Spanish group defeats Shkreli in Chagas voucher race

The US Food and Drug Administration (FDA) approved for the first time a small-molecule drug to treat Chagas disease or American trypanosomiasis in children. The anti-parasitic benznidazole, has been around for over 40 years but until now it lacked an official go-ahead. With the approval of benznidazole on August 29, its manufacturer Chemo Research, with Mundo Sano and Drugs for Neglected Diseases initiative earned a lucrative Tropical Disease Priority Review Voucher (PRV). It's a fitting prize for a global consortium that managed to pool their resources in time to beat notorious Martin Shkreli, recently found guilty of securities fraud, to the finish line.

The 'kissing bug disease', so-called because it is spread by an insect that tends to bite victims in the face while they sleep, affects around 300,000 people in the US and about 8 million people worldwide, mainly in Latin America. Chagas disease is caused by the *Trypanosoma cruzi* parasite, which is transmitted mainly by the blood-sucking insect vector, but people also become infected congenitally and by blood transfusion. The initial stages of infection are those most responsive to drug treatment. If left untreated, however, parasites persist in tissues and organs, and may result, decades later, in cardiomyopathy and gastrointestinal disease. About 30% of untreated patients eventually die of heart failure.

Two drugs are used to treat Chagas: benznidazole, and the drug nifurtimox manufactured by Bayer. Both have similar mechanisms of action; they generate free radicals, which damage the parasite's capacity to reproduce. But patients have a low tolerance to the Bayer molecule so benznidazole remains the first-line treatment.

Benznidazole is an old treatment: Roche introduced it to the market in 1971. But drug sales were weak, mostly because governments preferred vector control, and the Swiss pharma eventually sold rights to the drug in 2003 to Brazilian company Lafape, based in Recife. Although Lafape undertook to supply the region, the firm struggled to keep up with growing demand. The drug's manufacture moved to Argentine company Elea Laboratories (later acquired by the Madrid-based Chemo).

Access has remained problematic. In the US, for instance, the only way infected people can access the drug is through an investigational protocol from the Centers for Disease Control and Prevention in Atlanta. Chemo's Argentine owners were committed to solving supply and access issues, so they began discussions with the FDA in 2013 to register the drug in collaboration with Mundo Sano Foundation, a non-profit which they set up a decade earlier.

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An old drug to treat parasitic infections caused by *Trypanosoma cruzi* (pictured) suddenly became a hot commodity.

Then all changed abruptly in 2015 when the FDA included Chagas in a list of diseases that qualified for a priority review voucher (PRV). This PRV scheme was set up by the FDA to encourage pharma investment in neglected tropical diseases (*Nat. Biotechnol.* **26**, 1315–1316, 2008). "Although benznidazole has been used for decades, this was the first registration in the US," says Isabela Ribeiro, scientific lead at the DNDi, explaining why the drug would qualify for a voucher on approval.

Shkreli took note. PRVs can be used to speed up the drug review process, and companies might choose to use them themselves or sell them. Since the FDA introduced PVRs, they have fetched \$25–350 million (*Nat. Biotechnol.* **33**, 1120, 2015).

Shkreli's company KaloBios (later renamed Humanigen) acquired rights to one version of benznidazole from small pharma Savant. Shkreli not only expected to snag a voucher for its drug, but also intended to raise the prize to almost \$100,000 (the drug now costs \$60–100 a treatment).

The Chagas community was alarmed. Activists, medical groups and the DNDi came together and summoned investigators to gather existing raw clinical data from randomized controlled clinical trials that had been performed over the years. The agency expected to see the full package: old and new clinical trials and preclinical data, says Ribeiro.

Chemo submitted that package to the FDA, gaining an approval and a PRV. "We were already working with the regulator to set out the requirements for registration," says DNDi's Ribeiro. "For us it was a great outcome," says DNDi's Ribeiro. Once the voucher is sold, Chemo has agreed to invest half the money to increase access and raise awareness of Chagas disease and to advance biomarker and diagnostic work. Brisbane, California-based Humanigen, which is no longer associated with Shkreli, was contacted for this article but spokesperson Heather Anderson did not confirm whether development for the anti-parasitic drug continued, stating that the company is still assessing its options. The DNDi in collaboration with Tokyo-based Eisai also has a small molecule E1224, a prodrug of fosravuconazole, undergoing phase 2 trials in combination with benznidazole.

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“[Recruiting minorities] was always going to be a challenge, and [the 2016 election] hasn't helped. This study and its design and its legislative authority has always said that none of the info provided can be used for any other purpose.” Adolph Falcón, of the National Alliance for Hispanic Health, a partner of NIH's massive genome study, was alluding to minority groups' mistrust of government programs. (STAT News, 22 September 2017)