricide (Filaria) ⁽¹⁴⁾	997,411	311,988
TOTAL TRANSLATION PROJECTS	8,599,939	7,077,754
RESEARCH PROJECTS (SCREEN; HIT TO LEAD; LEAD OPTIMIZATION)		
Lead Optimization Consortia ⁽¹⁵⁾	4,667,142	4,376,032
Screening Resources & Reference Screening Centers ⁽¹⁶⁾	1,359,345	1,086,970
Screening Filaria ⁽¹⁷⁾	823,924	759,976
TOTAL RESEARCH PROJECTS	6,850,411	6,222,978
Project-related variable expenditure		
HCV, Mycetoma, and Anti-infective	187,268	0
Coordination & Supervision ⁽¹⁸⁾	3,109,458	2,656,917
TOTAL OF PROJECTS RELATED EXPENDITURE	27,646,111	23,206,749

MAIN R&D PARTNERS & SUB-CONTRACTORS:

Partners and service providers with financial compensation above EUR 5,000 in 2014 are:

(1) Sanofi, France / AEDES, Belgium / Zenufa, Tanzania / Bertin Pharma, France / IPCA, India / VINPA Accessories, India

(2) National Institute of Medical Research, Tanzania / Catalent, UK / CNRPF, Burkina Faso / KEMRI, Kenya / Ifakara, Tanzania / Epicentre, France / Cardinal Systems, France / Venn life, France / Centre Hospitalier Universitaire Valésan (CHUV), Switzerland

(3) PNLTHA, Democratic Republic of Congo / Swiss Tropical and Public Health Institute (Swiss TPH) / HAT Platform partners (PNLTHA, Republic of the Congo / TMRI, Sudan / ICCT, Angola / COCTU, Uganda; PNLTHA Central African Republic / PNLTHA, Chad)

(4) Kenya Medical Research Institute, Kenya / Institute of Endemic Diseases (IEND) and University of Khartoum, Sudan / Addis Ababa University, Ethiopia / University of Makerere, Uganda / Amudat Hospital, Uganda / LSHTM, UK / i+solutions, The Netherlands / IDA Solutions, The Netherlands / Abugarja Pharma, Sudan / Mohi Eldin Elrayah, Sudan / MSF Logistique, France / Royal Tropical Institute, The Netherlands / Gland Pharma, India / Médecins Sans Frontières / BIO RAD Laboratories, South Africa / Phinc Development, France / SGS, Belgium and France / Slotervaart Hospital, The Netherlands / Uppsala UNIVERSITY, Sweden / Aptuit, UK / Appledown, UK

(5) MSF-Supply, Belgium / MSF-Logistique, France / Gilead, Ireland / Médecins Sans Frontières / GVK Biosciences, India / Shaheed Surawhady Medical College Hospital (SHSMC), Bangladesh / International Centre for Disease Diarrheal Research (ICDDR), Bangladesh / Rajendra Memorial Research Institute of Medical Sciences (RMRI), India

(6) Laboratorio ELEA, Argentina

(7) Sanofi, France / Swiss TPH / HAT Platform partners [see point 3 above] / Aptuit, UK / SGS, Belgium and France / Vanga CBCO Clinic, DRC / Médecins Sans Frontières / MSF-Logistique, France / Bertin Pharma, France / Institute of Tropical Medicine-Antwerp, Belgium / Cardiabase, France / Phinc Development, France / Cardinal Systems, France / Venn Life, France / INRB, RDC / UBC United Biosource, Switzerland / Hopital du Cinquantenaire, RDC / Theradis Pharma, France / Accelera, Italy / Jeffery travels, RDC / RCTS, France / La Référence Médicale, RDC

(8) Gondar University, Ethiopia / Addis Ababa University, Ethiopia / Institut Tropical Medicine (ITM), Belgium / MSF-Logistique, France / Slotervaart Hospital, The Netherlands / LSHTM, UK / Uppsala UNIVERSITY, Sweden

(9) SCYNEXIS, USA / Drugabilis, France / Penn Pharma, UK / SGS, Belgium & France / Cardiabase, France / Patheon, UK / Wuxi, China / Bertin Pharma, France / Accelera, Italy / Eurofins Optimed, France / Phinc, France / Sunnikan, UK / MC Toxicology Consulting, Austria / M Benton UK

(10) PECET Universidade de Antioquia, Colombia / JSS, Canada / CECIF, Colombia / Genedesign Inc, Japan / FCSAI, Spain

(11) Barcelona Center for International Health Research (CRESIB), Spain / Texas Biomedical Research Institute, USA / McGill University, Canada / University of Georgia, USA / Fundacion Ingebi, Argentina / Phinc Development, France / Fundacion Instituto De Biologica Y Medicinal, Argentina / Núcleo de Desenvolvimento Farmacêutico e Cosmético (NUDFAC), Brazil / J Altcheh, Argentina / LAT Research, Argentina / F.P. Clinical, Argentina / ELEA, Argentina /

JSS, Canada / Aptuit Verona, Italy / SGS, Belgium / Cardiabase, France / Creapharm, France

(12) WuXi AppTech, China / CIPLA, India / University of Stellenbosch, South Africa / Associated Medical Sciences, Thailand

(13) Advinus Therapeutics, India / Huntingdon, USA / APTUIT, UK / SELCIA, UK / Accelera, Italy / Endolytics LLC, USA / Mission Cadres, Haddous, France / Wuxi, China / D Creasy, US

(14) Michigan State University, USA / McGill University, Canada / Covance, UK / Molecular Profiles, UK / WuXi AppTec, China

(15) Epichem Pty Ltd, Australia / Griffith University, Australia / Monash University, Australia / WuXi AppTech, China / Pace University, USA / LSHTM, UK / iThemba Pharma, South Africa / Antwerp University, Belgium / STA Pharmaceutical Hong Kong Ltd, China / Centro Nacional de Energia em Energia e Materiais (CNPEM), Brazil / CEMSA Laboratory Brasil / Advinus, India / CEREP, France / TCG Life Science Ltd, India / Pharmaterials Limited, UK / Syngene, India / Dundee University, UK / Sandexis, UK

(16) Swiss TPH, Switzerland / University of Antwerp, Belgium / GlaxoSmithKline (GSK-Tres Cantos), Spain / IPK, South Korea / Dundee University, UK / eMolecules Inc., USA / Axxam, Italy / SPECS Compound Handling BV, The Netherlands

(17) Northwick Park Institute for Medical Research (NPIMR), UK / Swiss TPH / WuXi AppTec, China / University Hospital of Bonn, Germany / MC Toxicology Consulting, Austria / Museum National History Natura, France

(18) R&D Coordination & Supervision: Sunnikan, UK / VOLT Europe Limited: UK / M Benton, UK

Breakdown of R&D coordination expenditure per activities

<i>(Expressed in EUR)</i>	2014	2013
Coordination	1,790,898	1,703,404
Scientific Advisory Committee	94,713	93,269
Business Development	847,990	668,082
Japan Representation Office	255,461	192,162
Medical and Access Coordination Latin America	120,396	
TOTAL	3,109,458	2,656,917

CONSULTANTS AND PROJECT STAFF INVOLVED IN R&D PROJECTS:

Alonso-Vega, Cristina; Ansong, Daniel; Babingwa Wilsonja, Delon; Bacchi, Cyrus; Barboza Marques, Tanya; Benton, Marcus; Bern, Caryn; Bessis, Anne-Sophie; Besson, Dominique; den Boer, Margriet; Bonnet, Béatrice; Bordbar, Céline; Borges, Marineide; Boulet, Pascale; Bray, Mike; Brenner, Jennifer; Burger, Albert; Bush, Jacob; Campbell, Simon; Carmody, Lesley; Chagas, Francisca; Chang, Shing; Chappuis, François; Christmann, Leandro; Clay, Robert; Dam, Hanne; Dessoy, Marco; Dinanga Muzadi, Jose; Dormeyer, Matthias; Dorre, Daniel; Dos Santos, Pamela Tamiris; Dos Santos, Rodrigues; Dos Santos Pinheiro, Eloan; Drappeau, Guillaume; Duke, Jeff; Elango, Varalakshmi; Evans, Dean; Fernandes, Jayme;

Fiorio, Valéria; French, Edward; Fontes, Raissa; Gardner, Mark; Garcia, Facundo; Grant, Ali; Gonçalves, Luciana; Hailu, Asrat; Juma, Rashid; Kabangu Mundidimbi, Patrice; Kanza, Eric; Khalil, Eltahir; Kuemmerle, Andrea; Last, Paul; Levin, Leon; Lotrowska, Michel; Maki Dir Onguku, Baudouin; Martin, Denis; Martin, Jorge; Mazué, Guy; Mbui, Jane; Mc Kenna, Ceri; Mechali, Daniel; Modabber, Farrokh; Montezuma, Juliana; Mutombo Kalonji, Wilfried; Larrey, Dominique; Mudawi Musa, Ahmed; Muthoni Nyawira, Agnes; Naim, Jennifer; Olobo, Joseph; O'Reilly, Terry; Parkinson, Tanya; Pedrique, Belén;

Pereira, Teresinha de Jesus; Peláez, Lúcia Enciso; Praciano, Claudenia; Rithea, Leang; Rodrigues, Belaine; Rosenkranz, Bernd; Scherrer, Bruno; Schijmann, Alejandro; Schneider, Manfred; Seltzer, Jonathan; Silva, Rosangela; Smith, Dennis; Solomos, Alexandra; Sosa Estani, Sergio; Speed, Bill; Tadoori, Leela Pavan; Taylor, Bob; Thenot, Jean-Paul; Tshimanga Kabongo, Dieudonné; Tweats, David; Vaillant, Michel; Vanraes, Joelle; Vieira, Marcela; Von Geldern, Thomas; Walker, Don; Wemeau, Jean-Louis; Westwick, John; Williams, Mike; Zawadi, Fifi; Zicker, Fabio; Zijlstra, Eduard; Zwang, Julien.

b) Presentation of the DNDi expenditure per nature of expenses

Recognized in (Expressed in EUR)	2014	2013
PERSONNEL		
Personnel at Headquarters	8,892,611	7,237,139
Personnel at Regional Offices	2,429,564	2,053,184
Consultants	1,762,857	1,673,558
Travel and Accommodation	1,386,652	1,207,433
TOTAL PERSONNEL	14,471,684	12,171,314
OPERATIONAL R&D		
Purchase & Logistics	1,360,232	734,297
Equipment	621,995	344,241
Discovery & Lead Optimization (partners & service)	5,484,863	5,257,020
Pre-clinical (partners & service)	1,844,174	1,424,967
Training for partners	200,516	89,956
Clinical & post-clinical (partners & service)	7,520,002	6,728,740
Product manufacturing & CMC (partners & service)	749,349	522,554
TOTAL OPERATIONAL R&D	17,781,131	15,101,774
OTHER		
Communication (tools, meetings, organization of documents)	1,371,668	1,305,394
Administration & IT (depreciation, furniture, service providers)	2,772,625	2,432,023
TOTAL OTHER	4,144,293	3,737,417
GRAND TOTAL	36,397,108	31,010,505

9 STRENGTHENING CAPACITIES EXPENDITURE

DNDi expenditure on strengthening existing capacities in developing countries aims to:

- build networks around specific projects between researchers from developing and developed countries;
- establish working partnerships, including technology transfers, with public and private institutions, and researchers from developing and developed countries; and
- invest in sustainable capacity and leadership in developing countries at all stages of research and development.

(Expressed in EUR)	2014	2013
Regional Offices, management costs: Rio, Delhi, Nairobi, Penang	1,267,631	1,027,453
Leishmaniasis East Africa Platform (LEAP)	737,444	181,528
Human African Trypanosomiasis (HAT) Platform	355,522	290,366
Chagas Clinical Research Platform [CCRP]	185,928	176,318
Exceptional expenditure (HAT platform)	-	56,260
Filariasis Platform	28,422	
TOTAL	2,574,948	1,731,925

For partners, see page 34 related to key financial performance indicators for strengthening existing capacities

10 ADVOCACY, FUNDRAISING AND GENERAL & ADMINISTRATION EXPENSES

(Expressed in EUR)	Advocacy		Fundraising		General & Administration	
	2014	2013	2014	2013	2014	2013
Human resources	1,171,479	1,143,122	1,253,638	1,204,755	1,907,229	1,586,919
Office charges	50,895	43,524	89,464	80,757	127,237	108,811
Travel expenses	76,479	67,530	97,766	86,297	116,276	141,019
Administration	38,215	45,859	66,411	60,170	252,576	279,486
IT & telecommunications	44,906	34,296	43,743	32,062	419,772	436,694
Communication	266,171	529,761	19,377	20,498	104,075	106,408
Depreciation	5,337	8,972	6,404	10,766	13,342	18,015
Exceptional expenses	7	2,823	2,979	22,749	2,270	537
TOTAL	1,653,489	1,875,887	1,579,783	1,518,054	2,942,777	2,677,889

Consultants and project staff: Alapenha, Julia; Alibert, Aude; Atekindoy Varne, Alida; Benmabrouk, Charles; Bloemen, Sophie; Bolton, Samantha; Bolton Jones, Helena; Carpenter Genesca, Pedro; Cavedon, Felipe; Cherkaoui, Sylvain; Childs, Michelle; Curtis, Jodie; El Tahir Ghada, Hatim; t Hoen, Elisabeth; Katz, Jennifer; George, Richard; Goel, Sunil Prakash; Langbein, Lena; Lucas Subirats, Marta; Leal Teixeira, Anderson; Matsudaira, Masako; Midori, Morioka; Morikawa, Mitsuyo; Morton, Erin; Moon, Suerie; Murakami, Akiko; Preve, Ricardo; Power, Christine; Rouijel, Fatima; Sarumaru, Michiko; Vieira, Marcela.

11 INDEMNITIES & REMUNERATIONS GIVEN TO BOARD MEMBERS

All members of the Board are appointed on a voluntary basis. The Board members have received no remuneration for their mandate in 2014, nor in 2013.

12 ASSETS PLEDGED AS GUARANTEE FOR COMMITMENTS

At year end, a bank of the Foundation provided two letters guaranteeing rental deposits of CHF 70,000 (EUR 58,205) and CHF 20,000 (EUR 16,630) in favour of a third party. Cash for an equivalent amount is pledged at the corresponding bank.

13 CONTRIBUTIONS IN-KIND

Drugs for Neglected Diseases *initiative* (DNDi) operations are funded through financial contributions and donations. In addition to financial funding, generous partners, private companies, academic groups and individuals provide DNDi with goods and services at no cost as gifts-in-kind (see note 20, DNDi In-Kind Policy). DNDi aims at reflecting this contribution in the 2014 financial statements in order to present a comprehensive picture of its activities. The in-kind contribution of DNDi partners decreased between 2013 and 2014 from EUR 7,352,524 in 2013 to EUR 3,366,543 in 2014. The reduction is mainly related to the end of the development of a formulation for flubendazole Macrofilicide for the filarial programme (minus EUR 3.1 M).

Gifts-in-kind evaluated for the year 2014 per category and per project:

(Expressed in EUR)	Staff Scientific	Staff non-Scientific	R&D Services	Office, furniture & admin.	TOTAL
Lead Optimization Consortia (Australia)	32,314	105,539		95,091	232,944
Screening Resources & Reference Screening Centres	382,612	13,332	201,506	159,214	756,665
Macrofilicide Filaria	899,526	10,507	301,133		1,211,166
Regional Offices	3,883	7,650	2,187	14,173	27,893
New VL treatments: Asia, America	90,554				90,554
ASMQ Fixed-dose Artesunate - Mefloquine (Malaria)	178	1,067	5,335		6,579
Paediatric HIV ('4-in-1' LPV/r-based fixed-dose combination)	49,411	28,498	28,579	46,506	152,993
Azoles E1224 (Chagas)	766,831	52,734	68,184		887,749
TOTAL	2,225,310	219,327	606,923	314,984	3,366,543

Main in-kind contributors: Eisai Ltd, Japan; ARC-Australian Research Council, Australia; University of Dundee, UK; FIOCRUZ, Brazil; Monash University, Australia; Saran District Hospital, India; KEMRI, Kenya; Astellas Pharma Inc, Japan; Cipla, India; Tait Weller & Baker, USA; Abbvie Inc, USA

Our thanks go to Barbara Kessler for her support as an Audit Committee member

14 SUBSEQUENT EVENTS

The Swiss National Bank dropped the 1.20 EUR/CHF floor on Thursday 15/01/2015

DNDi operates in a complex multi-currency environment where income currencies do not match expenses currencies. The donations are received mostly in USD, EUR, GBP and CHF. Two thirds of our expenses are naturally covered, as donations received enable

DNDi to fund expenses in the same currency. About one third of our operational expenses are in Swiss Francs (CHF), meaning about CHF 12 M is exposed to forex risk for 2015.

In this particular context, the finance and executive team is developing hedging measures that will be reviewed by the Audit Committee before Board approval in June 2015.

REPORT OF THE STATUTORY AUDITOR



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Report of the Statutory Auditor

To the Board of
Drugs for Neglected Diseases initiative (DNDi), Geneva

Report of the Statutory Auditor on the Financial Statements

As statutory auditor, we have audited the accompanying financial statements of Drugs for Neglected Diseases initiative (DNDi), which comprise the balance sheet as at 31 December 2014, statement of operations, funds flow statement, statement of changes in capital and notes, presented on pages 63 to 79, for the year then ended. In accordance with Swiss GAAP FER 21, the content of the performance report presented on pages 6 to 61 is not audited.

Board's Responsibility

The Board is responsible for the preparation of these financial statements in accordance with the requirements of Swiss law and the charter of the foundation. This responsibility includes designing, implementing and maintaining an internal control system relevant to the preparation of financial statements that are free from material misstatement, whether due to fraud or error. The Board is further responsible for selecting and applying appropriate accounting policies and making accounting estimates that are reasonable in the circumstances.

Auditor's Responsibility

Our responsibility is to express an opinion on these financial statements based on our audit. We conducted our audit in accordance with Swiss law and Swiss Auditing Standards. Those standards require that we plan and perform the audit to obtain reasonable assurance whether the financial statements are free from material misstatement.

An audit involves performing procedures to obtain audit evidence about the amounts and disclosures in the financial statements. The procedures selected depend on the auditor's judgment, including the assessment of the risks of material misstatement of the financial statements, whether due to fraud or error. In making those risk assessments, the auditor considers the internal control system relevant to the entity's preparation of the financial statements in order to design audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the entity's internal control system. An audit also includes evaluating the appropriateness of the accounting policies used and the reasonableness of accounting estimates made, as well as evaluating the overall presentation of the financial statements. We believe that the audit evidence we have obtained is sufficient and appropriate to provide a basis for our audit opinion.

Opinion

In our opinion, the financial statements for the year ended 31 December 2014 give a true and fair view of the financial position, the results of operations and the cash flows in accordance with Swiss GAAP FER and comply with Swiss law and the charter of the foundation.

Report on Other Legal Requirements

We confirm that we meet the legal requirements on licensing according to the Auditor Oversight Act (AOA) and independence (article 83b Civil Code (CC) in connection with article 728 Code of Obligations (CO)) and that there are no circumstances incompatible with our independence.

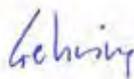
In accordance with article 728a para. 1 item 3 CO and Swiss Auditing Standard 890, we confirm that an internal control system exists, which has been designed for the preparation of financial statements according to the instructions of the Board.

We recommend that the financial statements submitted to you be approved.

Deloitte SA



Annik Jaton Hüni
Licensed Audit Expert
Auditor in Charge



Jürg Gehring
Licensed Audit Expert

Geneva, 20 May 2015

A WORD OF THANKS

DNDi is grateful for the support received from the following donors who contributed toward the advancement of its mission and goals. To date, DNDi has delivered six new treatments and aims to bring 11-13 treatments in total to patients suffering from neglected diseases by 2018. DNDi would like to thank all of the donors and partners for their loyal commitment and collaboration since 2003. Listed are supporters who have given a contribution of USD or EUR 5,000 cumulatively.

Public institutional support

- Department for International Development (DFID), UK
- Dutch Ministry of Foreign Affairs (DGIS), The Netherlands
- European Union – Framework Programmes 5, 6 and 7, International
- European and Developing Countries Clinical Trials Partnerships (EDCTP) with co-funding from Member States, International
- Federal Ministry of Education and Research (BMBF) through KfW and part of the EDCTP 2 Programme supported by the European Union, Germany
- French Development Agency (AFD), France
- German International Cooperation (GIZ) on behalf of the Government of the Federal Republic of Germany, Germany
- Global Health Innovative Technology Fund (GHIT Fund), Japan
- The Global Fund to Fight AIDS, Tuberculosis and Malaria (AMFm), International
- Minister of Foreign Affairs and International Development (MAEDI), France
- Ministry of Health, Brazil
- National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID), USA
- Norwegian Agency for Development Cooperation (Norad), Norway
- Republic and Canton of Geneva, Switzerland
- Region of Tuscany, Italy
- Ruta-N, City of Medellin, Colombia
- Science and Technology Innovation Agency (FINEP), Brazil
- Spanish Agency for International Development Cooperation (AECID), Spain
- Swiss Agency for Development and Cooperation (SDC), Switzerland
- UNITAID, International
- United States Agency for International Development (USAID), USA
- United States Agency for International Development (USAID), via the 4th Sector Health Project implemented by Abt Associates, Inc., USA

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- Bennett Shapiro and Fredericka Foster, USA
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- Brian Mercer Charitable Trust, UK
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- David and Lisa U'Prichard, USA
- Family of Richard Rockefeller, USA
- Fondation André & Cyprien, Switzerland
- Fondation ARPE, Switzerland
- Fondation de bienfaisance du groupe Pictet, Switzerland
- Fondation Pro Victimis, Switzerland
- George H. Stout, USA
- Goldman, Sachs & Co., USA
- Guy's, King's and St Thomas', Giving Week, UK
- Harlan Weisman, USA
- Jeffrey Nelson, USA
- Leopold Bachmann Foundation, Switzerland
- Marsha Fanucci, USA
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- Medicor Foundation, Liechtenstein
- Moreau Family, Brazil
- Rockefeller Brothers Fund, USA
- Rockefeller Foundation (through the 'Next Century Innovators Award'), USA
- The Peter and Carmen Lucia Buck Foundation, USA
- The Stainman Family Foundation, USA
- The Wellcome Trust, UK
- Steve Rabin and Jonathan Winslow, USA
- Sandoz Family Foundation, Switzerland
- Sasakawa Peace Foundation, Japan
- Starr International Foundation, Switzerland
- UBS Optimus Foundation, Switzerland
- Other private foundations and individuals who would like to remain anonymous

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Drugs for Neglected Diseases *initiative*

The Drugs for Neglected Diseases *initiative* (DNDi) is a patient-needs driven, not-for-profit research and development (R&D) organization that develops safe, effective, and affordable treatments for neglected diseases that afflict millions of the world's poorest people, notably human African trypanosomiasis (sleeping sickness), leishmaniasis, Chagas disease, paediatric HIV, filaria, and malaria.

DNDi's primary objective is to:

→ Deliver 11 to 13 new treatments by 2018 for targeted neglected diseases and establish a strong R&D portfolio 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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