NEWSLETTER n.1

CHAGAS DISEASE CLINICAL RESEARCH PLATFORM

PLATAFORMA DE INVESTIGACIÓN CLÍNICA EN ENFERMEDAD DE CHAGAS

RIO DE JANEIRO, SEPTEMBER, 2011

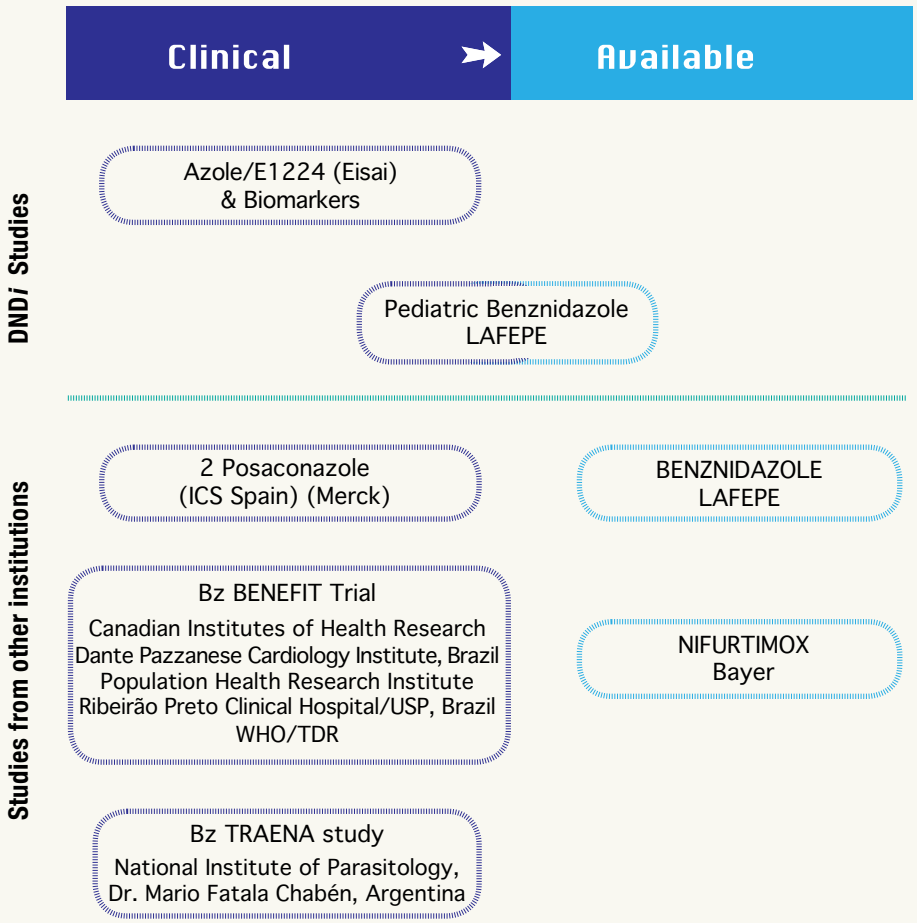
The year 2009 marked the 100th anniversary of the discovery of Chagas disease. On this occasion, DNDi together with other partners started the Chagas Clinical Research Platform (CCRP), whose main objective is to develop new drugs for the treatment of the infection caused by *T. cruzi,* in the belief that a flexible, needs-oriented network is able to support in a concrete manner the challenges mentioned at the Investigation and Development (I&D) application.

In 2011, the development of new drugs for Chagas disease moved forward with the start of several clinical trials in Latin America and Spain. Such studies may provide new hope for thousands of people affected by the disease. Under these circumstances, the Platform should be adapted to current challenges and support the above mentioned studies, as well as provide a space for discussion and exchange of experiences for clinical research on Chagas disease. The objective of the first newsletter of the Platform is to present the current status of key trials this year and so contribute to understanding and awareness of the network. The debate on innovation for neglected diseases is not limited to a purely technical discussion; it has also faced a number of challenges in relation to concrete access to new technologies. Access barriers are related to cost, regulatory issues, and implementation of new tools.

Therefore, 2011 represents an opportunity for all people concerned about the development of new drugs for Chagas disease to jointly search for solutions in order that new technologies may be produced and become accessible to the individuals most in need.

Enjoy your reading!

CHAGAS PORTFOLIO



SUMMARY

Target Product Profile (TPP) for Chagas Disease

- **A new treatment for adults and children for acute and chronic disease**
  - **priority is a pediatric formulation**
  - **useful against parasite species in all regions**
- **Better safety profile than existing drugs**
  - **ideally requiring little or no monitoring**
- **Equal or better efficacy profile than existing drugs**
- **Easy-to-use treatment**
  - **ideally less than 30 days**
  - **oral**
  - **preferably once daily treatment, ideally outpatient**
- **Stable in tropical climate**
- **Affordable**

DNDi AMÉRICA LATINA
Drugs for Neglected Diseases *initiative*
Iniciativa Medicamentos para Doenças Negligenciadas

Published by **Drugs for Neglected Diseases** *initiative* - Latin America

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Publishing: Vento Sul Design
Printing: www.stamppa.com.br
Photos: DND*i*

A BRIEF BACKGROUND ON THE CHAGAS CLINICAL RESEARCH PLATFORM

In 2005, DND*i* organized a first expert meeting to discuss the specific needs for the treatment of Chagas disease. This led to the creation of the Chagas Clinical Research Platform (CCRP).

The meeting focused on discussing the development of the paediatric formulation of benznidazole, which is being made available now, in 2011 (see pages 6 & 7). Two other meetings in 2006 dealt with the development of a Target Product Profile (TPP) for Chagas disease, both for the acute as well as chronic stages of the disease; and with the definition of a clinical research strategy, including the selection of effect measures and the identification of potential research centers and investigators.

In 2009, the 100th anniversary of the discovery of Chagas disease, DND*i* considered it time to strengthen an already established network and launched CCRP.

Although other networks exist for Chagas disease, none were focused on research and development for new Chagas drugs. This is the main purpose of the Platform.

During the last five years, the TPP for Chagas disease was updated a couple of times until reaching the present version, validated in the CCRP meeting held in Buenos Aires, Argentina (see next Box).

The Platform also organized training and standardized methodology courses to evaluate the effectiveness of drugs used for treating the infection caused by *T. cruzi*.

In 2011, several Chagas clinical studies began which generated challenges, not only from a technical and operational point of view, but also in relation to access to technologies by the populations who require them.

Within this spirit, DND*i* decided to invest in a process of consolidation by forming the CCRP, with the aim of greater integration and exchange among platform members.

CHAGAS PATIENTS CREATE AN INTERNATIONAL FEDERATION TO FIGHT FOR THEIR RIGHTS

Manuel Gutiérrez

Associations of Chagas disease patients from different countries met in October 2010 in Recife, Brazil, to create an International Federation of People Suffering from Chagas Disease (Findechagas). This is a milestone in the fight against the disease, insofar as the voices of patients and of scientists gather with the purpose of encouraging both public and private sectors to make more investment in R&D of new tools for diagnosing and treating the disease. The Federation, which has been legally established and involves Chagas patients from different countries, including Argentina, Brazil, Bolivia, Venezuela, Colombia, Spain, and Australia, intends to extend the fight for the rights of individuals suffering from this silent condition. From Bolivia, Manuel Gutierrez, President of Findechagas, tells us about his personal experience as a patient and explains the reasons behind this movement.

How and when did you find you had contracted Chagas disease?

It was four years ago, when my second child was born and diagnosed with the disease. Soon all family members were subject to lab tests, which proved positive.

How was your first contact with Chagas patients' associations?

It was through Fedebol (Federation of Bolivian Entities in Cataluña, Spain) and Asapecha (Association of Chagas Disease Patients), of which I am a member. This is a section of Fedebol that encourages actions in relation to Chagas disease in the Bolivian community living in Spain.

What caused the creation of the Federation? How did different associations get together to fight Chagas disease?

The reason was a need to join associations together under a single, international entity to represent us.

What are the main objectives of the new entity?

The main purpose is to fight Chagas, looking for international support to benefit all individuals who are suffering as a result of the disease. We are no longer invisible and are becoming direct spokespersons of Chagas disease, and that is important.

What are patients demanding today?

Main demands today include treatment, disease monitoring, and new and more efficient drugs, particularly for already infected patients undergoing the chronic phase of the disease. Moreover, we want to encourage people, especially pregnant women, to perform the Chagas lab test in newborn babies.

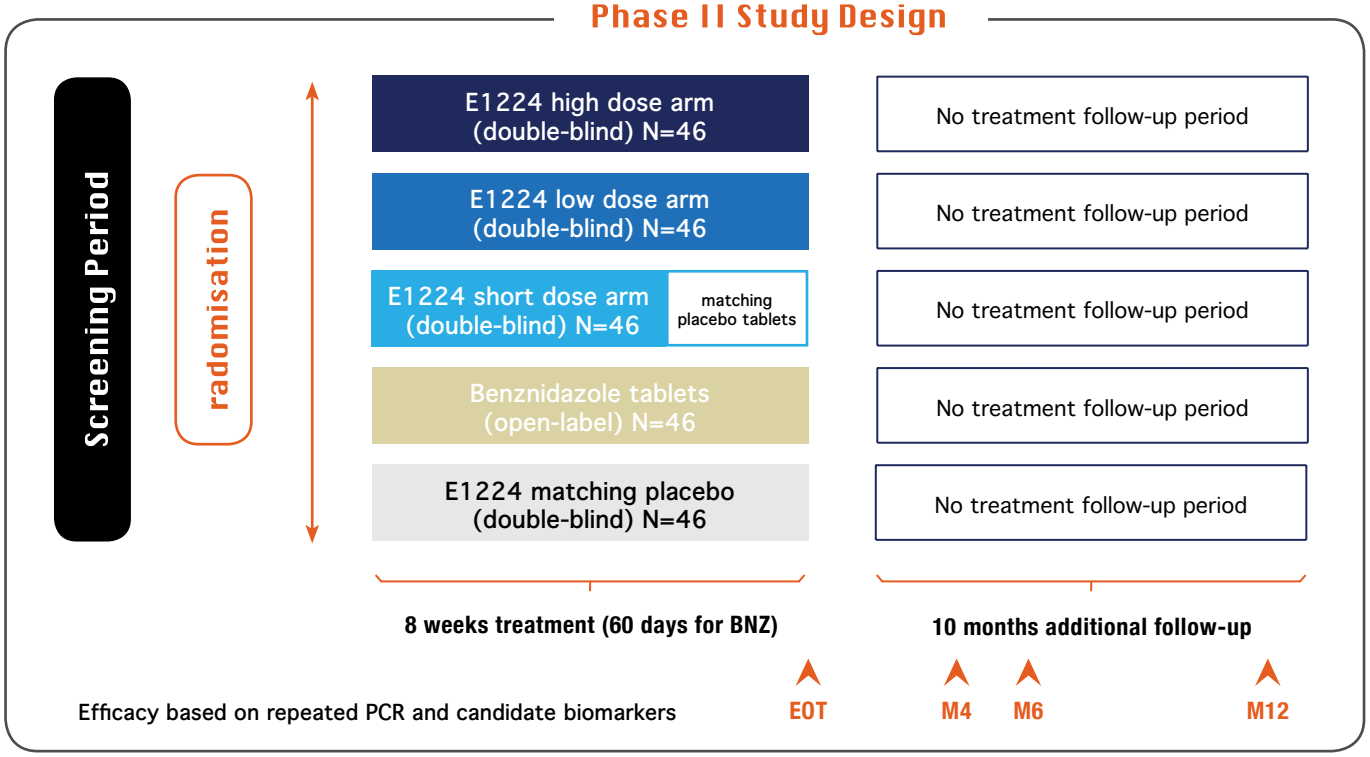
E1224: A PROMISING DRUG CANDIDATE FOR TREATING CHAGAS DISEASE

The only two drugs known to be effective against Chagas disease, benznidazole and nifurtimox, have serious limitations, especially when used for treating the chronic phase of the disease in adult patients. As an alternative to the existing drugs, triazol antifungal derivatives are able to inhibit *Trypanosoma cruzi* ergosterol biosynthesis, an essential component for the growth and survival of the parasite that causes Chagas disease. Studies were performed that confirmed the specific potential of ravuconazole, an antifungal compound shown to have important activity both *in vitro* and *in vivo*.

In association with the Japanese pharmaceutical laboratory Eisai, DNDi is working on the clinical development of E1224, a promising pro-drug of ravuconazole. This is the first new compound in the last 40 years to potentially treat Chagas disease. With the purpose of assessing safety and efficacy of the drug in individuals undergoing the chronic, indeterminate phase of the disease, DNDi will carry out a Phase II clinical trial in investigation centres in Cochabamba, Bolivia. This Latin American country has been elected for the study due to the high prevalence of the disease there and because of the existence of the *Platform for Integrated Assistance to Chagas Disease Patients* – a partner of DNDi in this clinical trial, which resulted from cooperation between San Simón University in Cochabamba and Barcelona International Health Research Centre (CRESIB, in Spanish).

E1224 was subject to toxicology and pharmacology safety studies, in addition to five Phase I clinical trials. Featuring a satisfactory safety profile and favourable pharmacokinetics, this compound is considered a priority prospective candidate for Chagas disease. The study has started in July 2011 and is expected to end by December 2012. •

Phase II Study Design



OPTIMIZATION OF PCR TECHNIQUE TO ASSESS TREATMENT RESPONSE IN CHAGAS DISEASE

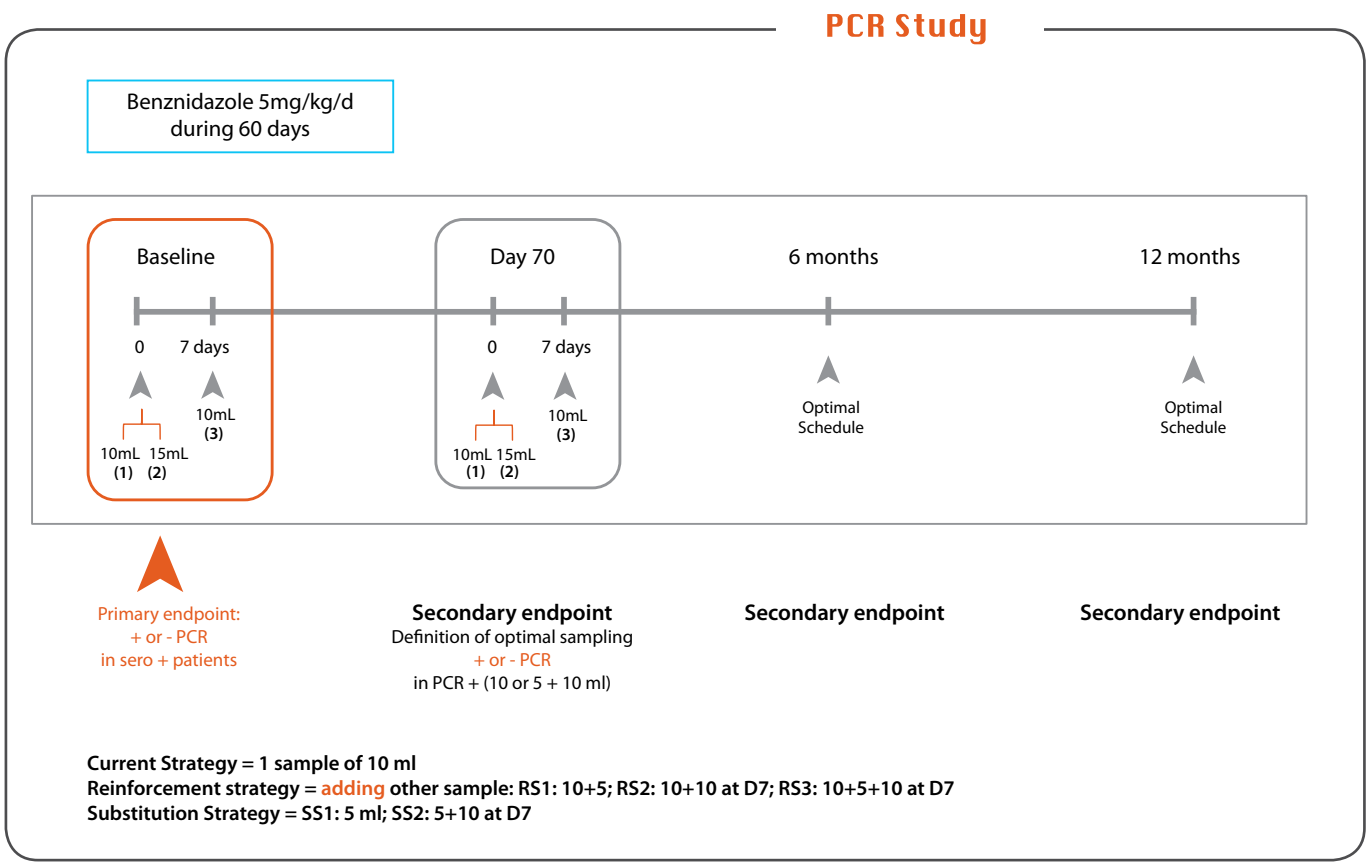
In the absence of a test of cure, many are the challenges for the development of new drugs for Chagas disease. A test of cure is a key parameter to compare therapeutic response against different treatment options under investigation. This is why we should be creative and continue our search for viable alternatives that provide answers about the effectiveness of drugs on Chagas infection control. The standardization of methods and tools now in use is a starting point and a path to compare studies and trials performed across the world.

To this end, Médecins Sans Frontières (MSF), Drugs for Neglected Diseases initiative (DNDi), and the Universidad Mayor de San Simón (UMSS) in Cochabamba, Bolivia have joined forces to perform a clinical research study called "Optimization of PCR technique sampling procedure to assess parasitological response in patients undergoing the chronic phase of Chagas disease who are treated with benznidazole in Aiquile, Bolivia".

After extensive consultations with experts, consensus was reached about PCR as the selected technique to measure primary therapeutic results (main variable for detection of therapeutic failures) in clinical studies. However, from a feasibility standpoint about the use of PCR in different settings for Chagas disease, it has been found to be complex and expensive. Thus, PCR is considered an intermediate solution until a more effective tool is developed to measure therapeutic responses.

PCR sensitivity must be improved through sampling procedures, and the improvement of logistics and viability of PCR are also important. Therefore, the purpose of the study is to estimate sensitivity variation based on several PCR sampling strategies and compare this with the standard technique of a single 10-mL sample to detect the chronic form of Chagas disease in blood (see graphic of the study design). Also, PCR sensitivity for 6- and 12-month post-treatment assessments of early detected therapeutic failure will be measured.

The study protocol was approved by two ethics committees (MSF Ethics Review Board and CEADES [Collective of Applied Studies and Social Development]) and the National Program for Chagas Disease Control in Bolivia. The first patients were recruited in April 2011. The study is to be completed in the second half of 2012. •



DND*i* AND LAFEPE LAUNCH PAEDIATRIC FORMULATION AGAINST CHAGAS PARASITE

Chagas disease affects over 10 million people around the world, many of them children. In countries where vectorial transmission is one of the main pathways of infection by *Trypanosoma cruzi,* children are the primary victims. Although there are only two drugs to treat the infection – one being benznidazole – evidence shows that treatment in children may result in parasitological cure in 60-85% of acute cases and in over 90% of cases of congenital infection of infants treated during their first year of life[1].

Benznidazole has been developed for 30 years now but is only available in 100-mg tablets for the treatment of adults. At present, it must be macerated, diluted, or fractionated into small pieces for children. (See photo).

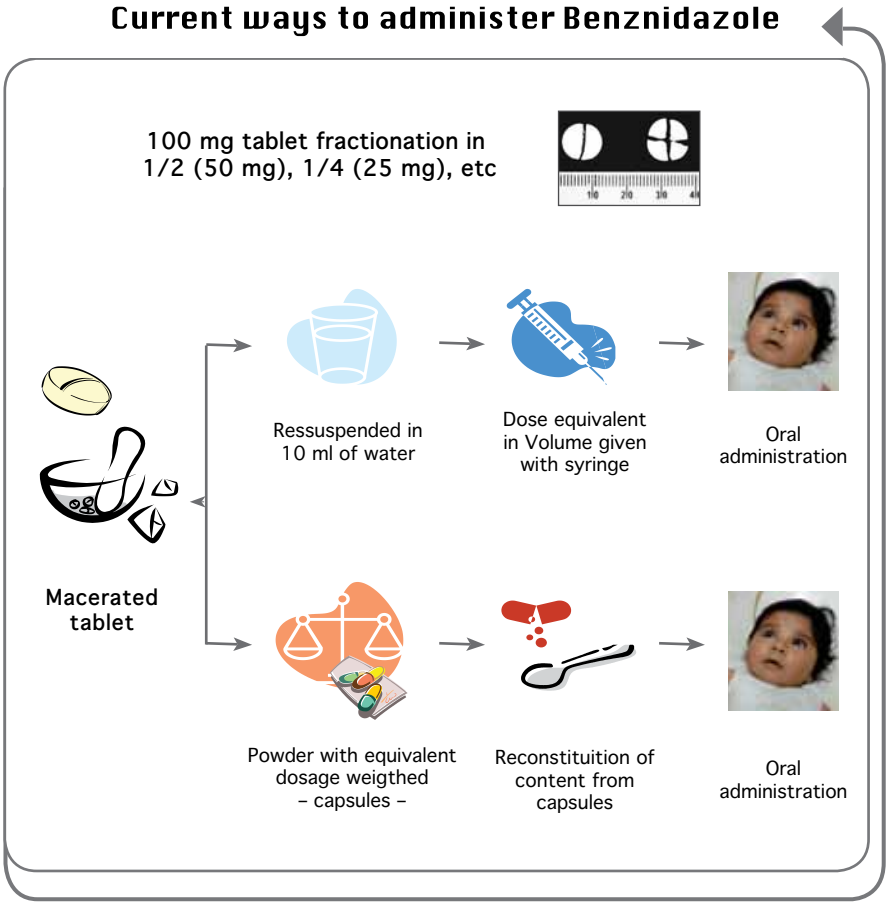
To fill this gap, Drugs for Neglected Diseases initiative (DNDi) and Pernambuco Pharmaceutical Laboratory (LAFEPE) joined together in 2008 to develop the first paediatric formulation of benznidazole. The drug, to be launched in late 2011, is undergoing the final industrial production stage. The product has been designed for patients up to 2 years old and weighing up to 20 kg. The 12.5-mg tablets will be sold at cost to endemic countries with high need. A health record has already been requested from the Health Vigilance Agency. •

1 Bern C, Montgomery S et al, ´Evaluation and treatment of Chagas disease in the united states: A systematic review´, Jama, Nov 14, 2007 – Vol 298, No 18

Voices from the field

Cecilia Centurión

"We hope that a paediatric formulation of benznidazole may meet the demand for treatment by health care providers, who are increasingly aware of the long-term benefits that result from treating children younger than 14 with a specific formulation for each age group. It is necessary that lack of formulation no longer be an excuse not to indicate treatment," comments Cecilia Centurión, from the Chagas Disease Alliance, a network active in Argentina and Mexico that deals with people who directly or indirectly suffer from Chagas disease.



Tools designed to broaden access to benznidazole

Two new tools have been created to facilitate more sustainable access to benznidazole (both adult and pediatric formulations) for people with Chagas disease.

The first tool is a Procurement Guide, a virtual step-by-step guide for purchasing benznidazole, which is manufactured by just one pharmaceutical company (LAFEPE). The guide will be updated periodically.
Visit: www.guiadecomprasbenznidazol.org.

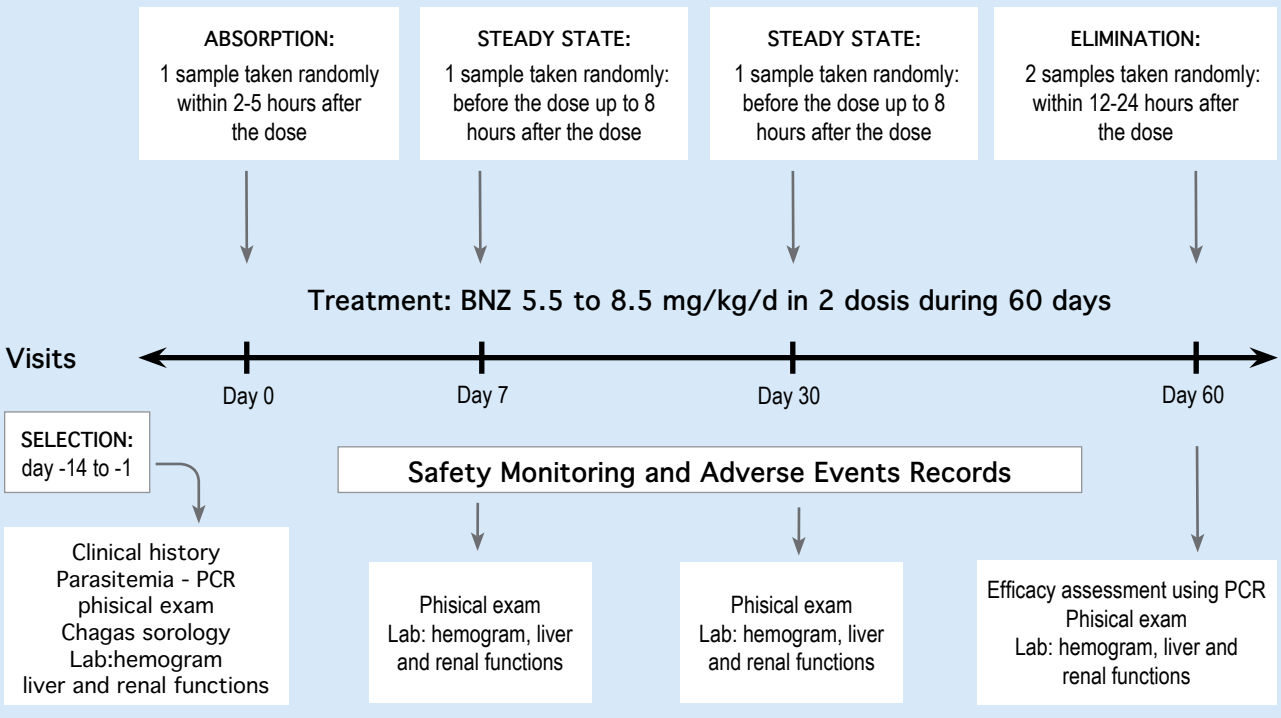
The second tool is the Benznidazole Demand Estimate, which resulted from collaboration among PAHO, MSF, and DNDi. Working with LAFEPE, this tool estimates the demand for benznidazole to contribute to improved production planning, both for the active substance and the final drug product. Directors of domestic programs and civil servants are being trained in the use of this tool at Chagas initiative meetings organized by PAHO. Thus, with this tool, national and local Chagas programs will be able to establish the demand for benznidazole for Chagas treatment and contribute to rationa planning for each country.

Population pharmacokinetics study to be performed in Argentina

To attain population pharmacokinetics data of children treated with benznidazole, a phase IV study will be conducted at research centers in Buenos Aires and endemic areas of northern Argentina, such as the provinces of Jujuy, Salta, and Santiago del Estero. An estimated 1.5-2 million Argentineans have already contracted the disease.

"No pharmacokinetics information has been obtained about benznidazole since 1970, and no study like this has ever been performed with children", says Jaime Altcheh, MD, Principal Investigator and member of the Parasitology Division at Ricardo Gutiérrez Children Hospital in Buenos Aires. According to Dr. Altcheh, the results will contribute to better knowledge about existing drugs against Chagas disease.

In April 2011, an open study will be conducted with 80 recruited patients. The patient group will include congenital cases, children at the beginning of the chronic indeterminate stage of the disease, and acute cases caused by vectorial transmission. Children of up to 12 years old will take part in the study.



POSACONAZOLE

Two new phase II clinical trials are currently being performed to assess the efficacy of the oral antifungal drug posaconazole for the treatment of patients with chronic Chagas disease. These studies are supported by STOP Chagas, funded by Merck and CHAGASAZOL, and led by Barcelona Hospital Universitari Vall d'Hebron Research Institute.

The study funded by Merck (STOP Chagas) is a test-of-concept, randomized, placebo-controlled study, in which posaconazole, oral suspension (400mg BID), is administered for 60 days, both as monotherapy and together with benznidazole. Benznidazole monotherapy will be employed as a monitoring arm. The objective of the study is to recruit 160 adults (men and women over 18 years of age) with chronic indeterminate Chagas disease, in several research centres of South America with a follow-up term of up to 360 days. STOP Chagas uses PCR to evaluate *T. cruzi* levels in blood as the main assessment criterion of response to treatment.

Safety will be periodically, monitored by the external, independent Data and Safety Monitoring Board (DSMB), which will make any required recommendations. The study results are expected by 2012. In a press release, Merck reported that they would work jointly with their associader to facilitate access o posaconazole, provided that the studies show benefits in the treatment of chronic Chagas disase.

The CHAGASAZOL study by the University Hospital Vall d'Hebron Research Institute in Barcelona, Spain is a phase II, randomized, open study designed to test the efficacy of posaconazole for the etiological treatment of chronic Chagas. The study began in August 2010 and includes three arms: low-dose posaconazole, high-dose posaconazole and benznidazole control arm.

The primary endpoint of this study is parasitological cure, measured by PCR at 12 months after treatment start, and negative PCR at end of treatment. A secondary endpoint is to assess sustainable parasite control, and evaluate safety and tolerability of both drugs used in the trial after two months of treatment.

Preliminary results are expected by December 2011.

Posaconazole has already been approved and is marketed in many countries, including Brazil, where it is available in oral suspension dosage form under the name of NOXAFIL).

BENEFIT

BENEFIT (BEN*znidazole Evaluation For Interruption of Trypanosomiases*) is a multicenter, randomized, double blind, placebo-controlled study, with the objective of studying about 3,000 patients with Chagas cardiomyopathy in Latin America.

The study design involves randomized allocation of patients to receive either benznidazole (5mg/kg/day) or placebo, for 60 days. Patients are being followed up for up to five years. The study has 90% probability of identifying a reduction of relative risk in 25% of the patients.

BENEFIT includes two substudies to assess the effects of benznidazole in the elimination of the parasite and in the impact of etiological treatment on left ventricular heart function. This is one of the most ambitious clinical trials ever conducted for Chagas disease and should help clarify the role of this trypanocidal drug treatment in preventing disease progression and death as a result of heart conditions caused by Chagas.

Recruitment began in 2004 in research centres in Brazil, Argentina, and Colombia. Ninety-six percent of the patients from all locations received over 75% of the indicated treatment for 60 days. The aggregate dropout rate is 14.5%, considering that 6.6% of the patients resumed taking the medication.

The study is funded by Hamilton Health Sciences Corporation (Hamilton, Canada) and supported by Dante Pazzanese Hospital (São Paulo, Brazil), Hospital das Clínicas de Ribeirão Preto (Brazil), Bunge y Born Foundation (Argentina), Ministry of Health of Argentina, and WHO.

The primary endpoints of the study are as follows:

PRIMARY ENDPOINTS First appearance of clinically significant effects, including: death, cardiac arrest, necessary defibrillation and cardioversion, sustained, documented ventricular tachycardia, development of symptomatic congestive heart failure, pacemakers, or stroke, implantation of a cardiac defibrillator or any other thromboembolic event in patients with no previous episodes of thromboembolism.

Source: www.clinicaltrials.gov / www.trialscentral.org / www.businesswire.com

GLOBAL HEALTH DEBATE ON INNOVATION AND ACCESS AND CHALLENGES FOR CHAGAS DISEASE

Michelle Childs *

In the past twelve years, Médecins Sans Frontières (MSF) has been implementing treatment projects to respond to Chagas disease in several countries in Latin America. In 2009, the centenary year of the discovery of Chagas disease, MSF launched the international campaign "Break the Silence"[1]. The heart of this campaign was to advocate for access to treatment and diagnostic tools - a critical part of the response to Chagas.

MSF has been able to diagnose and treat Chagas using existing technologies[2], but we are painfully aware of their constraints. The development of a test of cure, better rapid diagnostic tests, and better treatments are essential to improve the response. This gap in the innovation landscape for Chagas is a direct result of the imbalance in the way in which research and development (R&D) is funded. Companies fund R&D through charging high prices for the products once they are developed. As a result, the current medical innovation system not only leads to expensive and therefore often inaccessible products, but it primarily focuses on areas of greatest financial return rather than on medical needs.

The adoption by WHO Member States of the Global Strategy and Plan of Action for Public Health, Innovation and Intellectual Property (GSPA) in May 2008 marked widespread recognition of the need for new approaches to address urgent medical needs for diseases predominantly affecting people in developing countries. Building on this to accelerate scientific advances for essential health technologies, alternative funding mechanisms are urgently needed that de-link the costs of R&D from the price of the products.

As part of the implementation of the GSPA, a group of experts was established as the Consultative Expert Working Group (CEWG) to explore R&D financing and coordination and report back to the World Health Assembly in 2012. This is a key opportunity for exploring proposals presented by WHO Member States and others, which include proposals for new ways to fund innovation for Chagas. In assessing these proposals, two issues should be considered as a priorities: whether the proposals respond to a determined medical need, and whether they facilitate or allow for sustainable access to the resulting innovation.

Research alone will not ensure access to drugs, diagnostics, and vaccines for the poorest people. The stark reality is that even if research does take place, access to the fruits of innovation is far from guaranteed because it depends on affordable pricing and registration policies. When appropriate tools do exist, MSF all too often struggles to access them – with devastating consequences for patients.

It is vital that the CEWG, when assessing proposals for R&D financing, examines carefully how access to the resulting products will be achieved. Financing essential health R&D in a new, sustainable manner will require the separation or "delinkage" of R&D costs from the final price of products. Proposals should be analysed for their ability to both drive innovation and ensure sustainable access to the resulting products.

MSF believes that only in addressing these systemic challenges will we be able to find a sustainable solution to the current lack of early, low-cost access to products, or to the imbalance of medical innovation that is currently focused on market needs and not medical needs.

The international momentum for innovation for neglected diseases presents an opportunity to address the neglected technological needs for improving the detection and treatment of Chagas disease. This is an opportunity that cannot be missed. •

1 MSF Campaign "Break the Silence" - http://www.chagas-break-the-silence.com/

2 Yun et al. Feasibility, Drug Safety, and Effectiveness of Etiological Treatment Programs for Chagas Disease in Honduras, Guatemala, and Bolivia: 10-Year Experience of Médecins Sans Frontières. **PLoS Neglected Tropical Diseases**, v.3, n.7, jul 2009.

**Director of Policy Advocacy of the MSF Access Campaign for Essential Medicines*

NHEPACHA NETWORK AND THE CHAGAS CLINICAL RESEARCH PLATFORM

Joaquim Gascon*

Several circumstances remind us that Chagas disease is still one of the most neglected diseases. Only until recently were misunderstandings revealed about the ultimate cause of chronic complications of the disease, access to the only two antiparasitic drugs in the market since the last 50 years remains problematic, and clinical trials for new drugs are very few.

Only vector control programs in endemic countries have reminded us of the existence of Chagas disease. More recently, the efforts of certain research groups and initiatives, such as the BENEFIT trial (see pg. 8), has led to an increased concern for the disease.

For years, the theory that Chagas disease had a autoimmune origin stopped basic investigation and the need to find improved antiparasitic drugs. Now that the persistence of the parasite in affected tissues has been recognized as causing physiopathological and clinical events suffered by Chagas patients, we face other, but no less important barriers, among them, the lack of biomarkers for disease cure. This makes both patient follow-up and clinical trials for new drugs difficult. The Iberoamerican NHEPACHA network (*Nuevas HErramientas el diagnóstico y la evaluación de PAcientes con enfermedades CHAgas,* or "new tools for diagnosing and evaluating Chagas disease patients") has been organized around the needs for research on biomarkers for cure or disease progression, access to treatments, and clinical trials of new drugs. Other objectives of the network include fostering the exchange of scientific knowledge and preparing operational studies and multicenter clinical trials to assess newly designed tools.

NHEPACHA network is born at a time when research on Chagas can and needs to occupy a privileged position in the international agenda. For this reason, it has also been included in DNDi's Chagas Clinical Research Platform (CCRP), and through the joint action of these groups we want to contribute to these efforts. •

** NHEPACHA Network Coordinator*

Groups forming part of NHEPACHA network:

- **Belkisyole Alarcón de Noya. IMT-UCV (*Instituto Medicina Tropical, Universidad Central de Venezuela* /Tropical Medicine Institute, Central University of Venezuela), Venezuela.**
- **Tania Araujo-Jorge. FIOCRUZ-IOC. (*Fundaçao Oswaldo Cruz* – Instituto Oswaldo Cruz /Oswaldo Cruz Foundation–Oswaldo Cruz Institute), Brazil.**
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- **Isabela Ribeiro. DND*i* (Drugs for Neglected Diseases initiative).**
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- **Rodolfo Viotti. HIGAEP. (*Hospital Eva Perón* /Eva Perón Hospital), Argentina**

NEW CLINICAL TRIALS SCENARIO AND FUTURE PERSPECTIVES FOR THE TREATMENT AGAINST *T.CRUZI*

By Sergio Sosa-Estani*

Actions for interrupting vectoral transmission of *Trypanosoma cruzi* have reached an appropriate development level as well as significant implementation levels. The focus now should be on health care and proper access to infected people, whose chances for cure must be improved, avoiding Chagas disease progression and offering an adequate quality of life. Two actions are required to accomplish this: quality implementation of treatment and diagnostic tools and procedures whose effectiveness is well known, and finding new ways to improve available tools (diagnosis methods, therapeutic response monitoring, and treatments).

Three historic spans of time define the search for better solutions to cure *T. cruzi*-infected people. During the 60s-70s the only drugs available today were developed. In view of the existing tools and standards then used, long follow-up periods were needed for assessing treatment effectiveness.

During the 80s, the treatments indicated for the chronic phase were abandoned and clinical trials suspended due to a strong belief that etiological treatment was not useful in this disease phase. This concept was based on the idea that the evolution of pathology was almost exclusively determined by self-immunity phenomena, a physiopathogenesis basis prevailing at the time. However, some groups insisted that etiological treatment has beneficial effects in the chronic phase and carried out observational studies. These studies also required a long follow-up period to obtain valuable, though evidence-limited, results for the treatment of adults.

In the 90s, clinical trials were restarted during this time, providing evidence about the effectiveness of treatment of children and adolescents in the chronic phase of infection, and so expanding therapeutic indication criteria. This new scenario, together with the progress made in disease transmission prevention actions in the region through vector control, encouraged the search for new treatment possibilities for chronically infected people.

The recognition of etiological treatment as useful against *T. cruzi* infection should be viewed based on the impact it can have on Chagas disease control. It is necessary to stress that etiological treatment acts at different prevention levels, such as secondary prevention, curing both acute and chronic infection before organ damage, based on the essential role of the parasite in physiopathogenesis; and primary prevention, by mainly treating children, thus reducing the number of future infected mothers, blood donors, and organ donors, and so avoiding blood transmission (congenital or through transplantation). The object of a specific treatment against *T. cruzi* consists then of eliminating the parasite from the infected individual, reducing the probability of developing cardiovascular, gastrointestinal, or other condition and interrupting the transmission chain.

New available tools to measure therapeutic response have led reviewing the concept of effective treatment against the infection. This is based on other chronic infection cases, where positive therapeutic response is considered as reduced antigenic response (health improvement) and not necessarily as total cure, defined as clearance of the etiologic agent, in this case *T. cruzi.*

The above-mentioned scenario encourages the search for new treatment alternatives through different strategies, including assessment of new treatment schemes using old drugs; assessment of old and new drugs under other trypanocidal activity indications (*in vitro* and *in vivo*); and development of new drugs.

Inovations must come together with other equally important and innovative measures are required, such as increased practice of treatment currently indicated as mandatory (cases of acute and chronic infection of no more than 15-20 years evolution), and updating of new treatment effectiveness criteria in regulatory organizations. Said processes will pave the way for the incorporation of new therapeutic products under investigation, whose results are expected over the next five years, as well as other new tools still in preliminary stages or that may come up in the future.

National and international forums are now making a point about the need for caring for a group of diseases that have been defined as neglected, some of them being categorized as diseases that could be eliminated. This is the case of Chagas disease, the concern for which has returned in the last few years and is included in the agendas of a number of institutional initiatives. Notwithstanding, such concern must be increased and become sustainable.

While preventive control actions will reduce the occurrence of new cases, early diagnosis and timely treatment will be the essential tools to eliminate Chagas disease from the list of public health problems, reducing personal, social, and economic impact in both communities and health systems, and providing welfare for treated individuals and the surrounding community. •

** Director of the National Institute of Parasitology Dr. Mario Fatala Chabén, Argentina and Platform Coordinator*

Glossary

Primary endpoint: result measured at the end of the study to check efficacy of a certain treatment (e.g. number of deaths, or difference in survivors between control and treatment groups). Primary endpoints are always established before the study is started.

Preclinical trials: studies of the biological and chemical characteristics of a compound. These studies may be performed *in vitro*, on animal models (*in vivo*), or on isolated tissues or cells, to define pharmacology, toxicology, metabolism, and pharmacokinetics of a given compound. Preclinical trials determine if sufficient evidence exists of appropriate safety and potential efficacy before testing the compound in humans.

Phase I clinical trial: establishes the initial safety of a chemical or biological compound in healthy humans. Phase I studies typically start with one single dose of the study compound and progress to multiple or higher doses, once the previous dose administration proves to be safe. These trials require constant, close monitoring of the subjects. The pharmacokinetic profile of the compound when used in humans is defined in this phase. Other key data are also obtained in phase I, such as the maximum dose tolerated by humans and a preliminary profile of potential toxicity of the compound. This phase may likewise include test-of-concept studies to verify that the efficacy seen in preclinical studies is also observed in humans.

Phase II clinical trial: establishes the safety of using a given compound in human beings. Phase II studies are generally controlled, employing multiple doses of the compound under investigation in order to identify the appropriate dose to achieve the desired therapeutic effect, acceptably balanced between therapeutic benefits and risks, as evidenced by adverse events and other safety measures.

Phase III clinical trial: establishes the safety and efficacy of a compound in a relatively large number of human patients. These large, multicentre studies typically recruit hundreds or thousands of patients. Generally, the dose employed is the optimum dose identified in phase II trials. Phase III trials almost always use placebo or other active-compound control arms. The results obtained are used by regulatory authorities to determine if the safety and efficacy of the given drug compound are appropriate to approve for use in humans.

Phase IV clinical trial: investigations performed after the product has been marketed. Such investigations are based on the characteristics of the drug when it was authorized. Typically, phase IV trials are post-marketing surveillance studies, with the purpose of evaluating the therapeutic value of the drug, appearance of new adverse reactions, frequency of already known reactions, and strategies for optimal treatment. Phase IV studies require the same ethical and scientific standards applied to previous clinical phases.

Pharmacokinetics: branch of pharmacology focused on absorption, distribution, metabolism, and excretion of drugs in living organisms. Pharmacokinetics studies involve a restricted number of volunteers and require a large number of samples per patient. Such studies, however, contain little information about co-variables (e.g. age, gender, weight, etc.), provide limited data about variability in the population, and have a narrow predictive power.

Population pharmacokinetics: this area of pharmacokinetics seeks to quantify the typical parameters of a given population, as opposed to those of a single individual. Population pharmacokinetics models provide information about the population values of pharmacokinetic parameters of a drug, variability among individuals (i.e. differences among individuals within a common population), inter-individual variability (i.e. differences observed in the same individual under different circumstances), and the effect of co-variables (e.g. gender, age, weight, etc.).

In vitro: Latin expression of all biological processes occurring outside living systems, in a controlled, closed, laboratory environment and that are generally performed in glass vessels. *In vitro* processes became popular because they were used for assisted reproduction techniques (IVF, *in vitro* fertilization).

In vivo: Latin expression meaning "that occurs or is performed within an organism". *In vivo* studies relate to experimentation within or inside living tissues of a living organism. Animal testing and clinical trials are forms of *in vivo* research.

Polymerase chain reaction (PCR): method to amplify (create multiple copies of) DNA (deoxyribonucleic acid) with no need to use a living organism, for instance, *Escherichia coli* (bacterium) or yeasts. PCR is mainly applied where available quantities of DNA are limited. In theory, any DNA sequence can be amplified. PCR can be used to identify pathogens existing in samples. PCR is a highly sensitive analysis method, requiring great care to avoid contamination. PCR results are displayed using agarose or polyacrylamide gel electrophoresis, and require analysis and interpretation by a trained professional.