

Drug trial for top parasitic killer of the Americas: Mixed results, new evidence to improve therapy

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According to results of the first-ever Phase 2 clinical trial in Bolivia, conducted by the Drugs for Neglected Diseases initiative (DNDi), the experimental drug candidate E1224 showed good safety and was effective at clearing the parasite that causes Chagas disease, but had little to no sustained efficacy one year after treatment as a single medication. On the other hand, standard therapy for Chagas, benznidazole, was shown to be effective in the long term but continued to be associated with side effects. The results, presented today at the Annual Meeting of the American Society of Tropical Medicine and Hygiene (ASTMH), highlight the need to investigate alternative dosing regimens and possible combination therapies to improve patient care.

Less than 1% of [patients](#) living with Chagas disease currently receive treatment. The new findings fill a long-standing knowledge gap, providing evidence that will help to inform public health policies and help to increase access to treatment now, as well as shaping the direction of future research for new Chagas therapies.

E1224 is a new antifungal compound discovered and manufactured by the Japanese pharmaceutical company Eisai that is being developed as a treatment for Chagas disease with support from the Wellcome Trust. The Phase 2 double-blind, randomized, controlled trial evaluated the safety and efficacy of E1224 at three different dose regimens and was the first study to collect comprehensive clinical data on the current

approach to treatment, benznidazole. Both treatments were compared to a placebo control.

A total of 231 adult patients with chronic indeterminate (showing no symptoms) Chagas disease were treated for a maximum of 60 days and evaluated at treatment completion and at several different time points up to a 12-month follow-up assessment. The study took place at two sites (Cochabamba and Tarija) in Bolivia, which have the world's highest incidence of Chagas disease.

At end of treatment, E1224 was found to be safe and efficacious in clearing the Chagas parasite in patients when compared to placebo and to benznidazole. Few patients receiving the highest dose stopped treatment with E1224 due to side effects, less than in the benznidazole group. However, at 12 months after treatment, less than one third of patients treated with E1224 continued to maintain parasite clearance compared with over 80% of patients treated with benznidazole, demonstrating relatively low sustained eradication rates with E1224 in this study.

"In this prospective placebo-controlled study, these mixed results actually have provided very important scientific evidence on new drug development for Chagas disease, which has long been ignored," said Dr Isabela Ribeiro, Head of the Chagas Clinical Programme at DNDi, and the E1224 Project Leader. "We now have clear safety and efficacy data on two compounds that will be very useful in guiding future Chagas disease drug research efforts."

Although E1224 was found to be ineffective as a single-treatment agent (monotherapy), it holds promise for use in combination with existing drugs, since it showed strong positive activity during treatment, with a third of patients having a sustained treatment response at the higher dose. E1224 will no longer be tested as monotherapy for Chagas disease, but DNDi and Eisai are exploring the possibility of testing E1224 in

combination therapy with benznidazole

"Eisai remains committed towards the elimination of neglected tropical diseases and hopes to continue collaboration with DNDi in future studies that could determine the role that E1224 may play in the treatment of chronic indeterminate Chagas disease and provide newer and better treatment options for patients suffering from this disease," stated Dr Frederick P. Duncanson, Senior Director of Chief Innovation Officer Group at Eisai Inc., and the E1224 Project Leader at Eisai.

In addition to evaluating E1224, the study was the first to compare the clearance of Chagas parasites (*Trypanosoma cruzi*) with benznidazole treatment versus placebo in adults with chronic indeterminate Chagas disease. Benznidazole had a rapid and sustained effect, with significant drop in parasite counts after just one week of treatment. Some patients experienced adverse events, mostly nausea, skin reactions, and muscle and nerve pain. Since benznidazole treatment is typically 60 days long and undesirable side effects are common, shorter courses of the drug may be safer yet still effective. Based on these study findings, DNDi will investigate shorter-course treatments with benznidazole.

The study was the first Phase 2 clinical trial conducted in Bolivia, exemplifying the strengthening and sustaining of research capacity in a resource-limited, developing-country setting. A total of 97% of the enrolled patients completed follow-up at 12 months post-treatment, with only 7 of the 231 patients being lost to follow-up. Important Chagas patient data were collected on pharmacokinetics and pharmacodynamics, characterization of the parasite population before and after treatment, and candidate biological markers for evaluation of treatment response.

"The completion of this drug trial was a success story for Chagas patients, doctors, and researchers in Bolivia, demonstrating that excellent clinical testing can be carried out in endemic countries," said Dr

Faustino Torrico of Universidad Mayor de San Simon in Cochabamba, Bolivia, and one of the lead investigators. "The data generated were of high quality, and our clinical sites and research teams gained valuable experience and are ready to perform future studies."

"Chagas disease is one of world's most neglected illnesses, and millions of patients continue to be ignored and many needlessly die from the lack of treatment access and options," said Dr Bernard Pécoul, Executive Director of DNDi. "We have to take advantage of these important study results to scale up [treatment](#) access now, while we maintain momentum in developing safer, more effective, life-saving new treatments for Chagas patients around the world."

Provided by Drugs for Neglected Diseases Initiative

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