



2011 ANNUAL
REPORT

**TOWARDS
SUSTAINABLE
CHANGE FOR
NEGLECTED
PATIENTS**

DNDi

Drugs for Neglected Diseases *initiative*



VISION

To improve the quality of life and the health of people suffering from neglected diseases by using an alternative model to develop drugs for these diseases and by ensuring equitable access to new and field-relevant health tools. In this not-for-profit model, driven by the public sector, a variety of players collaborate to raise awareness of the need to research and develop drugs for those neglected diseases that fall outside the scope of market-driven 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, DNDi 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.

DNDi'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. DNDi 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, DNDi 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, DNDi will help to build additional capacity in a sustainable manner through technology transfer in the field of drug research and development for neglected diseases.

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 helminth infections, 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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Dr Bernard Pécoul
Executive Director



Prof. Marcel Tanner
Chair of the Board
of Directors

MESSAGE FROM THE CHAIR OF THE BOARD AND THE EXECUTIVE DIRECTOR

The year 2011 was a very important year for the neglected disease landscape, in general, and for DNDi, in particular. The revised DNDi Business Plan for the period 2011 to 2018 was released mid-year and – in addition to detailing our activities in the areas of African trypanosomiasis, Chagas disease, leishmaniasis, and malaria – it integrated earlier decisions (December 2010) to launch two new mini-portfolios: paediatric HIV and specific helminth infections.

At the close of the year, DNDi registered what is now its sixth treatment in implementation: a paediatric dosage form of benznidazole for children with Chagas disease, thanks to the approval by the Brazilian regulatory authority ANVISA. Both challenging and fruitful, the year 2011 was witness to a growing network of public and private partners committed to DNDi's vision and mission. We were fortunate to have benefited from increasing support, particularly through grants received from public and private donors committed to innovation for neglected diseases, despite a period of financial constraints owing to the foreign currency and debt crisis.

Best science & urgent needs

In 2011, DNDi's R&D pipeline showed important advances, with a total of eleven new chemical entities (NCEs) at various stages of development – as compared to what was a virtually empty pipeline just a decade ago – five programmes at the implementation phase, and the new treatment registered for Chagas disease. The latter, part of our short-term strategy to improve existing treatments, was particularly important as it filled an immense gap to become the only child-adapted dosage form to treat Chagas disease.

With the investments made over the past nine years, we hope to significantly change the course of history for some neglected diseases as promising programmes move into the clinical stages of development: fexinidazole for sleeping sickness; E1224 and biomarkers for Chagas

disease; and new visceral leishmaniasis treatments in Africa, Latin America, and Asia.

Since 2009, NECT has increasingly replaced the arsenic drug melarsoprol as first-line treatment for stage 2 HAT patients. For clinicians in African HAT-endemic countries engaged in the fight against this deadly disease, NECT represents a major breakthrough. Yet, NECT is what we consider an 'improved option therapy' for sleeping sickness, which is meant to respond to urgent patient needs in the short term, while we also strengthen our efforts to work towards an oral treatment that can support control or sustainable elimination programmes in the longer term.

Forging strong partnerships

Our partnerships with public and private partners are essential to developing new treatments: building new partnerships and strengthening existing partnerships are vital to our activities. Indeed, partnerships are the *raison d'être* of Product Development Partnerships (PDPs).

The year culminated with an initiative that marked a turning point in the neglected disease landscape: in early 2012, a high-level event in London, 'Uniting to Combat Neglected Tropical Diseases', was organized in support of the new World Health Organization (WHO) Neglected Tropical Disease (NTD) 2020 Roadmap for Implementation, which aims at control or elimination of 10 neglected tropical diseases (NTDs) by the end of the decade. The meeting, and the resulting 'London



In Memory of John Kinuthia

John Kinuthia passed away on 28 May 2011. He was the victim of a tragic road accident in Nairobi, as he was returning from a field visit in Sudan. John joined DNDi in 2007 as Assistant Data Manager and rose to the position of Data Manager, where he was instrumental in the operations of the Data Centre in Nairobi. With his passing away, we have lost a dedicated and passionate member of the DNDi Africa team. John is deeply missed by his family, friends, and colleagues.

Declaration on NTDs', brought together an unprecedented group of actors including DNDi, NTD-endemic country governments, the US, UK, and UAE governments, over a dozen pharmaceutical companies, the Bill & Melinda Gates Foundation, the World Bank, and other global health organizations which pledged to work together to defeat these diseases.

The initiative bolstered commitments from several pharmaceutical companies, particularly to share knowledge and compound libraries with DNDi. The impact of this event was comparable to that of the first report on neglected diseases, 'Working to overcome the global impact of neglected tropical diseases', published by WHO in 2010, which aimed to increase awareness on neglected and hidden diseases and the need for innovation.

Sharing knowledge & expertise

Since its inception, DNDi and its founders strongly believe that open source models, initiatives, and practices are critical to boosting innovation, reducing duplication and costs of R&D, and speeding up delivery of new medicines to patients. As an 'incubator of R&D pathways', we are pleased that DNDi's R&D model has allowed for new ways of working with private companies, by which access to compound libraries is given to DNDi, in addition to the necessary freedom to operate and agreement to produce drugs at cost and on a non-exclusive basis. The latter enables technology transfer and local production, both of which can lead to increased patient access to much-needed treatments.

Endemic country involvement from the outset

Strong and increased involvement of disease-endemic countries in defining our R&D priorities, especially in ensuring that such priorities are rooted in patient needs, is

one of the most important lessons learned by DNDi thus far. The role of our founding partners and the establishment of three regional disease-specific platforms have been vital to the development and success of our activities and ultimately to the implementation of new treatments.

Sustainable & increased funding

The R&D pipeline for neglected diseases is now beginning to replenish with over 150 products in development and managed by PDPs, but promising candidates will not progress and generate public health breakthroughs without increased and sustained funding, new incentives, and innovative collaboration models to ensure further development. The WHO initiative to assess mechanisms for R&D Financing and Coordination offers what could pave the way to a global and sustainable framework for neglected disease innovation.

To conclude, behind all of the work we do to effectively address the challenges of boosting innovation for neglected disease R&D, is a network of devoted staff, engaged partners, and committed donors, who together make it all happen. We would like to thank particularly the distinguished Board and SAC Members whose mandates came to completion in 2011, notably Reto Brun, Bruce Mahin, Lalit Kant, Gill Samuels, Marleen Boelaert, and Haruki Yamada, for all the excellence they brought to DNDi.

On behalf of DNDi, we would also like to thank all of you who share our commitment to bringing the best science to the most neglected, and who have supported us throughout this challenging and successful year.



Dr Bernard Pécoul



Prof. Marcel Tanner

DNDi is an alternative model
to develop drugs for neglected
diseases and ensure equitable
access for all patients.



SIXTH TREATMENT DELIVERED IN 2011 AND TWO NEW MINI-PORTFOLIOS

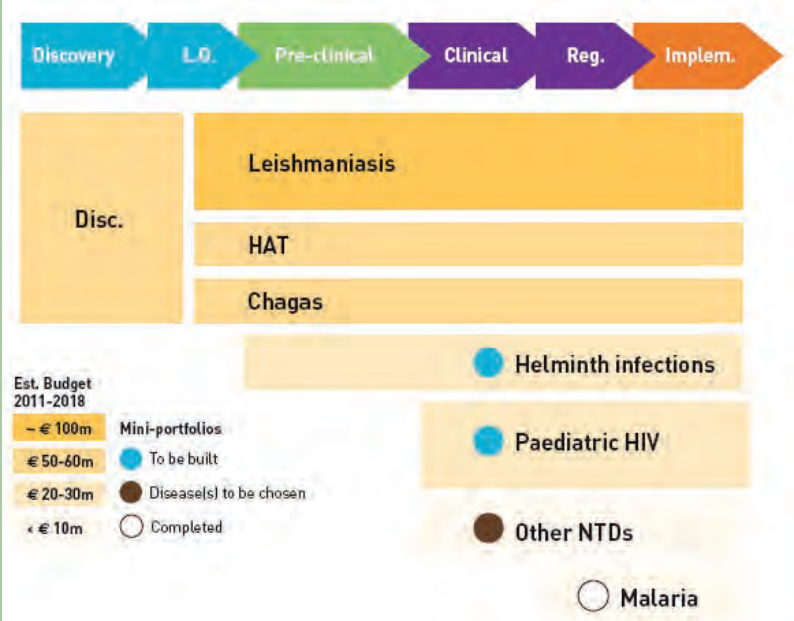
Six treatments delivered, a paediatric dosage form of benznidazole registered in 2011, two new mini-portfolios, and growing momentum of partnerships to address neglected patient needs... both today and tomorrow.

In 2011, DNDi and its partners delivered the sixth treatment for neglected patients: a paediatric dosage form of benznidazole for children with Chagas disease. This treatment was developed through a partnership with Brazil's Pernambuco State Pharmaceutical Laboratory (LAFEPE), and was registered by the Brazilian regulatory agency ANVISA in December 2011.

The new Business Plan for the period 2011 to 2018 was released in October 2011, paving the way for DNDi to take on more ambitious objectives, notably with the inclusion of two mini-portfolios to address patient needs in the fields of paediatric HIV and specific helminth infections, as well as the expansion of activities in DNDi's Regional Offices.

According to the updated plan, DNDi's primary objective is to deliver 11 to 13 new treatments by 2018 for leishmaniasis, human African trypanosomiasis (sleeping sickness), Chagas disease, malaria, paediatric HIV, and specific helminth

DNDi PROCESS



infections, as well as to establish a strong R&D portfolio. The plan stipulates that the malaria portfolio will be completed and transferred to partners by 2014.

STRIVING FOR INCREASINGLY OPEN INNOVATION MODELS

Since the year 2000, the R&D landscape for neglected diseases has improved, with a growing number of players now involved in the R&D process through partnerships between not-for-profit organizations and private companies. In addition, this improving landscape is supported by public donors and philanthropists and has led to a replenishing pipeline of health tools.

The year 2011, with new agreements to access compounds and expertise of pharmaceutical companies and new open innovation initiatives, marks a turning point in the landscape for neglected disease R&D.

In order to foster innovation for neglected diseases and deliver major scientific breakthroughs as quickly and efficiently as possible, gaining access to knowledge and compounds and encouraging open innovation models form the cornerstone of DNDi's efforts to advance global health by supporting the research community in the field of neglected diseases.

Aiming for 'gold standard' research and licensing agreements

The year 2011 and early 2012 were fruitful for DNDi in terms of partnerships with pharmaceutical and biotechnology companies, as well as with other PDPs, with new agreements either signed or underway. Several of these partnerships were highlighted during the 'Uniting to Combat NTDs' event in London in January 2012, where public and private partners pledged to boost efforts to combat ten neglected tropical diseases. DNDi's research and licensing agreements secure access to compound libraries, data, and knowledge in order to boost innovation and jumpstart the expensive and time-consuming discovery phase of R&D to identify promising drug candidates.

Today, DNDi works with over a dozen companies. In 2011, a three-year research collaboration agreement was signed with Sanofi to undertake research on new treatments for nine neglected tropical diseases (NTDs).

The rights to results produced by this partnership will be co-owned by Sanofi and DNDi and publication of the results will be facilitated to ensure access to the wider community of NTD research. The public sector will benefit from the drugs developed through this agreement under the best possible conditions to facilitate patient access in all endemic countries, irrespective of income level.

In early 2012, a four-year joint research and non-exclusive licensing agreement was signed with Abbott to undertake research on new treatments for Chagas disease, helminth infections, leishmaniasis, and sleeping sickness. Under the agreement, Abbott provides DNDi access to molecule classes and accompanying data. In addition to a non-exclusive licensing structure for relevant IP, the products resulting from the agreement will be provided in all endemic countries, irrespective of income level, at the lowest sustainable price.

Several years of experience have led DNDi to define what can be deemed the 'gold standard' of licensing terms, which includes four key components:

- perpetual royalty-free non-exclusive sub-licensable licenses in the specific disease areas determined in the agreement
- worldwide research and manufacturing rights
- commitment to make the final product available at cost, plus a minimal margin, in all endemic countries, regardless of income level
- non-exclusivity, enabling technology transfer and local production.

ChEMBL





Encouraging innovation through sharing of data and knowledge

Neglected disease R&D requires new and open models for sharing knowledge and research data. As demonstrated by the Open Source Drug Discovery consortium in India, ChEMBL-NTD, WIPO Re:Search, the Medicines for Malaria Venture's open access Malaria Box, GSK's Open Lab, and the Medicines Patent Pool, initiatives for open innovation are flourishing, and while it may be too early to evaluate their impact, they demonstrate increasingly open approaches to boosting innovation. DNDi welcomes this trend and took steps in the year 2011 in this direction.

With eight pharmaceutical companies and nearly a dozen not-for-profit or public research institutions, including Fiocruz, DNDi joined WIPO Re:Search as both a 'user' and a 'provider' of the public database and open innovation platform, launched in October 2011. WIPO Re:Search provides access to intellectual property (IP) for pharmaceutical compounds, technologies, and other data and knowledge for R&D on neglected tropical diseases, tuberculosis, and malaria. In 2011, DNDi posted data on over 5,500 compounds from two of its lead optimization consortia on sleeping sickness and Chagas disease, both on the WIPO Re:Search and on yet another public database: the ChEMBL-NTD medicinal chemistry database. The latter provides open access to primary screening and medicinal chemistry data relevant to neglected diseases.

A special 'Open Innovation Portal' was created to render these datasets easily accessible on the DNDi website. These two public databases represent a move towards more open mechanisms that have the potential to facilitate and foster sharing of IP and knowledge to boost neglected disease innovation, notably by avoiding duplication in research and by reducing costs and development timelines for the benefit of patients.

The data that DNDi makes available is the fruit of collaboration between DNDi and its partners and is part of a constant effort to render accessible to entire scientific community, whenever possible:

- both positive and negative research results, as negative results can offer a wealth of information, allow for new research approaches to the same series with potentially different outcomes, and eliminate duplication of efforts; and
- data that DNDi and its partners have willfully agreed to place in the public domain, free of any and all IP constraints.



2011 KEY MILESTONES

JANUARY 2011

Two new diseases areas

DNDi takes on specific mini-portfolio projects for two new disease areas: paediatric HIV and specific helminth infections.

MAY 2011

Research agreement with Sanofi

DNDi and Sanofi announce a three-year research collaboration agreement for the research of new treatments for nine neglected tropical diseases.

OCTOBER 2011

11 to 13 by 2018!

DNDi's updated Business Plan 2011-2018 is published, explaining the strategy to achieve the new objective to deliver 11 to 13 treatments by 2018, including two mini-portfolios, at an event the 7th European Congress on Tropical Medicine and International Health (ECTMIH) in Barcelona, co-hosted with Cresib and ISGlobal.

Open innovation

DNDi joins the WIPO Re:Search Platform, while calling for more ambitious provisions for innovation and access.

SEPTEMBER 2011



Ahmed Mohamed El Hassan, University of Khartoum, Sudan; Mounir Christo Lado Lugga, Ministry of Health, South Sudan; Mercé Herrero, WHO Ethiopia (from left to right)

New VL treatment implemented

LEAP platform meeting holds a press conference calling for support and uptake of SSG&PM, an improved and recommended treatment for VL in East Africa.

DECEMBER 2011

Paediatric dosage for Chagas patients

Treatment developed with the Brazilian laboratory Lafepe is granted registration in Brazil. New hope for children with Chagas disease, as this is the only existing child-adapted dosage form to facilitate early treatment.

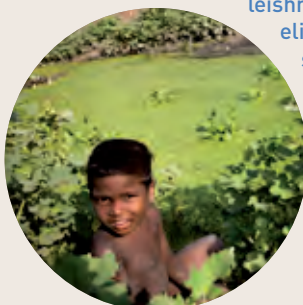
NOVEMBER 2011

Vast implementation study in India & Bangladesh

Launch of a four-year study to include over 10,000 patients to support India and Bangladesh's National Control Programmes in implementing new treatments to boost visceral

leishmaniasis elimination strategies.

VL Asia Consortium is launched with DNDi, OWH, and TDR.



120 million ASAQ treatments

ASAQ reaches 120 million fixed-dose treatments implemented in Africa to fight against malaria.

ASMQ registered in India



The Drugs Controller General of India (DCGI) registers the anti-malarial

treatment artesunate-mefloquine fixed-dose combination (ASMQ FDC).



JUNE 2011



New hope for HAT patients

Anacor, SCYNEXIS, and DNDi announce successful completion of pre-clinical studies for the first new oral drug candidate discovered specifically to combat sleeping sickness.

WHO

DNDi presents a contribution to the WHO Consultative Expert Working Group (CEWG) on R&D: Financing and Coordination.

JULY 2011



E1224 for Chagas disease

Start of the Phase II study in Bolivia to test the Eisai compound E1224 for adult chronic Chagas patients.

AUGUST 2011

Paediatric HIV still neglected

'Pediatric HIV – A Neglected Disease?' DNDi alerts the scientific community through an article in the *New England Journal of Medicine*, announcing its plan to undertake activities in this field.

... JANUARY 2012

London: Uniting to Combat Neglected Tropical Diseases



Margaret Chan, WHO; Stephen O'Brien, DFID; Donan Mmbando, Ministry of Health, Tanzania; Andrew Witty, GSK; Bill Gates, B&MGF (from left to right)

High-level meeting organized in support of the WHO NTD Roadmap, with new or expanded commitments from 13 pharmaceutical companies, the USA, UK, and UAE governments, the Bill & Melinda Gates Foundation, the World Bank, and other health organizations, including DNDi, announcing a new, coordinated push to accelerate progress for neglected patients.

DECEMBER 2011

Call to Action in Latin America



Carlos Gadelha, Ministry of Health, Brazil; Marcel Tanner, Swiss TPH and DNDi Board of Directors; Paulo Gadelha, Fiocruz, Brazil (from left to right)

NGOs, patient groups, private industry, and other key stakeholders, to boost innovation and access for neglected patients in the region.

Resulting from the momentum at the DNDi Partners' Meeting in Rio de Janeiro, with over 260 regional partners and members of its global network, DNDi and partners call on Latin American governments, but also academia,

NECT treatment for sleeping sickness patients

In 2011, approx. 93% of the stage 2 HAT patients in Democratic Republic of Congo were treated with NECT, reducing considerably the use of the toxic drug, melarsoprol (an arsenic derivative that is fatal for 5% of those who receive it).



Research agreement with Abbott

DNDi and Abbott sign a four-year joint research and non-exclusive licensing agreement to undertake research on new treatments for several of the world's most neglected tropical diseases, including Chagas disease, helminth infections, leishmaniasis, and sleeping sickness.

Governance

BOARD OF DIRECTORS

The Board of Directors is composed of ten to thirteen members, including at least one patient representative, who serve four-year terms. Each of the founding partners nominates one Board Member.

DNDi Board Members



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



Reto Brun
Secretary; Swiss Tropical and Public Health Institute (Swiss TPH) (until December 2011)



Els Torreele
Secretary; Open Society Foundations, USA (as from December 2011)



Bruce Mahin
Treasurer; formerly with Médecins Sans Frontières (MSF) (until December 2011)



Derrick Wong
Treasurer; non-profit management consultant, France (as from December 2011)



Alice Dautry
Institut Pasteur, France



Abul Faiz
Patient Representative; Sir Salimullah Medical College, Bangladesh



Lalit Kant
Indian Council of Medical Research (ICMR) (until June 2011)



Unni Karunakara
Médecins Sans Frontières (MSF)– International



Datuk Mohd Ismail Merican
Ministry of Health, Malaysia



Carlos Morel
Oswaldo Cruz Foundation (Fiocruz) Brazil



Paulina Tindana
Patient Representative; Navrongo Health Research Centre, Ghana



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



Gill Samuels
Global Forum for Health Research, Foundation Council, Switzerland, formerly with Pfizer, UK (until June 2011)



Robert G. Ridley
WHO-TDR (Permanent Observer)

- **Position currently vacant**, Kenya Medical Research Institute (KEMRI)
- **Position currently vacant**, Indian Council of Medical Research (ICMR)

SCIENTIFIC ADVISORY COMMITTEE (SAC)

DNDi's Scientific Advisory Committee (SAC) is composed of eighteen prominent scientists with expertise in various scientific disciplines related to drug discovery and development, and/or the specific reality of neglected diseases and neglected patients. They operate independently of the Board of Directors and the Executive Team. The SAC has the mandate to advise the Board of Directors on matters related to research and development and choice of projects, as well as the quality of the scientific output.

DNDi Scientific Advisory Committee Members

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

Khirana Bhatt, University of Nairobi, Kenya

Chris Bruenger, IDEC, Japan

François Chappuis, Médecins Sans Frontières & Geneva University Hospitals, Switzerland

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

Simon Croft, London School of Hygiene and Tropical Medicine (LSHTM), UK

Federico Gomez de las Heras, formerly with GlaxoSmithKline, Spain

Chitar Mal Gupta, Central Drug Research Institute, India

Maria das Graças Henriquez, Oswaldo Cruz Foundation (Fiocruz), Brazil

Paul Herrling, Novartis International AG, Switzerland

Dale Kempf, Abbott, USA

Nor Shahidah Khairullah, Infectious Diseases Research Center, 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, Bolivia

Mervyn Turner, formerly with Merck Research Laboratories, USA

Muriel Vray, Institut Pasteur, France

Krisantha Weerasuriya, World Health Organization (WHO), Switzerland

AFFILIATE AND REGIONAL OFFICE BOARDS

DNDi North America Board of Directors

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

Hellen Gelband, Center for Disease Dynamics, Economics & Policy, USA

Joelle Tanguy, Global Alliance for Vaccines and Immunization (GAVI), Switzerland

James Orbinski, University of Toronto, Canada

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

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

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

DNDi Latin America Board, Executive Members

Michel Lotrowska, Chair; Brazil

Carlos Morel, Oswaldo Cruz Foundation (Fiocruz), Brazil

Tyler Fainstat, Médecins Sans Frontières (MSF), Brazil

DNDi Japan Board of Directors

Haruki Yamada, Chair, Kitasato Institute for Life Sciences, Japan

Koshin Nakahira, Nakahira Certified Tax Accounting Office, Japan

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

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



EXECUTIVE TEAM

Bernard Pécoul, Executive Director

Shing Chang, Research & Development Director

(in alphabetical order)

Jean-François Alessandrini, Fundraising & Advocacy Director

Ralf de Coulon, Finance, Human Resources & Administration Director

Robert Don, Discovery & Pre-clinical Director

Jean-Pierre Paccaud, Business Development Director

Thomas Saugnac, Operations Director

Nathalie Strub Wourgaft, Medical Director

DNDi Regional Offices and Affiliate

Rachel Cohen, Regional Executive Director, North America

Fumiko Hirabayashi, DNDi Representative in Japan

Visweswaran Navaratnam, Head of Regional Office, Malaysia

Bhawna Sharma, Head of Regional Office, India

Eric Stobbaerts, Director of Regional Office, Latin America

Monique Wasunna, Head of Regional Office, Africa

DNDi Team Worldwide

DNDi's global team consists of permanent staff based in Geneva, five regional offices, one affiliate, and one liaison office. The team coordinates a broad base of consultants and volunteers worldwide. In total, 94 people (88.8 FTEs) contributed to DNDi's activities in 2011: 49 (46.6 FTEs) of which were based at headquarters in Geneva and 45 (42.2 FTEs) of which were based at the regional offices and affiliate.



HEADQUARTERS

Manica Balasegaram; Clélia Bardonneau; Hana Bilak; Séverine Blesson; Pascale Boulet; Phouttasone Bouppha; Stéphanie Braillard; Gwenaelle Carn; Eric Chatelain; Christine Crettenand; Brigitte Crotty; Violaine Dällenbach; Graciela Diap; Julia Fährmann; Anna Fitzgerald; Sally Ellis; Caroline Gaere Gardaz; Karin Gènevaux; Nina Holzhauer; Jean-Robert Ioset; Dominique Junod-Moser; Jean-René Kiechel; Marc Lallemand; Gabrielle Landry Chappuis; Delphine Launay; Janice Lee; Sandrine Lo Iacono; Denis Martin; Christofine Marty-Moreau; Janine Millier; Farrokh Modabber; Béatrice Mouton; Charles Mowbray; Emmanuel Pinget; Sylvie Renaudin; Ivan Scandale; Jérôme St-Denis; Olena Sushchenko; Antoine Tarral; Donia Tourki; Olaf Valverde; Laurence Vielfaure.

REGIONAL OFFICES & AFFILIATE

AFRICA

DRC: Mamie Thérèse Benyi; Arthur Bongo; Augustin Kadima Ebeja; Richard Mbumba Mvumbi. **KENYA:** Nicholas Bonyo; Simon Bolo; Robert Kimutai; Joy Malongo; Josephine Kesusu; The late John Kimani; Michael Ochieng; Seth Okeyo; Raymond Omollo; Truphosa Omollo; Rhoda Owiti; Rehma Nanfuka.

ASIA

INDIA: Sharmila Das; Vishal Goyal; Pankaj Kumar; Vikash Kumar; Babita Papneja; Abhijit Sharma; Vikash Sharma.

JAPAN: Emi Nakamura. **MALAYSIA:** Gan Eng Seong.

LATIN AMERICA

BRAZIL: Mariana Abi-Saab; Fabiana Alves; Bethania Blum de Oliveira; Alexandra Dias; Carolina Frossard; Gabriela Gazola; Igor de Moraes; Maristela de Oliveira Soares; Flavio Pontes; Isabela Ribeiro; Joëlle Rode; Glaucia Santana.

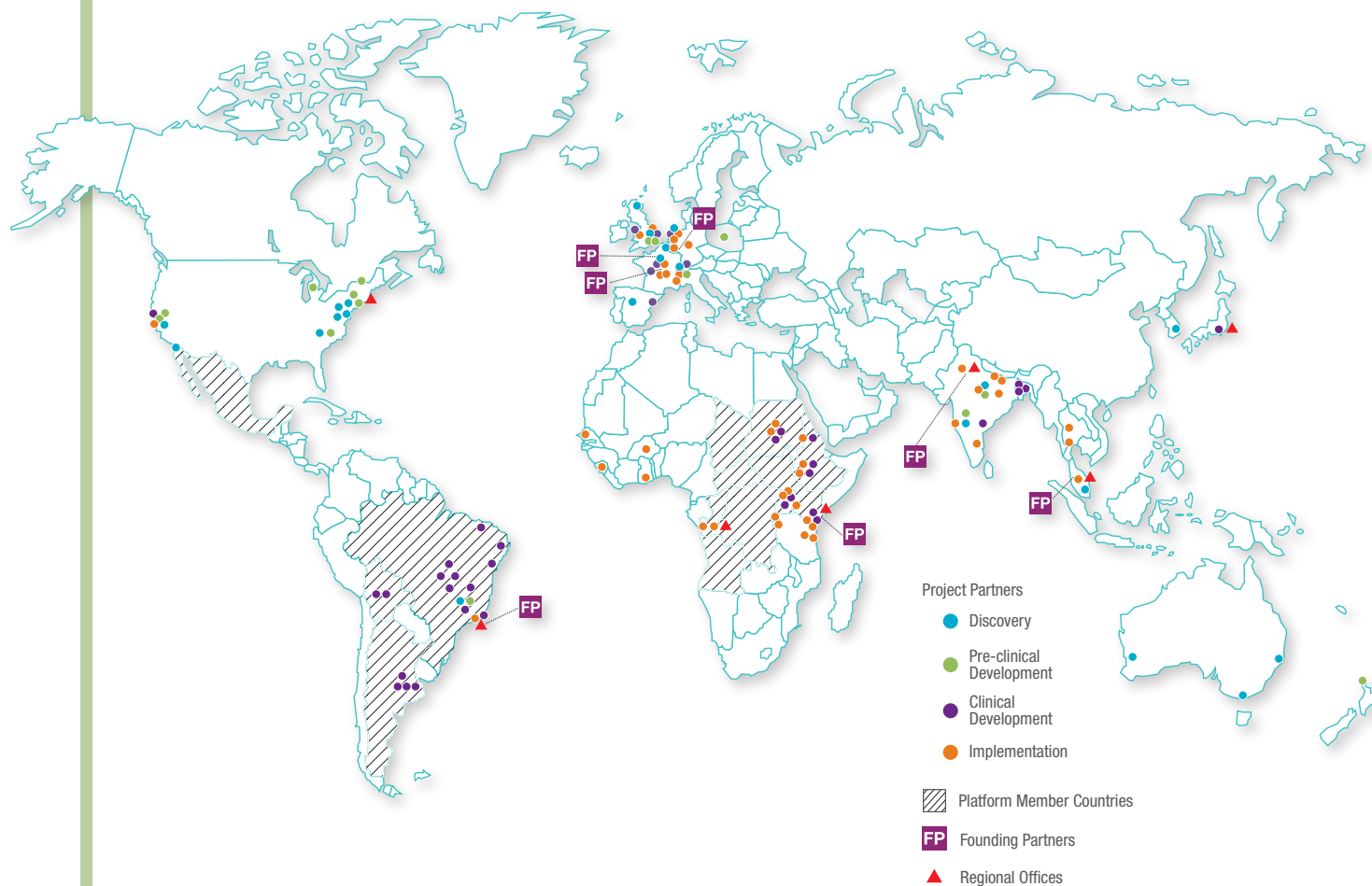
NORTH AMERICA

USA: Erin Conklin; Jennifer Duran; Jennifer Katz; Oliver Yun.

DNDi around the world

At the founding of DNDi in 2003, seven key stakeholders joined forces to propel the initiative.

Each Founding Partner is a centre of excellence in neglected disease research and/or patient care. In addition, DNDi has secured its regional rooting in countries where neglected diseases are endemic, as well as in other countries where its activities are prominent.



SEVEN FOUNDING PARTNERS **FP**

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
- WHO/TDR – The special programme for research and training in Tropical Diseases (TDR)

THREE PLATFORMS



LEAP
PLATFORM



HAT
PLATFORM



CHAGAS
CLINICAL RESEARCH
PLATFORM

SIX REGIONAL OFFICES

- DNDi Latin America (Rio) ▲
- DNDi Africa (Nairobi) ▲
- DNDi India (Delhi) ▲
- DNDi Malaysia (Penang) ▲
- DNDi Japan (Tokyo) ▲
- DNDi in DRC (Kinshasa) ▲

ONE AFFILIATE

- DNDi North America (New York) ▲

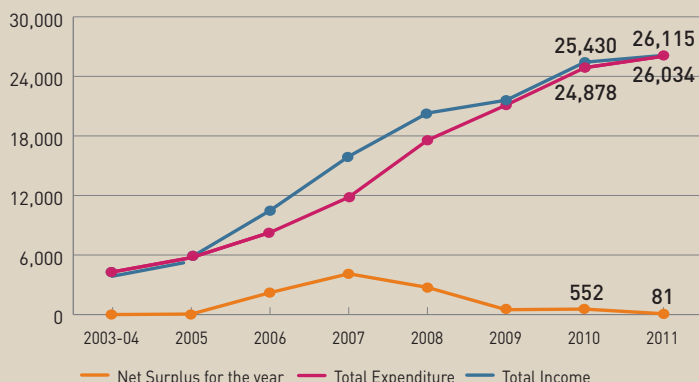
2011 KEY FINANCIAL PERFORMANCE INDICATORS



Supporting expansion of DNDi activities by reinforcing the team, partnerships, and processes

Statement of activities 2004-2011

Budget of EUR 26 million in 2011



DNDi expenditure totals **EUR 120 million since its inception in 2003**. In 2011, expenditure amounted to **EUR 26 million**, + 4.6% as compared to 2010. The operating loss of EUR 0.2 million was compensated by a positive exchange rate gain, mainly due to the weakness of the Euro against the US dollar.

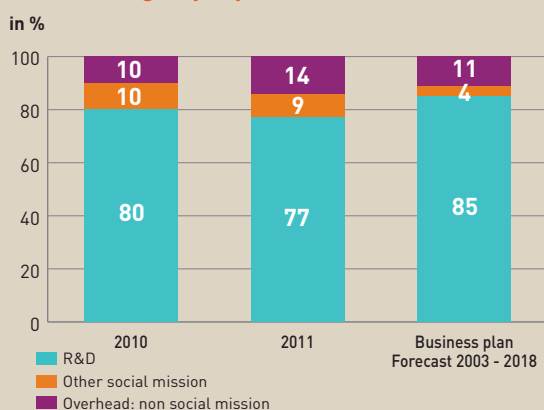
- The number of R&D projects increased by 30% (from 20 in 2010 to 24 in 2011) at all stages of the R&D process.
- R&D expenditure increased slightly in 2011 (+ 1.5% between 2010 and 2011 as compared to +20% between 2009 and 2010) due to: several projects having reached key transition points or at preparation stage – e.g. fexinidazole (preparation of Phase II); Oxaborole (preparation of Phase II); Nitroimidazole (VL) project selected VL-2098 for in-depth evaluation; new VL therapies in South Asia, including preparation of large implementation studies; start of activities for paediatric HIV and helminth infections; start of implementation for cutaneous leishmaniasis; and entry in the non-regulatory pre-clinical phase for fenarimol for Chagas.

To support these transitions, DNDi management and coordination were key:

- To identify and select **new partners**: from 81 in 2010 to 102 in 2011.
- To strengthen the **DNDi team**: + 8 FTEs in Regional Offices and + 7 FTEs at Headquarters.
- To improve **internal processes**: general management from 6% to 8% of annual expenditure.

2011 Social mission breakdown

Transitioning to prepare for the future



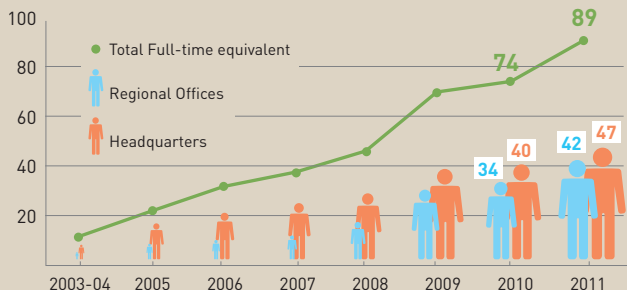
In 2011, the non social mission ratio increased temporarily as new resources were dedicated to improve processes to match the growth of DNDi (R&D portfolio is expected to grow by 30% in the coming years) notably by:

- Supporting the elaboration of the new Business Plan 2011-2018 (issued in September 2011); Recruiting an Operational Director to support empowerment of Regional Offices as well as operational practices and policies; and a Coordinator to support increased financial requests and reporting duties.
- IT support was adjusted to meet the increase of staff worldwide.
- Fundraising expenses increased by 26% to reinforce activities in Regional Offices.

Other social mission expenditure – which includes capacity strengthening and advocacy activities – remained stable in 2011 (- 1%). Cost savings were generated at the Partner's Meeting in December 2011 by holding other key meetings at the same occasion: launch of the paediatric dosage form of benznidazole; advocacy workshop; malaria expert meeting; Chagas Clinical Research Platform meeting; VL expert meeting; and the DNDi Board meeting.

Human Resources Evolution 2004-2011

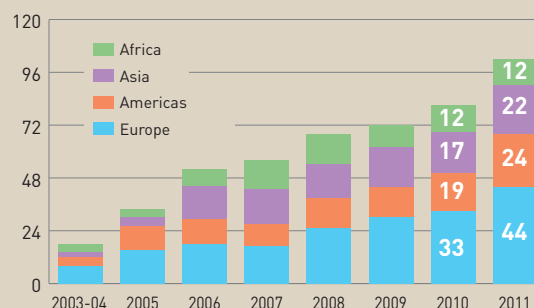
Reinforcing the team to match growth



In 2011, DNDi recruited an additional 15 FTEs. Seven new staff joined DNDi Headquarters (+18%) in order to: lead the new paediatric HIV formulation programme; complete the drug discovery team; and reinforce the finance and fundraising departments as well as the management team. In Regional Offices, eight staff joined DNDi in New Delhi, Rio de Janeiro, Kinshasa, and New York (+24%). The new staff members reinforce clinical teams in the endemic regions and support the expansion of DNDi's fundraising strategy in the USA and in emerging economies.

R&D Partners & subcontractors per continent

Strong increase in partners worldwide



In 2011, 102 partners and subcontractors participated in advancing the DNDi portfolio, + 24% as compared with 2011. New partners were identified and selected to progress DNDi projects through the R&D pipeline and start new projects [e.g. large implementation studies for new VL therapies in South Asia, paediatric HIV, helminth infections, and CL activities].



DNDi's objective is to deliver
11 to 13 new treatments by 2018
and to maintain a robust pipeline
to support long-term objectives.



A MATURING PORTFOLIO AND EXTENSION TO PAEDIATRIC HIV AND HELMINTH INFECTIONS

At the end of 2011, DNDi had delivered six new treatments and built a robust pipeline with 11 new chemical entities at pre-clinical and clinical stages, a major achievement in the field of R&D for neglected diseases. DNDi also added two diseases to its portfolio in 2011, specific helminth infections and paediatric HIV.

The year 2011 has been one of transitions for DNDi, with a maturing portfolio of molecules progressing through the development pipeline, including 11 new chemical entities (NCEs) at various stages of development for the kinetoplastid diseases (human African trypanosomiasis (HAT), visceral leishmaniasis (VL), and Chagas) and helminth infections, one new treatment registered, and five at the implementation phase.

At its inception in 2003, DNDi's Business Plan aimed to deliver between six and eight new treatments for patients in need by 2014. By the end of 2011, this objective was achieved, as six new treatments have been registered or made available to patients – the paediatric dosage form of benznidazole for the treatment of Chagas disease was registered by the Brazilian regulatory authorities in December 2011.

DNDi's R&D strategy relies on the combination of long-term goals, through the development of NCEs to support sustainable control or elimination of neglected diseases, with short-term goals based on the optimization of existing drugs, to address immediate and urgent patient needs. Building the future of novel and effective treatments for neglected diseases includes progressing promising compounds through the development pipeline, establishing collaborations with the pharmaceutical industry, biotech, academia, and increasingly with other PDPs

to access new chemical libraries or compounds, using cutting-edge technologies, such as high-throughput screening (an imaging technology-based high-content screening assay against intracellular *Leishmania* and *T. cruzi*), as well as developing strong lead optimization consortia. DNDi also builds capacity for clinical research in the field by supporting regional platforms for each kinetoplastid disease.

Each year, DNDi updates its target disease strategies, defining the need and desired outcome, and taking into account the current research landscape. Target product profiles (TPPs) define the key features of the new drugs/treatments and are developed with input from disease

BY KEEPING THE FOCUS ON PATIENTS AND THEIR NEEDS, DNDI'S PROJECT PORTFOLIOS BALANCE LONG-TERM AND SHORT/MEDIUM-TERM PROJECTS

- **Long-term projects** – to develop innovative medicines with new chemical entities.
- **Medium-term projects** – to identify existing pre-clinical or clinical stage compounds suitable for therapeutic switching, or for further improvements via improved formulations.
- **Short-term projects** – to make existing drugs available in broader geographic areas and to develop better treatments, including combinations, from existing drugs.

experts, representatives of Ministries of Health and National Control Programmes in endemic countries, WHO representatives, leading clinicians and researchers, as well as health workers who deal with the realities of the diseases in the field. DNDi's TPPs are publicly available on the website.

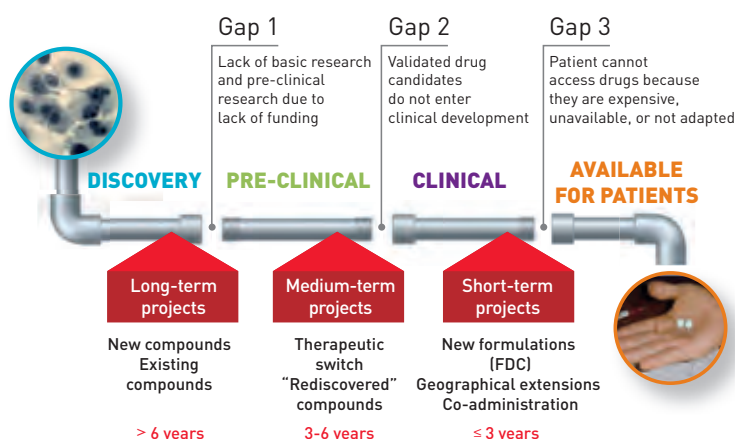
So far, DNDi has delivered six new treatments for malaria, sleeping sickness, visceral leishmaniasis, and Chagas disease.

The latest is a paediatric dosage form of benznidazole, developed in partnership with LAFEPE and registered in Brazil in December 2011 (see page 37), a real progress in that it enables accurate, easier-to-administer, and safer treatment of Chagas disease in infants and children under the age of two.

DNDi is working with its partners to ensure that these new treatments are effectively available to patients.

The past year was marked by projects progressing through the pipeline. Successful advancement of new leads and optimized leads in the discovery and pre-clinical phases is the key to building a robust pipeline for the coming years. Taking into account the realities of the field is an essential element when progressing candidates from the pre-clinical to the clinical phase. And finally, successfully completing the transition from the clinical phase to the implementation phase is the guarantee that patients will benefit from new, optimal treatments.

DNDi'S R&D PROJECTS – FILLING THE GAPS



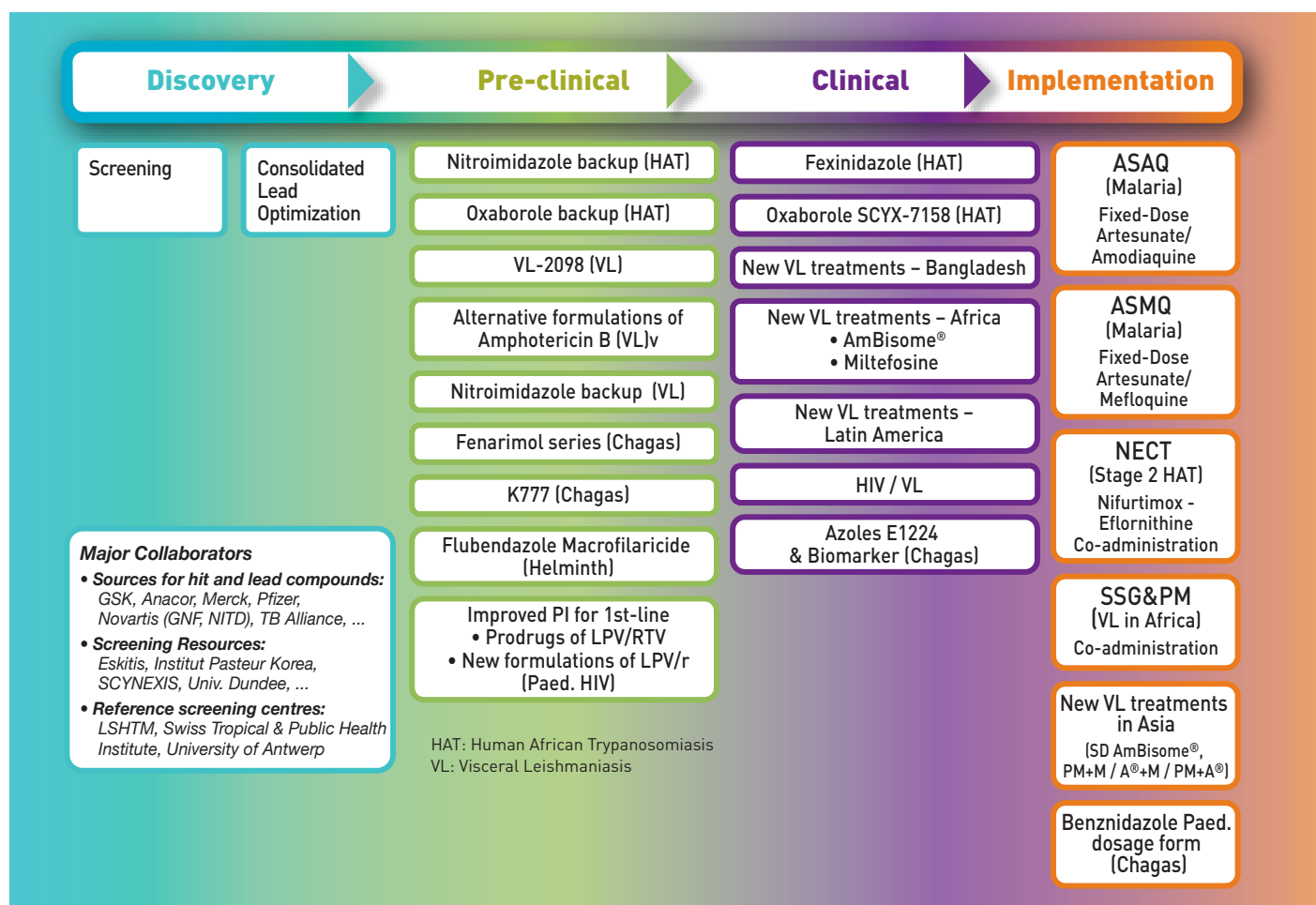
TARGET PRODUCT PROFILE (TPP)

- **Indications:** Which diseases?
- **Population:** Which type of patients and where?
- **Clinical Efficacy:** Does it treat the parasitic infection effectively?
- **Safety and Tolerability:** What level of acceptability for adverse events?
- **Stability:** How long is the shelf life of the drug(s), and necessary storage conditions?
- **Route of Administration:** How is it administered to patients?
- **Dosing Frequency and Treatment Duration:** How often and how long must it be given?
- **Cost:** Will it be affordable to target population?
- **Time to Availability:** How long will it take to develop?





DNDi portfolio (as of December 2011)



In 2011, DNDi's portfolio was extended to integrate two new diseases, specific helminth infections (see page 42) and paediatric HIV (see page 45). Both programmes are at the pre-clinical phase.

Key accomplishments 2011:

HAT: NECT is now on the national essential medicines lists of 12 countries across Africa and increasingly replacing treatment with melarsoprol and eflornithine monotherapy; Phase I studies for fexinidazole were completed in 2011; SCYX-7158, an oxaborole, is ready for Phase I studies. Promising backups are in lead optimization and pre-clinical phases.

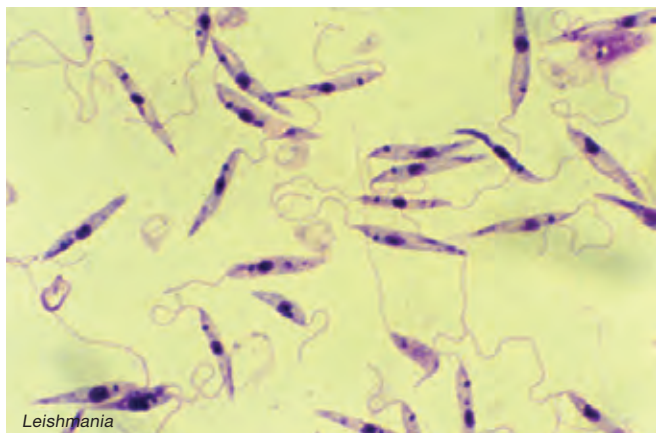
VL: SSG&PM is available and implemented in Sudan and Uganda. New drug combination therapies are available for Asia. Three backup compounds are at the pre-clinical stage and promising leads are in the lead optimization phase.

Chagas disease: The paediatric dosage form of benznidazole was registered in Brazil at the end of 2011. DNDi

has one project in the clinical phase and two in the pre-clinical phase, as well as promising perspectives in lead optimization.

Malaria: Both treatments are in the implementation phase. ASAQ Winthrop: by the end of 2011, 120 million ASAQ treatments had been distributed in 30 African countries. In addition, more than 20 million treatments were ordered for the private sector in 7 countries in Africa within the Affordable Medicines Facility – malaria (AMFm). ASMQ was registered in India after completion of the technology transfer between Brazilian and Indian partners. WHO pre-qualification, registration, and launch of the product in member countries of the Association of Southeast Asia Nations (ASEAN) are planned for 2012.

In 2011, DNDi decided to evolve its discovery strategy and lead optimization platforms toward a more efficient mode to better integrate knowledge, data, and resources from its partners.



The earliest stages of drug discovery consist of three phases, sourcing and screening compounds, hit-to-lead expansion up to lead selection, and lead optimization (LO). In its early days, DNDi relied on opportunities arising from academic and biotechnology collaborations to fill its discovery pipeline. Even though this model successfully delivered several leads, its intrinsic challenges (low throughput for drug screening, limited capacity for compound evaluation, and insufficient resources) led DNDi to restructure its drug discovery model and adopt a more pragmatic and structured discovery strategy that relies on partnerships with public (e.g. universities and academia) and private partners (pharmaceutical and biotechnology companies).

In addition, in 2011, DNDi restructured its LO activities to enable more flexibility and increase cost effectiveness, and moved from three disease-specific LO consortia to two, which work across all three kinetoplastid diseases. This reorganization enables greater cross-talk between diseases for each compound series being investigated.

In recent years, DNDi has also taken steps to address two main concerns: the low throughput in screening against intracellular protozoa (such as *Leishmania* and *Trypanosoma cruzi*) and the sourcing of quality compounds. DNDi now relies mainly on phenotypic screening to gen-

erate hits, and has successfully supported the development and validation of medium- to high-throughput *in vitro* assays using whole-cell assays against *Trypanosoma brucei brucei*⁽¹⁾ at Griffith University in Australia.

In addition, the Institut Pasteur Korea has developed, in partnership with DNDi, imaging technology-based high-content screening assays against intracellular *Leishmania* and *T. cruzi*. These newly developed assays have significantly increased DNDi's capacity to screen compound collections against its target pathogens.

In 2011,
DNDi screened
over 250,000
compounds in
more than 430,000
screening assays.

Main partners: Anacor Pharmaceuticals, USA; Drug Discovery Unit (DDU) at the University of Dundee, UK; Eskitis Institute (Griffith University), Australia; Genomics Institute of the Novartis Research Foundation (GNF), USA; GlaxoSmithKline, Tres Cantos, Spain; Institut Pasteur Korea (IPK), South Korea; London School of Hygiene & Tropical Medicine (LSHTM), UK; Merck, USA; Pfizer, USA; Sanofi, France; SCYNEXIS Inc., USA; Swiss Tropical and Public Health Institute (Swiss TPH); TB Alliance, USA; TI Pharma, The Netherlands; University of Antwerp, Belgium; Special Programme for Research and Training in Tropical Diseases (WHO-TDR).

Management: Discovery and Pre-Clinical Director: Robert Don; Discovery Manager: Jean-Robert Ioset.

(1) Sykes ML, Avery VM. Development of an Alamar Blue™ viability assay in 384-well format for high throughput whole cell screening of *Trypanosoma brucei* bloodstream form strain 427. Am. J. Trop. Med. Hyg. 81(4), 665–674 (2009).



→ Compound-mining

This approach is based on proactive acquisition and investigation of compounds from selected series associated with a significant level of available information (biological activities, pre-clinical dossier, published data, safety profile, among others) in order to identify candidates with a potential for further development – ideally ready to enter into pre-clinical or later stage without further optimization – for the target diseases. Following the successful example of fexinidazole, DNDi has extended this approach in collaboration with its pharmaceutical partners, including Sanofi (repositioning collection of 300 marketed drugs and clinical candidates, an initiative of Sanofi for Neglected Diseases) and GSK (collections of marketed drug sets, as well as terminated leads and candidates).

→ Chemical diversity

This approach aims to mine new chemical territories to identify additional classes of molecules of potential interest in terms of drug development for DNDi's target diseases. Illustrating this approach is the recent research collaboration with Pfizer to screen the Pfizer GDRS II set (representative of the entire Pfizer library in terms of chemical diversity, i.e. 150,000 compounds) against all three kinetoplastid diseases at the ESKITIS Institute (HAT) and IPK (VL and Chagas disease). More recently, DNDi has started evaluating various libraries based on chemical diversity with its pharmaceutical partners, including, among others, Sanofi and GSK.

→ Mining for chemical classes

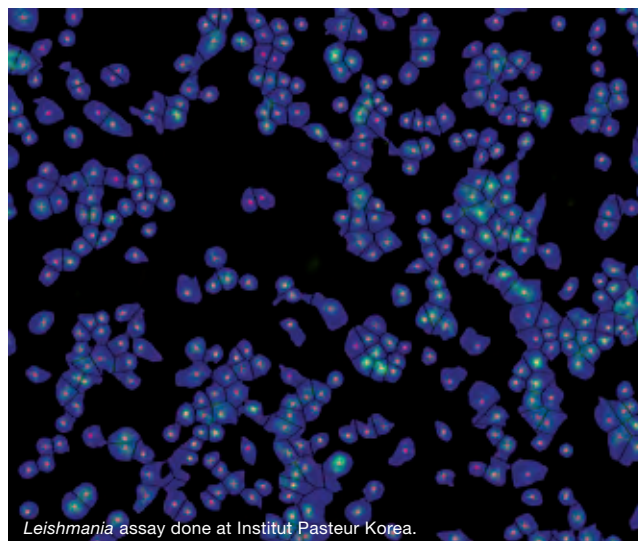
Discovery activities are typically associated with high attrition rates, especially in the case of candidates not associated with any pre-clinical data other than *in vitro* efficacy. In order to lower this attrition rate, mining for chemical classes relies on the identification of promising chemical classes of which a member has been successfully advanced in drug development for other disease indications. From libraries of collaborating pharmaceutical and biotech companies, promising compound classes can be identified by sampling a subset of representative compounds and testing them for antiparasitic activities. Examples of interesting classes include oxaboroles (Anacor Pharmaceuticals), pyridones (GSK), and nitroimidazoles (TB Alliance).

→ Target-based

This early discovery approach is based on screening compounds and assessing their activity against a specific target essential for parasite growth. In collaboration

with the Drug Discovery Unit (DDU) at the University of Dundee, DNDi aims to discover and, through hit-to-lead efforts, deliver one to three leads active against *Leishmania donovani*. This collaboration takes advantage of the unique existing capabilities of the partner in lead generation and their active engagement in high-throughput molecular target screening.

Additional capabilities at DDU have also been applied to the drug discovery efforts, such as cell and organism-based phenotypic screening (including high-content platforms), structure-based drug design, computational and medicinal chemistry, drug metabolism and pharmacokinetics, and *in vivo* animal models of infection.



Leishmania assay done at Institut Pasteur Korea.

→ High-throughput screening

High-throughput screening of large libraries for *Leishmania*, *T. cruzi* (IPK) and *T. brucei* (ESKITIS) have been developed and are used to identify novel hit compounds. Adequate screening capacity is a key element of DNDi's discovery strategy, as it enables the screening of large libraries/series of compounds and therefore a quicker identification of hits/leads.

→ Reference screening centres

The Swiss TPH, the University of Antwerp, and the LSHTM serve as reference screening centres to ensure that screening methodologies are comparable, and that *in vitro* and *in vivo* assays at different sites and with different groups meet the same standards. The centres also provide expert parasitology advice that ensures the quality of DNDi's data and work.

Eliminating sleeping sickness by 2020: An achievable goal?

Of the three kinetoplastid diseases, HAT is the only one slated for global elimination by the year 2020 in the WHO roadmap for implementation published in early 2012.⁽¹⁾ Thanks to the efforts and successes of National Control Programmes (NCPs), together with WHO, MSF, Sanofi, Bayer, DNDi, and others, there is indeed reason to hope: the number of reported cases has substantially decreased within the past years, dropping below 10,000 for the first time in 50 years in 2009. A new combination therapy, NECT, that simplifies treatment, was introduced in 2009 for patients with stage 2 HAT.

However, additional efforts and new treatments are still needed to make elimination possible and sustainable: surveillance and control programmes need to be maintained and expanded to all endemic areas and field-adapted tools need to be developed to detect and treat, in primary healthcare settings, those patients who are not reached by current strategies.

Treatments for HAT are toxic or complex to administer. Treatment is stage-specific, and requires in-hospital infusions for stage 2 of the disease, which is the life-threatening, neurologic phase. Together with complicated and invasive diagnostic methods, such as the lumbar puncture, the reality of HAT management remains challenging, even more so in the most remote, low-resource settings. In addition, the possibility of disease resurgence, together with that of emerging resistance to existing treatments, call for the development of new drugs, compatible with the realities of the disease in the field.

The ideal treatment is a safe, effective, and orally administered drug active against both stages of the disease.

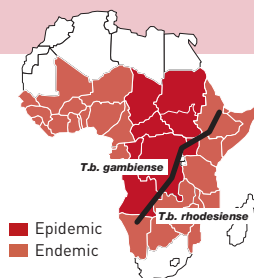
(1) *Accelerating Work to Overcome the Global Impact of Neglected Tropical Diseases – A Roadmap for Implementation*, World Health Organization, 2012.

IDEAL TARGET PRODUCT PROFILE FOR HAT

A new treatment for adults and children

- Effective against **both stages** of the disease
- Active against **both causative parasite sub-species**: *Trypanosoma brucei gambiense* and *T.b. rhodesiense*
- With less than 0.1% drug-related mortality
- With at least 95% efficacy at 18 months follow-up
- Safe for pregnant and lactating women
- **Easy to use**: short-course (7, maximum 10 days), oral, once a day, requiring no monitoring
- **Affordable**
- **Adapted to tropical climates** (three-year shelf-life)





Human African Trypanosomiasis (HAT)

A fatal disease threatening millions in sub-Saharan Africa

WHAT IS THE IMPACT OF HAT?

The number of reported cases in 2010 was just over 7,000, but the estimated number of actual cases is currently approximately 30,000.⁽¹⁾

Fatal if untreated, the disease affects mainly those living in remote areas with limited access to adequate health services. Almost eliminated in 1960, transmission increased again as a result of war, population displacement, poverty, and the collapse of health systems.

Recent successes and an impressive drop in the number of reported cases call for renewed hope, but there is still work to be done, as some areas are not covered by surveillance and control efforts.

HOW IS HAT TRANSMITTED?



HAT is transmitted to humans by two sub-species of the parasite *Trypanosoma brucei* (*T. b.*) through the bite of the tsetse

fly: *T. b. gambiense* (West and Central Africa, responsible for the vast majority of cases) and *T. b. rhodesiense* (East Africa). The disease affects 36 countries in sub-Saharan Africa, but 8 countries report 97% of all cases (see map), and over two-thirds of those are reported in the Democratic Republic of the Congo (DRC).⁽²⁾

WHAT ARE THE SYMPTOMS?

HAT occurs in two stages:

→ **Stage 1:** the hemolymphatic stage – includes non-specific symptoms like headaches and bouts of fever (and generally goes undiagnosed without active HAT surveillance).

→ **Stage 2:** the later, neurologic stage – occurs when the parasite crosses the blood-brain barrier and can lead to serious sleep cycle disruptions, paralysis, progressive mental deterioration, and ultimately, without effective treatment, death.

A lumbar puncture is needed to differentiate between the two stages for the administration of proper treatment.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

Available treatments are limited, difficult to administer, often toxic, and stage-specific.

→ **Stage 1:** pentamidine and suramin are fairly well-tolerated treatments, but require injections and are ineffective for stage 2.

→ **Stage 2:** melarsoprol is a toxic arsenic derivative that causes pain and fatal encephalopathies in up to 5% of those who receive it⁽³⁾, and is increasingly ineffective, with reports of drug resistance and treatment failure in some foci;

eflornithine is difficult to administer: treatment requires trained health staff and an extended hospital stay (56 intravenous infusions taking two hours each to administer, over 14 days and four times each day); **NECT** (nifurtimox-eflornithine combination therapy) is a simplified therapy option for stage 2 *T. b. gambiense* sleeping sickness, with only 14 injections of eflornithine over 7 days and 10 days of oral treatment with nifurtimox. While not the most appropriate treatment to support elimination efforts, it provides an incremental improvement in case management at the field level.

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 was included on the WHO Essential Medicines List in 2009 and is now recommended as first-line treatment for HAT in 12 endemic countries.

As a medium-term strategy, DNDi initiated a proactive compound mining effort to identify existing chemical compounds with potential against kinetoplastid diseases. This resulted in the rediscovery of fexinidazole, which completed Phase I clinical development in 2011. Fexinidazole is now ready to be assessed in a pivotal Phase II/III study in 2012. An agreement was signed in 2009 with Sanofi as the industrial partner for this project.

In order to build a strong pipeline for long-term drug discovery, DNDi established the HAT Lead Optimization Consortium. The identification of the Oxaborole SCYX-7158 represents the first success of this consortium. SCYX-7158 successfully progressed through pre-clinical development and at the end of 2011, all necessary documentation was submitted to relevant authorities for the start of Phase I clinical development in early 2012. Other backup compounds continue to be evaluated by the consortium.

Finally, DNDi supports the HAT Platform (see page 50) that was launched in Kinshasa (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 from Angola, the Central African Republic, Chad, DRC, Republic of the Congo, Sudan, South Sudan, and Uganda.

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

→ An oral, safe, effective treatment for stage 2 HAT, ideally to be used with the same regimen for stage 1 HAT

(1) <http://www.who.int/mediacentre/factsheets/fs259/en/> (2) Simarro PP, Jannin J, Cattand P (2008) Eliminating human African trypanosomiasis: where do we stand and what comes next? PLoS Med 5: e55. doi:10.1371/journal.pmed.0050055. (3) Blum J, Nkunku S, Burri C. (2001) Clinical description of encephalopathic syndromes and risk factors for their occurrence and outcome during melarsoprol treatment of human African trypanosomiasis. Trop Med Int Health;6:390-400.



Partners:

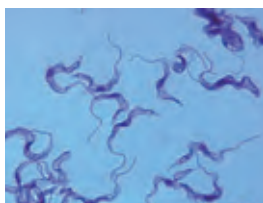
TB Alliance, USA;
University of Auckland, New Zealand;
SCYNEXIS Inc., USA;
Pace University, USA;
Wuxi AppTech, China;

Management:

Discovery and Pre-clinical Director:
Robert Don;
Head of Drug Discovery: Charles Mowbray;
Project Manager: Ivan Scandale;
Project Coordinator: Delphine Launay

Project start:

April 2007



HAT Lead Optimization Consortium – Nitroimidazoles backup – Oxaboroles backup

2011 OBJECTIVES:

- To develop backups from the oxaborole and nitroimidazole series
- To facilitate transition of discovery research to the new consolidated lead optimization programme during the second semester

DNDi's strategy for the lead optimization consortia is to develop a backup compound in each of the oxaborole and nitroimidazole series, whilst also advancing new chemical classes from the screening programmes. In case of failure of one of the current developed compounds, the backup should be able to replace it rapidly. These consortia bring together expertise in chemistry, biology, drug metabolism, and pharmacokinetics (DMPK), *in vivo* screening, drug safety assessment and pre-formulation development. Optimization efforts are focused on improving the molecule's characteristics to be absorbed into the bloodstream, to be distributed effectively to the infection sites, to survive in the body, to kill the parasite, and not to harm the patient.

In 2011, potential backup oxaboroles for HAT were identified and profiled *in vivo* for efficacy. The most advanced compounds were selected for exploratory toxicity studies. Potential backup nitroimidazoles for HAT were selected for further *in vitro* and *in vivo* DMPK studies. Promising leads were progressed towards *in vivo* efficacy studies. All selected compounds have the attributes described in discovery manuals and could match the aims of the TPP for HAT.

They are being assessed to ensure that they offer quality backups to SCYX-7158 and fexinidazole, should these two compounds not succeed through clinical development. Work will continue in 2012, with the aim to complete exploratory toxicity studies and further PK studies with the leading oxaborole backups for HAT, such that an optimized lead could be presented by end 2012.

Nitroimidazoles will continue to be triaged and profiled to provide an optimized lead backup to fexinidazole by the end of 2012. In addition, DNDi and its partners aim to bring at least one new hit series through hit-to-lead studies into lead optimization.

Nota Bene: the lead optimization (LO) consortia were re-organized in 2011, from three separate HAT, VL, and Chagas disease-specific consortia, into two consolidated consortia, LO USA and LO Australia, for all three diseases.



Partners:

SCYNEXIS Inc., USA;
Anacor Pharmaceuticals Inc., USA;
Advinus Therapeutics, India;
Penn Pharma, UK

Management:

Discovery and Pre-clinical Director:
Robert Don;
Head of HAT Clinical Programme:
Antoine Tarral;
Clinical Manager: Séverine Blesson;
Project Manager: Ivan Scandale;
Project Coordinator: Delphine Launay

Project start:

January 2010

Oxaborole SCYX-7158

2011 OBJECTIVES:

- Complete a GLP pre-clinical package, develop a process for drug formulation, manufacture the Active Pharmaceutical Ingredient (API)
- Submit regulatory files for Phase I clinical trials

SCYX-7158 belongs to a unique boron-based chemical class, the oxaboroles, which was originally provided by Anacor Pharmaceuticals and screened for activity against *T. brucei* at the University of California San Francisco. A unique collaboration between DNDi, Anacor Pharmaceuticals (a biopharmaceutical company in Palo Alto, California, USA) and SCYNEXIS (a drug discovery and development company based in Research Triangle Park, North Carolina, USA), within a consortium that also included Pace University (USA) and the Swiss TPH, enabled the identification of SCYX-7158, selected as a promising pre-clinical candidate in late 2009. In pre-clinical studies, SCYX-7158 was shown to be safe and efficacious to treat stage 2 of the disease, as it is able to cross the blood-brain barrier.



PRE-CLINICAL STUDIES completed

1ST DNDi LEAD OPTIMIZATION CONSORTIUM CANDIDATE to enter Phase I

120 VOLUNTEERS to be recruited in clinical trials

Pre-clinical development progressed successfully through 2010, and all pre-clinical data were published in PLoS NTD in June 2011.⁽¹⁾ In 2011, regulatory toxicology studies were performed to assess the compound's safety. Batches of drug substance and drug product were produced according to current good manufacturing practices (cGMP).

Finally, the Investigational Medicinal Product Dossier (IMPD) and the study protocol were submitted to the ethics committee and to the French regulatory authority, AFSSAPS. Following their clearance, SCYX-7158 is set to enter First-in-Human studies in early 2012 and become DNDi's first entity resulting from lead optimization efforts to enter Phase I clinical studies. These studies will assess its safety, tolerability, pharmacokinetics, and pharmacodynamics in healthy volunteers of sub-Saharan origin.

(1) Jacobs RT, Nare B, Wring SA, Orr MD, Chen D, et al. (2011) SCYX-7158, an Orally-Active Benzoxaborole for the Treatment of Stage 2 Human African Trypanosomiasis. PLoS Negl Trop Dis 5(6): e1151. doi:10.1371/journal.pntd.0001151





Partners:
Sanofi, France;
Swiss Tropical and
Public Health Institute (Swiss TPH);
HAT Platform members

Management:
Head of HAT Clinical Programme:
Antoine Tarral;
Medical Manager: Olaf Valverde;
Clinical Manager: Séverine Blesson;
Project Coordinator: Clélia Bardonneau

Project start:
2007



Fexinidazole

2011 OBJECTIVES:

- Complete Phase I clinical studies
- Determine the therapeutic dose to use in the subsequent pivotal Phase II/III study
- Develop an analytical method to measure pharmacokinetics (PK) in field conditions (dry blood spots)
- Finalize the protocol for the pivotal Phase II/III study

Fexinidazole is the first success of the extensive compound mining efforts pursued by DNDi within the nitroimidazole project initiated in 2005 to explore new and old nitroimidazole drug leads. This rediscovered drug entered Phase I First-in-Human studies in September 2009 and is now ready to enter Phase II/III. In addition to the single ascending dose, food effect, and multiple ascending dose studies carried out in 2010, studies to determine the optimal treatment dose and duration were performed in 2011. An analytical method to measure the PK of fexinidazole was completed during the year. In early



PHASE I
completed

510 PATIENTS
to be recruited
for Phase II/III
at **6 SITES**
in 3 countries

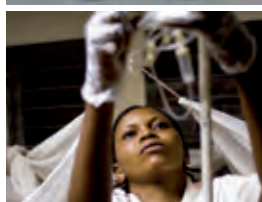
2011, DNDi and Sanofi requested joint scientific advice from the FDA and the EMA (through Article 58), on the clinical development plan for fexinidazole, which led to the development of a protocol for a single pivotal Phase II/III study to prove the safety and efficacy of fexinidazole, with NECT as the active comparator. Preparatory activities to conduct trials in the Democratic Republic of the Congo, the Central African Republic, and possibly South Sudan have taken place, such as selection of trial sites and training in good clinical practices (GCP). The protocol was submitted for review to an international ethics working group meeting convened by the Société Française et Francophone d'Ethique Médicale (SFFEM) with WHO support in early 2012, and the trial is expected to start in the second quarter of 2012.



Partners:
Médecins Sans Frontières (MSF), International;
Swiss TPH;
National Trypanosomiasis
Control Programmes of the
Democratic Republic of Congo;
HAT Platform members

Management:
Head of HAT Clinical Programme:
Antoine Tarral;
Medical Manager: Olaf Valverde;
Clinical Manager: Séverine Blesson

Project start:
2004



NECT

Nifurtimox-Eflornithine Combination Therapy

2011 OBJECTIVES:

- Support the inclusion of Nifurtimox-Eflornithine Combination Therapy (NECT) in the Essential Medicines List of all HAT Platform countries
- Continue follow-up of patients included in the NECT-Field trial initiated in 2009 (Q2 2012)

NECT was developed by DNDi, MSF, Epicentre, Swiss TPH, and the National Trypanosomiasis Programmes of the Republic of the Congo and DRC as a combination of eflornithine and nifurtimox. Available since late 2009, it reduces the number of eflornithine infusions needed, has a higher cure rate than eflornithine alone and fewer severe adverse events. By reducing the quantity of eflornithine needed to treat each patient, it also significantly lessens the cost of treatment. NECT also reduces the burden on health systems, as it is much simpler to administer, making it much more adapted to the field conditions where it is used.



93% OF STAGE 2
HAT patients
treated with NECT
in DRC (2011)

>4,000
TREATMENTS
distributed
in 2011 alone

12 COUNTRIES
with NECT in EML

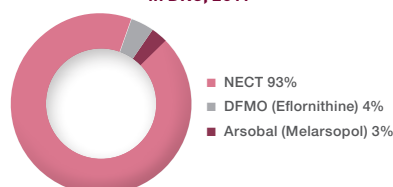
630 PATIENTS
in NECT-Field
in total

NECT was included on the WHO Essential Medicines List in 2009. Since then, melarsoprol and eflornithine monotherapy are increasingly being replaced by NECT – in 2010, only 12% of cases were treated with melarsoprol; as of December 2011, 12 countries had added NECT to their national essential medicines list: Angola, Cameroon, Central African Republic, Chad, DRC, the Republic of the Congo,

Equatorial Guinea, Guinea Conakry, Gabon, Ivory Coast, South Sudan, and Uganda. All of them have received supplies from WHO – over 4,000 treatments in 2011. The HAT Platform continues to advocate for the use of NECT, a more field-adapted, simpler and safer treatment for stage 2 sleeping sickness.

DNDi and its partners continue follow-up of patients included in the 'NECT-Field' study launched in 2009. This Phase IIIb study will further document the safety and ease of use in real-life conditions, in specific populations such as children, and pregnant and breastfeeding women. A total of 630 patients were enrolled in the study, including 100 children, 13 pregnant women, and 34 breastfeeding women. The two-year follow-up period will end in mid-2012.

**Distribution of HAT treatments
in DRC, 2011**



Implementing new VL treatment options is crucial to disease management, notably in Africa and in Asia.

Main clinical manifestations of leishmaniasis include visceral leishmaniasis (VL) (also known as kala-azar), cutaneous leishmaniasis (CL), and post-kala-azar dermal leishmaniasis (PKDL). VL is characterized by prolonged fever, enlarged spleen and liver, substantial weight loss, and progressive anemia, and is generally fatal if left untreated. CL is characterized by lesions of the skin that can become chronic and/or disfiguring. PKDL is a disseminated skin infection; a common sequel of VL, it serves as a parasite reservoir, thus contributing to the transmission of the disease.

While the last decade has seen improvements in the treatment, diagnosis, and prevention of leishmaniasis mostly in South Asia, much more remains to be done to reach the WHO aim of eliminating visceral leishmaniasis from the Indian sub-continent by 2020.⁽¹⁾ The disease still remains one of the world's most neglected, affecting the poorest of the poor. More work is needed to consolidate the progress achieved in South Asia and extend it to other parts of the world, in particular East Africa and Latin America. Chemotherapy remains one of the most important tools in the control of visceral leishmaniasis, but existing treatments have serious drawbacks: potential of resistance development, low tolerability, long treatment duration and difficulty in administration, as well as high cost. New treatments that address these issues and

cater for geographical variations and local realities are essential. Effective treatments for cutaneous leishmaniasis have yet to be discovered.

The ideal treatment for VL is a safe, effective, oral, short-course (10 days maximum) drug that would also be efficacious against PKDL. The ideal treatment for CL is a safe, short course, affordable, field-friendly topical or oral agent that cures lesions fast, with minimal scarring.

(1) Accelerating Work to Overcome the Global Impact of Neglected Tropical Diseases – A Roadmap for Implementation, World Health Organization, 2012.

IDEAL TARGET PRODUCT PROFILE FOR VL

A new treatment for adults and children

- Efficacious against **all species** of parasite in all regions
- Safe in pregnant and lactating women
- **Affordable**
- At least 95% efficacy after two months
- **Adapted to tropical climates** (minimum three-year shelf life)
- **Easy-to-use:** Short course, oral or topical, requiring no monitoring

IDEAL TARGET PRODUCT PROFILE FOR CL

A new topical or oral treatment

- Efficacious against ***L. tropica* and *L. braziliensis***
- Safe in pregnant and lactating women
- **Affordable**
- At least 95% efficacy
- **Adapted to tropical climates** (minimum three-year shelf-life)
- Minimal scarring





Leishmaniasis

A still neglected disease affecting five continents

WHAT IS THE IMPACT OF LEISHMANIASIS?

Leishmaniasis occurs on five continents with endemic transmission reported in 98 countries and three territories. Among parasitic diseases, morbidity and mortality caused by leishmaniasis are surpassed only by malaria and lymphatic filariasis.

It is estimated that 350 million people are at risk of the disease, most of them children. The annual incidence is estimated at over 1.5 million cases (400,000 for VL and 1.2 million for CL)⁽¹⁾, with 40,000 VL deaths each year.⁽²⁾ However, due to underreporting and misdiagnosis, estimation of the leishmaniasis disease burden is challenging and actual case loads are expected to be higher.

In addition, co-infection with other infectious diseases is an increasing concern: HIV-VL co-infection has been reported in 35 countries worldwide. The risk of death from VL is nine times higher in those who are co-infected with HIV.



HOW IS LEISHMANIASIS TRANSMITTED?

More than 20 species of the kinetoplastid protozoan parasite *Leishmania* can be transmitted to humans via

some 30 species of phlebotomine sandflies.

CL is most frequently caused by *Leishmania major*, *L. tropica* and *L. aethiopica* in the Old World, and *L. braziliensis*, *L. mexicana*, and related species in the New World.

VL is usually caused by *L. donovani* and *L. infantum*.

PKDL occurs during, or more often after, recovery from VL. It is caused by *L. donovani* and is believed to be a reservoir of parasites for human VL.

WHAT ARE THE SYMPTOMS?

CL is a small erythema that develops after a variable period at the site where an infected sandfly has bitten the host. The erythema develops into a papule, then a nodule that progressively ulcerates to become the lesion characteristic of the disease. CL usually heals spontaneously within one to two years, but results in a lifelong scar, which, depending on its size and location, may cause substantial trauma in affected individuals, particularly children.

VL is characterized by progressive fever, weight loss, enlarged spleen and liver, and anemia. Untreated VL is fatal in almost all cases.

PKDL is characterized by a macular, maculopapular and nodular rash; starting from the face, it spreads to other parts of the body.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

Existing therapies have serious drawbacks in terms of safety, drug resistance, stability and cost.⁽³⁾ They have low tolerability, long treatment duration, and are difficult to administer.

→ **Pentavalent antimonials** (sodium stibogluconate – SSG – and meglumine antimoniate) have been used in the treatment of VL and CL for more than 60 years. Acquired resistance has developed in areas of high prevalence and high transmission. Cardiotoxicity has been reported as a drug-induced effect and serious cardiotoxicity leading to death is well documented.

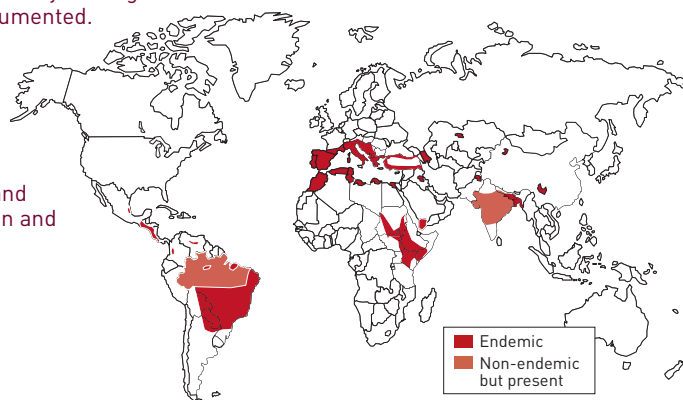
In addition, these drugs require a 30-day parenteral treatment. They are registered in Southeast Asia, and some Mediterranean and African countries.

→ **Amphotericin B** is used as first-line treatment for VL in areas with high rates of unresponsiveness to antimonials and second-line treatment elsewhere. Need for hospitalization, constant monitoring of patients, prolonged duration of treatment and infusion-related adverse events are notable drawbacks. Amphotericin B displays dose-limiting toxicity and requires 15-20 day treatment. It is registered in South Asia and some African countries.

→ **AmBisome®**: a liposomal formulation of amphotericin B, it is much safer and also highly efficacious. However, high cost limits its widespread use in many VL-endemic regions⁽⁴⁾. It is registered for VL in India, USA, and Europe and used as a second-line drug for the treatment of PKDL in East Africa and for CL in Brazil.

→ **Miltefosine** is the first orally administered drug registered in India for the treatment of VL but it is expensive⁽⁵⁾ and requires a 28-day treatment. The major limitation of miltefosine is its contraindication in pregnancy and mandatory contraception for women of child-bearing age for the duration of therapy and 2-3 months beyond. It is also registered in Colombia for treatment of CL.

→ **Paromomycin (PM)**: a low-cost parenteral formulation registered in India in 2007 by Gland Pharma in collaboration with OneWorld Health (OWH). It requires 3 weeks of intramuscular administration.



(1) http://www.who.int/leishmaniasis/burden/magnitude/burden_magnitude/en/index.html. (2) Reithinger R, Dujardin JC, Louzir H, Pirmez C, Alexander B, Brooker S. (2007) Cutaneous leishmaniasis. Lancet Infect Dis; 7:581–96. (3) Seifert K. (2011) Structures, Targets and Recent Approaches in Anti-Leishmanial Drug Discovery and Development. Open Med Chem J.; 5:31–39. (4) Through the WHO, significant cost reduction of both AmBisome® and miltefosine is available for the public sector of key endemic countries as of 2007. (5) Ibid.

Leishmaniasis

A still neglected disease affecting five continents

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?

DNDi's **short-term** approach is 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 short-term objective is to assess efficacy and safety of existing drugs in other countries and regions to extend their registration and availability to more patients.

In 2010, DNDi and partners **delivered the SSG&PM combination therapy for East Africa** that is now recommended as first-line treatment for VL in the region by the WHO Expert Committee on the Control of Leishmaniases. In India, together with its partners, DNDi also conducted a Phase III trial to evaluate the combination of already registered drugs: AmBisome®, miltefosine, and paromomycin. The study showed that the three possible 2-drug combinations were all **highly efficacious**, and they are now, together with single-dose AmBisome®, recommended by the WHO Expert Committee. Together with OWH and TDR, DNDi will collaborate with the National Control Programmes of India and Bangladesh, MSF, the Bihar State Health Society, and the Indian Council for Medical Research to facilitate the introduction of these new treatments for VL in South Asia. In Latin America, DNDi is participating in a study sponsored by the Brazilian Innovation Agency (FINEP) to evaluate the safety and efficacy of Glucantime®, AmBisome®, amphotericin B, and AmBisome® + Glucantime® combination to treat VL patients in Brazil.

As a **medium-term** approach, DNDi is looking into **new formulations** of amphotericin B.

In order to develop new drugs for the treatment of leishmaniasis, DNDi's **long-term** strategy is to bring **new candidates** into clinical development through its lead optimization programme.

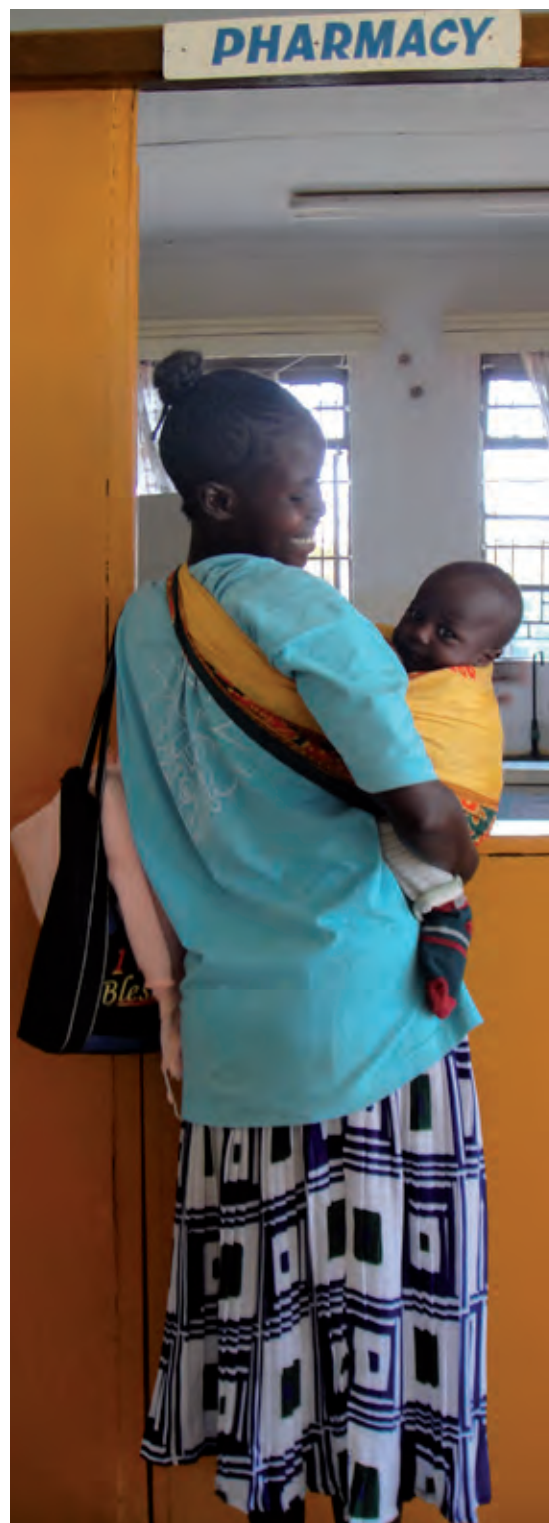
Finally, DNDi supports the Leishmaniasis East Africa Platform (LEAP, see page 50) that aims to geographically extend all currently available VL drugs to East Africa and to develop new therapies suitable for the region, as well as to build capacity in the region for conducting clinical trials.

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

- An oral, safe, effective, low-cost and short-course treatment
- A new treatment for PKDL that is shorter course and better tolerated than current options
- Treatment options for HIV-VL co-infected patients that would limit recurrences

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

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





DISCOVERY

LEISHMANIASIS

Partners:

SCYNEXIS Inc., USA;
Laboratory of Microbiology, Parasitology
and Hygiene, University of Antwerp, Belgium;
London School of Hygiene &
Tropical Medicine (LSHTM), UK;
Wuxi AppTech, China

Management:

Discovery and Pre-clinical Director:
Robert Don;
Head of Drug Discovery: Charles Mowbray;
Project Manager: Ivan Scandale;
Project Coordinator: Delphine Launay

VL Lead Optimization Consortium

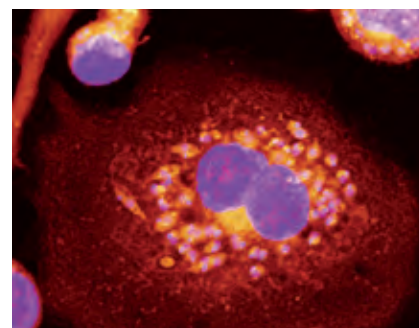
2011 OBJECTIVES:

- To develop new chemical entities (NCEs) with the aim of advancing two candidates into clinical development by 2014
- To facilitate transition of discovery research to the new consolidated lead optimization programme during the second semester

DNDi's strategy for the lead optimization consortia is to advance new chemical classes from the screening programmes, as well as to develop backup compounds that can rapidly replace currently developed compounds in case of failure. These consortia bring together expertise in chemistry, biology, drug metabolism, and pharmacokinetics (DMPK), *in vivo* screening, drug safety assessment, and pre-formulation. Optimization efforts are focused on improving the molecule's capacity to be absorbed into the bloodstream, to be distributed effectively to the infection sites, to survive in the body, to kill the parasite, and not to harm the patient.

In 2011, oxaboroles with promising pre-clinical *in vivo* activity for treating VL were identified. Selected compounds have the attributes described in discovery manuals and could match the TPP for VL. This class of molecules could provide a possible prototype candidate in a new chemical class. A decision will be made on their potential by mid-2012.

Nitroimidazoles are also being assessed as potential backups for VL-2098 (see below).



Nota Bene: the lead optimization (LO) consortia were re-organized in 2011, from three separate HAT, VL, and Chagas disease-specific consortia, into two consolidated consortia, LO USA and LO Australia, for all three diseases.

PRE-CLINICAL

LEISHMANIASIS

Partners:

TB Alliance, USA; Advinus Therapeutics, India;
Central Drug Research Institute, India; London
School of Hygiene & Tropical Medicine
(LSHTM), UK; Auckland University,
New Zealand

Management:

Head of Chagas Discovery
and Pre-clinical Programme: Eric Chatelain;
Project Coordinator: Delphine Launay

Project start:

July 2010

Nitroimidazole backup

2011 OBJECTIVE:

- Maintain a limited and focused backup programme to identify a backup compound for VL-2098, improving compound solubility and adjusting PK parameters

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. The TB Alliance granted rights to DNDi to develop a class of potential anti-TB compounds that also show significant promise for treating 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 below). A focused programme is ongoing to identify a backup pre-clinical candidate in case VL-2098 does not successfully complete pre-clinical testing. Over 150 have been prepared so far.



A few of these were identified as potential leads with an *in vitro* potency comparable to that of VL-2098, improved solubility, metabolically stable, and with reduced hERG channel binding. Work is ongoing to improve *in vivo* efficacy.



VL-2098

2011 OBJECTIVE:

→ Undertake the pre-clinical assessment of VL-2098

From the initially selected 70 nitroimidazoles belonging to four chemical subclasses, 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 and selective *in vitro* and shows efficacy in acute and chronic VL animal models. Appropriate exposure is obtained after oral dosing in rodents and the compound does not induce major acute toxicity after multiple administrations at several multiples of the efficacious dose. Ongoing safety studies and pharmaceutical development are planned for 2012.

Partners:

TB Alliance, USA; Advinus Therapeutics, India; Central Drug Research Institute, India; London School of Hygiene & Tropical Medicine (LSHTM), UK; Auckland University, New Zealand; Bertin Pharma, France.

Management:

Discovery & Pre-clinical Director: Robert Don; Head of Visceral Leishmaniasis Discovery & Pre-clinical Programme: Denis Martin; Project Coordinator: Stéphanie Brailard

Project start:

July 2010



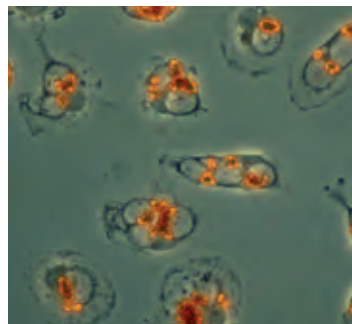
Alternative formulations of amphotericin B

2011 OBJECTIVES:

→ Recommend a novel amphotericin B formulation for advanced evaluation
→ Develop a polymer-based formulation active through intra-venous or intra-muscular administration

The goal of this project is to identify an improved formulation of amphotericin B that shows the most promise in terms of *in vivo* efficacy, safety, heat stability, and cost. Amphotericin B, under various formulations, is one of the most efficacious treatments for VL. The standard formulations (oily suspension) have side effects. AmBisome®, a liposomal formulation, has overcome these limitations, but its high cost and lack of heat stability limit its utility in disease-endemic countries. Recently, new formulations have emerged and have either been approved or are under clinical development in India. However, they are still not field-adapted and there is no safety and VL efficacy data available yet. DNDi and its UK partners are investigating improved polymer-based formulations to replace the lipid-based component with a narrow molecular weight range

polymer. Ideally, the selected polymer can form an amphotericin B conjugate that is soluble, cheaper, better tolerated, and has increased thermal stability. Initial results show that reproducible *in vivo* activity could be achieved without signs of amphotericin-induced toxicity in test animals. A biodegradable polyglutamic acid polymer has been selected and will be assessed for safety, efficacy, and scalability in the first half of 2012.





LEISHMANIASIS

PRE-CLINICAL

Partners:

Mashhad University of Medical Sciences
Mashhad, Iran; Institut Pasteur, Iran; PECET,
Universidad de Antioquia Medellín, Colombia;
Imperial College of Science, Technology and
Medicine, UK; Centro de Pesquisas René
Rachou, Brazil; Laboratory of Intracellular
Parasite Biology, NIH, USA; Laboratory of
Immunology, Division of Therapeutic Proteins,
OBP, CDER, FDA, USA

Management:

Senior Advisor for Leishmaniasis:
Farrokh Modabber; Clinical Managers:
Gwenaëlle Carn, Fabiana Alves

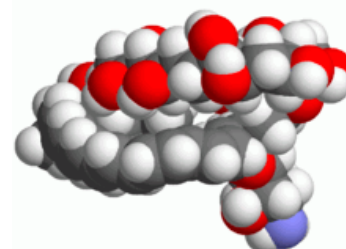
Project start:

September 2011

Cutaneous leishmaniasis

DNDi's objective is to develop a new treatment for CL based on three components – anti-parasitic, wound-healing, and immune modifying. As an ultimate goal to be achieved stepwise, the strategy is to select an already-developed wound-healing agent, to be combined with an anti-parasitic drug, identified by one of two approaches:

- Development of a topical treatment containing amphotericin B
- Screening of selected oral drugs used for other indications



In the long term, DNDi will seek to combine these two elements with an immune-modifier, such as an oligo-deoxy-nucleotide (CpG, or CpG-containing agents – with TLR-9 agonist activities). At each step, an incremental benefit may be achieved over what is currently available for treating CL.

LEISHMANIASIS

CLINICAL

Partners:

Kenya Medical Research
Institute (KEMRI), Kenya;
Institute of Endemic Diseases (IED), University
of Khartoum, Sudan;
Addis Ababa University, Ethiopia;
Gondar University, Ethiopia;
University of Makerere, Uganda;
London School of Hygiene &
Tropical Medicine (LSHTM), UK;
ASK (AMC, Slotervaart Hospital, KIT),
The Netherlands;
Ministries of Health of Ethiopia,
Sudan, Kenya, and Uganda;
Médecins Sans Frontières
(MSF), International;
i+solutions, The Netherlands;
OneWorld Health (OWH), USA;
LEAP (Leishmaniasis East Africa Platform);
Institute of Tropical
Medicine-Antwerp, Belgium

Management:

Head of DNDi Africa, Monique Wasunna;
Head of VL Clinical Programme:
Manica Balasegaram;
Clinical Manager: Sally Ellis;
Project Coordinator: Clélia Bardonneau

Project start:

November 2004

New VL treatments – Africa

2011 OBJECTIVES:

- Finish recruitment of the Phase II/III trial assessing single dose AmBisome®
- Complete exploratory Phase II trial assessing miltefosine combinations in East Africa
- Apply for registration of miltefosine in Sudan, Kenya, and Uganda
- Continue to evaluate and monitor parasite drug sensitivity to current treatments
- Apply for registration of paromomycin (PM) in Uganda, Sudan, Ethiopia, and Kenya

Due to toxicity, difficulty of use, and high cost of existing drugs, VL is complex to treat in Africa. SSG&PM is now recommended as the first-line treatment for VL in East Africa. Other drugs, such as miltefosine, are neither registered nor available in the region. Since 2004, DNDi and LEAP have embarked on a clinical research programme with two specific objectives: to geographically extend all currently available VL drugs and to develop one to two new treatments.

In order to achieve these objectives, DNDi and LEAP conducted two clinical trials in the region during 2011:

AmBisome® / AMBI 0106 Study

AmBisome®, a liposomal formulation of amphotericin B manufactured by Gilead, is approved to treat VL in India, USA, and Europe. Gilead has worked with the WHO and NGOs to provide AmBisome® at a pref-

erential price for the treatment of leishmaniasis in resource-limited settings. This study aims at determining the minimum dose of AmBisome® that is efficacious, safe, and cost-effective to treat VL in Africa, to reduce duration of hospitalization and to facilitate the registration and adoption of the drug in the region. Recruitment for the study was closed at the end of 2010. Patient follow-up and data collection and analysis were completed in 2011 and publication is planned for 2012.



Miltefosine-AmBisome® / LEAP 0208 Study

This study is conducted to evaluate the safety and efficacy of miltefosine and AmBisome®

combination treatment. Recruitment started in Kenya and Sudan in 2010. Miltefosine, a drug originally developed for the treatment of cancer, is the only orally administered drug against VL. It is registered and used in India and in some countries in Latin America. The trial will collect safety, efficacy, and pharmacokinetic data on miltefosine to geographically extend the use of the drug into East Africa. In addition, combination treatments of AmBisome® with either miltefosine or SSG are being evaluated. If the results are promising, one of the combinations will be taken into Phase III development.

LEISHMANIASIS

CLINICAL

New VL treatments – Bangladesh

See Implementation 'New VL treatments Asia', page 31.



New VL treatments – Latin America

2011 OBJECTIVE:

→ Support the Brazilian Ministry of Health and its partners to conduct a Phase III trial assessing the efficacy and safety of amphotericin B, AmBisome®, and the combination of AmBisome® + Glucantime®



70 PATIENTS
recruited in 2011

at 4 SITES

implemented in 2011 in VL reference centres throughout different regions of the country, and is expected to be completed by 2014. Evidence provided by this project will guide policies on the treatment of VL caused by *L. chagasi* in Brazil.

Partners:
René Rachou Research Institution – Fiocruz-MG, Brazil;
Paediatric Hospital João Paulo II – FHEMIG, Brazil;
Brasília University, Brazil;
Montes Claros State University, Brazil;
Piauí Federal University, Brazil;
Sergipe Federal University, Brazil;
Leishmaniasis Control Programme/ Brazilian Ministry of Health, Brazil;
Universidade Estadual do Rio de Janeiro, Brazil

Management:
Head of VL Clinical Programme: Manica Balasegaram;
Clinical Manager: Fabiana Alves

Project start:
February 2011

About 90% of VL cases in Latin America occur in Brazil, and most of them affect children. In 2009, Brazil reported 3,693 new cases with a fatality rate of 5.8%. DNDi is supporting the implementation of a Phase III clinical trial sponsored by the Brazilian Ministry of Health to assess treatments for VL. The primary objective of the study, led by Dr Gustavo Romero of the University of Brasília, is to 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. The project was



HIV/VL

2011 OBJECTIVE:

→ Develop study synopsis and identify partners and sites

Partners:
London School of Hygiene & Tropical Medicine (LSHTM), UK;
Institute of Tropical Medicine-Antwerp, Belgium;
Médecins Sans Frontières – The Netherlands;
Addis Ababa University, Ethiopia;
Gondar University, Ethiopia;
LEAP (Leishmaniasis East Africa Platform)

Management:
Head of VL Clinical Programme: Manica Balasegaram;
Clinical Manager: Sally Ellis;
Project Coordinator: Clélia Bardonneau

Project start:
September 2011

HIV/VL co-infection has important clinical, diagnostic, and epidemiological implications and represents one of the major threats to control visceral leishmaniasis (VL). In Ethiopia for example, in some highly endemic areas for VL, the rate of HIV co-infection among VL patients is 15–30%. This study will aim to identify a safe and effective treatment for VL in HIV co-infected patients.

The trial will evaluate the efficacy of two treatments at day 28: a combination regi-

men of AmBisome® + miltefosine and AmBisome® monotherapy in Ethiopian patients co-infected with VL and HIV. The study will assess relapse-free survival at day 390 (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 anti-retrovirals, AmBisome® and miltefosine, as well as immune function markers, will be examined in a subset of patients.

A second 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.





LEISHMANIASIS

IMPLEMENTATION

Partners:

National Vector Borne Disease Control Programme (NVBDCP), Delhi, India; Indian Medical Research Council (ICMR), Delhi, India; Rajendra Memorial Research Institute of Medical Sciences (RMRIMS), Patna, India; Bihar State Health Society (BSHS), Patna, India; Ministry of Health, Bangladesh; International Centre for Diarrhoeal Disease Research (ICDDR,B), Dhaka, Bangladesh; Shaheed Suhrawardy Medical College and Hospital (ShSMC), Dhaka, Bangladesh; Community Based Medical College (CBMC), Mymensingh, India; University of Tokyo, Japan; OneWorld Health (OWH), USA; Institute Tropical Medicine-Antwerp, Belgium; LSHTM, UK; Special Programme for Research and Training in Tropical Diseases (WHO-TDR); WHO (SEARO, Geneva); Médecins Sans Frontières, International

Management:

Head of VL Clinical Programme: Manica Balasegaram; Clinical Manager: Sally Ellis; Head of DNDi India: Bhawna Sharma; Project Coordinator: Vishal Goyal; Assistants: Pankaj Kumar, Abhijit Sharma

Project start:

2006

New VL treatments – Asia

2011 OBJECTIVE:

→ Implement effectiveness studies in the region to demonstrate feasibility in implementing new treatment modalities in primary healthcare settings in both the public and private sectors

The Phase III trial conducted by DNDi and its partners in 2010 demonstrated the efficacy of combination therapies based on AmBisome®, miltefosine, and paromomycin. An additional study by Sundar *et al.*⁽¹⁾ 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 developed a partnership consortium with TDR and OWH⁽²⁾, in collaboration with health authorities at state, national, and regional levels. DNDi will work to implement single



(1) Sundar S. *et al.* (2011) Comparison of short-course multidrug treatment with standard therapy for visceral leishmaniasis in India: an open-label, non-inferiority, randomized controlled trial. *The Lancet*; 377-9764:477-486.
(2) OneWorld Health (OWH) is an affiliate of PATH.



CONSORTIUM study:

10,000 PATIENTS to be recruited in total in 2 COUNTRIES

dose AmBisome® in the public sector in India (with TDR) and new combination therapies in the private sector (with OWH).

Effectiveness studies are being implemented in the region to demonstrate that such treat-

ments can be safely implemented through primary healthcare systems in both the public and the private sectors. These studies include:

- 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 has two main components, surveillance and pharmacovigilance to monitor treatment effectiveness and safety in the public sector. In 2011, approvals were obtained from key stakeholders in India, an agreement was signed with the Bihar State, and partnerships were established with local implementing organizations. The study is expected to begin mid-2012.

- A two-step Phase III study (first in hospital settings, then in primary healthcare centres) using the combination therapies in Bangladesh; recruitment started in July 2010 and continued in 2011.

LEISHMANIASIS

IMPLEMENTATION

Partners:

Kenya Medical Research Institute (KEMRI), Kenya; Institute of Endemic Diseases (IED), University of Khartoum, Sudan; University of Makerere, Uganda; Ministries of Health of Sudan, Kenya, and Uganda; Médecins Sans Frontières (MSF); i+ solutions, The Netherlands; OWH, India; LEAP (Leishmaniasis East Africa Platform)

Management:

Head of VL Clinical Programme: Manica Balasegaram; Clinical Manager: Sally Ellis; Head of DNDi Africa: Monique Wasunna

Project start:

November 2004



SSG&PM

Sodium stibogluconate & paromomycin

2011 OBJECTIVES:

→ Continue registration of paromomycin (PM) in East Africa
→ Facilitate uptake and implementation in key endemic areas of East Africa with local partners
→ Facilitate pharmacovigilance activities for SSG&PM to monitor safety and effectiveness post-implementation

In 2010, DNDi and LEAP successfully showed that the combination of sodium stibogluconate (SSG) and PM was as efficacious as single-dose SSG, with the advantage of being shorter course, therefore lessening the burden on health systems, and more cost-effective. Since then, DNDi and LEAP have worked with local ministries of health to ensure recommendation and uptake of the new treatment. First registration (of PM) was obtained in Uganda at the end of 2011, and registration is ongoing in Kenya, Sudan, and Ethiopia. Imple-



>10,000 DOSES of SSG&PM distributed since end of Phase III

Pharmacovigilance study at 4 SITES (3 countries)

mentation has already begun in the region, as the treatment was recommended as first-line therapy for VL patients in East Africa by the WHO Expert Committee on the Control of Leishmaniasis. In addition, it has been added to the national drugs lists of Sudan, South Sudan, and Ethiopia. SSG&PM treatment has been rolled out in Sudan and Uganda in public health structures, as well as in important NGO centres. Over 10,000 doses of SSG&PM have been distributed since the end of the Phase III trial – principally in South Sudan.

A pharmacovigilance study to monitor safety and effectiveness of SSG&PM was initiated in 2011 and will be completed in 2013.

A replenished pipeline and a new paediatric dosage form registered in 2011.

Of all the neglected diseases, Chagas disease is among those that receive the least investment for R&D. In 2010, reported funding for R&D for neglected diseases totalled just over USD 3 Billion. Of this amount, only USD 20 Million went to Chagas disease, and only USD 4.5 Million was invested in drug discovery for the disease.⁽¹⁾ The only two drugs approved for treating acute Chagas disease were developed over 40 years ago and are far from ideal. Until recently, the main focus of the fight against Chagas disease was to interrupt transmission through the deployment of vector-control strategies and the screening of blood donors. Whilst sustained vector control has largely contributed to reducing transmission in Latin America, the Pan American Health Organization (PAHO) currently estimates that approximately 8 million people are infected in the region, and that tens of thousands of new cases occur each year.⁽²⁾ Imported Chagas disease is increasingly recognized as an emerging problem in the USA and Europe, due to immigration from Latin America. The US Center for Disease Control (CDC) estimates that over 300,000 persons with *Trypanosoma cruzi* infection live in the USA.

The existing drugs, benznidazole and nifurtimox, have been used for decades, but because their efficacy against the chronic phase of the infection is poorly documented, they are of limited use in disease control strategies. In addition, long treatment periods (60-90 days) make patient compliance challenging, with increased risk of drug resistance development. Side-effects range from skin rashes to seizures and other nervous system disorders.⁽³⁾

In order to effectively fight the disease, new treatments that are safe, efficacious, and effective against the chronic phase of the disease – which is when most patients are diagnosed – are sorely needed. In addition, to gain understanding of the disease progression and ease the development of test-of-cure diagnosis tools that support drug development, a better understanding of biomarkers is essential.

(1) http://polycycures.org/downloads/g-finder_2011.pdf (2) http://new.paho.org/hq/index.php?option=com_content&task=blogcategory&id=3591&Itemid=3921&lang=en (3) Clayton, J. (2010) Chagas disease: pushing through the pipeline. *Nature* 465; S12–S15 doi:10.1038/nature09224.

IDEAL TARGET PRODUCT PROFILE FOR CHAGAS DISEASE

A new treatment for **both acute and chronic** phases:

- Useful against most parasite species in all regions
- Better **safety** profile than existing drugs
- Non-inferior **efficacy** to benznidazole
- **Easy-to-use** treatment: oral, once-a-day for less than 30 days, requiring no hospitalization and little or no monitoring
- **Affordable**
- **Adapted to** tropical climates (minimum three-year shelf-life)





American Trypanosomiasis – Chagas Disease

A 'silent killer' that remains hidden and under-acknowledged

WHAT IS THE IMPACT OF CHAGAS DISEASE?

Chagas disease is endemic to 21 countries in Latin America, where 100 million people are at risk. It is estimated that eight million people are infected, leading to approximately 12,000 deaths every year.⁽¹⁾ Hundreds of thousands of people across the world, in Europe, North America, Japan, and Australia also carry the disease,⁽²⁾ often without knowing it.



HOW IS CHAGAS DISEASE TRANSMITTED?

Chagas disease is related to infection by the kinetoplastid protozoan parasite

Trypanosoma cruzi, transmitted through the bite of a triatomine vector known as the 'kissing bug'. Other routes of transmission include blood transfusion, organ transplantation, as well as congenital and, less often, oral routes through ingestion of contaminated food or beverage.

WHAT ARE THE SYMPTOMS?

The disease has two clinical phases:

→ The acute phase (fatal for 2-8% of children⁽³⁾) is often asymptomatic or unrecognized due to non-specific symptoms, such as fever, malaise, and enlarged lymph nodes, spleen, and liver. In less than half the cases, first visible signs can be a skin lesion or a purplish swelling of one eyelid (known as Romaña's sign). These symptoms spontaneously resolve in 4-6 weeks.

→ The chronic phase that can be divided into two stages:

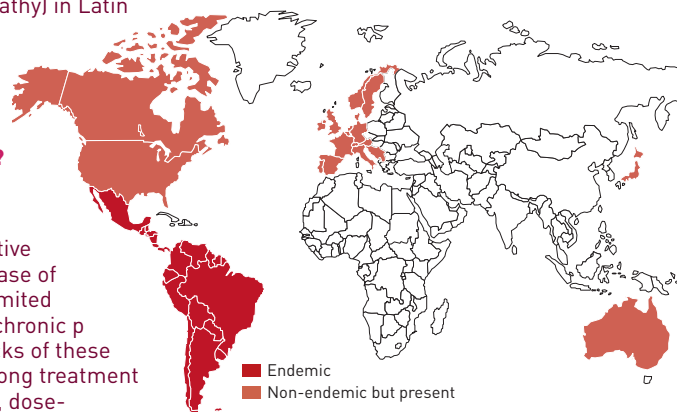
– The chronic, silent, and asymptomatic 'indeterminate' stage, during which patients can transmit the parasite to others, especially through vertical transmission or transfusion, while showing no signs of the disease, and which may last decades after infection.

– The chronic, symptomatic stage, which develops later in up to 30% of infected patients, and causes cardiopathies, digestive tract pathologies, and nervous system irregularities.⁽⁴⁾ Chagas disease

is the leading cause of infectious heart disease (cardiomyopathy) in Latin America.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

Current treatments, benznidazole and nifurtimox, are effective against the acute phase of infection, but have limited efficacy against the chronic phase. Other drawbacks of these treatments 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 chronic disease with target organ involvement and until



recently, there was no adapted paediatric dosage form for either of the existing drugs.

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?

DNDi's short-term goal was to make better use of existing treatments, notably through the development of a paediatric dosage form of benznidazole – a goal which was achieved: This treatment was granted registration by the Brazilian regulatory authorities in December 2011 and DNDi is working with LAFEPE, the manufacturer, to ensure it is widely accessible to all those in need.

As a medium-term strategy, DNDi is assessing known compounds already in development against fungal infections, such as the new azole antifungal drug, E1224, active against *T. cruzi* in adult chronic patients, as well as biomarkers of treatment response.

As part of its long-term strategy, DNDi continues to identify and engage partners from private and public sectors within the Chagas lead optimization consortium in order to identify, characterize, and advance the development of promising compounds.

In addition, DNDi supports clinical research capabilities through the Chagas Clinical Research Platform (see page 50), which was launched in 2009.

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

- An effective and safe oral treatment for the treatment of chronic Chagas disease, ideally effective also against the acute form of the disease
- Biomarkers to gain understanding of the disease progression, ease the development of test-of-cure diagnosis tools that support drug development

(1) http://new.paho.org/hq/index.php?option=com_content&task=view&id=5856&Itemid=4196. (2) Schmunis, G.A. (2007) The globalization of Chagas disease. ISBT Science; 2 – 1; 6–11. (3) Parada H, Carrasco HA, Anez N, Fuenmayor C, Inglessis I. (1997) Cardiac involvement is a constant finding in acute Chagas' disease: a clinical, parasitological and histopathological study. Int J Cardiol. 60: 49–54. (4) http://www.msfaaccess.org/sites/default/files/MSF_assets/NegDis/Docs/NEGDIS_report_Chagas_UpdateOnProgress_ENG_2006.pdf.



Chagas Lead Optimization Consortium



2011 OBJECTIVE:

→ Further characterize fenarimols and oxaboroles as potential pre-clinical candidates

The Chagas lead optimization consortium was set up by DNDi in 2008, bringing together analytical and medicinal chemists, pharmacologists, and parasitologists, with the objective of developing at least one new optimized series for Chagas disease by the first quarter of 2012 and to identify a new chemical series of interest.

The consortium has been working on the fenarimol series, from which two candidates have been characterized as potential pre-clinical candidates. The team had also been evaluating oxaboroles, taking advantage of the compounds generated within the HAT lead optimization programme. However, work on the oxaborole series has been stopped, as structure-activity relationship was mainly driven by *in vivo* models/data,

Nota Bene: the lead optimization (LO) consortia were re-organized in 2011, from three separate HAT, VL, and Chagas disease-specific consortia, into two consolidated consortia, LO USA and LO Australia, to address the needs for all three kinetoplastid diseases.



which is not suitable for a lead optimization programme.

The work of the consortium has provided a better understanding of the essential features for a drug to be efficacious for the treatment of Chagas disease. This insight will be used to propose a new pre-clinical candidate from the nitroimidazole class that is more potent and safer than the drugs currently used (nifurtimox and benznidazole). In parallel, hit series identified through the screening of the NIH library by the Broad Institute (Broad screen), as well as other series emanating from DNDi's screening efforts, will be profiled and prioritized according to their potential.

Partners:

Centre for Drug Candidate Optimisation (CDCO)/Monash University, Australia;
Epichem, Australia;
Murdoch University, Australia;
Federal University of Ouro Preto (UFOP), Brazil;
Institut Pasteur Korea (IPK), Korea;
WuXi AppTech, China.

Management:

Head of Chagas Discovery and Pre-clinical Programme: Eric Chatelain;
Project Manager: Ivan Scandale;
Project Coordinator: Delphine Launay

Project start:

end 2008



Fenarimol

2011 OBJECTIVE:

→ Further characterize the leads of the fenarimol series before candidate nomination

As mentioned above, the Chagas lead optimization consortium yielded two interesting candidates from the fenarimol series of compounds. The project is now in its non-regulatory pre-clinical phase, with further profiling of candidates before nominating one candidate for further regulatory pre-clinical development.

The objective is to perform Good Laboratory Practice (GLP) safety studies, as well as Chemistry, Manufacturing and Control (CMC) studies on the selected candidate compound in order to file a formal investigational new drug (IND) application and move the candidate to first-in-man studies in 2012.

Partners:

Centre for Drug Candidate Optimisation (CDCO)/Monash University, Australia;
Epichem, Australia;
Murdoch University, Australia;
Federal University of Ouro Preto (UFOP), Brazil;
Institut Pasteur Korea (IPK), Korea

Management:

Head of Chagas Discovery and Pre-clinical Programme: Eric Chatelain;
Project Coordinator: Delphine Launay

Project start:

end 2011



K777

2011 OBJECTIVE:

→ Progress IND enabling studies for K777

K777 is a vinyl sulfone cysteine protease inhibitor, which inhibits cruzain, a key protease required for the survival of *T. cruzi*. K777 was originally characterized by the Sandler Center for Research in Tropical Parasitic Disease at UCSF and has since been shown to be safe and efficacious in animal models of acute and chronic Chagas disease. The main objective of the project is to conduct pre-clinical safety and toxicology



studies in order to complete the IND package for clinical evaluation of K777 for the treatment of Chagas disease.

Partner:

University of California San Francisco (UCSF), USA

Management:

Head of Chagas Discovery and Pre-clinical Programme: Eric Chatelain

Project start:

September 2010

**Partners:**

Eisai Co. Ltd, Japan; Platform of Integral Care for Patients with Chagas Disease, Spain/Bolivia; Universidad Mayor de San Simon, Bolivia; Universidad Autónoma Juan Misael Saracho, Bolivia; Collective of Applied Studies and Social Development (CEADES), Bolivia; Cardinal Systems, France; Blanchard and Associates, Argentina; LAT Research, Argentina; McGill University, Canada; University Hospitals of Geneva, Switzerland; University of Georgia, USA; Texas Biomedical Research Institute, USA; University of Texas at El Paso, USA; Instituto Nacional de Parasitología Dr M Fátala Chabén, Argentina; NUDFAC – Nucleus of Pharmaceutical and Cosmetics Development, Brazil; CONICET (Consejo Nacional de Investigaciones Científicas y Técnicas) National Council for Scientific and Technological Research, Argentina; MSF-Spain; Oswaldo Cruz Foundation (Fiocruz), Brazil; Centre de Recerca en Salut Internacional de Barcelona (CRESIB), Spain

Management:

Head of Chagas Clinical Programme: Isabela Ribeiro; Head of Chagas Discovery and Pre-clinical Programme: Eric Chatelain; Clinical Trial Manager: Fabiana Alves; Project Coordinator: Bethania Blum

Project start:
2010

Azoles E1224 and Biomarkers

2011 OBJECTIVES:

- Evaluate the safety and efficacy of the azole compound E1224 for the treatment of adult patients with the chronic indeterminate form of Chagas disease
- Implement Phase II proof of concept clinical trial in adult patients with chronic indeterminate Chagas (single country, two sites): recruitment and follow-up for primary efficacy endpoint
- Harmonize a clinical trial design and success measurements in clinical development for Chagas disease
- Work on the validation of PCR as a marker of therapeutic response in preparation for Phase III studies
- Contribute to the selection and validation of biomarkers of therapeutic response in Chagas disease

In 2009, DNDi joined forces with Eisai Co. Ltd – the Japanese pharmaceutical company that discovered E1224 – to develop this new chemical entity for Chagas disease. E1224 is a pro-drug which converts to ravuconazole, leading to the drug's improved absorption and bioavailability

Previously studied to treat fungal diseases, E1224 has potent *in vivo* and *in vitro* activity against *T. cruzi*.

The Phase II proof-of-concept study started in July 2011 in Cochabamba and Tarija, Bolivia, the country which carries the world's largest Chagas disease burden.

The study, coordinated by DNDi and conducted by the Barcelona Centre for International Health Research (CRESIB), Spain, and the Platform of Integral Care for Patients with Chagas Disease at Universidad Mayor San Simon and Universidad Autónoma Juan Misael Saracho, Bolivia, will evaluate the potential of E1224 as an oral, easy-to-use, safe, and affordable treatment for Chagas disease. In addition, it will explore the currently most promising biomarkers of therapeutic response in Chagas disease.

This randomized, multicentre, placebo-controlled, safety and efficacy study will evaluate three oral E1224 dosing regimens (high dose for four weeks and eight weeks; low dose for eight weeks) and benznidazole (5mg/kg/day).

Recruitment for the study will include 230 adult patients with chronic indeterminate stage of Chagas disease. If E1224 progresses successfully through Phase III clinical trials, it could become one of the first new treatments for Chagas disease in 40 years.

SPECIAL
DNDi
CLINICAL
AWARD
2011



An additional study is ongoing to optimize procedures for the use of the polymerase chain reaction (PCR) blood test as a measure of treatment response in Chagas disease in collaboration with MSF-Spain, with PCR assay support provided by the UMSS in Bolivia and quality assurance from INGEBI-CONICET in Buenos Aires, Argentina. Patient recruitment was finalized in December 2011 and patients will be followed-up for 12 months.

In parallel, DNDi started the assessment of biomarkers for Chagas disease with respect to their potential for application to clinical research. Collaboration with different partners was initiated and a strategy is being defined for 2012 and the following years.

In the context of the E1224 study, markers of treatment response, such as conventional and non-conventional serology, selected pro-thrombotic factors and Apolipoprotein A1, will be assessed.



**230 ADULT
PATIENTS
to be recruited
in Phase II
at 2 SITES**

Additional activities were initiated in 2011 in collaboration with the University Hospitals of Geneva (Switzerland) and McGill University in Montreal (Canada) to evaluate proteomic signatures and identify potential new markers. The clinical samples collected during the TRAENA (Tratamiento en Adultos) trial will be tested by PCR for the presence of *T. cruzi* DNA.

In addition, funding from the Wellcome Trust was obtained in 2011 for a study on macaques to determine whether blood PCR assays can differentiate between parasitological cure and treatment failure. The study is due to start at the beginning of 2012.

Finally, DNDi is part of a new network of investigators (NHEPACHA) created for the long-term evaluation of potential biomarkers.

CHAGAS

IMPLEMENTATION

Major Partners:

Laboratório Farmacêutico do Estado de Pernambuco (LAFEPE), Brazil;
Hospital de Niños
Ricardo Gutierrez, Argentina;
Instituto Nacional de Parasitología Dr M Fátala Chabén, Argentina;
Hospital de Niños de Jujuy, Argentina;
Ministério 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

Management:

Head of Chagas Clinical Programme:
Isabela Ribeiro;
Project Coordinator: Bethania Blum

Project start:

May 2011

REGISTERED
IN 2011**Paediatric dosage form of benznidazole****2011 OBJECTIVES:**

- Submit registration dossier for paediatric dosage form of benznidazole
- Begin a population pharmacokinetic study in Argentina

Treatment of Chagas disease has always focused on paediatric patient populations, but initially, treatment was recommended only for acute and congenital cases (including newborns diagnosed at birth). Based on recent evidence, treatment recommendations were extended to children with the early chronic indeterminate form of Chagas disease up to 12-14 years of age. In 2002, the second report of the WHO Expert Committee on Etiological Treatment in the Chronic Phase recommended that all individuals with positive serology for Chagas disease be treated with specific drugs.

Despite these recommendations, adequate available treatment options for children have been lacking.

Benznidazole, a nitroimidazole introduced by Roche in 1971 and licensed to Brazil's Pernambuco State pharmaceutical laboratory (Laboratório Farmacêutico do Estado de Pernambuco, LAFEPE), is one of the two products registered for Chagas disease treatment and is included in the WHO Essential Medicines List. Benznidazole was only available as an adult tablet strength of 100 mg. Most treatments for infants and young children were based on the use of tablet fractions, macerated tablets, and other extemporaneous formulations, introducing variation and imprecision in drug dosing.

Policymakers and clinicians long stressed the urgent need for a paediatric drug formulation in Chagas control. Several international meetings (most notably the 2005 Scientific Working Group for Chagas Disease of the Special Programme for Research and Training in Tropical Diseases (WHO-TDR) and the 2007 TDR Working Group on Chagas Disease) highlighted the unmet medical need for new paediatric formulations for Chagas disease.

To respond to this need, 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.

The new 12.5 mg tablet is easily dispersible and adapted for babies and children up to two

years of age (20 kg body weight). Treatment is designed to use one, two, or three tablets, depending on weight (recommended dosage, 5-10 mg/kg bodyweight/day).

The new paediatric dosage form was granted registration from Brazil's National Health Surveillance Agency (ANVISA) in December 2011.

REGISTRATION
obtained in
BRAZIL

12.5 mg tablet

FOR CHILDREN
<2 years old

This new dosage form for children represents real progress for several reasons. Children are at especially high risk of infection, with a majority of them born from infected mothers. It is

known that early treatment using benznidazole in the first year of life can eliminate the parasite in more than 90% of infected newborns. Thus, babies infected with Chagas disease will benefit the most from this new paediatric tablet.

Tools to facilitate implementation of and access to the new treatment include a Demand Forecast, a Procurement Guide, and a Tool Box providing training and educational materials for doctors, other health professionals, mothers, and caregivers regarding appropriate use of the treatment.

DNDi is also collaborating with LAFEPE to make the drug widely available, notably by working to register the drug in Argentina, Bolivia, Colombia, and Paraguay – priority countries where Chagas disease prevalence is high and treatment is urgently needed.

In addition, a population pharmacokinetic study involving 80 paediatric Chagas disease patients was launched in Argentina to gain more information on pharmacokinetics, treatment safety, and efficacy in paediatric patients. The results of the study will be available by the end of 2012.





Sustained malaria control and elimination requires developing new tools, but also making good use of existing ACTs developed recently.

At the beginning of the new century, malaria was out of control throughout Africa and in many other parts of the world. With endemic countries implementing solid national strategies and increased levels of funding, major changes have occurred. In the past decade, hundreds of thousands of lives have been saved and child mortality rates are estimated to have fallen by 20%.⁽¹⁾

Despite these successes, according to the World Health Organization (WHO), malaria killed an estimated 655,000 people in 2010, 86% of which were children under the age of five.⁽²⁾ Other estimates are even higher.⁽³⁾ By all accounts, however, progress is fragile and the path to eliminating malaria is long and strenuous. Malaria remains a leading public health problem in a large number of countries, especially in Africa. Effective strategies that rely on effective tools are essential to continue the fight. The arsenal of strategies currently available for the control of malaria includes vector control, diagnosis, and prompt and effective treatment with effective antimalarials.

In 2001, in response to the increasing failure of *Plasmodium falciparum* malaria treatment with chloroquine, and to contain and control the spread of drug resistance in malaria-endemic regions, the WHO recommended worldwide abandonment of chloroquine and the use of artemisinin-based combination therapies (ACTs) as first-line treatment for uncomplicated *P. falciparum* malaria. Artemisinin derivatives available for oral administration include dihydroartemisinin, artesunate, and artemether. Fast-acting artemisinin-based compounds are combined with a drug from a different class, such as amodiaquine, lumefantrine, mefloquine, pyronaridine, piperaquine, and sulfadoxine/pyrimethamine. The advantages of ACTs are high efficacy, fast onset of action, and very good patient tolerance. They can be taken orally for a shorter duration than artemisinins alone and are safe to be used by pregnant women in their second and third trimester.

Recent evidence of resistance to artemisinin, first reported in 2009 at the Thai-Cambodia border region, today represents one of the major threats to progress achieved so

far. In Southeast Asia, ACTs are taking longer and longer to clear the parasite from patients. Expanded, intensified, and better coordinated actions at both the global and local levels are needed in order to prevent the loss of ACTs as effective treatment.⁽⁴⁾ These actions include consistent and accurate diagnostic testing, better access to ACTs for confirmed cases, compliance with ACT treatment and removal of artemisinin-based monotherapies as well as of substandard and counterfeit drugs. Expanding access to ACTs has been partially addressed by the AMFm (Affordable Medicines Facility – malaria), but many challenges remain in terms of supply, affordability, and availability of ACTs. Sustained malaria control and elimination requires developing new tools, but also, making good use of existing tools. In particular, making efficacious, easy-to-take ACTs available to the highest number is essential to winning the fight against malaria.

In 2002, the Fixed-dose Artesunate-Based Combination Therapies (FACT) Consortium, created by DNDi, started to develop two fixed-dose artesunate (AS)-based combination therapies (out of the four initially recommended by WHO):

- ASAQ, the fixed-dose combination of artesunate and amodiaquine (AQ) developed in partnership with Sanofi, was first registered in 2007 and pre-qualified by WHO in 2008.
- ASMQ, the fixed-dose combination of artesunate and mefloquine (MQ) developed in partnership with Farmaquinhos, was first registered in 2008.

Fixed-dose combinations (FDCs) enable simple treatment regimens, therefore increasing patient compliance. ASAQ and ASMQ, together with CoArtem®, the FDC of artemether and lumefantrine developed by Novartis, Pyramax®, the FDC of artesunate-pyronaridine and Eurartesim®, the FDC of dihydroartemisinin-piperaquine (DHA/PQP), both developed by the Medicines for Malaria Venture (MMV), strengthen the global ACT portfolio of FDCs now available for the treatment of uncomplicated *P. falciparum* malaria. Together with diagnosis and vector control tools, they represent a key element of the anti-malaria arsenal.

FDCs enable simple treatment regimens, therefore increasing patient compliance.

(1) A decade of partnerships and results, Progress and Impact Series number 7, World Health Organization, Geneva, 2011 (2) World Malaria Report 2011, World Health Organization, Geneva, 2011 (3) Murray, C.J.L. et al. (2012) Global malaria mortality between 1980 and 2010: a systematic analysis. Lancet; 379: 413–31 (4) http://www.who.int/malaria/publications/atoz/artemisinin_resistance_containment_2011.pdf



Malaria

Making available ACTs is essential to fight malaria

WHAT IS THE IMPACT OF MALARIA?

The WHO estimates that there were 216 million of cases of malaria in 2010, and that 655,000 deaths were attributable to the disease, 86% of which in children under five and 91% in sub-Saharan Africa. A recent study by C. Murray *et al.*, however, estimates that in 2010 malaria was the underlying cause of death for 1.24 million individuals, including 714,000 children younger than five years.⁽¹⁾

Recent successes and a reduction in the number of cases are reason for optimism, but many people at risk of malaria still lack access to critical treatment and prevention options, including to artemisinin-based combination therapies (ACTs), and malaria control continues to face serious challenges.⁽²⁾



HOW IS MALARIA TRANSMITTED?

Malaria is caused by *Plasmodium* parasites, spread to people through

the bite of an infected female anopheles mosquito. Four species of the parasite cause malaria in humans, *P. falciparum*, *P. vivax*, *P. malariae*, and *P. ovale*. *P. vivax* and *P. falciparum* are the most common, with *P. falciparum* the most deadly.

Approximately half of the world's population is at risk of malaria. Most malaria cases and deaths occur in sub-Saharan Africa, but Asia, Latin America, and to a lesser extent the Middle East and parts of Europe are also affected. In 2010, 99 countries and territories had ongoing malaria transmission.

WHAT ARE THE SYMPTOMS?

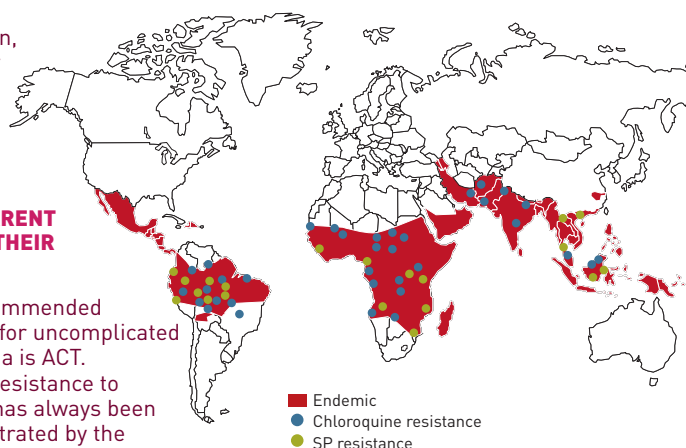
Malaria is an acute febrile illness, the initial symptoms of which can be difficult to recognize. Symptoms of uncomplicated malaria include fever, headache, chills, and vomiting. If treatment is not given within 24 hours, *P. falciparum* malaria can progress to severe illness, which can lead to death or serious brain damage,

especially in children, who are particularly vulnerable due to their lack of immunity to the parasite.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

Since 2001, the recommended first-line treatment for uncomplicated *P. falciparum* malaria is ACT. The appearance of resistance to antimalarial drugs has always been a challenge, as illustrated by the widespread resistance to drugs such as chloroquine, which greatly undermined previous efforts in combating malaria. Recent reports of resistance to artemisinin underlines the need for effective combination therapies, as the use of artemisinin oral monotherapies is believed to be an important factor in resistance development.

ACTs have been adopted as first-line treatment in 84 countries across the world, but access to these treatments is still limited in many parts of Africa and some parts of Asia, because of accessibility (proximity to health



facilities), affordability, availability (presence of the medicine at the service delivery point), acceptability (affected by a variety of socio-economic factors),⁽³⁾ and training of caregivers. Children, the primary victims of malaria worldwide, often do not have access to adequate paediatric formulations of ACTs. In addition, emerging evidence of artemisinin-resistance development threatens the world with the loss of the most effective treatment for malaria if nothing is done to contain resistance.

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?

Through 2014, DNDi aims at ensuring widespread access to the two ACTs developed within FACT, and to support their proper use to maintain the effectiveness of artemisinin-based therapies as first-line treatment for uncomplicated *P. falciparum* malaria. This includes facilitating registration in a growing number of countries, supporting policy and practice change, improving quality supply by facilitating technology transfers to second suppliers in Africa (ASAQ) and in Asia (ASMQ), as well as working to decrease drug costs by various mechanisms.

ASAQ: fixed-dose combination of artesunate and amodiaquine

ASMQ: fixed-dose combination of artesunate and mefloquine

(1) Murray, C.J.L. *et al.* (2012) Global malaria mortality between 1980 and 2010: a systematic analysis. *Lancet*; 379: 413–31 (2) A Decade of Partnerships and Results, Progress and Impact Series, number 7, World Health Organization, Geneva, 2011. (3) Matowe L and Adeyi O. (2010) The quest for universal access to effective malaria treatment: How can the AMFm contribute? *Malaria Journal*, 9:274.

MALARIA

IMPLEMENTATION

Partners:

Farmanguinhós, Brazil;
Cipla, 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, 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

Management:

Senior Pharma Advisor & Product Manager:
Jean-René Kiechel;
Clinical Manager: Gwenaëlle Carn;
Medical Coordinator FACT Project:
Graciela Diap

Project start:

January 2002



ASMQ FDC

2011 OBJECTIVES:

→ Technology transfer and registration:

- Support activities for pre-qualification by WHO and PAHO
- Obtain registration authorization for ASMQ FDC in India and Southeast Asia
- Reduce the cost of MQ to decrease the price of ASMQ FDC

→ Clinical studies

- Progress the multi-centre comparative study conducted in three African countries



Used in the field for many years, the combination of artesunate (AS) and mefloquine (MQ) is one of the five ACTs recommended by WHO for the treatment of uncomplicated *P. falciparum* malaria, preferably as a fixed-dose combination.

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, Farmanguinhós/Fiocruz, was the first manufacturer of ASMQ FDC. ASMQ FDC was registered in Brazil in March 2008 and adopted as treatment policy by the Ministry of Health, following excellent outcomes of a major intervention study with ASMQ in the Amazon Basin, sponsored by the National Malaria Control Programme (NMCP).⁽¹⁾ ASMQ FDC tablets (25/55 mg and 100/220 mg) offer an easy-to-use treatment regimen with one single daily dose of one or two tablets to be taken over three days. Following an agreement signed in 2008, the technology transfer between Farmanguinhós and the Indian generic pharmaceutical company Cipla was successfully completed in 2010 and will facilitate the availability of ASMQ throughout Asia and other parts of the world.

ASMQ was granted registration in India in November 2011, a crucial step towards further registration in Asian countries. A full dossier was submitted by DNDi and

partners for WHO pre-qualification in 2010 and is currently under final assessment for approval in 2012. ASMQ FDC is of particular relevance for Asia: mefloquine and artesunate therapy has been evaluated since 1991 in camps for displaced persons located along the Thai-Myanmar border. Since then, clinical data on the use of AS+MQ from almost 8,000 patients in Southeast Asia and more than 2,000 in the Western Pacific have been made available in the medical literature. The strategy of

artemisinin-based combination therapy with mefloquine was developed and adopted in 1994 in Thailand, where treatment of uncomplicated malaria has been modified several times during the past 30 years to counter the rapid emergence and spread of drug resistance. The deployment of the combination has led to a reduction in incidence of

P. falciparum malaria and has been associated with a halt of mefloquine resistance. Since the confirmation of resistance of *P. falciparum* to artemisinins at the Cambodia-Thailand border in 2009, containment activities to limit the spread of artemisinin-resistant parasites have been ongoing. One of the most urgent and challenging priorities in the Global Plan for Artemisinin Resistance Containment (GPARC) in Cambodia and Thailand is to replace the use of artemisinin monotherapy with an FDC, such as ASMQ.

Additional clinical studies using ASMQ FDC are ongoing and will provide information of ASMQ FDC use in children, adults, and pregnant women in Africa. According to WHO recommendation, AS+MQ could be considered for use in some countries in Africa. To provide key information on the efficacy and tolerability of ASMQ FDC, DNDi is sponsoring a multicentre Phase IV study in Tanzania, Burkina Faso, and Kenya to assess efficacy, safety, and pharmacokinetics of ASMQ FDC compared to artemether-lumefantrine in children below the age of 5 with uncomplicated *P. falciparum* malaria. Recruitment of patients is ongoing and expected to be completed by the end of 2012. Effectiveness data on ASMQ in field conditions are planned to be collected in India in a large implementation project conducted with partners.

REGISTRATION
obtained
in **INDIA**

PHASE IV
study:

400 PATIENTS
recruited
by end 2011
in
3 COUNTRIES

(1) Santelli A. C, et al. (2011) Effect of artesunate-mefloquine fixed-dose combination in malaria transmission in Amazon basin communities. Tropical Medicine and International Health. Volume 16 Suppl 1 pp 375-76.



MALARIA

IMPLEMENTATION

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;
Komfo Anokye Teaching
Hospital (KATH), Ghana

Management:

Senior Pharma Advisor & Product Manager:
Jean-René Kiechel ;
Clinical Manager: Gwenaëlle Carn;
Medical Coordinator FACT Project:
Graciela Diap

Project start:

January 2002

ASAQ Winthrop

2011 OBJECTIVES:

- Diversify ASAQ suppliers by transferring technology to a partner in Africa
- Facilitate implementation of ACT FDCs in general and specifically ASAQ, in all countries where it could benefit patients and abide local practices



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. By the end of 2011, over 120 million treatments had been distributed in 30 African countries. In addition, more than 20 million treatments of ASAQ FDC have been ordered for the private sector in seven countries in Africa within the Affordable Medicines Facility – malaria (AMFm).⁽¹⁾ First registered in Morocco, where it is manufactured, ASAQ is now registered in 30 African countries, as well as in India, Bangladesh, and Colombia.

ASAQ dosing is straightforward, based on four, optimized age-specific regimens and well adhered to, as demonstrated in a trial in Benin.⁽²⁾ ASAQ is available at less than USD 0.5 for children and USD 1 for adults.

In 2010, ASAQ Winthrop obtained WHO authorization for a three-year shelf life, giving the product the longest shelf-life of any pre-qualified FDC artemisinin-based treatment available for malaria. In partnership with Sanofi, MMV, and National Malaria Control Programmes, high-quality data on ASAQ effectiveness and safety

in the field is being collected, as part of a Risk Management Plan (RMP). This was the first RMP submitted to the WHO, and the first to be set up entirely in Africa. It is expected to contribute to building capacity on drug safety and efficacy monitoring in sub-Saharan African countries and could set the precedent for further real-life assessment studies of new ACTs.

>120 MILLION
treatments
distributed to date
in 30 African
countries
PHASE IV study:
7,000 PATIENTS
recruited
by end 2011
at 4 SITES

As part of this plan, the partners are undertaking a Phase IV implementation study, which will take place over two to three years in the health district of Agboville, Côte d'Ivoire, where ASAQ is used as first-line treatment. At the end of 2011, over 7,000 patients had been recruited at four different sites. Delays,

however, are expected due to recent instability in the country. Two additional clinical studies included in the above-mentioned plan have been managed by DNDi in collaboration with MSF, Epicentre, and the National Malaria Control Programme in Liberia, the results of which were made available in 2010. These studies show that ASAQ is highly efficacious, safe, and well tolerated in children and adults in Liberia.⁽³⁾

In parallel, DNDi, together with partners, is working on the transfer of technology to a second manufacturer in Africa, Zenufa, based in Tanzania. A project team consisting of members of participant organizations and the industrial partner has been set up for the duration of the transfer up to pre-qualification by WHO.

Following the antimalarial market assessments conducted by DNDi in Burundi⁽⁴⁾ and Sierra Leone in 2009,⁽⁵⁾ DNDi and its partner Komfo Anokye Teaching Hospital, Kumasi (KATH) performed outlet surveys in Ghana as part of the independent evaluation of the AMFm Phase I. The results, included in the AMFm Phase I Independent Evaluation Multi-Country Baseline Report, are publicly available.⁽⁶⁾



(1) <http://www.theglobalfund.org/en/amfm/> (2) Faucher J.F. et al., (2009) Comparison of sulfadoxine-pyrimethamine, unsupervised artemether-lumefantrine, and unsupervised artesunate-amodiaquine fixed-dose formulation for uncomplicated plasmodium falciparum malaria in Benin: a randomized effectiveness noninferiority trial. J Infect Dis. 200(1): p. 57-65. (3) Schramm B et al. (2010) A phase 4 randomized study to assess the tolerability of artesunate-amodiaquine (ASAQ) and artemether-lumefantrine (AL) fixed dose combinations (FDCs) for the treatment of uncomplicated P. falciparum malaria in Liberia. Am J Trop Med Hyg; 83(5): 371. (4) Amuasi JH et al. (2011) Access to artesunate-amodiaquine, quinine and other anti-malarials: policy and markets in Burundi. Malar J. 10;10:34. (5) Diap G et al. (2010) Anti-malarial market and policy surveys in sub-Saharan Africa Malar J. 23;9 Suppl 1:S1. (6) http://www.theglobalfund.org/documents/amfm/AMFm_PhaseIIndependentEvaluationMultiCountryBaseline_Report_en/.

Life-long disabilities, great suffering, and social stigmatization of those infected.

Helminths are parasitic worms and the most common infectious agents of humans in developing countries.

A sub-group of helminths, nematodes, cause filarial diseases, which are transmitted by insect vectors to humans. These diseases, namely Onchocerciasis (or river blindness), lymphatic filariasis (LF, or elephantiasis) and Loiasis (*Loa loa*, or African eye-worm) affect millions across the world, particularly in Africa.

Even though they do not kill, filarial diseases cause life-long disabilities, such as blindness (Onchocerciasis) and swelling of the limbs (LF), causing great suffering and social stigmatization of those infected.

Programmes to control and eliminate filarial diseases have been in place for over twenty years, such as the African Programme for Onchocerciasis Control (APOC) and the Global Programme to Eliminate Lymphatic Filariasis (GPELF).

These programmes rely on mass drug administration (MDA) of anti-helminthic drugs that are safe and donated: ivermectin for Onchocerciasis, diethylcarbamazine (DEC), as well as albendazole (ALB) in combination with ivermectin or DEC for LF. These drugs are effective because they kill the juvenile forms of the worms, the microfilariae, which cause most of the symptoms. However, they need to be administered repeatedly at regular intervals until adult forms (macrofilariae) die naturally and there are no more microfilariae in the body.

While these programmes have made enormous progress, they are not adapted to areas of Loiasis co-endemicity. Indeed, even though Loiasis is not life-threatening and is usually not treated, infected patients often have a high burden of microfilariae, and the sudden death of these juvenile forms causes a serious adverse reaction, known as *Loa loa* encephalopathy, which can be fatal or leave long-term sequelae.^[1]

Inclusion of patients in MDA programmes is therefore not recommended in regions of high *Loa loa* burden. There is an urgent need to develop a safe and highly efficacious macrofilaricide, with little or no effect on microfilariae, as an effective tool for the treatment of Onchocerciasis and LF in regions of Loiasis co-endemicity.

IDEAL TARGET PRODUCT PROFILE FOR HELMINTH INFECTIONS

A new treatment for adults and children

- **Macrofilaricide:** Efficacious against the adult form of worms
- **Oral**, short-course treatment
- **No side-effects** following death of worms
- **Safe** in pregnant and lactating women
- **Affordable**
- **Adapted to tropical climates** (minimum three-year shelf-life)





Helminth infections

Developing new tools to fill the gaps in existing treatment regimens

WHAT IS THE IMPACT OF HELMINTH INFECTIONS?

Helminth infections are caused by two sub-groups of helminths, nematodes and flatworms. Nematodes (also known as roundworms) include the major intestinal worms (also known as soil-transmitted helminths) and the filarial worms that cause Onchocerciasis, lymphatic filariasis (LF), and Loiasis.

Onchocerciasis (river blindness): A total of 18 million people are affected worldwide, in 36 countries in Africa, as well as in Guatemala, southern Mexico, some areas of Venezuela, small areas in Brazil, Colombia, and Ecuador, and in the Arabian Peninsula.⁽¹⁾

Lymphatic filariasis (LF, or elephantiasis): More than 1.3 billion people in 72 countries worldwide are threatened by LF, commonly known as elephantiasis. Over 120 million people are currently infected, with about 40 million disfigured and incapacitated by the disease.⁽²⁾

Loiasis (African eye-worm): The mapping of Loiasis endemic areas in affected countries is still ongoing, but it is estimated that in Onchocerciasis-endemic communities, over one-fifth of the population also has Loiasis.⁽³⁾ The disease burden of Loiasis is not significant enough to merit an elimination programme, but its co-endemicity with Onchocerciasis in certain areas of West and Central Africa and the fact that mass ivermectin treatment of Onchocerciasis can lead to serious adverse events in patients who have high *Loa loa* microfilarial densities, impedes the implementation of Onchocerciasis elimination programmes (see below).

HOW ARE FILARIAL DISEASES TRANSMITTED?



Filarial diseases are caused by parasitic worms transmitted by insect vectors to humans.

Onchocerciasis is a parasitic disease caused by *Onchocerca volvulus*, a thin parasitic worm that can live for up to 14 years in the human body. The disease is transmitted from one person to another through the bite of a blackfly.

The transmitted worm larvae develop into adult worms and settle into fibrous nodules in the human body close to the surface of the skin or near the joints.

Lymphatic filariasis is caused by nematodes of the Filariodidea family, mainly *Wuchereria bancrofti*, transmitted to humans through mosquitoes. When a mosquito with infective stage larvae bites a person, the parasites are deposited on the person's skin from where they enter the body. The larvae then migrate to the lymphatic vessels where they develop into adult worms in the human lymphatic system.

Loiasis is caused by the parasitic worm *Loa loa*. The adult worms migrate throughout the body just under the skin and sometimes cross into the subconjunctival tissue of the eye where they can easily be seen. It is transmitted through the repeated bites of deerflies (also known as mango flies or mangrove flies) of the genus *Chrysops*.

WHAT ARE THE SYMPTOMS?

Onchocerciasis is the world's second leading infectious cause of blindness and is often referred to as 'river blindness'. It also causes intense itching, skin discoloration, rashes, and eye disease.

Lymphatic filariasis can become chronic, and when it does, it leads to lymphoedema (tissue swelling) or elephantiasis (skin/tissue thickening) of limbs and hydrocele testes (fluid accumulation).

Such body deformities lead to social stigma, as well as financial hardship from loss of income and increased medical expenses. The socio-economic burdens of isolation and poverty are immense.

Loiasis leads to recurrent episodes of itchy swellings and to eye-worm, the visible migration of the adult worm across the surface of the eye, which resolves after a few days.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

Current treatments for Onchocerciasis and LF are based on mass drug administration (MDA) of anti-parasitic drugs through programmes directed by the WHO. Drugs used by MDA programmes include ivermectin for onchocerciasis, DEC and ALB in combination or DEC alone for LF. These drugs remove existing microfilariae from skin, thus preventing vector borne transmission, and provide long-term sterilization of adult worms, preventing re-population of the patient with microfilariae for six months or longer. However, in patients co-infected with *Loa loa*, the sudden death of large numbers of microfilariae can lead to serious adverse events, such as encephalopathy, which can be fatal or leave patients with severe sequelae. Patients infected only with *Loa loa* are not usually treated.

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?

DNDi's short-term strategy is to reformulate flubendazole, an anti-helminthic drug with proven efficacy against gastrointestinal infections of soil-transmitted helminths in animals and humans, into a safe, highly efficacious, and field-adapted macrofilaricidal drug candidate.

As a medium-term strategy, DNDi will assess additional opportunities through an active screening programme, with the goal of selecting one or two candidates emanating from the animal health industry or leads in development in pharmaceutical, biotechnology, and academic laboratories.

By 2015, DNDi aims to deliver from its helminth infections portfolio:

→ a new drug candidate available for clinical testing that could be used by mass drug administration programmes for filarial infections and/or case management of *Onchocerciasis* and lymphatic filariasis, especially in *Loa loa* co-endemic regions.

(1) http://www.who.int/water_sanitation_health/diseases/oncho/en/

(2) <http://www.who.int/mediacentre/factsheets/fs102/en/> (3) <http://www.who.int/apoc/cdti/raploa/en/index.html>



HELMINTH
INFECTIONS

PRE-CLINICAL

Partners:

Michigan State University, USA; Abbott
Laboratories, USA; McGill University, Canada;
University of Buea, Cameroon

Project management:

Discovery and Pre-clinical Director: Robert Don;
Project Manager: Ivan Scandale

Project start:

April 2011

Flubendazole

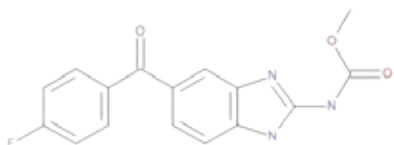
2011 OBJECTIVE:

→ Determine potential of flubendazole
as a pre-clinical candidate

This project aims to develop flubendazole as a safe, highly efficacious, and field-usable macrofilaricidal drug candidate for Onchocerciasis-*Loa loa* co-infections. If flubendazole meets the criteria specified for pre-clinical development, the project will also support the necessary studies required to draft an Investigational Medicinal Product Dossier (IMPD) followed by submission and subsequent approval of the IMPD.

In 2011, activities to extensively characterize the flubendazole API (active pharmaceutical ingredient) were conducted and four different formulation strategies to enhance its bioavailability were tested. The amorphous solid dispersion (ASD) formulation achieved sustained plasma levels of flubendazole and will be used for pre-clinical development. The safety profile of flubendazole is not yet defined, in particular with respect to genotoxicity. However, embryotoxicity has been observed at concentrations above 0.25 µg/mL and such levels are achieved with the

ASD formulation *in vivo*. Therefore, embryotoxicity is likely to be observed with flubendazole, which could be a limiting factor for its development as a mass drug administration programme. It will be essential to confirm these results in *in vivo* reproductive toxicology studies. In 2012, DNDi will conduct IMPD-enabling safety studies, develop an oral formulation suitable for human clinical use and conduct more extensive PK/PD studies to guide/refine the selection of human therapeutic doses.





Paediatric HIV: A neglected disease?

In the past years, good progress has been made in the rolling out of programmes to prevent new HIV infections in children, greatly reducing the global number of AIDS-related deaths. Despite these successes, in 2010, 390,000 children less than 15 years of age were newly infected with HIV and 250,000 children died from AIDS-related illnesses. Over three-quarters of HIV-infected children still do not have access to treatment.

Most children acquire HIV through perinatal transmission during foetal life, birth, or whilst breastfeeding. Whereas in high-income countries, HIV transmission in young children has largely been eliminated due to effective prevention of mother-to-child transmission (PMTCT) interventions, in low- to middle-income countries, the majority of pregnant women still do not have access to diagnosis or to timely, efficient drugs.⁽¹⁾

HIV-infected infants frequently develop illness within the first year of their life; approximately one-third of them die before their first birthday, and about half die before they are two years old.⁽²⁾ Therefore, while the best way of preventing deaths in young children remains prevention of HIV transmission in the first place, provision of adequate treatment to those who do become infected is vital.

In the past years, access to antiretroviral therapy (ART) has been rapidly scaled-up, resulting in remarkable progress in the global fight against HIV. However, provision of ART to HIV-infected children, especially to the very young, has been less successful, notably because of the lack of appropriate tools to diagnose HIV early in the child's life, and of easy-to-use, safe and stable paediatric ART formulations: in 2010, only 28% of infants had been tested for HIV in the first two months after birth in low- and middle-income countries, and only 23% of children in need of treatment had access to it, compared to 51% of adults.⁽¹⁾ Many of the drugs that are available for the treatment of adults have not been tested and approved for use in children, limiting the number of therapeutic

options for caregivers, especially in cases of treatment failure or adverse reactions. Some of the currently available paediatric HIV formulations have serious limitations for use in resource-poor settings, such as liquid formulations, which are difficult to administer, carry a high risk of dosing errors, have a poorly-tolerated taste, and display significant toxicity, in addition to severe logistical constraints linked to short shelf-life, cold chain requirement, large volumes, and high price. In addition, many children need to be treated for both HIV and tuberculosis (TB) and there are significant negative drug-drug interactions between anti-TB drugs and anti-HIV drugs. HIV-infected children co-infected with TB have particularly poor prognosis.⁽³⁾ Improved first-line therapies for children are urgently needed.

Available paediatric HIV formulations have serious limitations for use in resource-poor settings.

(1) Global HIV/AIDS response - Epidemic update and health sector progress towards Universal Access; Progress Report 2011. UNAIDS, Geneva, 2011. (2) Newell, M et al. (2004) Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. The Lancet, 364:9441. (3) Children and AIDS: Fifth Stocktaking Report. New York, UNICEF/UNAIDS/WHO/UNFPA/UNESCO.

IDEAL TARGET PRODUCT PROFILE FOR PAEDIATRIC HIV

A first-line, **all-in-one** antiretroviral regimen for HIV-infected children:

- **Safe and efficacious**
- **Adapted formulation** suitable for infants
- **Easy to use:** once-daily dosing preferred
- **Palatable**
- **Adapted to tropical climates** (heat stable)





Paediatric HIV

Millions of children, most of them in sub-Saharan Africa, are in need of an adapted treatment



WHAT IS THE IMPACT OF PAEDIATRIC HIV?

At the end of 2010, an estimated 3.4 million children below the age of 15 were living with HIV, more than 90% of which in sub-Saharan Africa. That same year, 2.02 million children were estimated to be in need of antiretroviral therapy.⁽¹⁾

An estimated 250,000 children less than 15 years died of AIDS-related illness in 2010.

HOW IS PAEDIATRIC HIV TRANSMITTED?

In children, HIV transmission can occur during pregnancy through the placenta, during delivery through exposure to body fluids and cervical secretions, and through breastfeeding. In the absence of antiretroviral preventive treatment, 30 to 40% of children born to an HIV-infected mother acquire infection themselves, but with antiretroviral prophylaxis throughout pregnancy, delivery, and breastfeeding, transmission can be decreased down to a few per cent.

WHAT ARE THE SYMPTOMS?

HIV is often difficult to diagnose in children and infants: indeed, symptoms rarely appear in the first few months, and when they do, they are often un-specific, such as weight loss and stunted growth. By the time children become ill, it is often too late and half die before their second birthday.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

Current WHO guidelines recommend early diagnosis and immediate treatment of HIV-positive infants and children under the age of two. The combination of a boosted protease inhibitor (PI) with two nucleoside reverse transcriptase inhibitors (NRTIs) is considered by many experts as the most effective first-line therapy, particularly in the case of infants and children with high viral loads who were previously exposed to antiretrovirals (ARVs) in the context of prevention of mother to child transmission (PMTCT).

However, this recommended combination therapy is not being widely used.

According to a WHO survey performed in 45 countries, only 12.2% of children with HIV were receiving a first-line treatment containing a PI (mostly lopinavir/ritonavir), 97% of whom were in South Africa. The current PI-based regimen requires use of multiple paediatric formulations. The only available PI for young children, lopinavir/ritonavir (LPV/r) does not come in a child-friendly formulation: the oral solution formulation is not palatable, contains 42% alcohol and is not adapted to resource-poor settings as it requires refrigeration, has a short shelf-life when exposed to heat, and poses logistical constraints due to its large volume.

In many areas, HIV-positive infants and children are co-infected with tuberculosis (TB). 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 treatment. In order to counteract this interaction, additional ritonavir needs to be added to the standard proportion of lopinavir and ritonavir (LPV/r). This is called 'super-boosting'. In order to do that, an infant-friendly formulation of ritonavir also needs to be developed. Currently available ritonavir formulation suffers the same limitations as LPV/r, with regard to taste, high alcohol content, short shelf-life (six months) and limited availability.

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?

In 2010, DNDi was called on by various organizations, including Médecins Sans Frontières and the international drug-purchase organization UNITAID, to apply its expertise to the development of paediatric HIV drugs. DNDi's position was published as a Perspective in the *New England Journal of Medicine* in August 2011.⁽²⁾

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

- Develop a first-line, all-in-one formulation containing a boosted PI (lopinavir/ritonavir) and two NRTIs, suitable for infants and young children
- Develop a stand-alone ritonavir booster formulation that 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.

In order to reach these objectives, DNDi has set up exploratory activities to investigate a number of options in terms of formulations of the PIs, ritonavir-boosted lopinavir (LPV/r). These include sprinkles, pro-drugs, nanoparticles, and nanodispersion. As part of its formulation work, DNDi will explore the feasibility of LPV/r sprinkles, in a sachet in association with NRTIs.

In order to address the needs of HIV-TB co-infected children, DNDi is committed to developing a formulation of ritonavir for super-boosting LPV/r at a 1:1 ratio. This strategy will be further investigated during a clinical study involving sites in South Africa.

Finally, DNDi is setting-up an HIV platform that will facilitate its clinical research programme in the longer term.

By 2015, DNDi aims to deliver from its paediatric HIV portfolio:

- One new all-in-one solid paediatric formulation
- One new treatment for HIV-TB co-infected children based on superboosting

(1) Global HIV/AIDS response - Epidemic update and health sector progress towards Universal Access; Progress report 2011. UNAIDS, Geneva, 2011 - the difference between the number of children living with HIV and those in need of antiretroviral therapy is based on eligibility criteria for this kind of treatment (e.g. CD4 count).
(2) Lallemand M, Chang S, Cohen R, and Péroul B. (2011) Paediatric HIV - A Neglected Disease? N Eng J Med 365;7.

2011 KEY FINANCIAL PERFORMANCE INDICATORS



R&D expenditure by disease

EUR 20.1 million in 2011 for R&D and a balanced kinetoplastid portfolio

2010: EUR 19.8 million



2011: EUR 20.1 million



■ Leishmaniasis Projects ■ Chagas disease Projects
■ HAT Projects ■ New Diseases: Helminth infections and paediatric HIV
■ Malaria Projects

Overall R&D expenditure remains stable between 2010 and 2011 (EUR 20.1 million). With two new treatments available and at least one product in clinical stage and one pre-clinical candidate for each of the three kinetoplastid diseases (Chagas, HAT, and VL), the breakdown of R&D expenditure by disease shows a balanced portfolio.

Leishmaniasis: The level of activities remains high with ten projects as of December 2011. Overall expenditure decreased due to slower patient recruitment in clinical trials and additional time required for preparation of the implementation study in Asia.

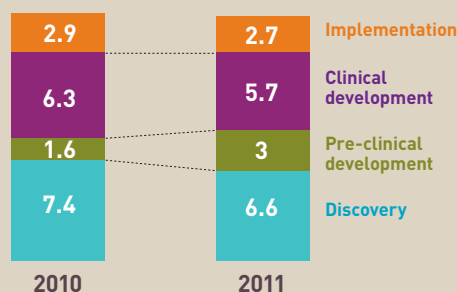
Chagas disease: Expenditure increased in 2011 by 62% with the registration of the paediatric dosage form of benznidazole (+ EUR 0.2 M), the launch of the Azole E1224 Phase II study (two sites in Bolivia, + EUR 0.6 M), the start of a test of cure project - PCR and biomarkers (+ EUR 0.2 M), and completion of the Chagas Lead Optimization Consortium development (+ EUR 0.7 M).

Malaria: In accordance with the Business Plan, expenditure continues to decrease (- EUR 200 K in 2011). The main activities were the Phase IV clinical trial in Burkina Faso, Kenya, and Tanzania (+ EUR 100 K) and technology transfer to Zenufa (Tanzania) for the production of ASAQ (+ EUR 150 K).

Portfolio expansion: Pre-clinical and screening activities started for the helminth infections project (flubendazole, macrofilaricide: + EUR 0.2 M) and in-kind contributions brought expenditures down in 2011. The paediatric HIV project (+ EUR 0.3 M) started pre-clinical activities following the TPP definition and the set-up of a network of clinical partners.

R&D expenditure by R&D stage

Seeking efficiency in building a robust portfolio



Discovery: Lead optimization programmes moved from 3 consortia (1 per disease) to an integrated model with 2 consortia for the 3 kinetoplastid diseases. Each consortium will implement 2 parallel programmes. A new partner was selected in China to work on chemistry, DMPK, and parasitology. This rationalization saves EUR 0.8 M in 2011 as compared to 2010.

Pre-clinical: Expenditure increased between 2010 and 2011 (+ EUR 1.4 M), due to progression of 4 drug candidates: completion of pre-

clinical studies of Oxaborole SCYX-7158 (+ EUR 0.4 M) for HAT; start of pre-clinical testing for VL-2098 (+ EUR 0.4 M) for VL; pre-clinical tests for flubendazole (+ EUR 0.2 M) for helminth infections; studies on the fenarimol series (+ EUR 0.1 M) for Chagas. Activities began on new formulations and prodrug development for paediatric HIV (+ EUR 0.3 M).

Clinical: Expenditure is stable compared to 2010, with **6 clinical studies** implemented in 2011: Patient recruitment started for Azole E1224 for Chagas disease (+ EUR 0.6 M); fexinidazole for HAT in transition phase before entering Phase II (- EUR 0.6 M); recruitment continued for new VL treatments (Africa, Bangladesh) but was slower than expected due to protocol criteria and implementation of new sites (- EUR 0.6 M).

Implementation: Expenditure is stable in 2011 as compared to 2010, whereas **two new treatments were delivered:** the paediatric dosage form of benznidazole was registered in December - therefore no implementation costs in 2011 - and VL Asia treatments, which required additional time for preparing the implementation study (+ EUR 0.3 M). Expenditure for malaria projects is decreasing (- EUR 0.3 M) as well as the NECT field study (- EUR 0.2 M) as both projects are entering the follow-up phase.

In-kind contributions

Leveraging EUR 5 million for R&D from partners

in EUR million



In-kind contributions are an integral part of the DNDi business model. To present a comprehensive view of activities, DNDi values the in-kind contribution of its partners (private companies, academic groups, individuals). Monitoring in order to more accurately value such contributions and thus obtain more accurate figures is a continually improving process. In six years, in-kind contributions have increased six-fold, reflecting DNDi's investment in consolidating partnerships.

The total of in-kind contributions in 2011 reached 20% of total operational expenses.

The major increase in 2011 in-kind contributions from those of 2010 (+100%) is due to pharmaceutical development of Azoles E1224 and fexinidazole with industrial partners.

DNDi works closely with partners in disease-endemic countries to strengthen existing clinical research capacity.





REINFORCING RESEARCH AND MANUFACTURING CAPACITIES IN ENDEMIC COUNTRIES

An integral part of its business model, DNDi has endeavoured to build regional disease networks to ensure that research capacity is where it needs to be – where the diseases occur – and that it is sustained. In addition, DNDi facilitates technology transfer as a vital means to sustaining production, notably in endemic countries, and increasing patient access to treatments.

The health R&D landscape in neglected disease-endemic countries has undergone a change over the past decade, with several initiatives being undertaken in and by developing countries. However, research capacity remains a hindrance to sustainable R&D in many such countries, which is why DNDi has maintained endemic country capacity utilization and strengthening at the core of its mission. By 2009, one disease-specific research platform per kinetoplastid disease (human African trypanosomiasis, leishmaniasis, and Chagas disease) was in



place. These platforms promote South-South collaboration and bring together the most important actors in each region to address patient needs from 'A to Z': from defining patient needs, to training clinical researchers, to facilitating registration, to expediting implementation. An integral part of the DNDi model, these platforms have achieved several important milestones, including: LEAP's delivery of SSG&PM for visceral leishmaniasis in East Africa; the HAT Platform's continued support for implementation of NECT for sleeping sickness in 11 endemic countries; and the Chagas Clinical Research Platform's network that oversaw three new clinical studies for Chagas disease in Argentina and Bolivia.

Disease platforms in 2011

Leishmaniasis East Africa Platform (LEAP)

Founded: 2003 in Khartoum, Sudan



Members: Center for Clinical Research, Kenya; Medical Research Institute, Kenya; Ministry of Health, Kenya; Institute of Endemic Diseases, University of Khartoum, Sudan; Federal Ministry of Health, Sudan; Addis Ababa University, Ethiopia; Gondar University, Ethiopia; Federal Bureau of Health, Ethiopia; Makerere University, Uganda; Ministry of Health, Uganda; Médecins Sans Frontières; i+ solutions; OneWorld Health (OWH); AMC/KIT/Slotervaart Hospital, The Netherlands; London School of Hygiene & Tropical Medicine (LSHTM), UK.

- Approx. 60 individual members, representing over 20 institutions
- Over 1,300 patients enrolled in clinical trials by the end of 2011
- Approx. 700-800 patients treated outside clinical trials in 2011
- 1,000 patients on Pharmacovigilance Phase IV study (all patients received SSG&PM combination therapy)

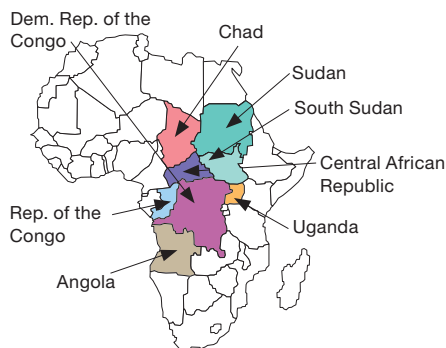
Overall objectives:

- Strengthen clinical research capacity, which is lacking in part due to the remoteness and geographic spread of the patients, most of whom live in the most impoverished regions of Africa
- Serve as a base for ongoing educational cooperation among East African countries and for standardization of procedures and practices in the region, as far as possible within the confines of local regulations
- Evaluate, validate, and facilitate registration of new treatments for VL in the region



Human African Trypanosomiasis HAT Platform

Founded: 2005 in Kinshasa, Democratic Republic of the Congo



Members from the following institutions:

National Control Programmes of most affected endemic countries: Angola, Central African Republic, Chad, Democratic Republic of the Congo, Republic of the Congo, South Sudan, Sudan, Uganda; Swiss Tropical and Public Health Institute (Swiss TPH); Institute of Tropical Medicine-Antwerp, Belgium; Institut National de Recherche Biomédicale (INRB), DRC; Kenya Agricultural Research Institute – Trypanosomiasis Research Centre (KARI-TRC), Kenya; Tropical Medicine Research Institute (TMRI), Sudan; Institut Pasteur Bangui, CAR; Médecins Sans Frontières (MSF); Epicentre; Foundation for Innovative New Diagnostics (FIND); regional networks such as Eastern Africa Network for



Trypanosomiasis (EANETT), Centre interdisciplinaire de Bioéthique pour l'Afrique Francophone (CIBAF); Special Programme for Research and Training in Tropical Diseases (WHO-TDR) as observer.

- With the independence of South Sudan in July 2011, the HAT Platform now counts eight member countries.

Overall objectives:

- Build and strengthen treatment methodologies and clinical trial capacity in HAT-endemic countries, so that new treatments can be rapidly and effectively evaluated, registered, and made available to patients
- Develop appropriate clinical trial methodologies for HAT and strengthen clinical trial capacity (human resources, infrastructure, equipment)
- Overcome system challenges related to administrative and regulatory requirements
- Share information and strengthen ties among endemic countries

Chagas Clinical Research Platform (CCRP)

Founded: 2009 in Uberaba, Brazil



The Platform includes representatives from:

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); Hospital de Niños Ricardo Gutiérrez, Argentina; Instituto Nacional de Parasitología Dr M Fátala Chabén, Argentina; Hospital de Niños de Jujuy, Argentina; Hospital Público Materno Infantil – Salta, Argentina; Centro de Chagas y Patología Regional, Santiago del Estero, Argentina; Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina; Instituto Oswaldo Cruz, Brazil; Instituto de Pesquisa Evandro Chagas-Fiocruz, Brazil; Centro de Pesquisas René Rachou-Fiocruz, Brazil; Universidad Mayor de San Simón – Platform of Integral Care for Patients with Chagas Disease, Bolivia; CRESIB – Hospital Clinic Barcelona, Spain; Médecins Sans Frontières; Institut de Recherche pour le Dével-

oppement, France; Eisai Co. Ltd, Japan; FINDECHAGAS; Mundo Sano, Argentina.

- More than 70 institutions represented from 20 countries

Overall objectives:

- Deliver concrete support for R&D, such as training, capacity building, definition and compliance to standards and regulations, integration of ethical principles across different populations and countries
- Discuss access challenges to new and existing technologies, through a flexible and needs-driven platform





Achievements and Activities in 2011

Treatments: Following the results of the study comparing paromomycin (PM) and sodium stibogluconate (SSG) in monotherapies, and the shorter course combination SSG&PM, the WHO Expert Committee on the Control of Leishmaniases recommended, in March 2010, the use of SSG&PM as first-line treatment for VL in East Africa. Sudan applied this recommendation at the close of 2010, implementing SSG&PM as first-line treatment. Since then, the process of registration of PM has been initiated in LEAP countries, of which Uganda will be the first (early 2012).

Clinical trials: Patient follow-up and data collection and analysis for DNDi and LEAP AmBisome®/AMBI 0106 Study were completed in 2011 (see page 29). In 2011, recruitment progressed for Miltefosine-AmBisome®/LEAP 0208 study (see page 29). In addition, a pharmacovigilance study to monitor safety and effective-

ness of SSG&PM was initiated (see page 31).

Another study, the Rapid Diagnostics Tests (RDT) study in Kenya (MSF and KEMRI) was completed.

Capacity strengthening: Good Clinical Practice (GCP), Good Clinical and Laboratory Practice (GCLP) and study-specific training courses were held in 2011 for lab technicians, nurses, pharmacists, monitors, and investigators. LEAP also provides post-graduate training to researchers and health workers: in 2011, one person from Uganda, three from Kenya, one from Sudan, and three from Ethiopia. A total of 108 people were trained in 2011. In addition, an exchange programme was initiated between the laboratory staff at the Kimalale site in Kenya and the Amudat site in Uganda. Launched in November 2011 in Kimalale, the programme will continue in 2012 in Amudat.

Infrastructure: In 2011, the renovation of laboratories at Gondar clinical site, Ethiopia, started and will be finalized in 2012.

Access: LEAP countries are in the process of reviewing National VL Guidelines in light of WHO recommendation of SSG&PM as first-line treatment for VL in the region. In parallel, the update of Essential Medicines Lists in each country is ongoing in order to reflect the addition of SSG&PM as a VL treatment.

Communication: The first LEAP brochure was released. SSG&PM treatment was featured in regional media following a press conference in Nairobi in September 2011.

Meetings: The 16th LEAP meeting & LEAP stakeholders workshop held in Nairobi, Kenya, in September 2011 brought together more than 150 participants for a week-long meeting. Principal investigators' meetings and DSMB & monitors' meetings took place at this occasion; other scientific congresses.



Achievements and Activities in 2011

Treatments: In December 2011, NECT was used in 11 African countries after becoming the first-line treatment for second stage *T.b. gambiense* infected patients. In 2011, the Republic of Congo was the latest country to adopt NECT as first-line treatment.

Clinical trials: **NECT:** Participation in the ongoing NECT-Field studies (six sites in DRC); **Exenidazole:** Preparation of the clinical trials for a new oral drug in DRC during 2011: discussions with ethical and regulatory authorities of DRC; training; and selection of sites. This study will start in 2012 in three countries: DRC, Central African Republic (CAR), and South Sudan. In addition, by strengthening collaboration with FIND, the platform contributed to a trial for a new Rapid Diagnostic Test. With ITM-Antwerp, it was involved

in the preparation of the trial for the neurological diagnosis decision trees (NIDIAG).

Capacity strengthening: In 2011, the platform organized two training courses in Kinshasa: A pharmacovigilance training with 40 participants (DRC, Chad, CAR, and Angola) and a Clinical Research and Good Clinical Practice training with 22 participants, mainly from DRC and CAR.

Infrastructure: The HAT Platform helps to identify the needs of each member country and sites involved in the clinical studies, namely by facilitating the selection of equipment and products to purchase. In 2011, Kwamouth and Katanda clinical sites in DRC benefited from several infrastructure upgrades, such as solar energy systems, kitchen, warehouses, and painting of rooms.

Access: Advocacy in member countries towards quick adoption of NECT as first-line treatment for second stage HAT. NECT is rapidly replacing previous treatments for stage 2 HAT: in 2011, 93% of stage 2 sleeping sickness patients in DRC were treated with NECT.

Communication: Two HAT platform newsletters were published in 2011; the first HAT platform brochure was released.

Meetings: The HAT Platform Steering Committee took place in Bangui, CAR, in May 2011, with 20 participants. The Annual Scientific Meeting of the HAT Platform was held in Bamako, Mali, in September 2011, with 37 participants. Other scientific congresses: presentations of HAT research activities at the 31st ISCTRC meeting (Bamako) and at the 7th ECTMIH (Barcelona, Spain).



Achievements and Activities in 2011

Clinical trials: In 2011, three studies that receive support from the Platform were initiated: a population pharmacokinetics (PK) study of the use of benznidazole in children, including the new paediatric dosage form (Argentina); a study to evaluate and optimize the polymerase chain reaction method (PCR) for diagnosis and assessment of therapeutic response in patients with chronic indeterminate Chagas disease (Bolivia); a study to evaluate the safety and efficacy of E1224, a pro-drug of ravuconazole (Bolivia, see page 36).

Capacity Strengthening: In 2011, Good Clinical Practice training courses and investigators meetings were held in Bolivia and Argentina for team members involved in the ongoing clinical studies on Chagas disease supported by the platform. 70 participants were trained in 2011.

Infrastructure: As part of the start-up and preparatory activities for the implementation of the clinical trials (E1224, Bolivia, and the paediatric dosage form of benznidazole, Argentina), equipment and infrastructure building took place in 2011 (upgrade of laboratory equipment and construction of separate laboratory areas of the Platform of Integral Care for Patients with Chagas Disease).

Access: The CCRP collaborated on the development of an Information, Education, and Communication (IEC) Tool Box for rational use of the paediatric dosage form of benznidazole. In addition, the Platform was active in mediating and addressing the 2011 crisis in the production of benznidazole.

Communication: The first edition of the CCRP Newsletter was published in August 2011 in

Portuguese, Spanish, and English, and a Web Forum was launched, bringing together over 120 members from 73 organizations and 20 countries within this virtual working space for discussions and sharing of information on access to treatments.

Meetings: In 2011, the Ibero-American research network NHEPACHA, member of the CCRP, organized two meetings in Spain and Argentina to launch the network and review priorities in research on biological markers for Chagas disease and facilitate long-term follow-up. The 2nd CCRP meeting took place end 2011 in Brazil with over 90 participants including PAHO, WHO, control programme managers from key endemic countries, investigators, and patient representatives. All the current projects on Chagas disease were reviewed and discussed.

TRANSFERRING TECHNOLOGY TO BOOST LOCAL INNOVATION CAPACITY

DNDi develops non-patented treatments notably to facilitate their production by different pharmaceutical partners, namely in endemic countries, to ensure the sustainability of production, to ensure a second source of treatments, and ultimately better support patient access to the treatments. To do so, a process of transfer of technology is needed to share the drug development know-how between industrial partners. DNDi is committed to two technology transfers (TT), for ASAQ and ASMQ, the two ACT fixed-dose combinations for malaria.

ASMQ: From Brazil to India

In order to facilitate access of the ASMQ fixed-dose combination (see page 40) in Southeast Asia, a South-South TT between Farmanguinhos/Fiocruz in Brazil and Cipla Ltd in India came to completion in 2010 with support from DNDi. The first TT of its kind between a company in Brazil and one in India – even more unique since it involved a public entity (Farmanguinhos) and a private company (Cipla) – the results of this transfer continue to bear fruits. An application for registration was submitted in India and ASEAN countries (Cambodia, Laos,



Malaysia, Myanmar, Philippines, Thailand, and Vietnam) in 2011. In addition, responses and complementary information for the submission to the WHO for pre-qualification were provided throughout the year. In November 2011, the registration of ASMQ by the Drugs Controller General of India (DCGI), launched the implementation process of ASMQ for Asia and the Southeast Asian region. More ASEAN countries are set to register ASMQ in 2012 in order to ensure wide-spread distribution of the life-saving treatment in the region.



ASAQ: From Morocco to Tanzania

Developed as a non-patented product, the ASAQ fixed-dose combination (see page 41) – produced by Sanofi in Morocco since 2007 – will undergo technology transfer. In 2010, DNDi, with support from a group of experts from OTECI, assessed potential partners in Africa to become the second producer of ASAQ in an endemic area of Africa. By the close of 2010, the Tanzanian industrial group Zenufa was selected, one of the critical characteristics of the partner being its ability to pass pre-qualification by WHO.



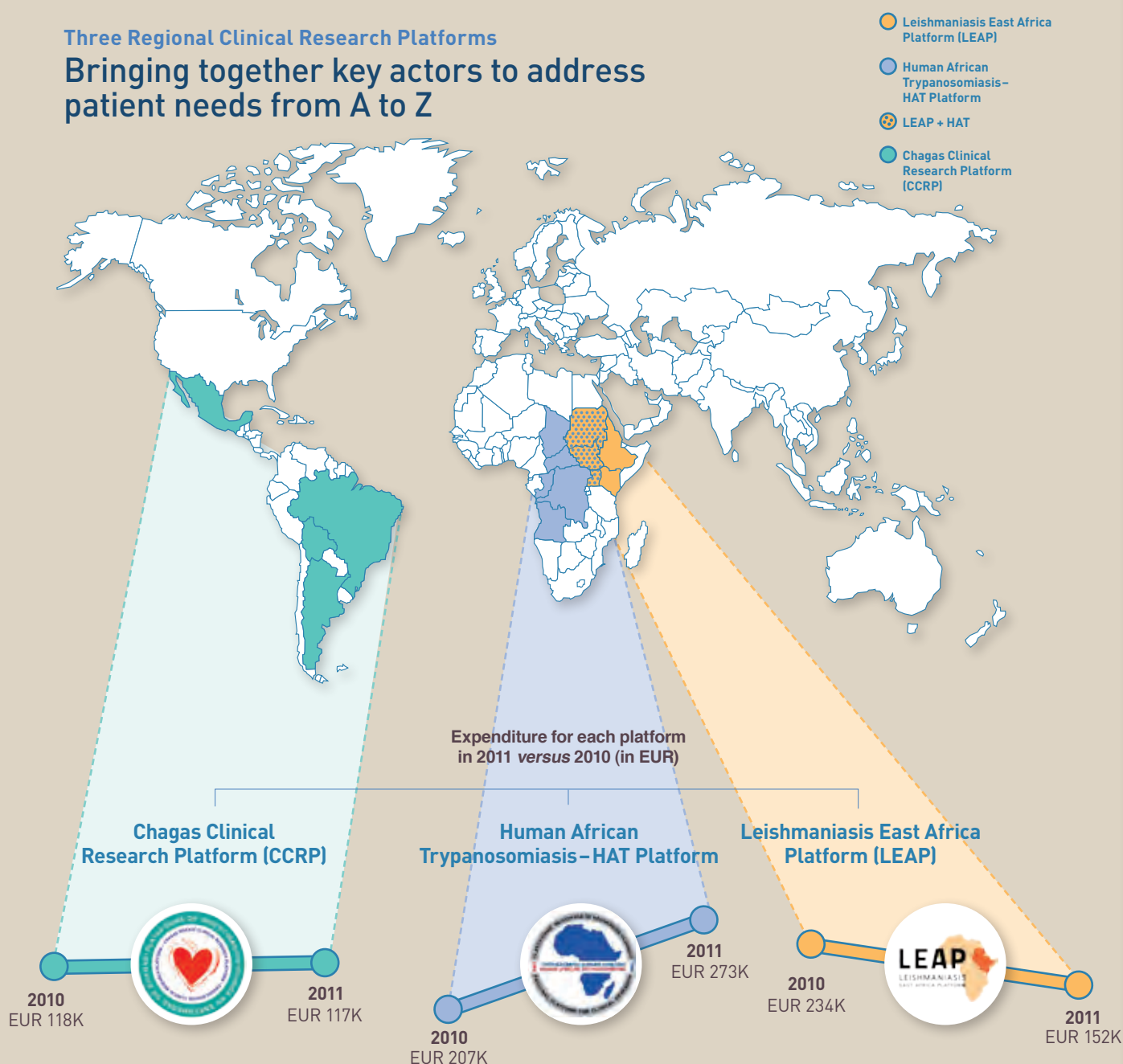
In 2011, the terms of the agreement were finalized and the contract with Zenufa was signed. The first transfer activities began, among them audits of Zenufa to define the steps of the analytical and technical transfer plans, to assess in detail Good Manufacturing Practice (GMP) for pre-qualification, and to develop a business plan. To manage the TT, a team formed by Aedes, Bertin Pharma, OTECI, DNDi, and Zenufa was formed.

2011 KEY FINANCIAL PERFORMANCE INDICATORS



Three Regional Clinical Research Platforms

Bringing together key actors to address patient needs from A to Z



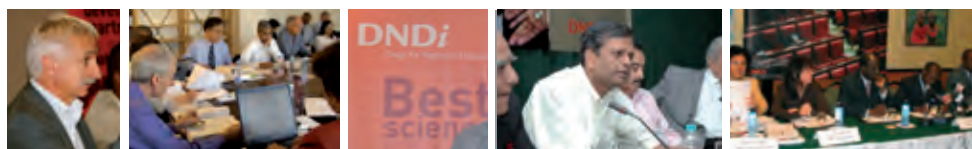
The **Chagas Clinical Research Platform (CCRP)** is operational at two sites for the E1224 Phase II study (Bolivia) and five sites for paediatric benznidazole pharmacokinetics (Argentina). The CCRP expenses remain stable, and include the organization of a platform meeting in December 2011 in Rio de Janeiro, Brazil. **In 2011, 70 people were trained.**

The **HAT Platform** is operational at six sites for the NECT study. In addition, five to six sites are in preparation in DRC (Bandundu-Ville, Vanga, Masi-Manbimba) and in CAR (Batangafo) for the fexinidazole Phase II/III study expected to start in 2012. The increase of expenses is due to human resource strengthening to support the preparation of clinical trial sites for this study. **In 2011, 62 people were trained.**

In 2011, clinical trial activities are conducted at seven sites managed by the **LEAP platform**: two in Sudan (Kassab, Dooka), one in Uganda (Amudat), one in Kenya (Kimallel), and two in Ethiopia (Arba Minch, Gondar). In addition, in 2011, MSF and MoH sites in Sudan have implemented studies for SSG&PM co-administration. No rehabilitation was undertaken in 2011, whereas the site in Dooka was rehabilitated in 2010 (EUR 0.1 Million) and opened as a new LEAP clinical site in 2011 for the VL studies. **Over 100 people were trained in 2011.**



DNDi advocates for increased public responsibility and a more enabling environment for neglected disease R&D.



A GLOBAL FRAMEWORK FOR NEGLECTED DISEASE R&D TO SUSTAIN INNOVATION AND RESOURCES

Since its inception in 2003, DNDi has **advocated for increased resources for neglected disease R&D**, new incentive mechanisms, and better coordination of R&D activities to compensate for market and policy failures.

During the year 2011, G20 governments, the WHO Consultative Expert Working Group (CEWG) on Research & Development: Financing and Coordination, and many international groups analysed and proposed a number of new ideas, including both 'push' mechanisms to finance R&D and 'pull' incentives to spur private-sector investment. Underlying all of these initiatives is the lack of sustainable funding and mechanisms to support long-term global health innovation for poverty-related diseases and the necessity for public health priorities to be set for work carried out by current initiatives, including Product Development Partnerships (PDPs) such as DNDi.

At this time, when many new actors, new policy proposals, and new funding initiatives have emerged in the field of essential health R&D, DNDi considers it vital that a sustainable strategy and plan be designed to empower existing initiatives and to implement more effective policies to boost innovation and ensure equitable access to the fruits of this innovation.

Based on nearly a decade of experience, DNDi endeavoured throughout 2011 to advocate specifically for the following:

→ greater boosting of innovation and more open sharing of research knowledge

→ stronger synergy, partnerships, and coordination across public and private sectors

→ engagement of partners in endemic countries from the outset and throughout the entire R&D process

→ sustainability and diversification of resources.

Coordination and financing for neglected disease R&D

In June 2011, DNDi released an analysis entitled 'Financing & Incentives for Neglected Disease R&D: Opportunities and Challenges', which was submitted to the WHO CEWG. This report concluded that '*[s]everal types of incentives and financing mechanisms tailored to particular stages of R&D, types of diseases and health technologies will*



[...] be necessary to address [the] various gaps and the unmet needs of neglected patients. [T]hese mechanisms should promote R&D according to public health needs, build and improve innovative capacity in developing countries, including through transfer of technology, ensure delivery and access to populations in need, and manage IP in a manner consistent with all these objectives.'

Regional approaches to addressing neglected patient needs

The DNDi/Partners' Meeting 2011, 'Moving Innovation to Access for Neglected Patients', held in Rio de Janeiro, Brazil, on 2 December 2011, in partnership with Fiocruz, marked nearly a decade of progress since the foundations for DNDi were set forth at a remarkable meeting in Rio in 2002. The meeting resulted in 'A Call to Action for Latin America to Boost Innovation and Access for Neglected Patients in the Region'. The call highlighted the fact that *'[i]n Latin America – a region unique in that it includes both endemic countries with pressing patient needs and emerging economies with substantial research and financing capacity – political leadership has deepened and the building blocks for regional coordination and harmonization in the health sector have been put into*



place. Institutions such as Fiocruz have taken a leading role in the struggle against neglected diseases, bringing excellence to research and development (R&D) for medicines and vaccines.' The call articulated six actions for 2012 and beyond in the areas of: implementation; R&D priority setting and coordination; regional regulatory harmonization; open innovation; innovative financing; and new R&D incentives. Over 260 regional and international partners participated in the meeting in presence of representatives of the Brazilian and Argentinian governments. In addition, 1,200 people worldwide participated via a live webcast.

Boosting innovation and open sharing of research knowledge

DNDi joined the WIPO Re:Search public database and open innovation platform at its launch in October 2011 (see pages 6-7). While welcoming the initiative as both a 'user' and a 'provider', DNDi called for more ambitious provisions for innovation and access. DNDi provided data on over 5,500 compounds from two of its lead optimization

consortia on sleeping sickness and Chagas disease, both on the WIPO Re:Search and the ChEMBL medicinal chemistry databases. A special 'Open Innovation Portal' was created to render these datasets easily accessible on the DNDi website. These two public databases represent a move towards more open mechanisms that have the potential to facilitate and foster knowledge sharing to boost neglected disease innovation, notably by avoiding duplication in research and by reducing costs and development timelines for the benefit of patients.



The London Declaration: Growing momentum and partnership building in support of the WHO NTD Roadmap

The year 2011 marked a major build-up of partners engaging in neglected disease R&D, notably with donors stepping up to the plate despite financial crisis and pharmaceutical and biotech partners placing more resources towards neglected disease R&D. The WHO issued a report in early 2012, *Accelerating Work to Overcome the Global Impact of Neglected Tropical Diseases: A Roadmap for Implementation*, which was supported by a coalition of actors in a landmark meeting in London: 'Uniting to Combat Neglected Tropical Diseases'. This meeting, in January 2012, gathered a diverse range of public and private partners to combat 10 neglected tropical diseases (NTDs) by 2020, including: 13 pharmaceutical companies, the US, UAE, and UK governments, the Bill & Melinda Gates Foundation, the World Bank, officials from NTD-endemic countries, and DNDi. Expanded existing drug donation programmes to meet demand through 2020; sharing of expertise and compounds with DNDi to accelerate R&D of new drugs; and USD 785 Million to support R&D efforts and strengthen drug distribution and implementation programmes, were the main outcomes of this event. The partners pledged to bring a unique focus to NTDs and to work together to improve the lives of the billion people worldwide affected by them, by signing on to the 'London Declaration on Neglected Tropical Diseases'.



EUR 184 Million Secured

Reinforcing donor commitments en 2011

Despite the effects of the on-going financial crisis, DNDi was able to generate a total of EUR 25.8 Million to cover its total expenses in 2011 (+ 4% compared to 2010). This is the result of on-going multi-year grants, renewed and increased commitments of past and current donors, as well as new partnerships with key institutions.

In 2011, two new funders entered into partnership with DNDi to support R&D programmes for neglected tropical diseases: the Federal Ministry of Education and Research (BMBF/KFW)* of Germany, which decided to join forces with other public donors to increase global resources for innovation against poverty-related diseases in support of specific Millennium Development Goals; and the Wellcome Trust.

Nine of DNDi's existing funders renewed or increased their commitments to DNDi in 2011.

The renewed commitments include the Dutch government, DGIS (new multi-year portfolio funding for a total of EUR 14 Million – highlighted in the DNDi Annual Report 2010); the Bill & Melinda Gates Foundation; the Spanish government, AECID; Médecins Sans Frontières (Norway, Italy, and Brazil sections with EUR 0.35 Million, EUR 0.3 Million, Real 1 Million, respectively); the Medicor Foundation (annual funding of USD 0.5 Million for leishmaniasis activities in Africa); and two Swiss foundations. The UK government, DFID, and the Global Fund (EUR 0.3 for the End Point Survey for AMFm), both increased their commitments to DNDi.

These commitments were essential to ensuring the continuation of activities and commencing key projects to fill essen-

Target:
**EUR
400
Million**

To date:
**EUR
184
Million**

tial R&D gaps, such as for helminth infections, cutaneous leishmaniasis, and biomarkers for Chagas disease.

In order to diversify its funding sources, resource mobilization activities were carried out in a more systematic manner through DNDi's regional offices.

By the end of 2011, funders committed a total of EUR 184 Million to DNDi, + 20% from December 2010. An additional EUR 216 Million is needed by 2018 to achieve DNDi's Business Plan objectives. Core funding – and alternatively portfolio funding – is critical to ensure the flexibility DNDi needs to adequately manage and progress, in a cost-efficient manner, its R&D activities through to patient use.

New Grants Received in 2011

UK Government (DFID)

GBP 3.4 Million

This additional core funding from DFID for 2011/2012 has allowed DNDi to start implementing new projects with a particular focus on leishmaniasis (e.g. start of cutaneous leishmaniasis and preparation for HIV-VL activities). It also has ensured progress of key activities (e.g. technical transfer for the production of ASAQ, optimization for innovative oral treatments for HAT, in-licensing well-characterized compound series from pharmaceutical companies, clinical study for the second combination treatment for VL in Africa). DFID has been supporting DNDi since 2006.

Federal Ministry of Education and Research of Germany (BMBF through KFW)

EUR 8 Million

This grant received by DNDi in 2011 will be disbursed over the period of 2011-2015 and is part of a larger funding programme of

EUR 20 Million allocated by the BMBF to three product development partnerships. The part applied to DNDi activities ranges from compound screening to clinical studies for new or improved products for sleeping sickness, visceral leishmaniasis, Chagas disease, and helminth infections.

Wellcome Trust

EUR 2 Million

The project aims to develop the azole compound E1224, a promising drug developed in partnership with Eisai Co. Ltd. to treat Chagas disease, which is being tested in adult patients in Bolivia. The award, the first that DNDi has received from the Wellcome Trust, will take the project to the end of Phase II clinical trials.

Bill & Melinda Gates Foundation

USD 9 Million

This grant is applied to implementing part of a comprehensive four-year project including over 10,000 patients in clinical and pharmacovigilance studies for diagnosis and treatment of visceral leishmaniasis in India and Bangladesh.

USD 5.8 Million

This grant is applied to a project that will assess, through pre-clinical activities, the potential of the drug flubendazole to treat a highly neglected subset of helminth infections, notably co-infection of two of the three filarial diseases: onchocerciasis (river blindness) and lymphatic filariasis (LF; elephantiasis), in co-infection with loiasis (African eyeworm or *Loa loa*).

USD 2 Million

This grant is applied to screening activities for leishmaniasis, human African trypanosomiasis, and helminth infections.

Spanish Government (AECID)

EUR 1 Million

In 2011 AECID supported, through core funding, various activities including the development of new treatments for visceral leishmaniasis in Asia, Africa, and Latin America and the Chagas lead optimization consortium, enabling DNDi and its partners to continue searching for innovative treatments for Chagas disease. AECID also contributed to capacity building, ensuring that sustainable scientific capacity is fostered in endemic countries. AECID has been supporting DNDi since 2007.

'We strongly believe that DNDi, through the development of cost-effective and easy-to-use treatments [...] will contribute to global efforts to control and/or eliminate certain NTDs.'

Dr Helge Braun,
Parliamentary State Secretary, Germany

FRIENDS OF DNDi

The 'Friends of DNDi' are internationally-renowned individuals who contribute to DNDi's mission and vision by engaging globally influential actors, policy-makers, and key supporters to further the work of DNDi. Each friend plays an important role based on his or her specific background, expertise, and position.

Paulo Buss, Professor of Health Planning, National School of Public Health, Oswaldo Cruz Foundation (Fiocruz), Brazil

Yves Champey, former Chair of DNDi Board of Directors. Served as Medical and Scientific Director, and then as Senior Vice President, International Drug Development, at Rhone Poulenc, France

Abdallah Daar, Professor of Public Health Sciences and Surgery, University of Toronto, and Senior Scientist and Director of Ethics and Commercialization at the McLaughlin-Rotman Centre for Global Health, University Health Network and University of Toronto, Canada

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

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

Nirmal K. Ganguly, former Director General of the Indian Council of Medical Research (ICMR), India

Rowan Gillies, former President of MSF International Council, Australia

Lalit Kant, former Head of the Division of Epidemiology & Communicable Diseases, Indian Council of Medical Research, India

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

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

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

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

José Gomes Temporão, former Minister of Health, Brazil

Rafael Vila San Juan, Director Laboratorio de Ideas, Institute for Global Health of Barcelona (ISGlobal), Spain

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

Yongyuth Yuthavong, former Minister of Science and Technology, Thailand

Outreach, advocacy & DNDi strives to give a voice to neglected patients

MAIN FEATURES IN THE MEDIA

- **IPS**, 'Child-Adapted Formula to Deal Major Blow to Chagas Disease', 8 DECEMBER 2011
- **La Nación**, 'Aprueban el primer medicamento pediátrico para Chagas', 3 DECEMBER 2011
- **The Times of India**, 'Study boost for elimination of kala-azar in India', 10 NOVEMBER 2011
- **New York Times**, 'Kala Azar: Four-Year Test Seeks Better Ways to Treat a Persistent Disease Spread by Sand Flies', 7 NOVEMBER 2011
- **El Mundo**, 'Un proyecto internacional para erradicar la leishmaniasis', 7 NOVEMBER 2011
- **SciDev.net**, 'Major patent pool opens up research on neglected disease', 31 OCTOBER 2011
- **La Vanguardia**, 'Millones de personas en el mundo siguen olvidadas', 29 OCTOBER 2011
- **Le Temps**, 'Union sacrée contre les maladies négligées', 27 OCTOBER 2011
- **Science**, 'Drug developers finally take aim at a Neglected Disease', 19 AUGUST 2011
- **Le Monde**, 'Les enfants des pays les plus pauvres sont les grands oubliés de la lutte contre le SIDA', 19 AUGUST 2011
- **JAMA**, 'Effort launched to adapt HIV/AIDS drugs for children', 10 AUGUST 2011
- **Financial Times**, 'Wake-up call for sleeping sickness', 8 JULY 2011
- **Science**, 'Hitting Sleeping Sickness Where It Lives', 28 JUNE 2011

The New York Times

KALA AZAR: Four-Year Test Seeks Better Ways to Treat a Persistent Disease Spread by Sand Flies

Aprueban el primer medicamento pediátrico para Chagas

LA NACION

Es producido en Brasil y ya está en trámite su aprobación en la Argentina

Study boost for elimination of kala-azar in India

THE TIMES OF INDIA

Science

Hitting Sleeping Sickness Where It Lives

Drug Developers Finally Take Aim At a Neglected Disease

New and recycled compounds target the parasite responsible for Chagas disease which afflicts millions in Latin America

LE TEMPS

Union sacrée contre les maladies négligées

Effort Launched to Adapt HIV/AIDS Drugs for Children

JAMA

awareness-raising

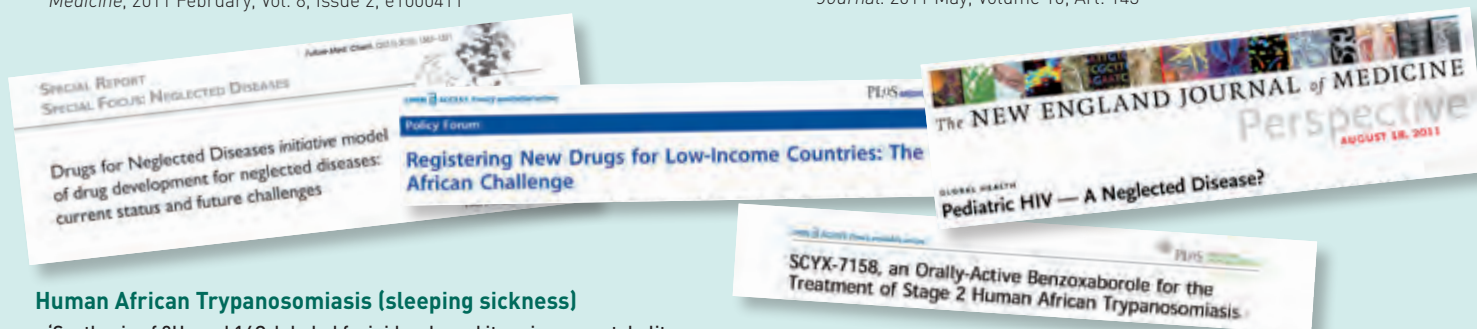
in both international and regional media, in addition to scientific publications

20 SCIENTIFIC PUBLICATIONS BY DNDi AND PARTNERS

DNDi enjoyed an increase in the number of scientific publications in 2011 as compared to 2010. This is an important marker of DNDi's activities and the progression of projects.

DNDi Model & Neglected Diseases

- 'Drugs for Neglected Diseases initiative model of drug development for neglected diseases: current status and future challenges' by Chang S and Ioset J-R. *Future Medicinal Chemistry*, 2011 September, Volume 3, Issue 11, pp. 1361-71
- 'Kinetoplastid Parasites' by Von Geldern T, Harhay MO, Scandale I and Don R. *Top Med Chem*. Volume 7, 181-241
- 'Drug discovery and development for neglected diseases: the DNDi model' by Chatelain E and Ioset J-R. *Drug Design, Development and Therapy*, 2011 March, Vol. 5, pp. 175-181
- 'Registering New Drugs for Low-Income Countries: The African Challenge' by Moran M, Strub Wourgaft N, Guzman J, Boulet P, Wu L, Pecoul B. *PLoS Medicine*, 2011 February, Vol. 8, Issue 2, e1000411



Human African Trypanosomiasis (sleeping sickness)

- 'Synthesis of 2H- and 14C-labeled fexinidazole and its primary metabolites labeled with 2H' by Fontana E, Pignatti A, Venegoni S, and Bray MA. *The Journal of labelled compounds and radiopharmaceuticals*. 2011 August, Volume 54, Issue 11, pp. 714-19
- 'SCYX-7158, an Orally-Active Benzoxaborole for the Treatment of Stage 2 Human African Trypanosomiasis' by Jacobs RT, Nare B, Wring S.A, Orr M.D, Chen D, Sligar JM, Jenks MX, Noe RA, Bowling TS, Mercer LT, Rewerts C, Gaukel E, Owens J, Parham R, Randolph R, Beaudet B, Bacchi CJ, Yarlett N, Plattner JJ, Freund Y, Ding C, Akama T, Zhang Y-K, Brun R, Kaiser M, Scandale I, Don R. *PLoS NTD*. 2011 June. Volume 5, Issue 6, e1151
- 'Challenges of controlling sleeping sickness in areas of violent conflict: experience in the Democratic Republic of Congo' by Tong J, Valverde O, Mahoudeau C, Yun O, Chappuis F. *Conflict and Health*. 2011 May, Volume 5, Issue 7
- '1-Aryl-4-nitro-1H-imidazoles, a new promising series for the treatment of human African trypanosomiasis' by Bourdin Trunz B, Jędrzyński R, Tweats D, Brun R, Kaiser M, Suwiński J and Torreele E. *European Journal of Medicinal Chemistry*, 2011 May, Volume 46, Issue 5, pp. 1524-1535

Leishmaniasis

- 'Who Is a Typical Patient with Visceral Leishmaniasis? Characterizing the Demographic and Nutritional Profile of Patients in Brazil, East Africa, and South Asia' by Harhay MO, Olliaro PL, Vaillant M, Chappuis F, Lima MA, Ritmeijer K, Costa CH, Costa DL, Rijal S, Sundar S, Balasegaram M. *Am. J. Trop. Med. Hyg.* 2011 Volume 84, Issue 4, pp. 543-550
- 'Comparison of short-course multidrug treatment with standard therapy for visceral leishmaniasis in India: an open-label, non-inferiority, randomised controlled trial' by Sundar S, Sinha PK, Rai M, Verma DK, Nawin K, Alam S, Chakravarty J, Vaillant M, Verma N, Pandey K, Kumari P, Lal CS, Arora R, Sharma B, Ellis S, Strub Wourgaft N, Balasegaram M, Olliaro P, Das P, Modabber F. *Lancet*, 2011 January, Volume 377, Issue 9764, pp. 477-486

Chagas disease

- 'Novel 3-Nitro-1H-1,2,4-triazole-based Aliphatic and Aromatic Amines as anti-Chagasic Agents' by Papadopoulou MV, Bourdin B, Bloomer WD, McKenzie C, Wilkinson SR, Prasittichai C, Brun R, Kaiser M, Torreele E. *Journal of Medicinal Chemistry*, 2011 October, Volume 54, Issue 23, pp. 8214-8223

Malaria

- 'Hematologic parameters in pediatric uncomplicated Plasmodium falciparum malaria in sub-Saharan Africa' by Olliaro P, Djimdé A, Dorsey G, Karema C, Mårtensson A, Ndiaye JL, Sirima SB, Vaillant M, Zwang J. *Am J Trop Med Hyg.* 2011 October; Volume 85, Issue 4, pp. 619-25
- 'Changing patterns of malaria during 1996-2010 in an area of moderate transmission in southern Senegal' by Brasseur P, Badiane M, Cisse M, Agnamey P, Vaillant MT, Olliaro P. *Malaria Journal*. 2011 July, Volume 10, Art. 203
- 'Innovative public-private partnerships to maximize the delivery of anti-malarial medicines: lessons learned from the ASAQ Winthrop experience' by Bompert F, Kiechel J-R, Sebbag R, Pecoul B. *Malaria Journal*. 2011 May, Volume 10, Art. 143

- 'The initial pharmaceutical development of an artesunate/amodiaquine oral formulation for the treatment of malaria: a public-private partnership' by Lacaze C, Kauss T, Kiechel J-R, Caminiti A, Fawaz F, Terrassin L, Cuart S, Grislain L, Navaratnam V, Ghezzoul B, Gaudin K, White NJ, Olliaro P, Millet P. *Malaria Journal*. 2011 May, Volume 10, Art. 142
- 'Standardised versus actual white cell counts in estimating thick film parasitaemia in African children under five' by Olliaro P, Djimdé A, Karema C, Mårtensson A, Ndiaye JL, Sirima SB, Dorsey G, Zwang J. *Tropical Medicine & International Health*. 2011 May. Volume 16, Issue 5, pp. 551-4
- 'Effect of artesunate and mefloquine in combination on the Fridericia corrected QT intervals in Plasmodium falciparum infected adults from Thailand' by Krudsood S, Looareesuwan S, Wilairatama P, Leowattana W, Tangpukdee N, Chalermrut K, Ramanathan S, Navaratnam V, Olliaro P, Vaillant M, Kiechel JR, Taylor WRJ. *Tropical Medicine & International Health*. 2011 April, Volume 16, Issue 4, pp. 458-465
- 'Access to artesunate-amodiaquine, quinine and other anti-malarials: policy and markets in Burundi' by Amuasi JH, Diap G, Blay-Nguah S, Boakye I, Karikari PE, Dismas B, Karenzo J, Nsabiyeumva L, Louie KS, Kiechel J. *Malaria Journal*, 2011 February, Volume 10, Issue 34

Helminth infections

- 'Potential Drug Development Candidates for Human Soil-Transmitted Helminthiasis' by Olliaro P, Seiler J, Kuesel A, Horton J, Clark J.N, Don R, Keiser J. *PLoS NTD*. 2011 June. Volume 5, Issue 6, e1138

Paediatric HIV

- 'Pediatric HIV - A Neglected Disease?' by Lallemand M, Chang S, Cohen R, and Pécoul B. *The New English Journal of Medicine*. 2011 August, 365:581-583

DNDi SYMPOSIA AND MAIN CONFERENCES

ASTMH 2011 (American Society of Tropical Medicine and Hygiene)

Philadelphia, USA, 4-8 December 2011

→ DNDi participated in the sessions 'CYP51 as a Target for Chagas Disease Drugs' and 'A Decade Later: Drug Development and the Promise of Health Care Impact', in addition to presenting several posters (Chagas disease, visceral leishmaniasis, malaria, helminth infections).

4th DNDi Partners' Meeting 2011: Moving Innovation to Access for Neglected Patients

Rio de Janeiro, Brazil, 30 Nov – 2 Dec 2011

→ DNDi brought together over 260 regional partners and members of its global network to Rio de Janeiro, and the main event on 2 December was webcast live to 1,240 viewers around the world.

→ Brazilian Ministry of Health announced the registration of the paediatric dosage form of benznidazole.

→ The meeting resulted in a 'Call to Action for Latin America to Boost Innovation and Access for Neglected Patients in the Region'.

Parallel meetings:

→ The annual meeting of the Chagas Clinical Research Platform gathered over 90 participants to review the Chagas R&D projects.

→ The meeting 'Artesunate-Mefloquine (ASMQ) Fixed-Dose Combination (FDC), an additional tool in the armamentarium to control malaria in Latin-America' was held in parallel.



ISID-NTD Meeting

Boston, USA, 8-10 July 2011

→ DNDi presented in the following sessions: 'Developing the Tools Needed to Fight NTDs' and 'Essential Elements: Drug Donations and Non-Governmental Development Programs'.

World Health Summit

Berlin, Germany, 23-26 October 2011

→ DNDi joint session with International Consortium on Antivirals (ICAV): 'Product Development for Neglected Patients: Where Are the Research Gaps and What Are the Priorities?'

→ Participation in the session: 'Innovation for Diseases of Global Health Importance: Adapting Innovation to Fit Local Conditions'

7th European Congress of Tropical Medicine and Hygiene (ECTMIH)

Barcelona, Spain, 3-6 October 2011

In total, 22 presentations from DNDi staff members and R&D partners, covering the NTD portfolio, in addition to several poster presentations.



→ DNDi session: 'Drug Development for Kinetoplastids'

→ DNDi joint session with Institute of Tropical Medicine, Antwerp, Belgium: 'Visceral Leishmaniasis - HIV Co-infection: Current Challenges and Perspectives'

→ DNDi also took part in various sessions on elimination, helminth infections, Chagas disease, sleeping sickness, and malaria, in addition to several poster presentations.

31st Conference of the International Scientific Council for Trypanosomiasis Research and Control (ISCTRC)

Bamako, Mali, 12-16 September 2011

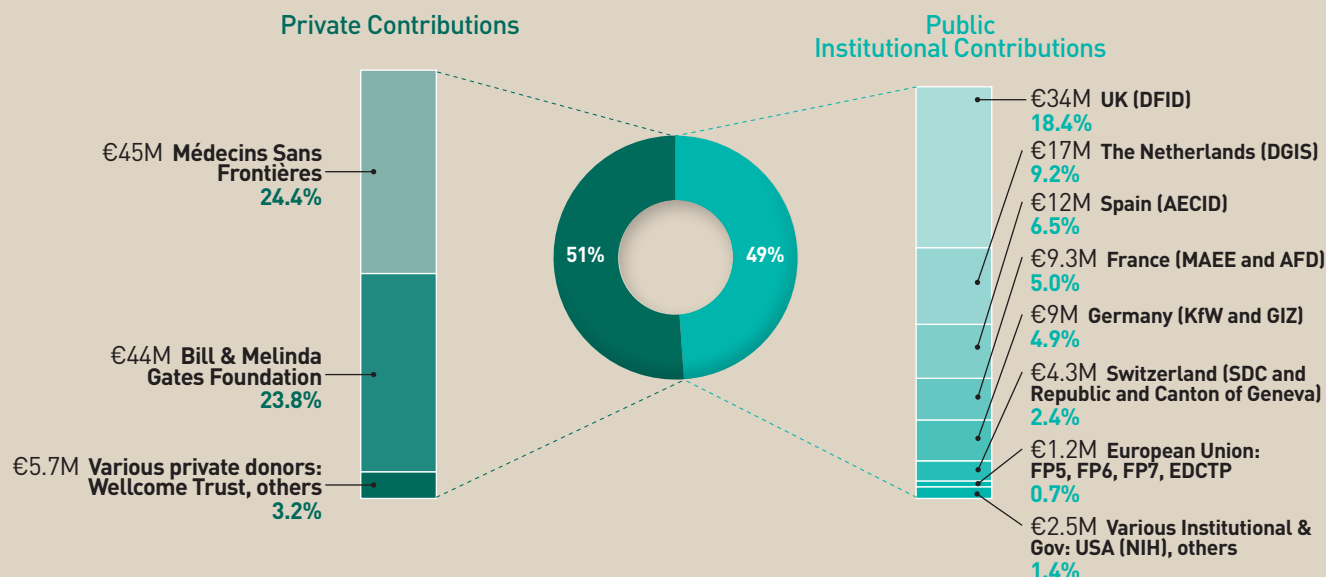
→ Four DNDi presentations were included in the session on HAT chemotherapy covering the whole process of drug development, notably on: discovery project entering Phase I clinical stage; a molecule starting Phase II; a project in Phase IIIb; the conditions and challenges of implementation of a treatment launched end 2009, NECT.

2011 KEY FINANCIAL PERFORMANCE INDICATORS



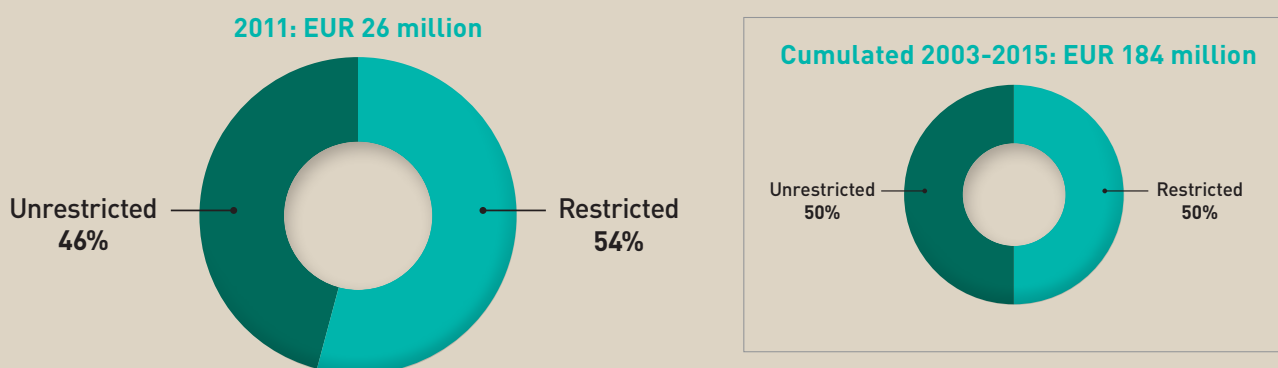
Balanced and diversified funding – key to DNDi's vision

EUR 184 Million committed to DNDi for 2003-2015 (as per January 2012)

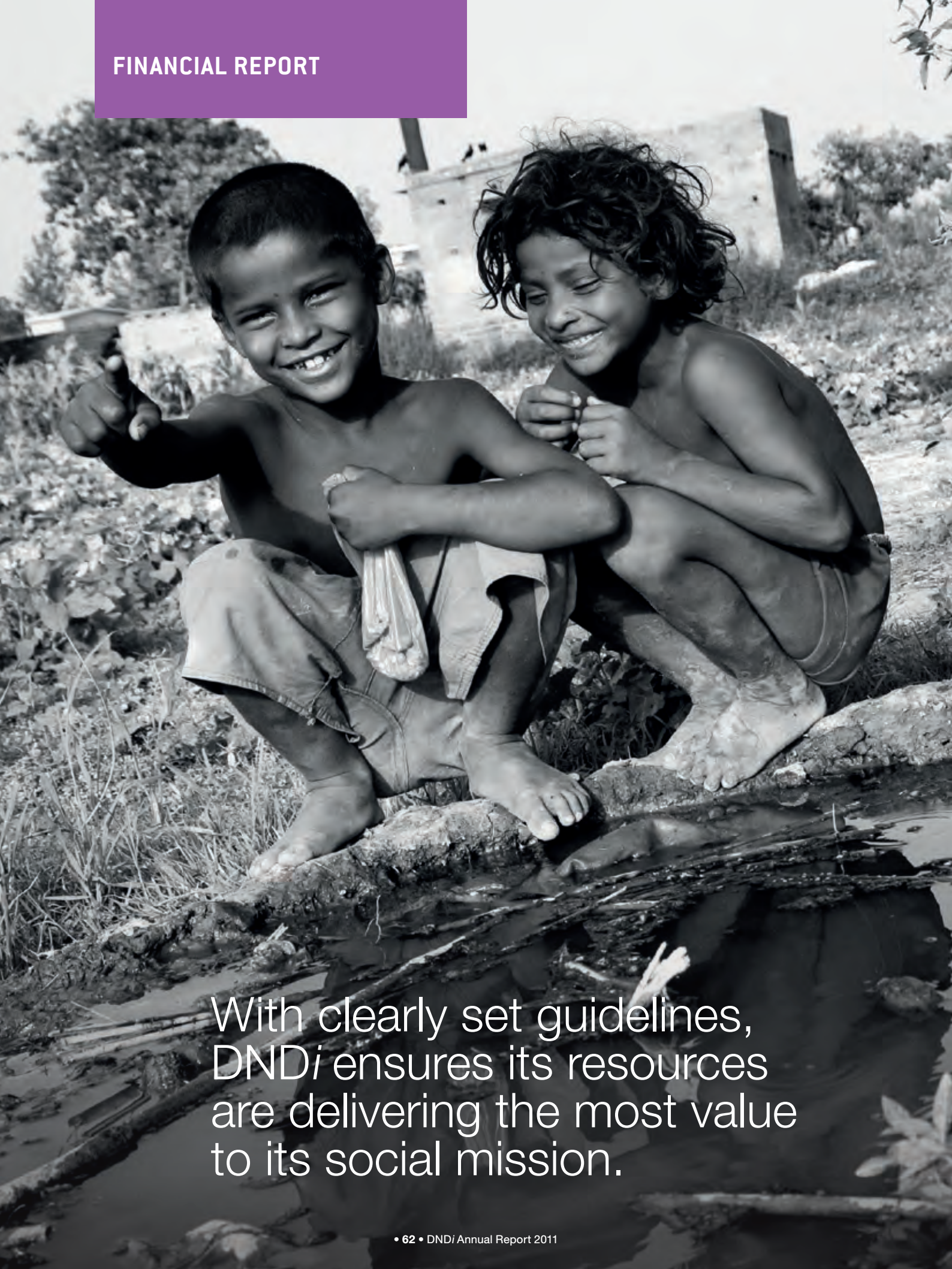


To realize its vision and mission, DNDi seeks to ensure balanced and diversified financial support from public and private donors, allowing the organization flexibility and sustainability, while also preserving its independence. The public-private balance has been maintained thus far, and the diversification of donors has increased – with two new donors in 2011 (Wellcome Trust and BMBF/KfW).

Unrestricted core funding vital to flexible portfolio management



The trend shows an increase in the number of restricted grants in 2011 (compared to 46% in 2010 and 34% in 2009). Under these restricted grants a new and more flexible category has emerged: portfolio grants. Covering various diseases and/or various projects, these grants are estimated at 18% of the 2011 total income. However, to maintain flexibility and independence in managing the scientific portfolio, it is critical that DNDi continues to raise unrestricted core funding in the coming years.



With clearly set guidelines,
DNDi ensures its resources
are delivering the most value
to its social mission.



FINANCIAL STATEMENTS AND AUDIT REPORT

BALANCE SHEET

AT 31 DECEMBER 2011 (with 2010 comparative figures)

(expressed in EUR)	NOTES	2011	2010
CURRENT ASSETS			
Cash and cash equivalents			
Cash and banks at headquarters		11,096,606	3,985,617
Cash and banks at regional offices and affiliates		347,002	285,943
Time deposits		8,182,670	12,815,450
Total cash and cash equivalents		19,626,278	17,087,010
Stocks of drugs	3	80,797	81,041
Current accounts and receivables			
Advances to officers and liaison offices		66,651	47,700
Receivables from public institutional donors		2,475,541	2,899,330
Receivables from Founding Partners		0	6,745
Other receivables		1,147,388	388,347
Prepaid expenses		380,290	75,862
Total current accounts and receivables		4,069,870	3,417,984
Total current assets		23,776,945	20,586,035
NON-CURRENT ASSETS			
Tangible fixed assets, net	4	85,459	86,051
Bank guarantee deposits		32,108	28,938
Total non-current assets		117,567	114,989
TOTAL		23,894,512	20,701,024
CURRENT LIABILITIES			
Payables		2,588,190	3,073,437
Accrued expenses		759,073	439,470
Deferred income		10,077,858	6,750,150
Provisions	5	199,347	248,614
Total current liabilities		13,624,468	10,511,671
CAPITAL OF THE ORGANIZATION			
Paid-in capital		32,510	32,510
Restricted operating funds	6	219,888	205,155
Internally generated unrestricted funds		10,017,646	9,951,688
Total capital of the organization		10,270,044	10,189,353
TOTAL		23,894,512	20,701,024

STATEMENT OF OPERATIONS

FOR THE YEAR ENDED 31 DECEMBER 2011 (with 2010 comparative figures)

(expressed in EUR)	NOTES	2011	2010
INCOME			
Public institutional funding:			
Govern. & public int. organiz. unrestricted		8,729,076	9,237,011
Govern. & public int. organiz. restricted		4,728,028	2,652,925
Total public institutional funding		13,457,104	11,889,936
Private resources:			
Private foundations, corporations, and individuals, unrestricted		71,060	36,689
Private foundations, corporations, and individuals, restricted		8,192,695	9,322,111
Royalties on drug sales	6	56,693	54,071
Total private resources		8,320,448	9,412,871
Resources from founding partners:			
Médecins Sans Frontières, unrestricted		3,091,937	3,165,075
Médecins Sans Frontières, restricted		864,557	465,000
Indian Council for Medical Research, unrestricted		0	1,266
Total resources from Founding Partners		3,956,494	3,631,341
Other income:			
Sundry income & reimbursements		96,894	84,033
Total income	7	25,830,940	25,018,181
SOCIAL MISSION EXPENDITURE			
RESEARCH & DEVELOPMENT EXPENDITURE:	8		
Research & development coordination and supervision		2,017,738	1,687,659
Human African trypanosomiasis projects		5,794,051	7,308,575
Leishmaniasis projects		4,466,885	4,678,495
Chagas disease projects		3,811,913	2,356,588
Other diseases projects (malaria, helminths infections, paed. HIV)		2,397,430	2,217,335
Portfolio building		1,595,323	1,561,311
Total research & development expenditure		20,083,340	19,809,963
STRENGTHENING CAPACITIES	9	1,460,091	1,414,184
ADVOCACY EXPENSES	10	866,543	941,318
Total social mission expenditure		22,409,974	22,165,465
NON-SOCIAL MISSION EXPENDITURE			
Fundraising	10	1,484,841	1,174,883
General and administration	10	2,139,433	1,538,043
Total non-social mission expenditure		3,624,274	2,712,926
Total expenditure		26,034,248	24,878,391
Operating surplus		(203,308)	139,790
OTHER INCOME (EXPENSES)			
Financial income, net		34,323	30,453
Exchange gain, net		249,676	381,468
Total other income, net		283,999	411,921
Net surplus for the year prior to allocations		80,691	551,711
Allocation to restricted operating funds	6	(14,733)	(54,071)
Allocation to internally gener. unrestricted funds		(65,958)	(497,640)
Net surplus for the year after allocations		-	-



FUNDS FLOW STATEMENT

FOR THE YEAR ENDED 31 DECEMBER 2011 (with 2010 comparative figures)

<i>(expressed in EUR)</i>	2011	2010
FUNDS FLOW FROM OPERATIONS		
Net surplus for the year, unrestricted	65,958	497,640
Net surplus for the year, restricted	14,733	54,071
Depreciation of fixed assets	105,153	88,815
Increase (decrease) in provisions	(49,267)	18,863
(Increase) decrease in stocks	244	(46,041)
(Increase) decrease in advances	(18,951)	324,231
(Increase) decrease in receivables from donors	423,790	(1,245,615)
(Increase) decrease in Founding Partners and other receivables	(752,296)	1,059
(Increase) decrease in prepaid expenses	(304,428)	1,693
Increase (decrease) in payables	(485,247)	325,819
Increase (decrease) in accrued expenses	319,603	1,645,323
Increase (decrease) in deferred income	3,327,708	1,679,102
Funds flow from operations	2,647,000	3,344,960
FUNDS FLOW FROM INVESTING ACTIVITIES		
(Increase) decrease of investments in tangible fixed assets	(104,562)	(21,700)
(Increase) decrease in bank guarantee deposits	(3,170)	(5,050)
Funds flow from investing activities	(107,732)	(26,750)
FUNDS FLOW FROM FINANCING ACTIVITIES	-	-
Cash increase (decrease)	2,539,268	3,318,210
Cash and cash equivalents - beginning of year	17,087,010	13,768,800
Cash and cash equivalents - end of year	19,626,278	17,087,010

STATEMENT OF CHANGES IN CAPITAL

FOR THE YEAR ENDED 31 DECEMBER 2011

Internally generated funds <i>(expressed in EUR)</i>	Opening balance	Allocation	Internal fund transfers	Closing balance
Paid-in capital	32,510	-	-	32,510
Surplus for the year	-	80,691	(80,691)	-
Restricted operating funds	205,155	-	14,733	219,888
Internally generated unrestricted funds	9,951,688	-	65,958	10,017,646
Capital of the organization	10,189,353	80,691	-	10,270,044

NOTES TO THE FINANCIAL STATEMENT

FOR THE YEAR ENDED 31 DECEMBER 2011

1. GENERAL INFORMATION

a) Legal aspects

The Drugs for Neglected Diseases *initiative* (DNDi) is a Swiss foundation, established as a not-for-profit legal entity, registered in Geneva under statutes dated 17 July 2003. DNDi is managed by a Board, an Executive Director, and six senior managers. In 2011, a seventh senior manager position was created to complete the Executive team.

With its headquarters in Geneva, DNDi aims to:

- 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 patient 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.

As with all Swiss foundations, DNDi is monitored by the Swiss Federal Supervisory Board for Foundations.

b) Income tax

DNDi is exonerated from income tax from the Swiss federal income tax and from the Geneva cantonal and communal taxes for a five-year period commencing 2003, which was renewed in September 2008 for a period of ten years until 2018.

c) Situation of Regional Offices (RO) and Affiliate

DNDi has seven Regional Offices and Affiliates to help identify patient needs, support heads of disease programmes, identify and support regional partners, and undertake regional advocacy work for DNDi. These offices, together with regional networks, ensure the participation of disease-endemic countries notably in clinical and post-clinical activities and foster South-South collaboration. In addition, Regional Offices can explore fundraising opportunities in their regions. Their tasks and duties are further developed in the DNDi Business Plan. Regional Offices (ROs) are usually hosted by a Founding Partner, often at no cost, and are represented by an experienced senior person as the RO Director, bearing a consultant contract with DNDi. For local or operational reasons, DNDi may deem necessary to establish the RO as a legal entity, usually a branch of DNDi Foundation or a corporation following needs and local regulations

and requirements. Establishment of a DNDi legal entity outside Switzerland requires the authorization of the Board of Directors.

As of December 2011, DNDi has established legal entities in Kenya (in 2006), in Brazil (in 2008), and in India (2009) in the form of branches. The fourth DNDi RO is in Penang, Malaysia and is still in the process of being registered there as a branch. Additionally, DNDi has one Liaison Office in the Democratic Republic of Congo. RO accounting is fully incorporated into DNDi accounts.

In June 2009, the Board of Directors approved the creation of a Regional 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.

The aim of DNDi Japan is exclusively charitable, and includes but shall not be limited to: assisting people in developing countries who are suffering from tropical diseases and contributing to the health and welfare of people in developing countries by supporting activities of the Drugs for Neglected Diseases *initiative* (DNDi) by promoting medical treatment; encouraging scientific research; and liaising, advising, and assisting entities performing these activities. The DNDi Japan Board of Directors met in February 2011.

DNDi Japan presents an annual report comprising the financial statements of the calendar year. This report is certified by an independent Certified Public Accounting (CPA) firm selected by its Board of Directors. The firm auditing DNDi Japan accounts in 2011 is Deloitte Touche Tohmatsu LLC Tokyo, Japan.

Start-up funding is provided via annual grants from DNDi and is accounted for in the DNDi financial statements by combining DNDi Japan accounts following the method of full integration (i.e. all income and expenditures are incorporated in the DNDi financial statement).

DNDi Japan's 2011 financial position as of 31 December 2011 is the following:

- Total liabilities and net assets: JPY 1,620,608
- Total revenue: JPY 12,536,494 which represents a grant from DNDi to DNDi Japan;
- Of this grant, there is JPY 0 carried forward for 2012.

Affiliate: 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.



The purposes for which it was formed are exclusively charitable and educational and include conducting activities to support or benefit the Drugs for Neglected Diseases *initiative* (DNDi), such as conferring grants to support programmes, projects, and activities to stimulate and support research and development of drugs for neglected diseases and raising awareness in the region about the need for increased research and development for neglected diseases.

DNDi NA presents an annual report comprising the financial statements of the calendar year. This report is certified by an independent Certified Public Accounting (CPA) firm selected by its Board of Directors. The firm auditing DNDi NA accounts as of 2008, is Tait, Weller & Baker LLP, Philadelphia, Pennsylvania, USA.

Start-up funding is provided via annual grants from DNDi and is accounted for in the DNDi financial statements by combining DNDi NA accounts following the method of full integration (i.e. all income and expenditures are incorporated in the DNDi financial statement).

DNDi NA's 2011 financial position as of 31 December 2011 is the following:

- ▶ Total liabilities and net assets: USD 184,892;

- ▶ Total revenue and other support: USD 1,924,059, of which a total grant from DNDi to DNDi NA, amounting to USD 672,970 and contributions (unrestricted) from individuals and private foundations (restricted) ranging from USD 25 to 1,102,830 for a total of USD 1,175,873. One donor provided approximately 57% of the total contributions, including seed funding from DNDi NA;
- ▶ Total expenses: USD 1,855,446, and an excess of revenue over the expenses (change of net assets) of USD 68,613.

In June 2009, the Board of Directors approved the change in legal status of DNDi in Brazil from a branch to a not-for-profit legal entity under the form of Associação de direito privado, sem fins lucrativos e de fins não econômicos, DNDi Latin America. The process was terminated during the first semester 2010.

Lastly, a legal entity has been set up in France in the form of a not-for-profit association for administrative purposes in September 2004, this legal entity is not a Regional Office.

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;
- f) Performance report.

These financial statements present all activities by the Foundation. A list of in-kind income and expenditures is disclosed in Note 12.

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 incurred 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:

	2011	2010
USD	0.7728	0.7496
CHF	0.8212	0.8006
GBP	1.1913	1.1597
100 CDF	0.0821	0.0801
100 INR	1.4536	1.6733
100 KES	0.9116	0.9287
100 JPY	0.9962	0.9210
100 BRL	41.4388	45.0999

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.

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, one or more 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 exceeding EUR 50,000, as detailed in the agreement signature process. Thereafter, funds are allocated to the partner(s) in charge of the project. Expenditures are recorded:

- a) according to a financial report presenting expenditures incurred during the year on an accrual basis; or
- b) if financial reports are unavailable as per the deadline of the 15 March of the following year, an estimated amount is calculated on a prorata temporis basis, based on the time between the contract signing date and 31 December. 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 are approved by the Board. They include funding for projects subcontracted to partners and current expenditures required to achieve the objectives for the year. A budget revision is approved by the Board at mid-year. All expenditures incurred on behalf of a project or for any activity of DNDi are recorded on an accrual basis.

i) Credit 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. The maximum exposure is primarily represented by the carrying amounts of the financial assets in the balance sheet, including accounts receivable and cash.

j) Tangible fixed assets

Tangible fixed assets are stated at cost 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 four guarantees representing three deposits related to office rental in Tokyo and New York, and parking rental in Geneva; and a letter of guarantee pertaining to the Geneva premises. It is recoverable, subject to prevailing contract terms, upon vacating the premises.

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.
- They must be recognizable as a visible contribution to DNDi's projects and activities, benefit DNDi, and be in-line with DNDi's mission and objectives.
- A partner's voluntary involvement in joint projects and activities, in particular if the Partner does not aim to achieve DNDi's project objectives, is not considered a gift-in-kind.
- For goods or services paid at prices below market prices, the difference between real payment and current market price is not considered a gift-in-kind, but the current market price reached after negotiations.
- Fair market value is defined as the price DNDi would have paid to utilize the good 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 RPC 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. DRUG INVENTORY

In 2011, DNDi purchased vials of SSG, AmBisome®, paromomycin (PM) and caps of miltefosine 10mg and 50mg for an estimated value of EUR 65,000 from various partners (IDA Foundation, Gilead, Gland Pharma, and Paladin), for use in the ongoing clinical trials

and the SSG&PM combination pharmaco-vigilance programme. Stocks of SSG, AmBisome®, miltefosine, and paromomycin at an estimated value of EUR 80,797 are stored at clinical trial sites in Ethiopia, Kenya, Sudan, Uganda, and Bangladesh.

Countries / drugs	Vials			Caps		Total in EUR
	SSG	AmBisome®	Paromomycin	Miltefosine 50mg	Miltefosine 10mg	
Uganda	1,201	280	2,620			11,935
Ethiopia	2,177	821		3,024		25,328
Kenya	852	453		2,077	832	12,899
Sudan	3,818	500	1,490	1,359	1,740	30,635
Total vials/caps	8,048	2,047	4,110	6,460	2,572	
Total in EUR	41,447	27,751	3,085	5,942	2,572	80,797

4. TANGIBLE FIXED ASSETS, net

<i>(expressed in EUR)</i>	Computer Equipment	Office fittings & Installations	Office Equipment	Total
Net carrying amounts 1.1.2010	34,186	48,162	70,820	153,168
Gross values of cost				
Beginning of the period 1.1.2010	209,998	126,485	137,261	473,744
Additions	16,358	5,342	-	21,700
Disposals	-	-	-	
End of the period 31.12.2010	226,356	131,827	137,261	495,444
Accumulated depreciation				
Beginning of the period 1.1.2010	(175,812)	(78,324)	(66,441)	(320,577)
Change of the year	(36,616)	(22,996)	(29,204)	(88,816)
End of the period 31.12.2010	(212,428)	(101,320)	(95,645)	(409,393)
Net carrying amounts 31.12.2010	13,928	30,507	41,616	86,051
Net carrying amounts 1.1.2011	13,928	30,507	41,616	86,051
Gross values of cost				
Beginning of the period 1.1.2011	226,357	131,828	137,260	495,445
Additions	77,811	6,697	20,053	104,561
Disposals				
End of the period 31.12.2011	304,168	138,525	157,313	600,006
Accumulated depreciation				
Beginning of the period 1.1.2011	(212,428)	(101,320)	(95,645)	(409,393)
Change of the year	(48,834)	(22,300)	(34,019)	(105,153)
End of the period 31.12.2011	(261,262)	(123,620)	(129,664)	(514,546)
Net carrying amounts 31.12.2011	42,906	14,905	27,649	85,460

5. PROVISIONS

<i>(expressed in EUR)</i>	Provision for taxes	Provision for HR expenses (holidays not taken)	Provision for running expenses (other)	Total
Carrying period as per 1.1.2010	140,408	65,718	23,624	229,750
Creation	42,963	75,624	14,588	133,175
Utilization	(24,507)	(62,985)	(26,819)	(114,311)
Reversal	-	-	-	-
Carrying period as per 31.12.2010	158,864	78,357	11,393	248,614
Carrying period as per 1.1.2011	158,864	78,357	11,393	248,614
Creation		73,815	9,818	83,633
Utilization	(45,840)	(75,624)	(11,435)	(132,899)
Reversal	-	-	-	-
Carrying period as per 31.12.2011	113,024	76,548	9,776	199,348



6. ROYALTIES

In December 2004, DNDi signed an agreement with sanofi-aventis, a pharmaceutical company (currently 'Sanofi'), pertaining to the implementation of co-formulation treatments against malaria developed originally by DNDi together with sanofi-aventis (ASAQ). 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 pharmaco-vigilance projects or activities such as the implementation of the ASAQ treatment in developing countries, notably in Africa.

The 3% royalties on the 2010 sales of CoArsucam® amounting to EUR 56,693 were allocated as follows: EUR 41,960 to the Artesunate + Amodiaquine (FACT-ASAQ in Africa) project; EUR 14,733 to the Restricted operating fund, which will be used for collaborative projects with various partners for observational studies and other access related expenses in Africa and in Asia. The total amount of this restricted fund amounted to EUR 219,888 as per 31 December 2011.

7. INCOME

a) Cumulative donations committed to DNDi and/or received by 2011 (in EUR)

DONORS		Total Commitment (in currencies)*	Total Commitment (in EUR)	As per Statement of Operations 2011 (in EUR)	To be used after 2011 (in EUR)
Médecins Sans Frontières	EUR	44,854,973	44,854,973	3,956,494	8,775,360
Bill & Melinda Gates Foundation	USD	59,016,944	43,720,379	7,087,764	18,449,534
UK Government DFID**	GBP	27,881,529	33,890,896	7,559,349	4,765,738
Dutch Government DGIS	EUR	16,975,000	16,975,000	2,000,000	12,000,000
Spanish Government AECID	EUR	12,000,000	12,000,000	1,000,000	1,000,000
French Government MAEE / AFD***	EUR	9,255,000	9,255,000	585,259	0
German Government	EUR	9,000,000	9,000,000	401,439	7,598,561
Swiss Government SDC	CHF	4,120,000	3,202,691	837,402	821,200
Wellcome Trust UK	EUR	1,999,801	1,999,801	719,497	1,280,304
USA Government NIH/NIAID	USD	2,488,363	1,833,189	326,810	716,636
Medicor Foundation	EUR	1,719,424	1,719,424	359,179	0
European Union, FP5, FP6, FP7, EDCTP	EUR	1,216,134	1,216,134	326,583	191,543
Canton of Geneva	CHF	1,600,000	1,117,401	161,624	164,240
UBS Optimus Foundation	CHF	1,250,000	791,045	0	0
Global Fund (AMFM)	EUR	518,205	518,205	258,638	98,399
Various private donors	EUR	436,417	436,417	97,315	4,661
Sandoz Family Foundation	CHF	500,000	308,700	0	0
Sasakawa Peace Foundation	EUR	241,336	241,336	0	0
Tuscany Region	EUR	200,000	200,000	0	0
Various other donor(s)	EUR	170,060	170,060	0	0
Starr International Foundation	USD	200,000	141,388	0	0
Anonymous donation	CHF	201,229	138,108	0	0
Total Donations (EUR)*			183,730,147	25,677,353	55,866,176

* Exchange rates used for 'Total Commitment in EUR' and 'As per Statement of Operations 2011', are real exchange rates following the DNDi exchange rate policy. Exchange rates used for 'To be used after 2011', appear in EUR at the USD/EUR, CHF/EUR and GBP/EUR exchange rates as per 31.12.2011 (see note 2). 'Total Donations' therefore yields an approximate value as exchange will vary over time.

** The UK Government, DFID, funded DNDi with 4 grants. A first unrestricted grant of 6,500,000 British pounds in 2006 for the period 2006 – 2008, a second unrestricted grant of 18,000,000 British pounds in 2009 for the period 2009 – 2013, a third restricted grant of 1,381,529 British pounds in 2010 for the period 2010 – 2011, and a fourth restricted grant of 2,000,000 British pounds in 2011 for 2011.

*** The French Government, Ministry of Foreign and European Affairs, funded DNDi with 4 grants. From the MAEE: EUR 5,955,000 in April 2007 for the period 2007-2010; from the MAEE: EUR 1,300,000 in December 2009 for the period 2009-2011; from the AFD: EUR 1,500,000 in June 2006 for the period 2006-2008 & from the AFD EUR 500,000 in December 2009 for the period 2009-2010.

b) Funding per project (restricted and unrestricted)

		Operational Income							
(expressed in EUR)		UK Government DFID ¹ (Restricted/ Unrestricted)	French Government MAEE (Restricted) ²	Spanish Government AECID (Unrestricted)	Dutch Government DGIS (Restricted)	German Government KfW-BMBF (Restricted) ³	United States Government NIH (Restricted) ⁴	Switzerland SDC (Unrestricted)	Switzerland Canton of Geneva (Restricted)
Clinical & Post-Clinical	FACT (ASAQ & ASMQ fixed dose) for Malaria	1,306,463							
	Nifurtimox + Eflornithine co-administration (NECT) for HAT	84,677		788				120,227	141,352
	Combination therapies/ new treatment for VL (Asia, Africa, Latin America)	431,666		137,911	582,628	54,703		354,393	
	Fexinidazole for HAT					6,657			
	Azole E1224 & Biomarker for Chagas	133,727		41,778	166,347				
	Benznidazole Paediatric dosage form for Chagas								
Pre-clinical	Alternative formulations of Amphotericin B for VL						166,178		
	Oxaborole SCYX 7158 (& Back-up) for HAT	152,695	1,523		103,520	10,351	735		
	Nitroimidazole (& Back-up) for VL	43,661				107,332			
	Flubendazole Macrofilaricide for Helminths								
	K777 for Chagas						119,236		
	Paediatric HIV (Exploratory)								
Discovery	VL Consortium Lead Optimization	171,975				15,649			
	Chagas Consortium (Including Fenarimol series) Lead Optimization	343,612	135,108	299,800	347,771	146,847			
	HAT Consortium Lead Optimization	638,420	194,854			2,098			
	Discovery & Exploratory activities	639,510	252,227		162,483	2,586			
	Exploratory CL	184,492		35,064					
	R&D Coordination, Supervision costs	844,523		131,256	240,582	11,686	27,252	88,436	
	HAT LEAP & Chagas Platforms	187,070		43,892	116,111	7,170		71,843	18,643
	Other Strengthening Capacity activities	473,007		13,388				55,973	
	Advocacy	687,645		80,161				33,953	
	Fundraising	468,940		115,321	153,854	11,566			
	General Management	767,266	1,547	100,641	126,704	24,794	13,409	112,577	1,629
	Net surplus allocated to restricted funds								
	Net surplus allocated to unrestricted funds								
	TOTAL Income	7,559,349	585,259	1,000,000	2,000,000	401,439	326,810	837,402	161,624

(1) DFID grants include: 1) An unrestricted grant of EUR4,579,526; 2) A restricted grant of EUR667,675 for Malaria projects (Jan-Mar 2011); 3) An unrestricted grant of EUR2,312,148 covering the period Oct-Dec 2011 only.

(2) MAEE restricted grant in 2011 was of EUR585,259 for discovery projects (Jan-Dec 2011), which finalises the allocation of the EUR1,300,000 contribution started in December 2009.

(3) German Government KfW-BMBF restricted multi year grant started as of December 2011 with an amount of EUR401,439.

(4) NIH grants include two multi year grants: 1) A restricted grant with a no cost extension for the entire year 2011 of EUR191,393 for Alternative formulations of Amphotericin B for VL project; 2) A restricted grant of EUR135,417 for K777 for Chagas project.

(5) AmfM - Global Fund include one restricted grant with a contract that has been amended and increased in 2011 with a total amount of EUR258,638.

(6) B&M Gates Foundation include five restricted grants in 2011: 1) A grant of EUR3,648,271 pertaining to Lead Optimization /Preclinical for HAT & VL & Nitroimidazole for VL projects; 2) A grant of EUR2,259,746 for Fexinidazole for HAT project; 3) A grant of EUR679,930 for new VL treatments in Asia project covering the period July to



e (Grand TOTAL = 25'830'940)									Financial income (Net) =283,998	TOTAL Expenses =26,034,048
AMfM - Global Fund (Restricted) ⁵	European Union EU FP7 (Restricted)	European Union EDCTP (Restricted)	Bill & Melinda Gates Foundation (Restricted) ⁶	Médecins S. Frontières (Restricted/Unrestricted) ⁷	Wellcome Trust (Restricted) ⁸	Medicor Foundation (Restricted) ⁸	Private Foundations, Individuals & Other Revenues (Restricted/Unrestricted) ⁹	Royalties on drug sales ¹⁰		
235,578		223,527		87,826			8,739	41,960		1,904,093
										347,044
			581,622	88,138		286,423	21,289			2,538,774
			2,030,994	5,420						2,043,071
				73,928	682,316		1,745			1,099,841
				466,080			35,539			501,619
										166,178
			935,166				60,867			1,264,857
			501,484	116,442						768,919
			196,297							196,297
				184						119,420
				292,630			82			292,712
			789,912	15,449			29			993,014
				801,658			16,237			2,091,033
			1,222,698	80,883			126			2,139,079
			178,196	144,184			149			1,379,335
	760									220,316
	1,929		140,937	523,497			7,640			2,017,738
			8,955	10,620	37,181	41,209				542,694
	65,693		23,460	285,876						917,397
			9,919	53,469			1,396			866,543
			52,638	678,177			4,345			1,484,841
23,060	11,167	23,507	415,486	232,033		31,547	36,026		218,040	2,139,433
								14,733		
									65,958	
258,638	79,549	247,034	7,087,764	3,956,494	719,497	359,179	194,209	56,693	283,998	

December 2011; 4) A grant of EUR269,259 for Flubendazole Macrofilaricide for Helminths project covering the period April to December 2011; 5) A grant of EUR200,558 for Screening NTD covering the period November to December 2011

(7) MSF include 4 grants in 2011: 1) An unrestricted grant of EUR3,091,937; 2) A restricted grant of EUR300,000 for Benznidazole Paediatric dosage form for Chagas project; 3) A restricted grant of EUR350,000 for Paediatric HIV (Exploratory) project; 4) A restricted grant of EUR214,557 for Benznidazole Paediatric dosage form for Chagas project.

(8) Wellcome Trust restricted multi year grant started as of April 2011 with an amount of EUR719,497.

(9) Private Foundations: ABT Association (EUR35,538); Buck Foundation (EUR17,516); Fondation ARPE (EUR8,739). Other Revenue: various individual donations for a total of EUR35,522, of which EUR33,810 come from North America and EUR1,711 come from Geneva. In addition Geneva has collected various reimbursements and participations of partners all along the year for a total amount of EUR96,894.

(10) Royalties from Sanofi for EUR56,693 earmarked to Monitoring study on pharmacovigilance of ASAQ (see note 6).

8. R&D PROJECTS RELATED EXPENDITURE

Recognized in <i>(expressed in EUR)</i>	2011	2010
CLINICAL/POST-REGISTRATION PROJECTS		
Artesunate + Amodiaquine (Malaria) ¹	649,207	678,703
Artesunate + Mefloquine (Malaria) ²	1,254,886	1,538,633
Nifurtimox - Eflornithine co-administration for stage ² T.b.gambiense (HAT) ³	347,044	500,066
Fexinidazole for (HAT) ⁴	2,043,071	2,662,577
Combination therapy (VL) in Africa ⁵	1,599,592	1,945,443
Combination therapy (VL) in Latin America ⁶	123,316	60,593
Combination therapy (VL) in Asia ⁶	815,866	841,405
Paediatric Benznidazole (Chagas) ⁷	501,619	403,882
Azole E1224 & Biomarkers (Chagas) ⁸	1,099,841	467,060
Total Clinical/Post-Registration Projects	8,434,442	9,098,362
PRE-CLINICAL PROJECTS		
Alternative formulations of Amphotericin B (VL) ⁹	166,178	181,302
Drug combination for Chagas ¹⁰	0	18,909
Oxaborole SCYX7158 (HAT) ¹¹	1,264,857	873,837
Nitroimidazole (VL) ¹²	768,919	397,432
Nitroimidazole backup (HAT)	0	34,620
K777 for Chagas ¹³	119,420	0
Flubendazole Macrofilaricide (Helminth) ¹⁴	196,297	0
Paediatric HIV (exploratory)	292,712	0
Total Preclinical Projects	2,808,383	1,506,100
DISCOVERY (SELECTION & OPTIMIZATION) PROJECTS		
Screening Resources (Dundee, Eskitis, IPK) ¹⁵	932,539	1,139,512
Reference Screening Centers (STPH, LSHTM, Antwerp) ¹⁶	442,467	336,945
Lead Optimization (HAT) Consortium ¹⁷	2,139,079	3,272,096
Lead Optimization (VL) Consortium ¹⁸	993,014	1,179,856
Lead Optimization (Chagas) Consortium ¹⁹	2,091,033	1,424,095
Total Discovery Projects	6,598,132	7,352,504
OTHER EXPLORATORY ACTIVITIES TO BUILD THE PORTFOLIO		
Other exploratory activities	224,645	165,338
Total Exploratory projects	224,645	165,338
PROJECT-RELATED VARIABLE EXPENDITURE		
Coordination & Supervision ²⁰	2,017,738	1,687,659
Total of Projects related expenditure	20,083,340	19,809,963



Main R&D Partners & Subcontractors

1. Sanofi, France / Medicines for Malaria Venture, Switzerland / National Centre for Research and Development on Malaria, Burkina Faso / Universiti Sains Malaysia / Institute of Research for Development (IRD), Senegal / Mahidol University, Thailand / Ellipse Pharmaceuticals, France / Médecins Sans Frontières / Epicentre, France / 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 / Komfo Anokye Teaching Hospital (KATH), Ghana.

2. Shoklo Malaria Research Unit, Thailand / Universiti Sains Malaysia / Indian Council of Medical Research (ICMR), India / Epicentre, France / Centre Hospitalier Universitaire Vaudois (CHUV), Switzerland / National Institute of Medical Research, Tanzania; Kenya Medical Research Institute (KEMRI), Kenya / Centre National de Recherche et de Formation sur le Paludisme (CNRFP), Burkina Faso / Cipla, India.

3. Epicentre, France; Médecins Sans Frontières (MSF) / Swiss Tropical and Public Health Institute (Swiss TPH) / National Trypanosomiasis Control Programmes of the Republic of Congo and the Democratic Republic of the Congo (DRC) / HAT Platform partners (PNLTH, the Republic of Congo / TMRI Sudan / ICCT, Angola / COCTU, Uganda / PNLTHA Centrafrique / PNLTHA Chad).

4. Sanofi, France / Swiss TPH / HAT Platform partners (see point 3 above) / Aptuit, UK / Accelera, Italy / SGS, Belgium and France / Epicentre, France / Covance, UK / Phinc Development, France / XCentipharm, France / Cardinal Systems, France.

5. Kenya Medical Research Institute, Kenya / Institute of Endemic Diseases (IED) and University of Khartoum, Sudan / Addis Ababa University, Ethiopia / Gondar University, Ethiopia / University of Makerere, Uganda / Amudat Hospital, Uganda / LSHTM, UK / ASK (AMC, Slotervaart Hospital, KIT), The Netherlands / GILEAD, Ireland / IDA Foundation, The Netherlands / OneWorld Health (OWH), USA / Institute of Tropical Medicine-Antwerp, Belgium / Médecins Sans Frontières, The Netherlands.

6. GVK, India / Sitaram Kala Azar Medical Centre, India / RMRIMS (ICMR), India / ICDDR,B, Bangladesh / SHSMC, Bangladesh / SK Hospital Bangladesh.

7. Pharmaceutical Laboratory of Pernambuco State (LAFEPE), Brazil / Centro Nacional de Diagnostico e Investigacion de Endemo-epidemias (CeNDIE) / LAT Research, Argentina / FITEC, Argentina.

8. Eisai Co., Ltd., Japan / Cardinal Systems, France / CRESIB, Spain / CEADES, Bolivia / CONICET, Argentina.

9. Polytherics, UK / London School of Pharmacy, UK / LSHTM, UK.

10. Federal University of Ouro Preto, Brazil.

11. SCYNEXIS, USA / Advinus Therapeutics, India / Drugabilis, France / Penn Pharma, UK.

12. TB Alliance, USA / Advinus Therapeutics, India.

13. Harlan, Switzerland / University of California in San Francisco (UCSF), USA.

14. Michigan State University, USA / McGill University, Canada / Drugabilis, France / Accelera, Italy / MSU, USA.

15. Eskitis Institut at Griffith University, Australia / Institut Pasteur Korea, South Korea / University of Washington, USA / Swiss TPH, Switzerland / GlaxoSmithKline (GSK-Tres Cantos), Spain / University of Dundee, UK.

16. Swiss TPH, Switzerland / LSHTM, UK / Institute of Tropical Medicine-Antwerp, Belgium.

17. SCYNEXIS, USA / Pace University, USA / WuXi, China / Drugabilis, France.

18. Advinus Therapeutics, India / TB Alliance, USA.

19. Epichem Pty Ltd, Australia / Murdoch University, Australia / Monash University, CDCO, Australia / WuXi, China / Institute of Tropical Medicine-Antwerp, Belgium.

20. R&D Coordination & Supervision in EUR

	2011	2010
Coordination	1,151,350	888,695
Scientific Advisory Committee	113,567	99,209
Business Development	420,761	377,565
Japan representation office	234,291	206,835
Research: IP & Regulatory affairs	97,769	115,355
Total	2,017,738	1,687,659

Consultants involved in R&D projects in alphabetical order:

Amuasi, John; Ansong, Daniel; Barros Gonçalves, Luciana; Baker, William; Bennett, John; Blay Nguah, Samuel; Bray Michael; Bruning, Karin; Daher, André; Dormeyer, Mathias; Dorre, Daniel; Espinoza, Emilia; Fernandes, Jaime; Ferreira Crato, Marguerite; Ghabri, Salah; Grislain, Luc; Hailu, Asrat; Holst, Marylise; Hudson, Alan; Khalil, Elthahir; Mazue, Guy; Mechali, Daniel; Moody, Anthony; Musa Mudawi, Ahmed; Pinheiro, Eloan; R.K. Singh; Sasella, Daniela; Scherrer, Bruno; Schijman, Alejandro; Seltzer, Jonathan; Smithuis, Frank; Sosa-Estani, Sergio; Taylor, Bob; Thenot, Jean-Paul; Tweats, David; Vaillant, Michel; Von Geldern, Thomas; Yardley, Vanessa; Zijlstra, Ed; Zwang, Julien.

East African Clinical Site Monitors: Bedru, Kinoti, Mwangi, Okello, Ogeti, Waweru.

Additional partners involved in DNDi R&D projects without financial implications:

Cipla, India; Oxford University, UK; WHO-TDR; Fiocruz-Farmanguinhos, Brazil; Genzyme, USA; Hospital de Ninos Ricardo Gutierrez, Argentina; Institut René Rachou, Brazil; Novartis Institute for Tropical Diseases NITD, Singapore; Pfizer, USA; University of Auckland, New Zealand; Universidade Federal do Piaui, UFP, Brazil; Universidade Federal de Tocantins, Brazil; Ministry of Health, Kenya / Federal Ministry of Health, Sudan / Federal Bureau of Health, Ethiopia / Ministry of Health, Uganda / Oxford University, UK / Université de Bordeaux, Faculté de Pharmacie, France / Univesidade de Brasilia (UNB), Brazil / CNPq, Brazil / Ministério de Salud, Provincia de Jujuy, Argentina / Centro de Chagas y Patologia Regional, Argentina / CONICET, Argentina / Ministry of Health, Argentina / University of Liverpool, UK / Hospital de Niños Ricardo Gutierrez, Argentina / Instituto Nacional de Parasitología, Dr M Fatale Chabén, Argentina / Hospital de Niños de Jujuy, Argentina / Hospital Público Materno Infantil – Salta, Argentina.

9. STRENGTHENING CAPACITIES EXPENDITURE

DNDi expenditures on strengthening existing capacities in developing countries aim 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)	2011	2010
Regional Offices: Brazil, India, Kenya, Malaysia	842,514	716,615
For VL combo, Ward Construction & Equipment in Ethiopia and in Sudan	0	78,654
Leishmaniasis East Africa Platform (LEAP)	151,760	155,355
Human African Trypanosomiasis (HAT) Platform	273,552	207,075
Chagas Clinical Research Platform	117,382	118,526
LeishDNAvac Consortium Agreement	74,883	99,183
Pan-Asian Natural Substances Network	0	38,776
TOTAL	1,460,091	1,414,184

Consultants: Cecilia Castillo, Gabriela Chaves, Vanessa Daniel-Boscoraj, Gan Eng Seong, Michel Lotrowska.

HAT Platform: WHO, Ministries of Health National Control Programmes of the major endemic countries (Angola, Democratic Republic of the Congo, Republic of Congo, Sudan, Uganda, Chad, and the Central African Republic), Swiss Tropical and Public Health Institute, Médecins Sans Frontières, DNDi.

Leishmaniasis East Africa Platform: University of Khartoum, Sudan; Addis Abeba University, Ethiopia; Makerere University, Uganda; Kenya Medical Research Institute; Ministries of Health of Kenya, Uganda, Ethiopia, and Sudan; London School of Hygiene and Tropical Medicine, UK; Médecins Sans Frontières; AMC-Slotervaart Hospital-KIT, The Netherlands; i+ Solutions, The Netherlands; DNDi.

10. ADVOCACY, FUNDRAISING AND GENERAL & ADMINISTRATION EXPENSES

(expressed in EUR)	ADVOCACY		FUNDRAISING		GENERAL & ADMINISTRATION	
	2011	2010	2011	2010	2011	2010
Human resources	453,778	487,445	1,170,773	919,307	1,215,285	938,799
Office charges	45,079	47,950	74,397	66,778	106,550	95,132
Travel expenses	39,506	29,072	86,787	46,559	141,789	103,848
Administration	26,861	31,820	86,989	92,905	284,561	160,719
IT & telecommunications	23,548	18,242	24,139	14,644	248,619	177,921
Communication	265,659	301,518	28,086	24,032	112,037	37,730
Depreciation	11,567	11,546	13,670	10,658	27,340	23,092
Other	545	13,725	0	0	3,253	802
TOTAL	866,543	941,318	1,484,840	1,174,883	2,139,433	1,538,043

Consultants: Samantha Bolton, Nina Holzhauser, Nicolette Jackson, Louie Karly, Ivan Maillet, Masako Matsudaira, Thomas Saugnac, Daniel Stein, Marta Lucas Subirats, Hans Van de Werde, Ulrike Von Pilar, Susan Wells.



11. INDEMNITIES & REMUNERATIONS GIVEN TO DIRECTORS

All members of the Board are appointed on a voluntary basis. The Board members have not received any remuneration for their mandate in 2011, nor in 2010.

12. VALUATION OF 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 zero cost as gifts-in-kind (see note 2.o, DNDi In-Kind Policy). DNDi aims at reflecting this increasing contribution in the 2011 financial statements in order to present a comprehensive picture of its activities. The In-Kind contribution of DNDi's partners was raised between 2010 and 2011 from EUR 2,300,000 in 2010 up to EUR 5,000,000 in 2011.

Gifts-in-kind in EUR evaluated for the year 2011 per category and per project:

<i>(expressed in EUR)</i>	Staff Scientific	Staff non-Scientific	R&D Services	Office, furniture & admin.	TOTAL
Lead Optimization (Chagas) Consortium	69,518	4,085	230,222		303,824
Screening Resources	513,596	14,923	318,840		847,359
Fexinidazole (HAT)	150,000		30,000		180,000
Flubendazole macro- filaricide (helminths)	410,440				410,440
Regional Offices	75,193	17,518		80,482	173,193
Combination therapy (VL)	116,485	86,661	42,927		246,073
Azole E1224 (Chagas)	1,071,731	120,333	1,640,036		2,832,101
Advocacy (Partners' meeting)		21,101			21,101
TOTAL	2,406,964	264,620	2,262,024	80,482	5,014,090

Main In-kind contributors: Eisai, Japan; Abbott, USA; Sanofi, France; CNPq-Brasilia University, Brazil; ARC-Australian Research Council, Australia; Dundee University, Scotland; University Federal Ouro Preto, Brazil; GSK, France; FIOCRUZ, Brazil; Epichem Pty Ltd, Australia; ICMR, India; KEMRI, Kenya; IDEC Inc, Japan; LAFEPE, Brazil

13. ASSETS PLEDGED AS GUARANTEE FOR COMMITMENTS

At year-end, a bank of the Foundation had provided two rental letters of guarantee of CHF 70,000 (EUR 57,484) and CHF 20,000 (EUR 16,424) in favour of a third party. Cash for an equivalent amount is pledged at the corresponding bank.

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, statement of operations, funds flow statement, statement of changes in capital and notes, presented on pages 63 to 77, for the year ended December 31, 2011. In accordance with Swiss GAAP FER 21, the content of the performance report is not audited.

Board's Responsibility

The Board is responsible for the preparation and the fair presentation of the financial statements in accordance with Swiss GAAP FER and 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 December 31, 2011 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.

Audit.Tax.Consulting.Corporate Finance.
Member of Deloitte Touche Tohmatsu



Drugs for Neglected Diseases initiative (DNDi)
Report of the statutory auditor
for the year ended
December 31, 2011

Report on other legal requirements

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

In accordance with article 728a paragraph 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

Peter Quigley
Licensed audit expert
Auditor in charge

Jürg Gehring
Licensed audit expert

Geneva, May 16, 2012

THANKS

DNDi would like to thank the following donors for supporting its activities since July 2003:

PUBLIC INSTITUTIONAL DONORS

- Department for International Development (DFID) / United Kingdom
- Dutch Ministry of Foreign Affairs (DGIS) / The Netherlands
- European Union – Framework Programmes 5, 6, and 7
- European and Developing Countries Clinical Trials Partnerships (EDCTP) with co-funding from Member States / International
- Federal Ministry of Education and Research (BMBF) through KfW / Germany
- French Development Agency (AFD) / France
- The Global Fund to Fight AIDS, Tuberculosis and Malaria (AMFm) / International
- German International Cooperation (GIZ) on behalf of the Government of the Federal Republic of Germany / Germany
- Ministry of Foreign and European Affairs (MAEE) / France
- National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID) / USA
- Region of Tuscany / Italy
- Republic and Canton of Geneva / Switzerland
- Spanish Agency of International Cooperation for Development (AECID) / Spain
- Swiss Agency for Development and Cooperation (SDC) / Switzerland
- United States Agency for International Development (USAID), via the 4th Sector Health Project implemented by Abt Associates, Inc. / USA

PRIVATE DONORS

- Bill & Melinda Gates Foundation / USA
- Médecins Sans Frontières (Doctors without Borders)
- Wellcome Trust / United Kingdom
- Fondation André & Cyprien / Switzerland
- Fondation ARPE / Switzerland
- Fondation de bienfaisance de la banque Pictet / Switzerland
- Fondation Pro Victimis / Switzerland
- Guy's, King's and St Thomas, Giving Week / UK
- Leopold Bachmann Foundation / Switzerland
- Medicor Foundation / Liechtenstein
- Peter and Carmen Lucia Buck Foundation / USA
- Sasakawa Peace Foundation / Japan
- Starr International Foundation / Switzerland
- UBS Optimus Foundation / Switzerland
- Steve Rabin
- Jonathan Winslow
- Other private foundations and individuals who would like to remain anonymous

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BEST
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