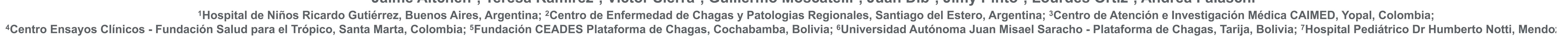
# LACK OF CONGENITAL TRANSMISSION IN INFANTS BORN OF FEMALE PATIENTS WITH CHAGAS DISEASE WHO BECAME PREGNANT DURING A NIFURTIMOX STUDY (CHICO AND CHICO SECURE)\*

Jaime Altcheh<sup>1</sup>, Teresa Ramirez<sup>2</sup>, Victor Sierra<sup>3</sup>, Guillermo Moscatelli<sup>1</sup>, Juan Dib<sup>4</sup>, Jimy Pinto<sup>5</sup>, Lourdes Ortiz<sup>6</sup>, Andrea Falaschi<sup>7</sup>

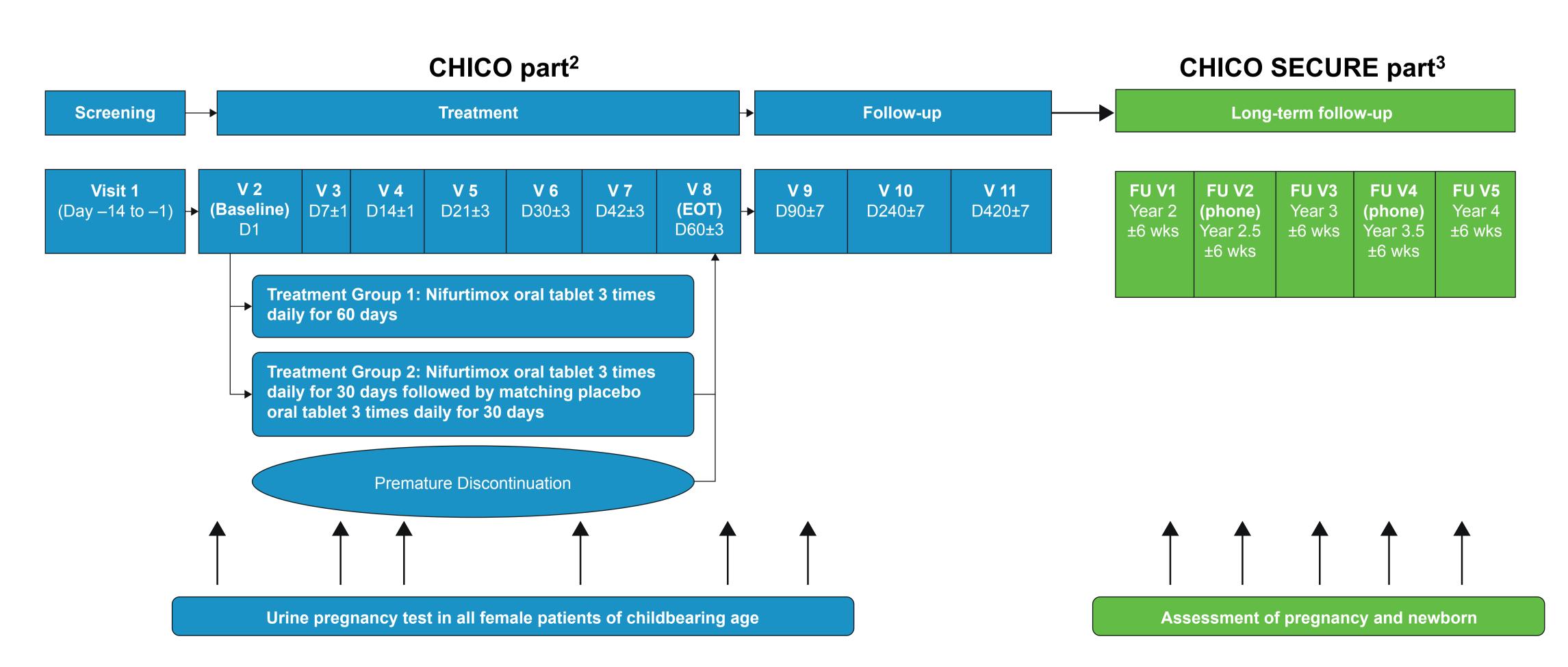




### Introduction

- Chagas disease (American trypanosomiasis) is a vector-borne neglected tropical disease caused by Trypanosoma cruzi. T. cruzi infection is endemic in Latin America, however, due to migration of infected individuals, Chagas disease is becoming a public health problem in non-endemic countries. Currently, around 300,000 T. cruzi-infected people live in the USA.
- Control of the spread of the disease via the triatomine insect vector and through blood transfusions has improved over recent years. However, controlling transplacental transmission remains a challenge. Currently, vertical transmission is the most common route of transmission in non-endemic countries, with the frequency of maternal-fetal transmission varying between 3.9% to 5.6%.
- The treatment of Chagas disease with nifurtimox or benznidazole is typically delayed until after pregnancy due to concerns around drug safety.
- Nifurtimox (Lampit, Bayer AG) has been shown to be safe and efficacious in the treatment of patients with Chagas disease. A new formulation was approved by the FDA under the provision of accelerated approval regulations (21 CFR 314.500) to treat Chagas disease in patients younger than 18 years of age and weighing at least 2.5 kg.
- Based on findings from animal studies, nifurtimox can cause fetal harm when administered to a pregnant woman. Pregnancy testing is recommended for women of childbearing age prior to initiating nifurtimox treatment, and the use of effective contraception during treatment and for 6 months after the last dose is also recommended.
- Women should be screened for *T. cruzi* infection before or during pregnancy. A previous study reported that benznidazole treatment prevented vertical transmission of Chagas disease to the offspring of mothers treated prior to their pregnancy. Evidence supporting similar efficacy for nifurtimox is lacking.
- We investigated the outcomes of pregnancies in female patients with Chagas disease after treatment with nifurtimox in a phase 3 clinical trial (CHICO<sup>2</sup> and CHICO SECURE<sup>3</sup>), with particular focus on the mother-to-child transmission of *T. cruzi*.

Figure 1. Study design overview



D, day; FU, follow-up; V, visit.

<sup>1</sup>Moscatelli G, Moroni S, Garcia-Bournissen F, et al. Prevention of congenital Chagas disease through treatment of girls and women of childbearing age. Mem Inst Oswaldo Cruz 2015;110(4):507-9.

<sup>2</sup>Altcheh J, Castro L, Dib JC, et al. Prospective, historically controlled study to evaluate the efficacy and safety of a new pediatric formulation of nifurtimox in children aged 0 to 17 years with Chagas disease one year after treatment (CHICO). PLoS Negl Trop Dis 2021;15(1):e0008912. <sup>3</sup>Atcheh J, Sierra V, Ramirez T, et al. Efficacy and safety of nifurtimox in pediatric patients with Chagas disease: results at 4 years follow-up in a prospective, historically controlled study (CHICO SECURE). Manuscript submitted for publication.

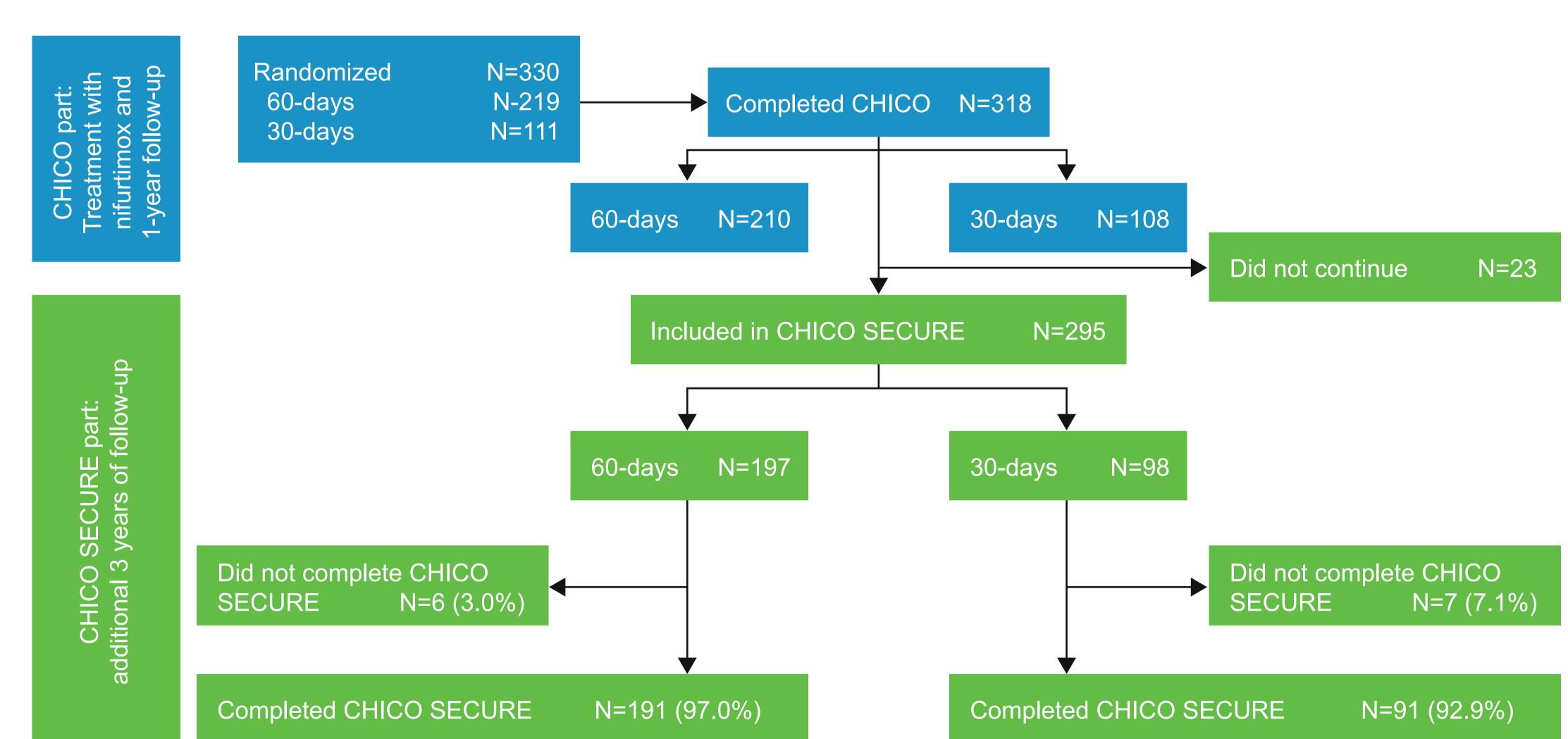
#### Methods

• CHICO<sup>2</sup> and CHICO SECURE<sup>3</sup> were the two parts of a multicenter, multinational, randomized, double-blind phase 3 clinical trial (NCT02625974) that evaluated the efficacy and safety of nifurtimox in the treatment of pediatric patients with Chagas disease

(Figure 1). Figure 2. Study countries

- Study population: male and female children (0 days to 17 years) with Chagas disease.
- Study sites: Argentina (18 centers), Bolivia (3 centers), and Colombia (4 centers) (Figure 2).
- Diagnosis of Chagas disease was confirmed by:
- direct observation of *T. cruzi* using a parasitological concentration test in patients aged <8 months
- positive results from both recombinant and total purified antigen conventional ELISA in patients aged betwen 8 months and <18 years.

Figure 3. Patient demographics (all enrolled patients)



- A total of 330 children were each randomly assigned to one of two treatment regimens: nifurtimox treatment for 60 days (n=219); or nifurtimox treatment for 30 days followed by matching placebo for 30 days (n=111) (Figure 3).
- Nifurtimox was administered in age- and body weight-adjusted doses three times daily:
  - <40 kg body weight: 10-20 mg/kg/day</li>
  - ≥40 kg body weight: 8-10 mg/kg/day.
- Patients had to agree to use an effective method of contraception until 3 months after the last administration of nifurtimox.
  - Pregnancy tests were performed at screening, during treatment, and 30 days after the end of treatment.
- At the post-treatment follow-up visits in CHICO SECURE, patients were asked about current pregnancies or births that took place during the study.
  - Patients that gave birth were invited to test their infants for *T. cruzi* infection.
- Patients were followed for 4 years after the end of nifurtimox treatment.

Principal investigators of the CHICO and CHICO SECURE Study Group: H. Abate (ARG), J Altcheh (ARG, L. Arce (ARG), A. Cancellara (ARG), A. Caruso (ARG), L. Castro (COL), R. De La Fuente, (ARG), M. Diaz Ariza (ARG), J. Dib (COL), C. Dominguez (ARG), R. Duarte (ARG), G. Ensinck (ARG), A. Falaschi (ARG), M. Jofre (ARG), C. Llapur (ARG), I. Menna (ARG), C. Monla (ARG), J. Morales (ARG), G. Moscatelli (ARG), L. Ortiz Daza (BOL), J. Pinto (BOL), F. Quiroz (COL), T. Ramirez (ARG), A. Romano (ARG), J. Sanchez (BOL), M. Serjan, (ARG), V. Sierra (COL), M. Sosa (ARG)

#### Results



Table 1. General pregnancy data					
	CHICO part		CHICO SECURE part		
Females of childbearing age	67				
	60-day regimen	30-day regimen	60-day regimen	30-day regimen	
Number of pregnancies*	3 (3 patients)	2 (2 patients)	14 (13 patients)	4 (4 patients)	
Argentina	2 (2 patients)	1 (1 patient)	7 (6 patients)	2 (2 patients)	
Bolivia	0	1 (1 patient)	2 (2 patients)	1 (1 patient)	
Colombia	1 (1 patient)	0	5 (5 patients)	1 (1 patient)	
Number of pregnancies during nifurtimox treatment	0	0	Not applicable	Not applicable	
Age at randomization in patients with pregnancies (range)	16 years	15 – 16 years	11 – 17 years	12 – 16 years	
General outcome of pregnancy	<ul> <li>2 full-term, healthy newborns</li> <li>1 full-term, low birth weight newborn</li> </ul>	<ul> <li>1 full-term, healthy newborn</li> <li>1 elective abortion</li> </ul>	<ul> <li>13 full-term, healthy newborns</li> <li>1 case with no information on health status of newborn</li> </ul>	<ul> <li>3 full-term, healthy newborns</li> <li>1 case with no information on health status of newborn</li> </ul>	

\*Two patients became pregnant twice during the study.

- Table 1 gives an overview of the pregnancies that occurred during the study and the health status of the newborns.
- No pregnancies were reported during nifurtimox treatment.
- 5 pregnancies were reported during the 1st year of post-treatment follow-up (CHICO).
  - The last menstrual period in those patients that became pregnant during CHICO was between 1 and 7 months after the end of treatment.
- Another 18 pregnancies were reported during the additional 3-year follow-up period in CHICO SECURE.
  - All mothers were T. cruzi RT-PCR negative at the end of the treatment period and remained negative during follow-up.
  - Two females did not consent to have their babies tested for *T. cruzi* infection.
- No maternal-fetal transmission of T. cruzi was observed (Table 2).

Table 2. Incidence of congenital *T. cruzi* infection in children born to CHICO SECURE study participants



Congenital infection*	Total N=19 (100%)		
Yes	0		
No	19 (100%)		
Confirmed by ELISA	14 (73.68%)		
Confirmed by microbial concentration	12 (63.16%)		

Some infants were tested for *T. cruzi* infection using both serology and parasitology In some infants, investigation of congenital infection with *T. cruzi* was performed outside of the clinical trial.

## Conclusions

- No cases of mother-to-child *T. cruzi* transmission were observed in female patients with Chagas disease who became pregnant after treatment with nifurtimox in a phase 3 clinical trial.
- Although the number of cases in our study is limited, our findings reinforce previously published data supporting the benefits of treating Chagas disease in females of childbearing age in the prevention of congenital *T. cruzi* transmission.

Mailing address: Hospital de Niños Ricardo Gutierrez, Gallo 1330, C1425, Buenos Aires, Argentina eMail: jaltcheh@gmail.com Phone number: + 54 11 4963 4122



<sup>\*</sup>The study was sponsored by Bayer AG, Leverkusen, Germany