

STRENGTHENING EXISTING CAPACITIES

EXPANDING AND CONSOLIDATING CLINICAL RESEARCH CAPACITIES

In line with its vision and mission, DNDi has worked closely with partners in disease-endemic countries to strengthen existing clinical research capacity and build new capacity where necessary.

The year 2015 has been a time for consolidation of the three existing platforms – LEAP, HAT Platform, and CCRP, which have been highly involved in clinical studies, treatment access, and personnel training – as well as of the recently created RedeLEISH network, which took off with a dense programme of activities mainly for R&D for cutaneous leishmaniasis.

DNDi has always been committed to putting in place processes that, if successful, will ensure a wide-spread distribution of new treatments, and maintain competitive prices, such as by the development of non-patented products. The technological and scientific capacities of endemic countries have been reinforced, including through technology

transfers, particularly of manufacturing processes, to industrial partners in endemic regions. The technology transfer of the antimalarial ASAQ – developed in partnership with Sanofi and others – to the Tanzanian drug company Zenufa, made significant progress in 2015. This required stability and bioequivalence studies, together with the preparation of the WHO prequalification and registration dossier to be submitted in 2016 which could ultimately result in the production of three to five million treatments per year for distribution in Africa.

Building strong R&D collaborations to answer the needs of filariasis patients

In 2015, DNDi's filariasis programme pursued its analysis of filariasis patients' needs. Clinical expert meetings held in May and October resulted in the definition of a Target Product Profile (TPP) of a new treatment for onchocerciasis, and the team visited research centres in Cameroon to assess possible sites for clinical studies. The team also attended two meetings of the African Programme for Onchocerciasis Control (APOC), its 40th Technical Consultative Committee in Burkina Faso (March) and the APOC closure meeting at its Joint Action Forum in Uganda (December).

Building strong R&D partnerships with disease experts is the first step towards answering patients' needs quickly and efficiently. To reach this common objective, DNDi has started collaborations in 2015, notably with

the Department of Public Health of the University Medical Center of Rotterdam, the Netherlands for an epidemiological modelling study on onchocerciasis and lymphatic filariasis; with CEA/LETI, France and the Research Foundation in Tropical Diseases and the Environment, Cameroon (REFOTDE), for an optical, non-invasive approach for clinical studies on drug effectiveness

for onchocerciasis; with CEA/LETI, REFOTDE, the Institut de Recherche pour le Développement (IRD), France, and the National Natural History Museum, France for research on biomarkers and surrogate endpoints, and has regular interactions with key stakeholders in clinical research for filarial diseases.

MISSION OF THE PLATFORMS

- Define patients' needs, taking into consideration the local settings
- Bring together key regional actors in the disease field, namely representatives of ministries of health, national control programmes, regulatory authorities, academia, civil society groups, and pharmaceutical companies, as well as clinicians and health professionals
- Utilize, capitalize upon, and reinforce clinical capacities in endemic regions, and address infrastructural requirements where necessary
- Provide on-site training in clinical research in sometimes very remote settings
- Contribute to regulatory processes, uptake, and sustainable access of new treatments.

redeLEISH FOUNDED: 2014 in Rio de Janeiro, Brazil

This network was built to give support and strengthen capacities for the implementation of clinical trials for the evaluation of new therapeutic tools for leishmaniasis, according to GCP, and to promote technical and scientific information sharing between participants. RedeLEISH also aims to promote consensus on research priorities and on harmonization of clinical trial design and methodology, and to promote discussion on the R&D challenges in leishmaniasis and on strategies to ensure the public health impact of the new treatment options developed.



Over 70 representatives from 38 institutions in 8 Latin American countries (Bolivia, Brazil, Colombia, Guatemala, Mexico, Peru, Panama, Venezuela).

2015 HIGHLIGHTS

- Originally created as a Brazilian network, redeLEISH included reference centres and experts from other Latin American countries.
- The second meeting was held in Medellin, Colombia with the collaboration of PECET (Programme for the Study and Control of Tropical Diseases/University of Antioquia), and Ruta N. 65 representatives from 35 institutions – namely PAHO, TDR/WHO, FIOCRUZ, and the Colombian and Brazilian MoHs – attended to identify the capacity of clinical research in Latin America. The agenda included discussions on the target product profile of a rapid diagnostic test for cutaneous leishmaniasis.
- A collaborative project for *Leishmania* species identification in three Brazilian States was implemented in 2015.



Second redeLEISH meeting in Medellin, Colombia.

Before starting the project, a GCP introduction training was given at Tomé-Açu Hospital and at Unidade Referência em Atenção Primária Dr Claudia Vitorino – Rio Branco

- The creation of a Web Forum, a virtual platform serving as a real space to share experiences in leishmaniasis R&D and access to treatments.

RedeLEISH is essential for the implementation of DNDi's strategy for cutaneous leishmaniasis (see p.28).



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

LEISHMANIASIS EAST AFRICA PLATFORM (LEAP)

Founded: 2003, Khartoum, Sudan

Over 60 individual members, representing over 20 institutions



2015 HIGHLIGHTS

- 22nd LEAP meeting in Khartoum, Sudan in October 2015, with 68 participants, with 22nd LEAP principal investigators (PIs) meeting and 1st Project Advisory Committee (PAC) of the AfriCoLeish Project
- “New combination treatments for VL in Africa” and Fexinidazole studies completed.

Treatments & Access

LEAP facilitated and organized the Stakeholders and MoH dissemination meetings regarding the pharmacovigilance results of SSG&PM, in Nairobi and in Kampala (Nov.) and reviewed the national guidelines for VL diagnosis and management to clearly state that SSG&PM combination is the new first line treatment for primary VL patients in Eastern Africa.

Clinical trials

- **Miltefosine pharmacokinetic and safety in children with VL:** Completed recruitment, with 30 patients in August 2015 (21 in Kacheliba, Kenya and 9 in Amudat, Uganda). 2 DSMB meetings (July and Oct.)
- **HIV/VL treatment study:** 60 patients recruited by end of 2015 (32 in Gondar and 28 in Abdurafi, Ethiopia). The study is evaluating the efficacy of AmBisome®+miltefosine combination and of a higher-dose AmBisome® monotherapy. 2 DSMB meetings (April and May).

Capacity strengthening

LEAP organized trainings in Marsabit (with 22 attendees) and Turkana (14) counties, Kenya on the National Diagnosis and Management of VL Guidelines. Protocol specific, Good Clinical Practice (GCP), and GCLP courses were provided to **363 health staff of clinical sites**, in Gondar and Abdurafi (Ethiopia), Amudat (Uganda), and Kacheliba (Kenya). Data management events were attended by LEAP members: the 4th ADMIT Workshop organized by the Institute of Tropical Medicine (ITM) in Antwerp,



Belgium (3), and the OpenClinica Global Conference 2015 in Amsterdam, Netherlands (6).

Communications

The fourth edition of the LEAP Newsletter was published in November 2015.

“I am proud to be part of a team that gained new knowledge through training and participation in a clinical trial for the first time.”

Martin Sunguti Kundu,
Lab. head, Kacheliba,
West Pokot, Kenya

MEMBERS: Center for Clinical Research, Kenya Medical Research Institute (KEMRI), 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; IDA Foundation, The Netherlands; OneWorld Health (OWH/PATH), USA; AMC/KIT/Slotervaart Hospital, The Netherlands; London School of Hygiene & Tropical Medicine (LSHTM), UK.



HUMAN AFRICAN TRYPANOSOMIASIS (HAT) PLATFORM



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

2015 HIGHLIGHTS

- Recruitment of patients to the fexinidazole Phase II/III study completed (394 patients)
- Participation in the 33rd International scientific council of research and control of trypanosomiasis in Ndjamena, Chad, with 53 attendees (Sept.)

Treatments & Access

In 2015, NECT improved therapy has been used as first-line treatment for stage 2 sleeping sickness in almost all *T. b. gambiense* detected patients. The platform attended the meeting of the Consultative Scientific Committee to the national control programme of DRC in Kinshasa, DRC (Sept.), where the DRC national HAT policy was reviewed and recommendations were issued. This could help other national programmes to revise and update their policies, particularly considering WHO's new target for elimination of the disease by 2020.

Clinical trials

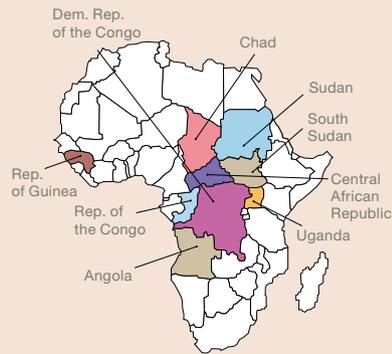
- **Fexinidazole Phase II/III study:** Inclusion of all 394 patients completed in April. Two additional cohort studies have enrolled the following: 230 stage 1 and early stage 2 adult patients and 125 children aged 6-14 years (all stages). A total of 749 patients have been included.
- **SCYX-7158 Phase II/III study:** This single dose oral treatment will be tested in 210 stage 2 and around 150 stage 1 patients in DRC. Recruitment is planned to start in 2016. Three new clinical sites, N'gandajika, Bolobo, and Kwamouth (DRC), were selected and prepared in 2015.

Capacity strengthening

Training on Trypanosomiasis management was co-organized between Chad's national sleeping sickness control programme and the HAT Platform in Dinamadji district (Chad) with the support of DRC national control programme; 22 doctors and nurses attended (August). The platform also supported HAT clinical training in South Sudan, with 36 attendees (Nov). An investigators' meeting on fexinidazole trials was organized in Kinshasa, DRC, with 18 attendees (July).

Communications

The 16th edition of the HAT Platform newsletter was published in 2015.



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

“The training in Good Clinical Practice and the site initiation of the clinical study help me on a daily basis to improve the way we take care of all patients.”

Tawaba Say Watson,
Nurse head, Bagata,
Kwilu province, RDC

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



Countries highlighted on the map represent Chagas disease-endemic Latin American countries with platform members. Other CCRP members' countries are listed below.

The CCRP brings together partners, experts, and stakeholders to provide support for the evaluation and development of new treatments for Chagas disease. This patient-centred platform aims to facilitate clinical research, provide a forum for technical discussions, develop a critical mass of expertise, and strengthen institutional research capacities. In addition, it identifies and reviews priority needs, works towards standardization of methodology to assess drug efficacy, and reviews alternatives for using current approved drugs (new schemes, doses, combination).

“Enabling discussions among researchers is an important tool for the improvement of efficiency, diagnosis, and treatment.”

Concepción Zúniga Valeriano,
Medical doctor, Head of CHAGAS-
Honduras

CHAGAS CLINICAL RESEARCH PLATFORM (CCRP)



Founded: 2009 in Uberaba, Brazil

Over 90 institutions represented from 23 countries, bringing together over 300 people

2015 HIGHLIGHTS

- Number of CCRP members grew by 23%; about 40% of new members come from non-endemic countries.
- The Annual Chagas Clinical Research Platform Meeting in Buenos Aires, Argentina (Aug.) in the context of the National Chagas Week, with 230 attendees (from 17 countries) from, among others, national programmes, patient associations, research and clinical care centres, NGOs, and pharmaceutical companies.

Treatments & Access

In 2015, the Platform continued its engagement on access issues, namely with Global Chagas Coalition and Regional Initiatives meetings convened by PAHO and the national programmes, for instance at the Andean Countries Initiative meeting (Peru, Sept.) or at the Central America & Mexico Initiative meeting (Costa Rica, Nov.) CCRP also contributed to the Chagas Access Implementation Project on access to diagnosis and treatment, through pilot projects in Colombia (as of April); Mexico, USA, Brazil, and Gran Chaco will follow in 2016-17. The CCRP continued to strongly support the registration process for benznidazole in Mexico.

Clinical Trials

- The Phase II **New Benznidazole Regimens** study: protocol finalization and study design definition, consensus on the study read-outs, and quality systems.
- The Phase II **Fexinidazole** study in Bolivia to evaluate the treatment of adult patients with chronic Chagas disease: in 2015, the enrolled patients were monitored for 12 months post-treatment.
- The Phase I **Drug-drug interaction** study of fosravuconazole with benznidazole in

Argentina was concluded: no clinically relevant PK, safety, or tolerability issues identified.

In addition, the CCRP worked towards integration of clinical trial results from different research groups and institutions, as well as harmonization of clinical trial designs in Chagas disease.

Capacity Strengthening

In 2015, 12 experts' and technical meetings were held in Mexico, Argentina, Bolivia, and Spain, namely a Target Product Profile workshop in Barcelona with 25 participants (March); the Experts' Meeting (NHEPACHA Network) in Barcelona & Buenos Aires; and the Latin-American Chagas Summit, organized by the National Programme in Mexico, with 235 attendees (July). The DNDi Chagas Team also taught two courses to CCRP members: Introduction to Clinical Trials (Córdoba, Argentina) and Introductory Course on Research (Tarija, Bolivia).

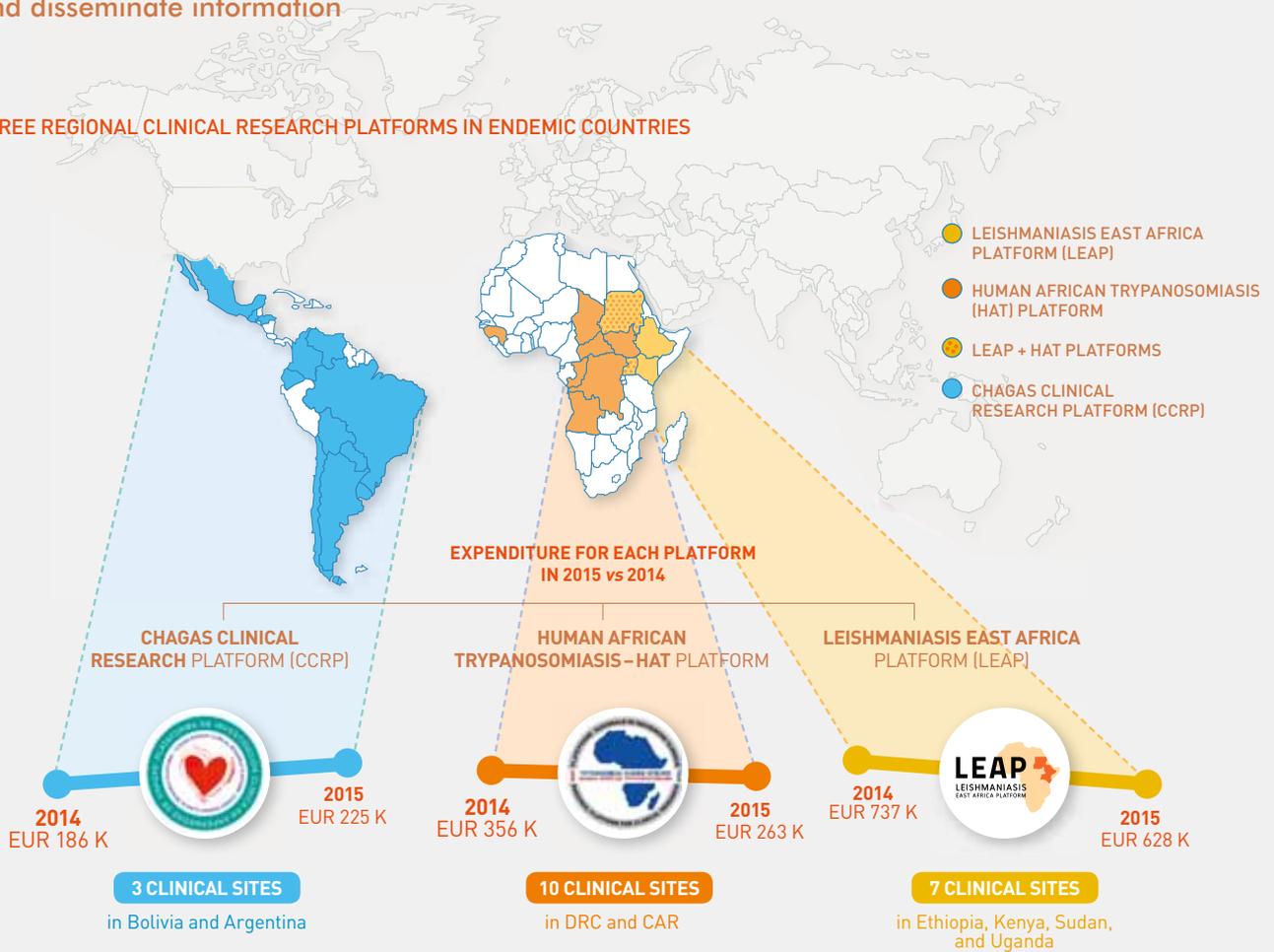
Communications

The fourth edition of the CCRP newsletter was published in July. The Web Forum has been actively used by CCRP members as an online workspace for discussion, sharing of information, and debate.

MEMBERS: 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, Colombia, Chile, Paraguay, Ecuador, Mexico, Honduras, Costa Rica, Guatemala); Global Chagas Coalition; NHEPACHA; Médecins Sans Frontières; International Federation of People Affected by Chagas Disease (FINDECHAGAS) and several patient associations **ARGENTINA:** Hospital de Niños Ricardo Gutiérrez; Instituto Nacional de Parasitología Dr. M. Fátala Chabén; Hospital Eva Perón; Hospital de Niños de Jujuy; Hospital Público Materno Infantil – Salta; Centro de Chagas y Patología Regional, Santiago del Estero; Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET); INGEBI; Fundación Mundo Sano; ELEA; Grupo Hablamos de Chagas **BRAZIL:** Instituto Oswaldo Cruz; Instituto de Pesquisa Evandro Chagas – Fiocruz; Centro de Pesquisas René Rachou – Fiocruz; IFSC – Universidade de São Paulo; UNICAMP; Universidade federal de Ouro Preto; Universidade de Pernambuco; Faculdade de Medicina – Universidade Federal do Ceará; LAFEPE **BOLIVIA:** Universidad Mayor de San Simón; Platform of Integral Care for Patients with Chagas Disease; CEADES **SPAIN:** ISGlobal and Barcelona Centre for International Health Research (CRESIB); Hospital Clinic Barcelona; Hospital Vall d'Hebron; Instituto de Parasitología y Biomedicina López Neyra; Consejo Superior de Investigaciones Científicas; Instituto Catalán de la Salud; Instituto de Salud Tropical, Universidad de Navarra **MEXICO:** Instituto Carlos Slim de la Salud; Instituto Nacional de Salud Pública de México; UADY; UNAM **COLOMBIA:** CIMPAT; CIDEIM; PECET; Universidad de los Andes; Chagas Network **VENEZUELA:** Venezuelan Institute for Scientific Research; Central University of Venezuela; IDEA **SWITZERLAND:** Geneva University Hospitals **FRANCE:** Institut de Recherche pour le Développement **USA:** Sabin Vaccine Institute; Broad Institute of MIT; TULANE University; Baker Institute; The University of Texas at El Paso; UCLA; Merck **JAPAN:** Eisai Co. Ltd **GERMANY:** Bayer **UNITED KINGDOM:** The Global Health Network **CANADA:** McMaster University; IRDC; EndoParagon **ITALY:** Centro per le Malattie Tropicali – Ospedale Sacro Cuore **OTHER:** Researchers from others Universities and media in endemic and non-endemic countries.

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

THREE REGIONAL CLINICAL RESEARCH PLATFORMS IN ENDEMIC COUNTRIES



The overall platform budgets decreased by 13% between 2014 and 2015 (from EUR 1'279 K in 2014 to EUR 1,115 K in 2015).

- The Chagas platform expenditure (CCRCP) increased by 21% because 2015 was a year of transition characterized by a consolidation of the main clinical research groups, with a specific agenda for each one. Consequently, the number of trainings between 2014 and 2015 increased by 129%. In addition the number of members of the platform grew by 23% (~40% of new members come from non-endemic countries) and this has a direct impact on the cost of the annual platform meeting.

- The HAT platform expenditure decreased by 26% while the recruitment of the new coordinator was ongoing. Since mid-2015, with the arrival of the new coordinator of the HAT platform, the activities have fully resumed.

- The Leishmaniasis East Africa platform (LEAP) costs decreased by 15%, due to the fact that the LEAP meeting was not organized together with a scientific day meeting as in 2014. LEAP continues to maintain clinical trial sites (mainly the team) even though they were not involved in R&D activities in 2015. The costs of these sites (Kimaltel clinical trial site of KEMRI in Kenya, Abdu Rafi in Ethiopia, Kassab and Dooka in Sudan) were removed from R&D expenditures and allocated toward the strengthening capacities budget. Patients treated outside clinical trials in 2015 in the seven VL clinical trial sites reached 1,363 (3,910 people screened).

People trained between 2014 and 2015 increased by almost 50%

DEVELOPING RESEARCH CAPACITIES IN ENDEMIC REGIONS

In six years, platforms have been able to multiply by 7 the number of people trained every year.

