



CHAGAS DISEASE

- *Trypanosoma cruzi* parasite transmitted by the bite of a triatomine vector known as the 'kissing bug'
- Congenital transmission, blood transfusion, organ transplantation, or ingestion of contaminated food or beverages also possible
- Endemic in 21 countries in Latin America but also in Europe, North America, Japan, and Australia
- Occurs in two phases:
 - the initial acute phase, with no or unspecific symptoms in most cases; lasts for about two months after infection, and
 - the chronic phase, where the parasites are hidden mainly in the heart and digestive muscles.
- Up to 30% of chronically infected people develop cardiac alterations and up to 10% develop digestive, neurological, or mixed alterations. In later years, can lead to sudden death due to cardiac complications

70

million people at risk,
mainly in Latin America

6 to 8

million people infected



About
12,000
deaths annually

Less than 1%
of infected people have
access to diagnosis
and current treatments



Current available treatments are more than 40 years old, and while they show good efficacy in the acute phase, they need to be used in long regimens and cause significant side effects. The efficacy and safety of shorter treatment courses and/or at lower doses need to be explored. New drugs and new combinations are also needed, and there is currently no approved treatment for the chronic form of the disease.

Lastly, the dire situation of access and extremely limited use of existing drugs needs to be tackled, caused by a lack of guidelines and policies supporting implementation and the poor availability of medicines.



“I am dedicated to informing my community about Chagas disease, especially the children and youth. But what can I say to those adults that access treatment?”

Duámaco Escribano

Chagas patient and community health activist, Palomino, Colombia

DNDi aims to deliver:

- Alternative regimens of existing drugs (lower doses, shorter treatment duration, and combinations)
- A safe and efficacious new drug treatment of chronic Chagas patients, ideally efficacious for acute Chagas patients, also safe to use during pregnancy
- An early test of cure and/or markers of therapeutic response



Chagas H2L

Hit-to-lead for Chagas disease

OBJECTIVE: Identify new lead series from current ongoing hit-to-lead activities by taking advantage of the optimization consortia and screening platforms for Chagas disease.

Background: The project evaluates hits identified from screening and begins the process of optimizing new chemical series. If promising activity can be demonstrated in *in vivo* models of Chagas disease, the series will be advanced into full lead optimization programmes. This process of hit-to-lead optimization is ongoing with multiple series identified following DNDi screening efforts and coming from several pharmaceutical companies.

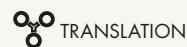


Chagas lead optimization

OBJECTIVE: Optimize leads issued from hit-to-lead series and identify pre-clinical candidates with the potential to fulfill the target product profile.

Background: In order to guarantee a robust pipeline for new drug candidates, a lead optimization strategy is being followed that explores a range of chemical scaffolds.

2016 Two new compounds issued from two new chemical classes showed curative activities against chronic infection of Chagas disease in a bioluminescence imaging mouse model developed by the London School of Hygiene & Tropical Medicine. It was the first time that non-nitroimidazoles compounds have been found to be curative in this model.



New benznidazole regimens +/- fosravuconazole



OBJECTIVE: Evaluate new therapeutic regimens of benznidazole, in monotherapy and in combination with fosravuconazole, for the treatment of adult patients with chronic indeterminate Chagas disease.

Background: Benznidazole, the standard treatment for Chagas, has sustained efficacy until 12 months post-therapy, but is associated with side effects that can result in treatment discontinuation. In 2013, a proof-of-concept trial showed that fosravuconazole, an azole-class antifungal drug discovered by Eisai, had good safety and was effective at clearing the parasite, but efficacy was not sustained. A Phase I drug-drug interaction study assessed the safety and pharmacokinetic interactions of fosravuconazole and benznidazole administered separately and in combination. No major clinically relevant safety or tolerability issues were identified.

2016 Regulatory approvals were secured in Bolivia to start a Phase II Proof of Concept study to determine if the safety and tolerability issues of benznidazole could be managed by reduced doses and treatment duration, or by combining it with fosravuconazole. Benznidazole in monotherapy or in combination with fosravuconazole at selected doses and treatment durations will be assessed versus placebo in 210 patients with chronic Chagas disease. Recruitment started at the end of November; 10 patients had been enrolled by the end of 2016.



Fexinidazole

OBJECTIVE: Evaluate fexinidazole for treatment of chronic Chagas disease.

Background: A Phase II Proof of Concept study of fexinidazole was initiated in 2014 in Cochabamba and Tarija, Bolivia. A total of 47 patients were included, but the study was interrupted due to safety and tolerability issues. Analyses of key outcomes demonstrated high efficacy findings at the lowest dose tested and for all treatment durations, with safety concerns about treatment at high doses tested for more than 14 days. In addition, acceptable safety and tolerability were found at low doses and short treatment durations. Taken together, these results warrant further investigation of fexinidazole for Chagas disease.

2016 A new PoC study has been designed and will be run in four sites in Spain. Recruitment of patients is planned for 2017.



Biomarkers

OBJECTIVE: Identify and evaluate new biological markers of therapeutic efficacy in chronic Chagas disease.

Background: DNDi has been seeking to identify and/or evaluate biomarkers of therapeutic response to treatment, as the only measurable outcomes to date have been the disappearance of anti-Chagas antibodies which, with the exception of children, can take several decades, and clinical benefit. The initial focus has been on optimizing blood sampling procedures and validation of DNA quantification through polymerase chain reaction, one of the key outcome measures in use for clinical trials in Chagas disease.

2016 Pre-clinical studies are ongoing to identify and validate potential biological markers of therapeutic response in Chagas disease patients. In addition, through the Ibero-American network NHEPACHA, DNDi is fostering and encouraging work on testing four biomarkers to assess the response to treatment of Chagas.





Bringing Treatment to the Forgotten 99%

The treatment access pilot programme in Colombia

Treatment of Chagas disease with existing drugs is recommended worldwide but less than 1% of those infected have access to diagnosis and treatment. There are over six million people around the globe infected with *T. cruzi*, the parasite that causes Chagas disease. The disease impact is high in the lives of those affected. It has an important economic burden on countries, with high health care costs and a significant loss of productivity from cardiovascular disease-induced early mortality. This represents a missed opportunity for adding to patients' healthy, productive years of life while reducing the economic burden on the public system.

People with Chagas disease are prevented from receiving the medical attention they need due to many factors that lead to a cycle of neglect. Political and economic inequalities offer structural barriers for access to diagnosis and treatment, as well as the gaps on the health systems, availability of diagnostic and treatment options, and the associated stigmatization, misconceptions, and prejudices about Chagas disease.

In different settings across the world, people are taking action to overcome these obstacles. In Colombia, stakeholders from Government, academia, NGOs, and patient organizations are working in partnership with DNDi aiming to eliminate barriers to diagnosis and treatment for Chagas disease in the country for its estimated 437,000 patients.

This cooperation started in 2015, with a seminar in Bogota that identified four different key barriers to access in Colombia: a lengthy, complex diagnostic process that created long delays; low awareness of Chagas disease among providers and patients; the absence of registered medications and availability; and the fact that specialists who were providing treatment were far from patients' communities.

This analysis led to two initiatives in 2016: first, a patient-centred roadmap was created for Chagas disease and implemented in pilot projects in selected endemic communities in Colombia. Four endemic municipalities volunteered and were selected to join the pilot project in the departments of Boyacá, Santander, Casanare, and Arauca. Second, a new diagnostic model was proposed to the health representatives of each department of the country.

The first capacity building training for health and laboratory workers from Casanare, one of the Colombian departments with the highest prevalence of Chagas disease in the country, took place in December.

Once the model has been tested, it is expected to be extended to the rest of the country – with the support of the Ministry of Health, territorial entities, the National Health Institute, and DNDi – in order to guarantee the diagnosis, care, and timely treatment of patients with Chagas disease. Also, this model could be replicated by other countries in Latin America after the identification of local barriers and a consideration of the contextual analysis ■

A young woman in the village of Jerusalem, close to Rio Claro in the Andes, Colombia

Partnering for Access

Drug registration is an important step to overcoming barriers to accessing medicine.

In June 2016, DNDi and the pharmaceutical company Chemo Group, together with non-profit foundation Mundo Sano, signed a formal collaboration to register benznidazole, the first-line treatment for Chagas disease, in affected countries mainly in Latin America. It also includes the USA, through the Food and Drug Administration (FDA).

DNDi and Mundo Sano's strategy, with partners, is, to scale up access to diagnostics and treatment for Chagas patients – supported by a comprehensive action plan – in both endemic and non-endemic countries.

Alejandro Gaviria

Minister of Health and Social Protection, Colombia



Colombia wants to lead the way in the fight against neglected diseases. Nobody can do this alone and the collaboration with DNDi has shown that it is feasible to address the long-term challenge of Chagas disease in the country. We want to step away from a legacy of human suffering and disease and pave the way to a better future. ■