The BENDITA study:

A Phase II study to assess safety, tolerability, and efficacy of different benznidazole regimens, alone and in combination with fosravuconazole

Background

Chagas disease, or American trypanosomiasis, is a neglected tropical disease endemic in 21 countries in Latin America, but present also in North America, Europe, Japan, and Australia. It is caused by the parasite *Trypanosoma cruzi* and transmitted mainly by blood-sucking triatomine insects known as "kissing bugs". Transmission is also possible from an infected mother to her baby, via blood transfusions and organ transplantation, and by eating food contaminated by the insect's feces.

As the disease usually remains asymptomatic for years after infection, most people with the disease are unaware of their condition. For 30-40% of people infected, the disease progresses to a late chronic stage. Of these, most will suffer cardiac damage, often leading to sudden death or progressive heart failure. The disease can also cause enlargement of the gastrointestinal tract and organs and gastrointestinal motor disorders.

There are currently only two drugs available to treat Chagas disease – nifurtimox and benznidazole – both discovered half a century ago. Treatment with the drug most commonly used, benznidazole, has proven effective in the acute and chronic indeterminate stages, with around 80% of patients showing no evidence of parasites in the blood 12 months after finishing treatment. However, this treatment has limitations: it lasts 60 days, and some 20% of patients stop treatment due to the side effects, which include gastric intolerance, skin rashes, or neuromuscular problems. Some patients do not even want to start the treatment as a result. The side effects and treatment duration are among the main barriers to treating more people with Chagas. Of the 6 million people estimated by the World Health Organization (WHO) to have Chagas disease, fewer than 10% have been diagnosed, and of those, very few receive the treatment they need.

1 Why have we done this study?

While searching for new and better drugs to treat Chagas disease, DND*i*, ISGlobal, and CEADES are also working to improve the efficacy, safety, and tolerability of treatment with existing drugs. New drug discovery and development take time, and patients need better treatment now, while research continues for new drugs.

Based on the idea that the side effects of the standard treatment may be related to the dose or treatment duration, DND*i* decided to test the efficacy of new regimens where the patient's exposure to benznidazole would be reduced, either due to shorter treatment, lower doses, or both. The objective of the BENDITA study (Benznidazole New Doses Improved Treatment & Therapeutic Associations) was to find regimens that were at least as effective as the standard treatment, while producing fewer side effects and, consequently, improving patients' adherence to treatment. Fewer side effects would make the treatment more acceptable not only to patients, but also to caregivers and physicians, removing one of the main barriers to treating more people with Chagas disease.

2 What exactly did we test?

BENDITA was a double-blind, Phase II, randomized, placebo-controlled study carried out in sites of the Chagas Platform that CEADES and ISGlobal coordinate in Cochabamba, Tarija, and Sucre, Bolivia, between 2016 and 2018. It tested, against a placebo, six benznidazole treatments of differing lengths and dosages, both as a monotherapy (i.e., benznidazole alone) and in combination with fosravuconazole, a broad-spectrum anti-fungal drug.

BENDITA is the first randomized controlled trial to assess the efficacy of different benznidazole regimens. **A total of 210 adult patients with chronic indeterminate Chagas disease participated in the study, randomized to one of the following six treatment regimens:**

- **The standard 8-week treatment**, with a daily dose of **300mg/day** of benznidazole in monotherapy
- **A shorter, 4-week treatment** with a **standard daily dose** of **300mg/day** of benznidazole in monotherapy
- **A shorter, 2-week treatment** with a **standard daily dose** of **300mg/day** of benznidazole in monotherapy
- **A shorter, 4-week treatment** with a **lower daily dose of 150mg/day** of benznidazole in monotherapy
- **A shorter, 4-week treatment** with a **lower daily dose of 150mg/day** of benznidazole, in combination with fosravuconazole
- **An 8-week treatment**, with a **lower weekly dose of 300mg** of benznidazole, in combination with fosravuconazole.

3 How did we measure treatment efficacy?

There is no test of cure for Chagas disease. In itself, this is a barrier to treatment and another area in which DND*i*, ISGlobal, and CEADES are conducting research. To assess treatment efficacy, we use molecular biology, which allows us to identify parasites present in the blood through blood tests done six and twelve months after the end of treatment. For BENDITA, efficacy was measured by testing for the absence of parasite DNA in the blood using PCR, a particular laboratory technique used to detect DNA in blood samples. Patients with no signs of the parasite in any blood tests up to 12 months after the end of the study were considered to have been successfully treated.

4 What were the results?

More than 80% of patients in all treatment groups responded to treatment (i.e., had no detectable parasite in blood tests after completing treatment or at the 12-month follow-up), compared to 3.3% in the placebo group. Sustained treatment responses 12 months after treatment was completed ranged from 82.1% of patients treated with the standard 300mg benznidazole dose for a shorter 2-week period to 88.9% of patients receiving the same dose for a 4-week period. The efficacy among patients receiving the standard 300mg benznidazole dose combined with fosravuconazole for 4 weeks was 83.3% and it was 84% in patients receiving a weekly dose of benznidazole combined with fosravuconazole for 8 weeks.

The new regimens were well-tolerated and had very good safety profiles. No severe adverse effects were observed in any of the patients who took 300mg benznidazole for 2 weeks. In the group that took 150mg benznidazole for 4 weeks, only one patient out of 30 had to discontinue treatment due to side effects. Among patients that took the standard regimen of 300mg/day benznidazole for 8 weeks, 6 out of 30 patients discontinued treatment due to side effects. This rate of treatment discontinuation was as expected and is consistent with other studies using standard regimens (5 mg/kg/day for 60 days).

5 What does it mean for the future of people with Chagas disease?

While all the new treatment regimens were efficacious and had good safety profiles, the 2-week treatment arm is particularly promising as it is significantly shorter than the standard treatment, and all patients were able to complete the course. Although this study was conducted with a small number of people, the fact that benznidazole is an old, well-known drug and that the results show a good safety profile for the shorter regimen gives us reason to believe that this new regimen should be proposed without delay for consideration for adults with chronic indeterminate Chagas. Meanwhile, the current regimens can continue to be prescribed and provide known benefits.

We are still completing the analysis of the combination arms (benznidazole combined with fosravuconazole) to assess its potential indication for certain groups of patients with specific needs.

Changing the treatment protocol to reduce treatment duration from 8 weeks to 2 weeks could help remove one of the main barriers to expanding access to Chagas treatment in the region. The shorter treatment would remove some common concerns of both caregivers and patients, and thus improve treatment adoption. It would also reduce treatment costs for national programmes. DND*i* will now work with the Pan-American Health Organization/WHO, national programmes, health ministries, and other partners to propose a policy change and registration of this new indication.

Analysis of parasitological response at 6-month follow-up and 12-month follow-up★

	BZN 300 mg 8 wks	BZN 300 mg 4 wks	BZN 300 mg 2 wks	BZN 150 mg 4 wks	BZN 150 mg 4 wks/ E1224 300 mg	BZN 300 mg (Weekly) 8 wks/ E1224 300 mg	Placebo
6-months of follow-up	89.3	89.3	82.8	83.3	85.2	82.8	3.3
12-months of follow-up	82.8	89.3	79.3	80.0	85.2	82.8	3.3
Subjects with treatment-related side effects leading to treatment discontinuation	6 (20.0)	2 (6.7)	0	1 (3.3)	3 (10.0)	4 (13.3)	0

★ *Intention to treat analysis, meaning that all patients enrolled in the study and randomized to a treatment arm were included in the analysis, whether or not they started or completed treatment.*

Who were the partners in the study?

The trial was conducted in partnership with CEADES (Fundacion Ciencia y Estudios Aplicados para el Desarrollo en Salud y Medio Ambiente), ISGlobal, Japanese pharmaceutical company and manufacturer of fosravuconazole Eisai Co. Ltd., Argentinian pharmaceutical company manufacturer of benznidazole Elea, and associated non-profit foundation Fundación Mundo Sano, among others, and funded by the Global Health Innovative Technology Fund (GHIT).