Tratamiento de la enfermedad de Chagas

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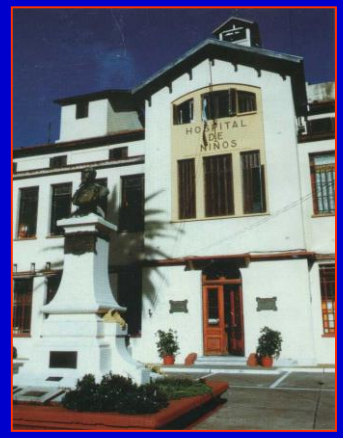

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Servicio de Parasitología-Chagas
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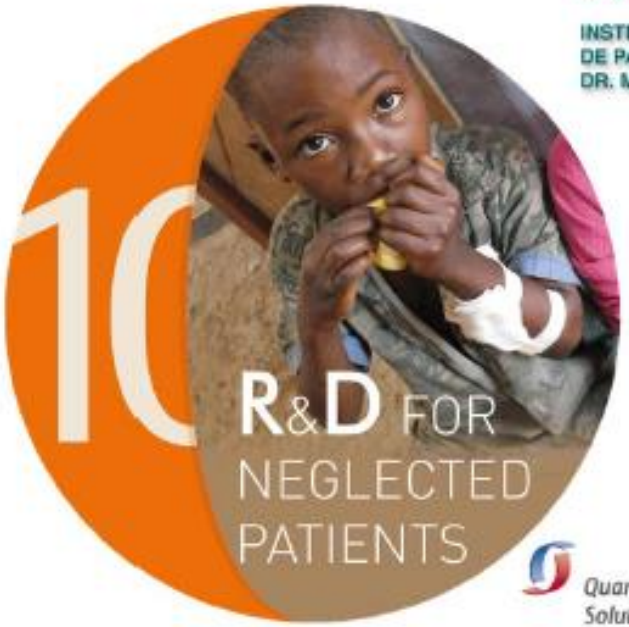
Buenos Aires, Argentina
Centro Colaborador OPS / OMS en Enfermedad de Chagas Pediátrica (2016)

Organización Panamericana de la Salud
Organización Mundial de la Salud Américas

PEDCHAGAS



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PEDCHAGAS

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gsk

Laboratorio ELEA


Falsa sensación de
Enfermedad de Chagas
Límites de país
Transmisión por el principal vector
Septiembre 2014
Área endémica donde la interrupción de la transmi vectorial no es una meta
Área endémica donde la transmisión por el vector ha sido interrumpida
Área donde la transmisión por el vector principal está cercana a la interrupción
Área donde la transmisión por el vector principal está interrumpida
Área donde el principal vector ha sido eliminado
Área no endémica sin evidencia de transmisión vectorial
Áreas no participantes
1,500 2,000
Datum: WGS 1984
Units: Degree
Fuente de Datos:
PAHO/CHA/CD
Control de Enfermedad de Chagas
Producción del Mapa:
PAHO/CHA/R

Table 1 **Estimated demographic and epidemiological parameters of Chagas disease in Latin America by country, 2010**
Tableau 1 **Estimation des paramètres démographiques et épidémiologiques de la maladie de Chagas en Amérique latine par pays, 2010**

Latin American countries – Pays d'Amérique latine	Population	Estimated no. of people infected by *T. cruzi* – Estimation du nombre de personnes infectées par *T. cruzi*	Estimated annual no. of new cases due to vectorial transmission – Estimation du nombre annuel de nouveaux cas dus à la transmission vectorielle	Estimated no. of women aged 15–44 years with *T. cruzi* infection – Estimation du nombre de femmes âgées de 15 à 44 ans infectées par *T. cruzi*	Estimated annual no. of cases of *T. cruzi* infection due to congenital transmission – Estimation du nombre annuel de cas d'infection à *T. cruzi* dus à la transmission congénitale	Estimated prevalence of *T. cruzi* infection per 100 habitants – Estimation de la prévalence des infections à *T. cruzi* pour 100 habitants	Estimated incidence due to vectorial transmission per 100 habitants – Estimation de l'incidence due à la transmission vectorielle pour 100 habitants	Estimated incidence of *T. cruzi* infection due to congenital transmission per 100 live births – Estimation de l'incidence des infections à *T. cruzi* dues à la transmission congénitale pour 100 naissances vivantes	Estimated population at risk of *T. cruzi* infection – Estimation de la population exposée au risque d'infection à *T. cruzi*	Estimated no. of people with Chagasic cardiopathy – Estimation du nombre de personnes atteintes de cardiopathie chagasique	Estimated prevalence of *T. cruzi* infection among blood donors – Estimation de la prévalence de l'infection à *T. cruzi* chez les donneurs de sang
Argentina – Argentine	41 343 000	1 505 235	1 078	211 102	1 457	3.640	0.0020	0.210	2 242 528	376 309	3.130
Belize	315 000	1 040	10	272	25	0.330	0.0030	0.333	70 252	200	N/A
Bolivia – Bolivie	9 947 000	607 186	8 087	199 351	616	6 104	0.0810	0.235	586 434	121 437	2.320
Brazil – Brésil	190 755 799	1 156 821	46	119 298	571	0.03	0.084 per 100.000 – 0.084 pour 100.000	0.020	25 474 365	231 364	0.180
Chile – Chili	17 095 000	119 660	0	11 771	115	0.699	0	0.046	0	35 898	0.160
Colombia – Colombie	45 805 000	437 960	5 274	116 221	1 046	0.956	0.0110	0.114	4 813 543	131 388	0.410
Costa Rica	4 516 000	7 667	10	1 728	61	0.169	0.0002	0.080	233 333	2 300	0.045
Ecuador – Équateur	14 483 499	199 872	2 042	62 898	696	1.379	0.0140	0.317	4 199 793	40 384	0.190
El Salvador	6 952 000	90 222	972	18 211	234	1.297	0.0130	0.187	1 019 000	18 044	1.610
Guatemala	13 550 000	166 667	1 275	32 759	164	1.230	0.0090	0.035	1 400 000	20 833	1.340

Urban Chagas disease in children and women in primary care centres in Buenos Aires, Argentina

Guillermo Moscatelli[1]/+, Ada Berenstein[2], Ana Tarlovsky[3], Susana Siniawski[2], Miguel Biancardi[1], Griselda Ballering[1], Samanta Moroni[1], Marta Schwarcz[4], Susana Hernández[4], Facundo García-Bournissen[1], Andrés Espejo Cozzi[4], Héctor Freilij[1], Jaime Altcheh[1]

[1]Ricardo Gutiérrez Children's Hospital, Department of Parasitology and Chagas, Buenos Aires, Argentina [2]Primary Care Centre, Community Action Centre 15, Buenos Aires, Argentina [3]Primary Care Centre, Community Action Centre 11, Buenos Aires, Argentina [4]Interamerican Open University, Centre of Studies on Human Science and Health, Buenos Aires, Argentina

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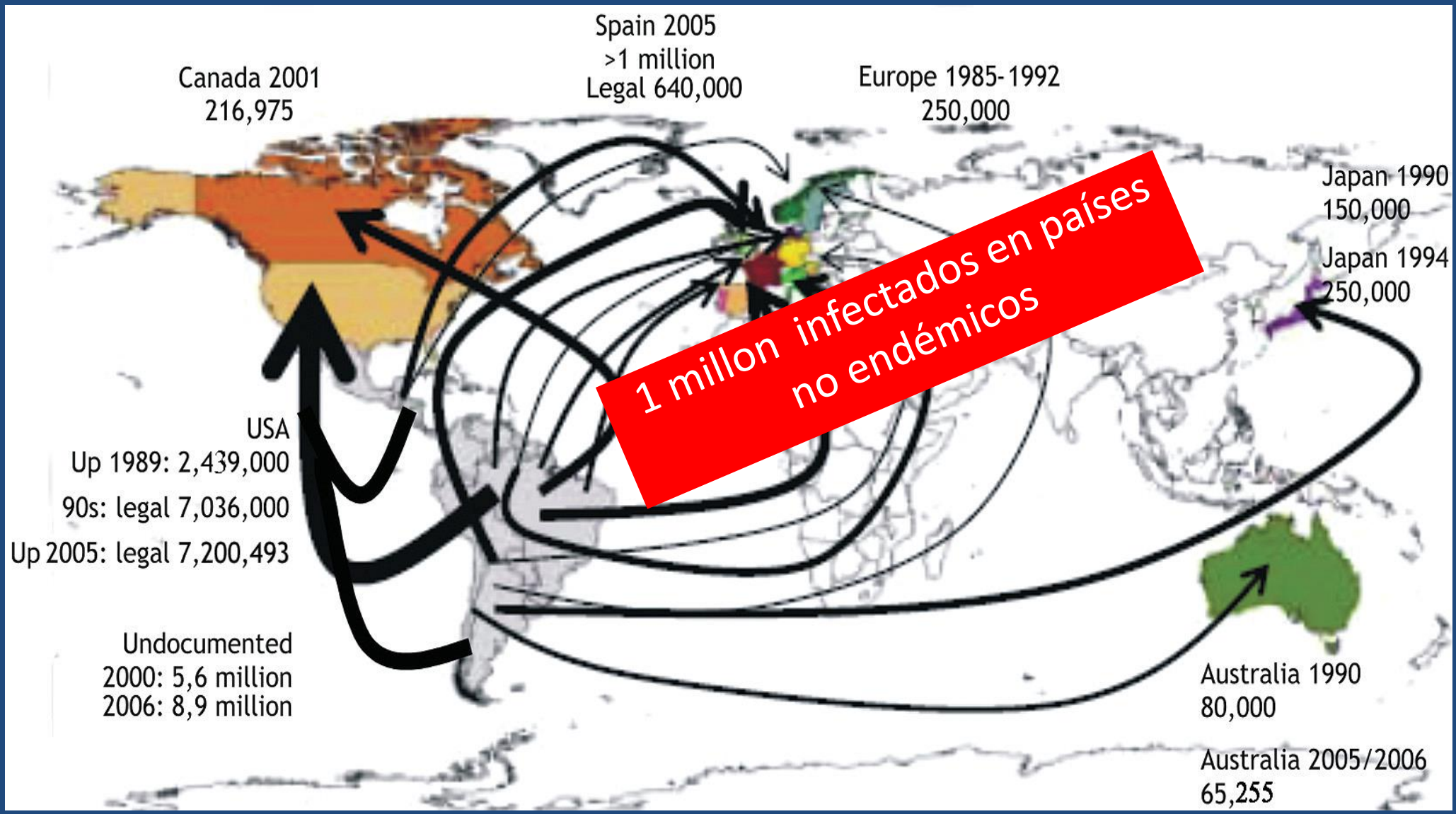
Flujo migratorio



Schmunis G. Mem Inst Oswaldo Cruz 2007. 102(Suppl. I):75

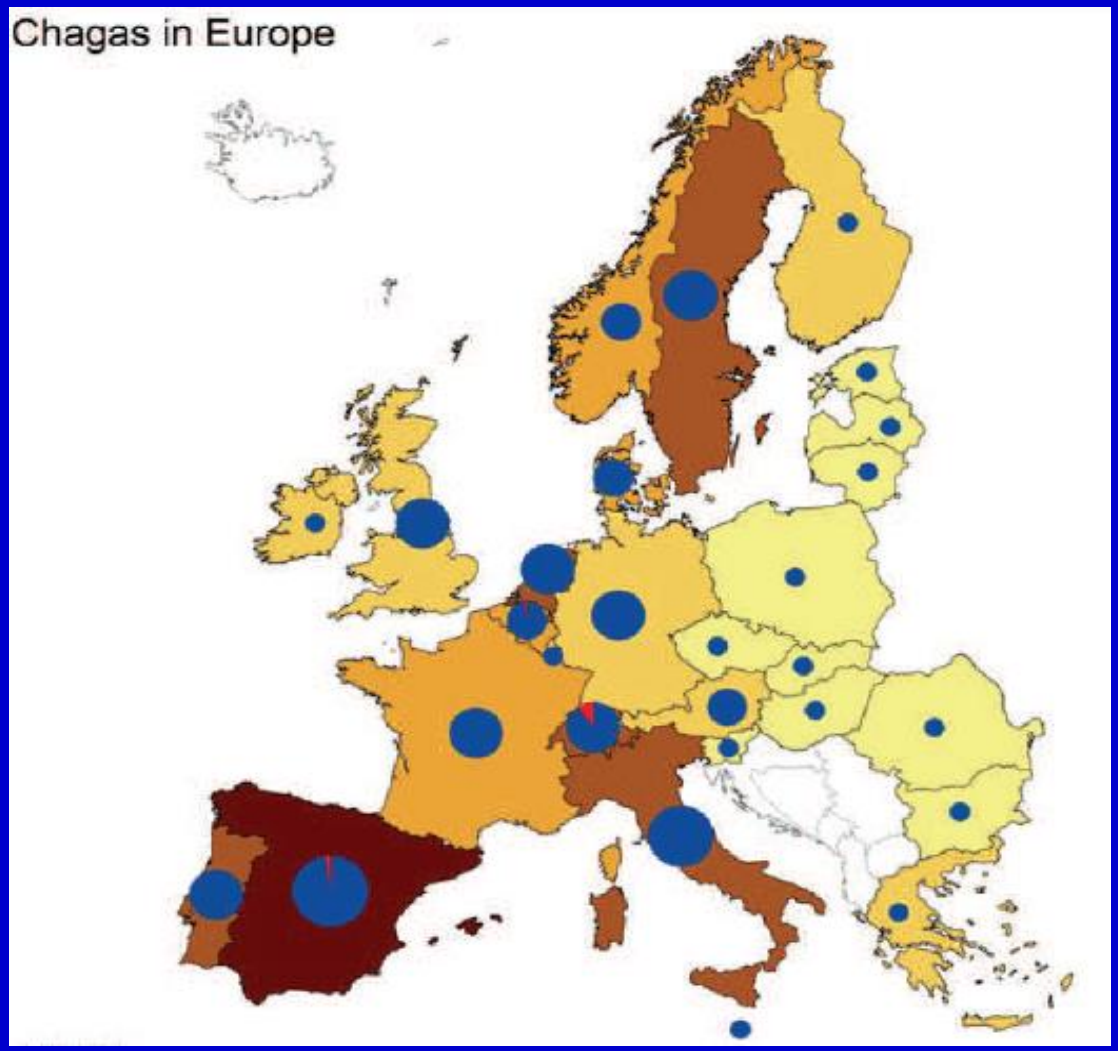
Estimated number of Chagas disease cases in North America.

40,000 embarazadas con *T. cruzi* ,
con 2,000 casos congenitos

Segun OPS los casos congenitos producen mas de un cuarto de los nuevos casos de enfermedad de Chagas

Hotez PJ, Dumonteil E, Betancourt Cravioto M, Bottazzi ME, et al. (2013) An Unfolding Tragedy of Chagas Disease in North America. PLoS Negl Trop Dis 7(10): e2300. doi:10.1371/journal.pntd.0002300
http://www.plosntd.org/article/info:doi/10.1371/journal.pntd.0002300

PLOS | NEGLECTED TROPICAL DISEASES



- **100.000 infectados**
  - **Mayor prevalencia en España**
- **75,000 casos (approx.60 % mujeres en edad fertil)**
- **94 centros diagnostican CD**
- **2014: approx. 1,800 pts tratados**

Source: "Epidemiology of Chagas' disease in Europe: many calculations, little knowledge": J. Strasen et al. Clin. Res. Cardiol.(2014), 103:1-10

Tratamiento

Benznidazol (Lafepe, Brasil, Abarax®, ELEA)

Dosis: 5-10 mg/Kg/día en 2 dosis.

Presentación: comprimidos 12.5?, 50 y 100 mg.

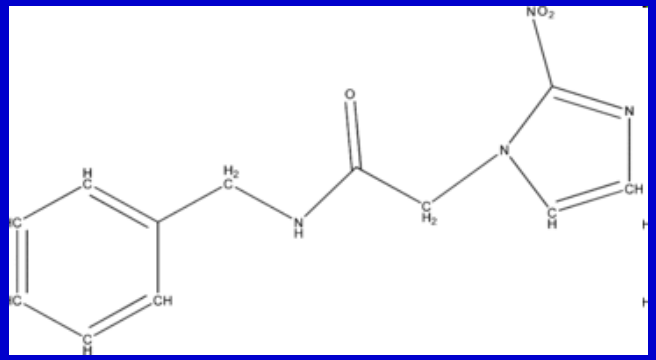
Nifurtimox (Lampit®, Bayer)

Dosis: 10-15 mg/Kg/día en 3 dosis.

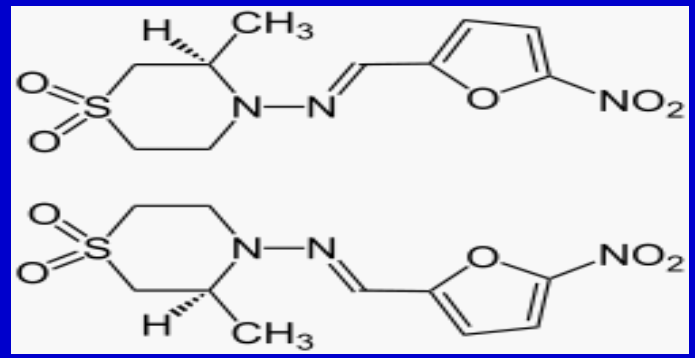
Presentación: comprimidos 120 mg. 30 mg ?

Duración: 60 días ?.

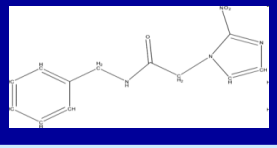
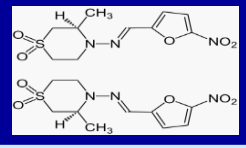
Benznidazol



Nifurtimox

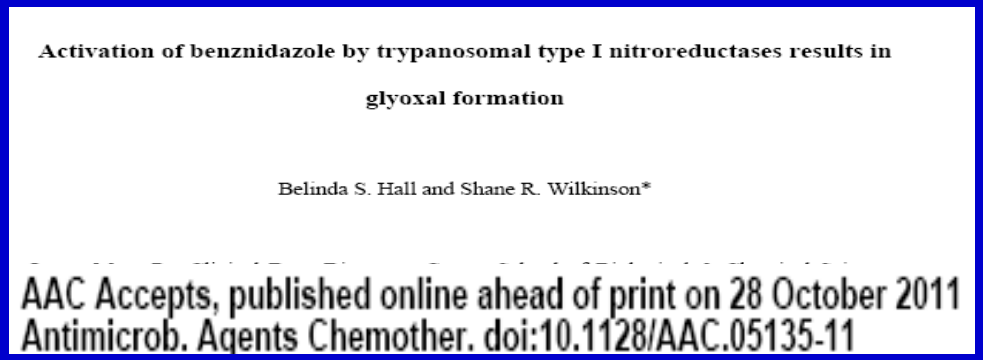


- Baja solubilidad en agua
- Alta liposolubilidad
- Buena distribucion en tejidos
- Cruza barrera hematoencefalica

	Benznidazol	Nifurtimox
		
Absorción	**Rápida** **>90% absorbido en <2hs.** **Metabolismo de primer paso 80%, y circulacion entero-hepatica (?)**	**Rápida** **90% absorcion <3hs.** **Muy alto primer paso 98% (hepatico? TD??) Circulacion enterohepatica**
Distribución	**Buena distribucion a los tejidos, incluyendo cerebro (brain/plasma ratio 69%)** **Tmax= 1.5 hs** **V/F = 0.56 L/kg** **Union a proteinas 44%** **Cruza la placenta (en animales)**	**Buena distribucion a tejidos, incluyendo cerebro** **Tmax = 2 hs** **V/F = ~13 L/kg ± 5.5)** **Union a proteinas ~60%** **Cruza la placenta (en animales)**

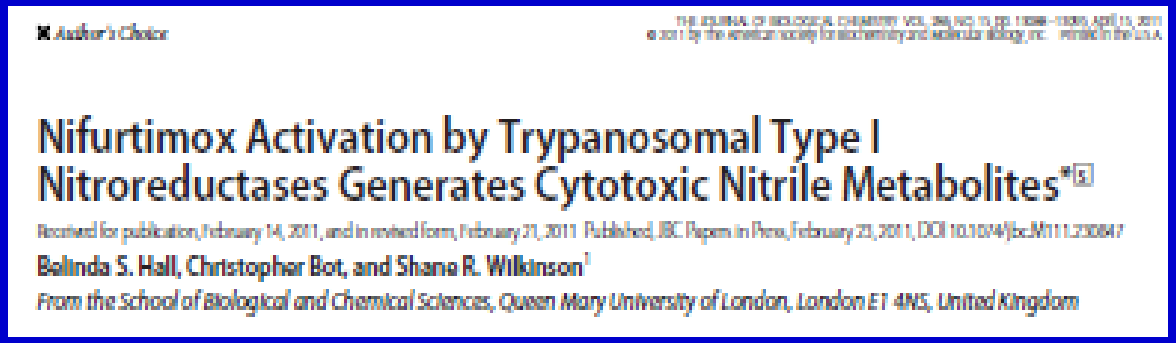
Nifurtimox y Benznidazol

- Pro-drogas: activadas a radicales nitro en el parasito → superoxido → daño oxidativo
- Activadas por nitroreductasa mitocondrial tipo I parasitaria (NTR), cuya inactivacion lleva a resistencia
- Mecanismo de proteccion del parasito (anti-oxidante) : Tripanotiona / Tripanotiona-disulfito reductasa


Activation of benznidazole by trypanosomal type I nitroreductases results in glyoxal formation

Belinda S. Hall and Shane R. Wilkinson*

AAC Accepts, published online ahead of print on 28 October 2011
Antimicrob. Agents Chemother. doi:10.1128/AAC.05135-11


Author's Choice

Nifurtimox Activation by Trypanosomal Type I Nitroreductases Generates Cytotoxic Nitrile Metabolites*

Received for publication, February 14, 2011, and in revised form, February 21, 2011 Published, JBC Papers in Press, February 23, 2011, DOI 10.1074/jbc.M111.230847

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Serological and parasitological response
Cerisola J. PAHO 1977.

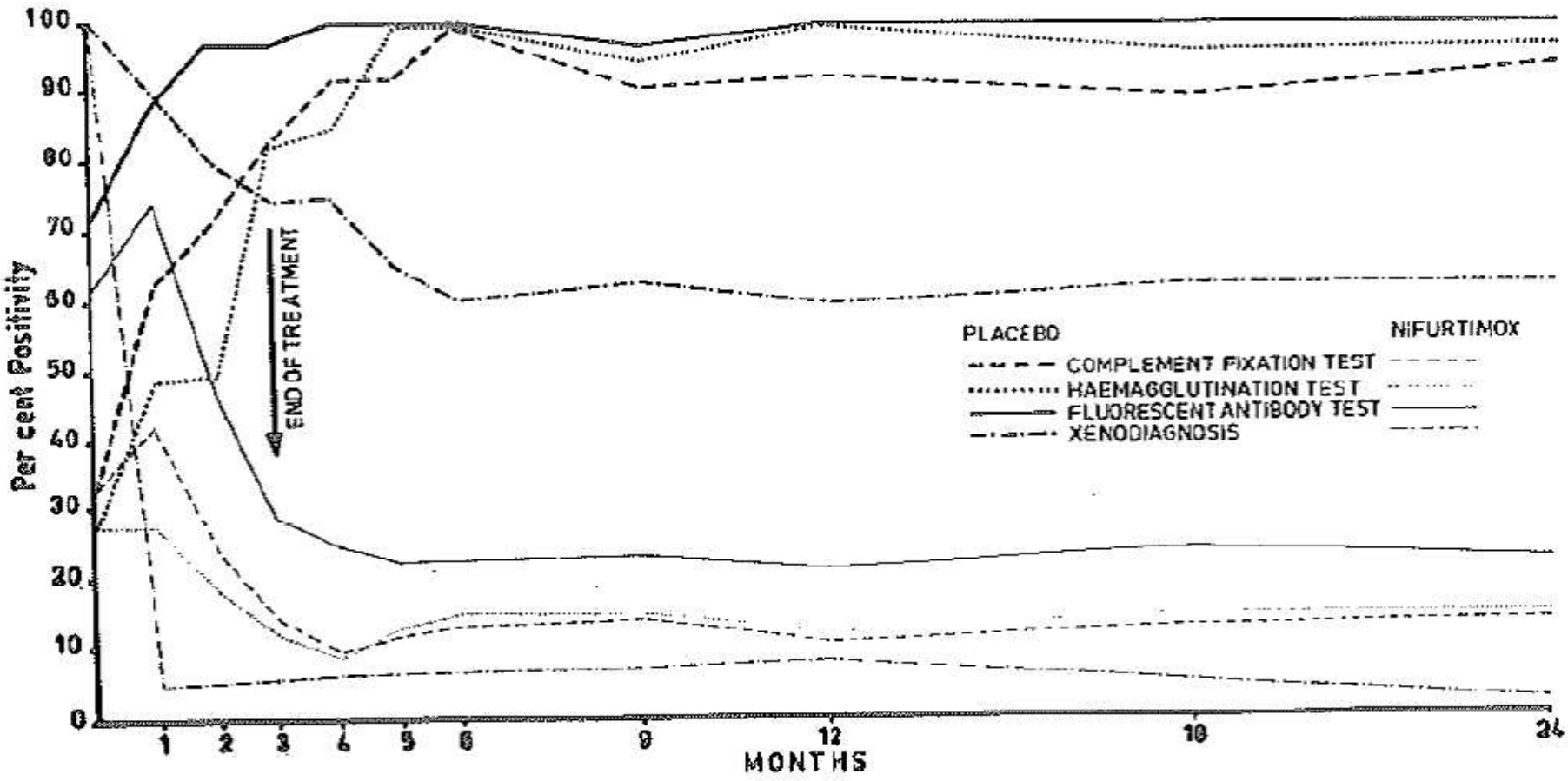

Figure 1. Serological and parasitological evolution in acute Chagas' infection (51 untreated patients and 550 treated with nifurtimox).

THE LANCET

Randomised trial of efficacy of benznidazole in treatment of early *Trypanosoma cruzi* infection

Ana Lucia S Sgambatti de Andrade, Fabio Zicker, Renato Mauricio de Oliveira, Simonne Almeida e Silva, Alejandro Luquetti, Luiz R Travassos, Igor C Almeida, Soraya S de Andrade, João Guimarães de Andrade, Celina M T Martelli

Summary

Background Benznidazole, a nitroimidazole derivative, has been recommended for the treatment of acute and congenital *Trypanosoma cruzi* infection (Chagas' disease). We have examined the safety and efficacy of this drug in the treatment of the early chronic phase of *T cruzi* infection.

Methods Between 1991 and 1995, we carried out a randomised, double-blind, placebo-controlled trial in a rural area of Brazil with endemic Chagas' disease. 82% of 2434 schoolchildren (aged 7–12 years) identified in a census were screened for antibodies to *T cruzi* by indirect immunofluorescence, indirect haemagglutination, and ELISA. 130 were positive in all tests and were randomly assigned benznidazole (7·5 mg/kg daily for 60 days by mouth) or placebo. The primary endpoint for efficacy was the disappearance of specific antibodies (negative seroconversion) by the end of 3-year follow-up. The secondary endpoint was the reduction of antibody titres on repeated serological tests. One child moved away from the area just after randomisation and was excluded from the analyses. Insecticidal measures were taken throughout the trial to reduce the risk of reinfection.

Findings Minor side-effects requiring no specific medication were recorded in a small proportion of individuals. On a chemiluminescent ELISA with purified trypomastigote glycoconjugate, serum from all participants was positive at the beginning of the trial. At the end of follow-up, 37 (58%) of the 64 benznidazole-treated participants and 3 (5%) of those who received placebo were negative for *T cruzi* antibodies. The efficacy of benznidazole treatment estimated by intention to treat was 55·8% (95% CI 40·8–67·0). At the end of follow-up, children who received benznidazole had five-fold lower geometric mean titres by indirect immunofluorescence than placebo-treated children (196 [147–256] *vs* 1068 [809–1408], p<0·00001).

Interpretation The trial showed that a 60-day course of benznidazole treatment of early chronic *T cruzi* infection was safe and 55·8% effective in producing negative seroconversion of specific antibodies. The results are very encouraging and justify the recommendation of treatment for seropositive children as public health policy.

Lancet 1996; **348:** 1407–13

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Introduction

American trypanosomiasis or Chagas' disease is a chronic disease caused by the parasite *Trypanosoma cruzi*. The disease is transmitted by a triatomine insect vector and also by blood transfusion and transplacentally. The infection may cause an acute self-limited disease, which evolves to a symptomless period, known as indeterminate phase. Several years after infection about 30% of individuals present clinical evidence of heart disease, and around 8% develop megavisceras. However, geographical variations in the frequency of the different clinical forms and in severity have been reported.[1] Chagas' heart disease is one of the main causes of disability and death in many Latin American cities. The control activities implemented in the endemic countries are based on elimination of the

Randomized controlled trials in children

Chronic indeterminate form, age ≤ 12 years

has been recommended for treatment of acute and congenital infection, as shown by the clearance of parasitaemia and the disappearance of antibodies to *T cruzi* (negative seroconversion).[4,5] The effect of treatment in the chronic phase is controversial and difficult to demonstrate because there are no specific criteria for success during this phase.[6] Clinical trials with drugs including nifurtimox, allopurinol, and benznidazole did not show any effect of treatment in preventing the development of chronic Chagas' disease.[3,4,7] The general assumption, however, is that the earlier the diagnosis is made and the specific treatment initiated, the greater the chance of parasitological cure.[7]

Before treatment of infected children as a public health measure can be recommended, full-scale investigation of drug safety and efficacy in this target group, preferably under field conditions,[8] is essential. An effective treatment might prevent the progression of infection to disease and its complications. Large-scale treatment might also decrease the pool of infected individuals in the population, thus reducing the risk of transmission.

We report the results of a phase III randomised double-blind placebo-controlled field trial of benznidazole in the early chronic phase of *T cruzi* infection carried out from 1991 to 1995 in an endemic area in Brazil.

Am. J. Trop. Med. Hyg., 59(4), 1998, pp. 526–529

EFFICACY OF CHEMOTHERAPY WITH BENZNIDAZOLE IN CHILDREN IN THE INDETERMINATE PHASE OF CHAGAS' DISEASE

SERGIO SOSA ESTANI, ELSA LEONOR SEGURA, ANDRES MARIANO RUIZ, ELSA VELAZQUEZ, BETINA MABEL PORCEL, AND CRISTINA YAMPOTIS

Centro Nacional de Diagnóstico e Investigación de Endemo-Epidemias/Administración Nacional de Laboratorios e Institutos de Salud (ANLIS) Dr. Carlos G. Malbrán, Buenos Aires, Argentina; Instituto Nacional de Parasitología Dr. Mario Fatala Chaben/ ANLIS, Secretaría de Salud, Ministerio de Salud y Acción Social de la Nación, Buenos Aires, Argentina; Hospital San Roque, Ministerio de Salud de la Provincia, Embarción Salta, Argentina

Abstract. A double-blind, randomized, clinical field trial was designed to test the efficacy and tolerance of a specific drug treatment in children in the indeterminate phase of infection by *Trypanosoma cruzi*. Children were treated with benznidazole at a dose of 5 mg/kg/day for 60 days or placebo and followed-up for 48 months. The treated children showed a significant decrease in geometric mean titers of antibodies against *T. cruzi* measured by indirect hemagglutination, indirect immunofluorescence, and ELISA. After a four year follow-up, 62% of the benznidazole-treated children and no placebo-treated child were seronegative for *T. cruzi* when tested by an ELISA using a *T. cruzi* flagellar calcium-binding protein (F29). Xenodiagnosis carried out after 48 months of follow-up was positive in 4.7% of the benznidazole-treated children and in 51.2% of the placebo-treated children. These results show the tolerance to and efficacy of benznidazole against *T. cruzi* in seropositive children six to 12 years of age. We used an early serologic marker of cure after treatment, consisting of a recombinant antigen implemented in a rapid, conventional serologic procedure.

Chagas' disease exists only in the American continents, and extends from Mexico to Argentina and Chile. In Argentina, there are approximately 2.3 million people infected with *Trypanosoma cruzi*.[1] The disease is transmitted by triatomine bugs and also by blood transfusion and transplacentally. The course of infection includes an acute phase that

in children less than three years of age.[4] The objective of this study was to test the efficacy and tolerance of a specific drug treatment in children infected with *T. cruzi* in the indeterminate phase of Chagas' disease who lived in rural areas of Salta, Argentina.

MATERIALS AND METHODS

Experimental design. This study was a double-blind, randomized, clinical field trial carried out in the Province of Salta in northwestern Argentina. The children lived in 14 localities in an area of approximately 200 km². Sixty-six percent of the children lived in rural areas. The area has been under continuous triatomine surveillance by sanitary agents since 1982 (i.e., they undertook regular insecticidal actions against infestations). This was a condition for the selection of the study area. We assumed that the children's infection with *T. cruzi* would be more than six years old. Children were excluded from the trial for any of the following reasons: 1) presence of any chronic health condition (such as epilepsy, malnutrition, asthma, severe anemia); 2) presence of any acute infectious disease; 3) lack of consent from their parents to participate in the study; and 4) unstable residence.

The children were matched in each locality by age to receive benznidazole, (Radanil®; Roche, Olivos, Argentina) (benznidazole-treated children [BTCh]) or placebo (placebo-treated children [PTCh]). Fifty-five children were allocated to the BTCh group and 51 children to the PTCh group. Benznidazole (5 mg/kg/day) was administered to each child for 60 days. The pills were administered by parents, teachers, or nurses from the health services who were specifically trained for such a task.

Informed consent was obtained twice, before screening and before recruitment into the trial. The protocol was reviewed and approved by the Ethical Committee of the Instituto Nacional de Chagas Dr. Mario Fatala Chaben.

Clinical examination. Continuous medical assistance (anamnesis, physical examinations, and electrocardiograms [ECGs]) was provided during the trial. Laboratory tests (red blood cell and leukocyte counts, hematocrit, erythrocyte sedimentation rate, bilirubin, creatinine, aspartate aminotransferase, and alanine aminotransferase levels, and urine tests) were performed at days 21 and 60 after initiation of treatment to assess drug toxicity. Side effects were considered mild if the patients showed some adverse effects but were able to complete the treatment; moderate if treatment had to be suspended because of some side effect; and severe if it was suspended and the patients needed special treatment.

Serology. Repeated serologic tests were carried out immediately before and at 3, 6, 12, 18, 24 and 48 months after the onset of treatment; these included an enzymatic immunoassay (EIA),[5] an indirect hemagglutination assay (IHA),[6] and an indirect immunofluorescence assay (IFA).[7] A new EIA (F29 EIA), using a *T. cruzi* flagellar calcium-binding protein (F29) as antigen, was used to assess parasitologic cure of patients.[8] The clone encoding the whole protein was subcloned in the pMAL-p2 expression vector and expressed in *Escherichia coli*.[8]

Xenodiagnosis. All children were tested by xenodiagnosis using two boxes with 10 *Triatoma infestans* third or fourth instar nymphs each at the end of the follow-up.[9]

Statistical analysis. The data were analyzed using Epi-

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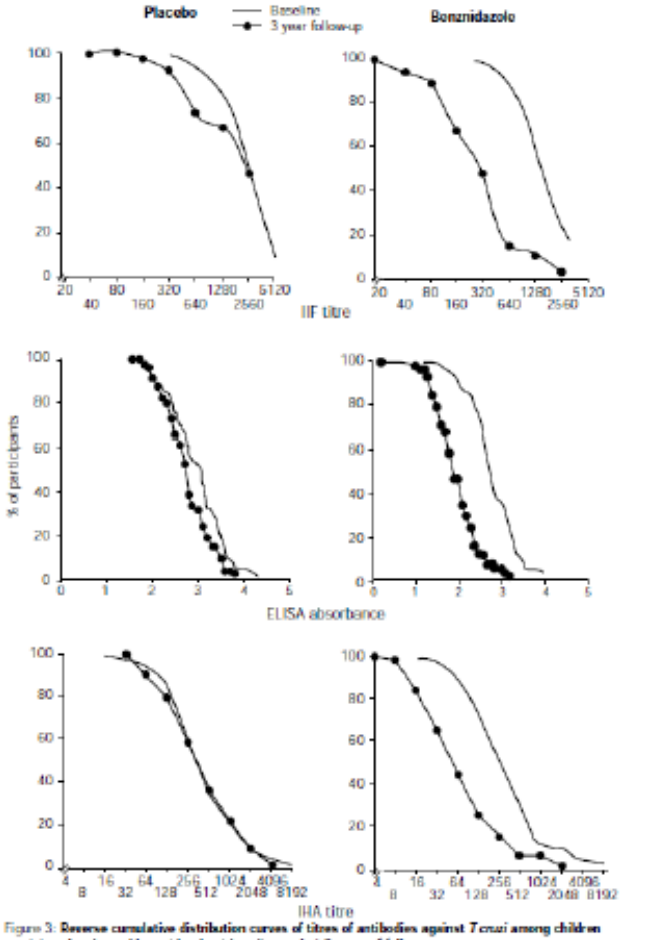


Figure 3: **Reverse cumulative distribution curves of titres of antibodies against *T cruzi* among children receiving placebo and benznidazole at baseline and at 3 years of follow-up.**
n=58 for benznidazole, 54 for placebo group. IIF=Indirect immunofluorescence; IHA=Indirect haemagglutination.

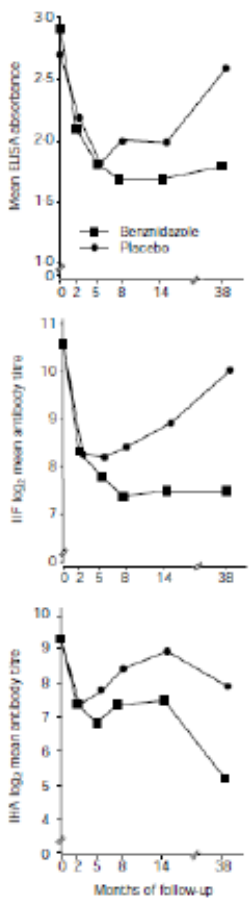


Figure 4: ***T cruzi* serological response in benznidazole and placebo groups by time**
Error bars indicate 95% CI. IIF=Indirect immunofluorescence; IHA=Indirect haemagglutination.

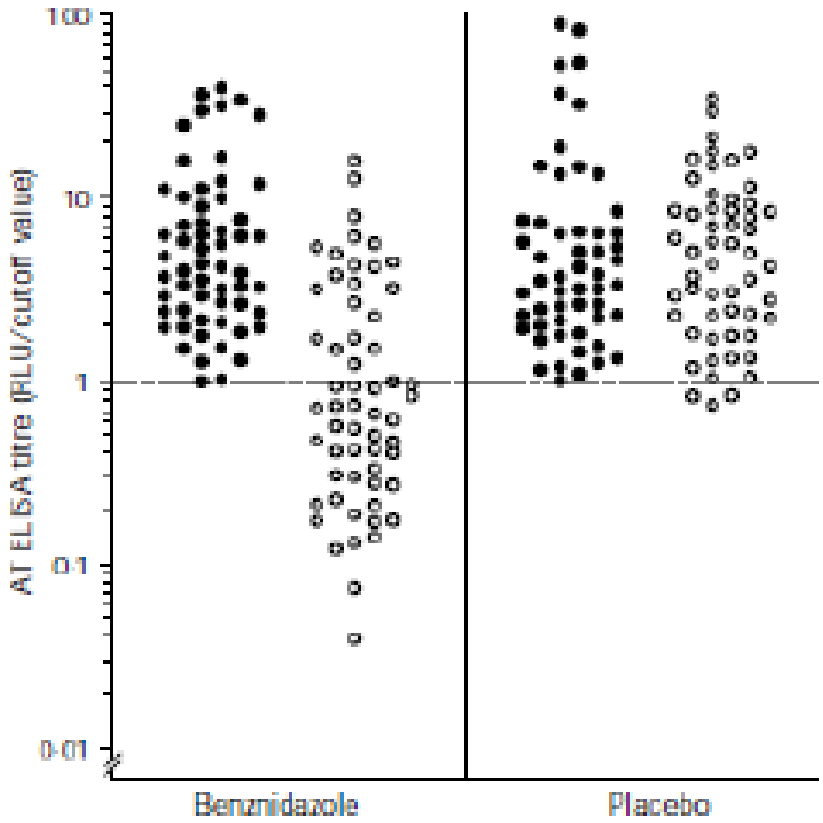


Figure 2: **AT ELISA results at trial entry (●) and at end of follow-up (○) for 58 benznidazole-treated and 54 placebo-treated children who completed trial treatment.**
Broken horizontal line=cut-off; values below this indicate seronegativity.

Am. J. Trop. Med. Hyg., 59(4), 1998, pp. 526–529

EFFICACY OF CHEMOTHERAPY WITH BENZNIDAZOLE IN CHILDREN IN THE INDETERMINATE PHASE OF CHAGAS' DISEASE

SERGIO SOSA ESTANI, ELSA LEONOR SEGURA, ANDRES MARIANO RUIZ, ELSA VELAZQUEZ, BETINA MABEL PORCEL, AND CRISTINA YAMPOTIS

Centro Nacional de Diagnóstico e Investigación de Endemo-Epidemias/Administración Nacional de Laboratorios e Institutos de Salud (ANLIS) Dr. Carlos G. Malbrán, Buenos Aires, Argentina; Instituto Nacional de Parasitología Dr. Mario Fatala Chaben/ ANLIS, Secretaría de Salud, Ministerio de Salud y Acción Social de la Nación, Buenos Aires, Argentina; Hospital San Roque, Ministerio de Salud de la Provincia, Embarción Salta, Argentina

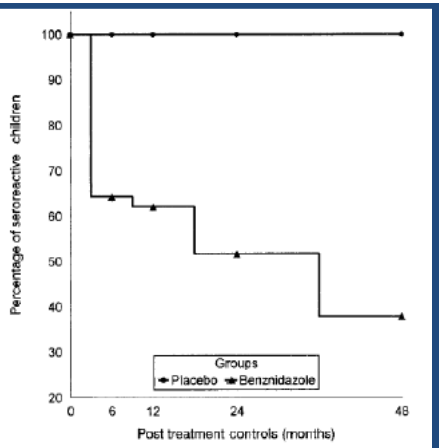


FIGURE 1. Decrease in the percentage of children with reactive serology against *Trypanosoma cruzi* (indeterminate phase of Chagas' disease) by enzyme immunoassay using the F29 protein after treatment with benznidazole or placebo in Salta, Argentina, 1991–1995.

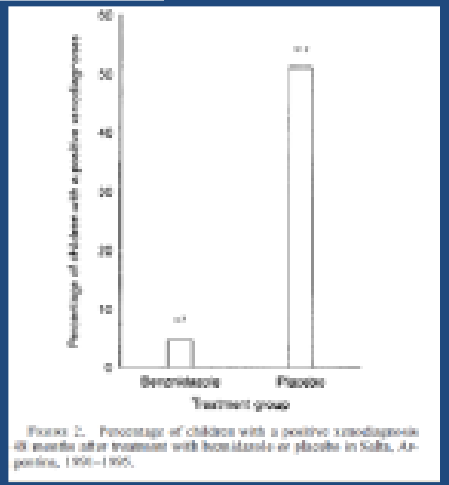


FIGURE 2. Percentage of children with a positive xenodiagnosis 48 months after treatment with benznidazole or placebo in Salta, Argentina, 1991–1995.

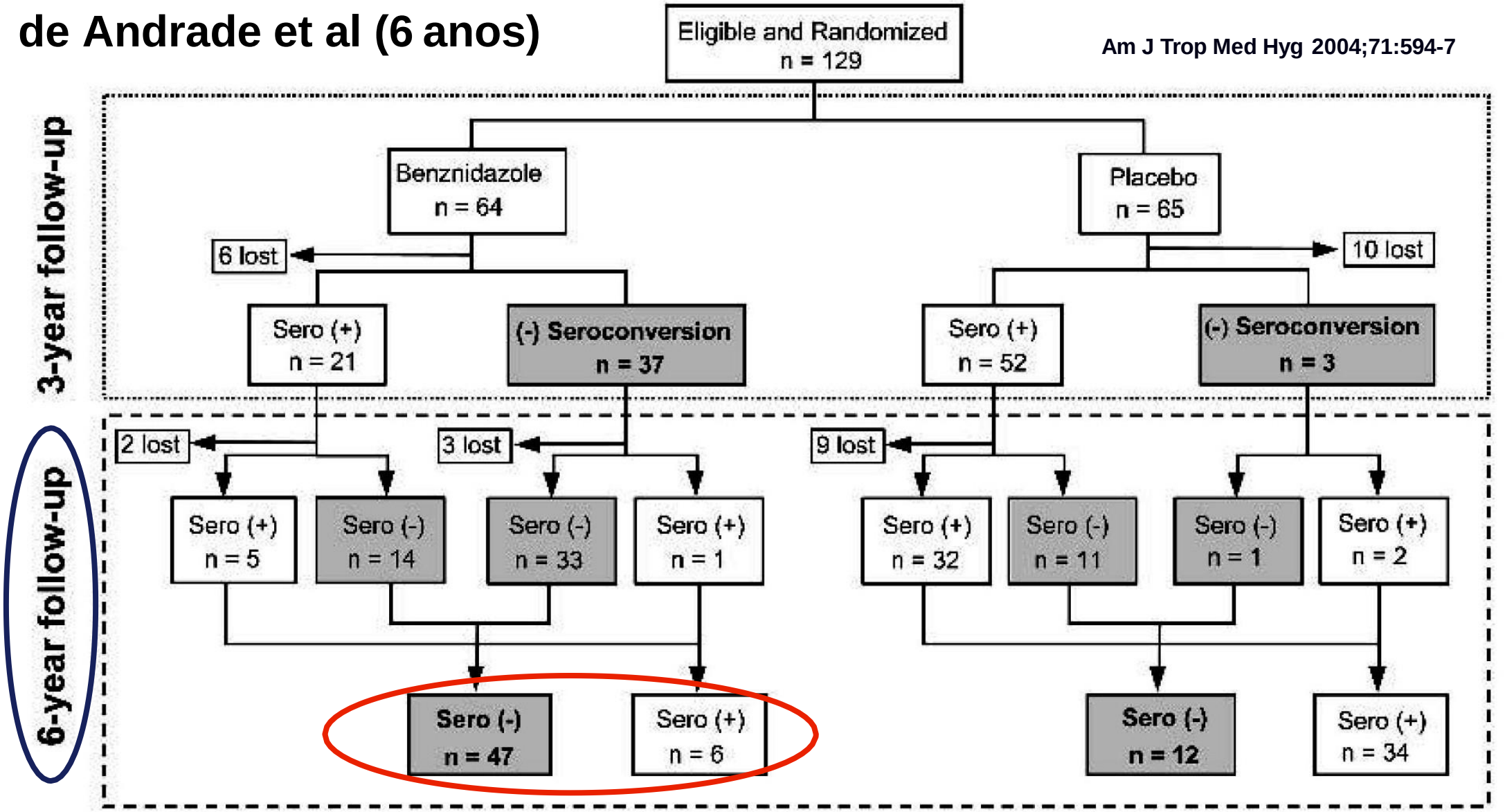
Serologic follow-up of children treated with benznidazole or placebo to 48 months post-treatment in Salta, Argentina, 1991–1995*

		IHA				IFA				EIA			
Treatment	n	Mean	SD	Test		Mean	SD	Test		Mean	SD	Test	
Benznidazole													
Pretreatment	51	7.98	1.82	7 DF	1 DF	7.05	1.12	7 DF	1 DF	0.467	0.099	7 DF	1 DF
End of treatment	47	7.68	2.14		NS	6.57	1.58		NS	0.433	0.110		NS
3 months	45	7.26	2.33		NS	6.27	1.28		$P<0.01$	0.409	0.112		$P<0.01$
6 months	45	7.00	2.53		$P<0.05$	6.11	1.57		$P<0.001$	0.371	0.115		$P<0.001$
12 months	48	7.00	2.27		$P<0.05$	5.87	1.56		$P<0.001$	0.369	0.107		$P<0.001$
18 months	47	6.53	2.62		$P<0.001$	5.80	1.82		$P<0.001$	0.358	0.120		$P<0.001$
24 months	46	6.80	2.26		$P<0.01$	5.32	2.03		$P<0.001$	0.330	0.098		$P<0.001$
48 months	44	5.93	2.11	$P<0.001$	$P<0.001$	5.65	2.18	$P<0.001$	$P<0.001$	0.343	0.094	$P<0.001$	$P<0.001$
Placebo													
Pretreatment	50	8.00	1.16	7 DF	1 DF	6.80	1.22	7 DF	1 DF	0.472	0.095	7 DF	1 DF
End of treatment	45	8.11	1.21		NS	6.80	1.07		NS	0.492	0.090		NS
3 months	44	8.11	1.10		NS	6.54	1.15		NS	0.489	0.098		NS
6 months	39	7.87	1.34		NS	6.61	1.60		NS	0.477	0.101		NS
12 months	47	8.08	1.26		NS	6.40	1.13		NS	0.476	0.113		NS
18 months	48	7.93	1.17		NS	6.47	1.16		NS	0.464	0.108		NS
24 months	49	7.77	1.22		NS	6.34	1.54		NS	0.479	0.104		NS
48 months	44	7.47	0.95	NS	$P<0.05$	6.97	2.21	$P<0.05$	$P<0.05$	0.501	0.115	NS	NS

* IHA = indirect hemagglutination assay; IFA = indirect immunofluorescence assay; EIA = enzyme immunoassay; Test = analysis of variance or Kruskal-Wallis test; df = degrees of freedom; NS = not significant ($P > 0.05$). The IFA and IHA values are means ($\log_2$ of two-fold dilutions of serum samples). The EIA values are mean optical densities.

de Andrade et al (6 anos)

Am J Trop Med Hyg 2004;71:594-7



Efficacy of benznidazole treatment of *Trypanosoma cruzi*–infected adolescents after a six-year follow-up*

Treatment group	A&T CL-ELISA		Total followed-up	Total randomized	Efficacy (95% CI)	
	Positive	Negative			Per protocol	Intention to treat
Benznidazole	6	47	53	64	84.7% (66.8–92.9)	64.7% (50.2–78.7)
Placebo	34	12	46	65		

ETIOLOGICAL TREATMENT OF CHAGAS DISEASE WITH BENZNIDAZOLE IN THE CHRONIC PHASE

Long term follow up and evolution to cardiopathy

Authors	Population	Follow up (years)	Development of Cardiopathy (ECG)	
			Drug	Control/Placebo
Macedo et al, 1987	Adults (n=171)*	7	6.7%	8.8%
Ianni et al, 1993	Adults (n=33)	8	13.3%	0.0%
Miranda et al, 1994	Ad. & Ch (n=120)	10-16	10.5%	63.6%
Viotti et al, 1994	Adults (n=201)	8	4.2%	30.0%
Fragata Fº et al, 1995	Adults (n=120)	7-8	7.0%	14.3%
Andrade et al, 1996	Children (n=129)	3	1.7%	6.9%

** Includes cases treated with Nifurtimox*

Rassi A. Arq Bras Cardiol 1998;71:643-6.

Annals of Internal Medicine | ARTICLE

Long-Term Cardiac Outcomes of Treating Chronic Chagas Disease with Benznidazole versus No Treatment

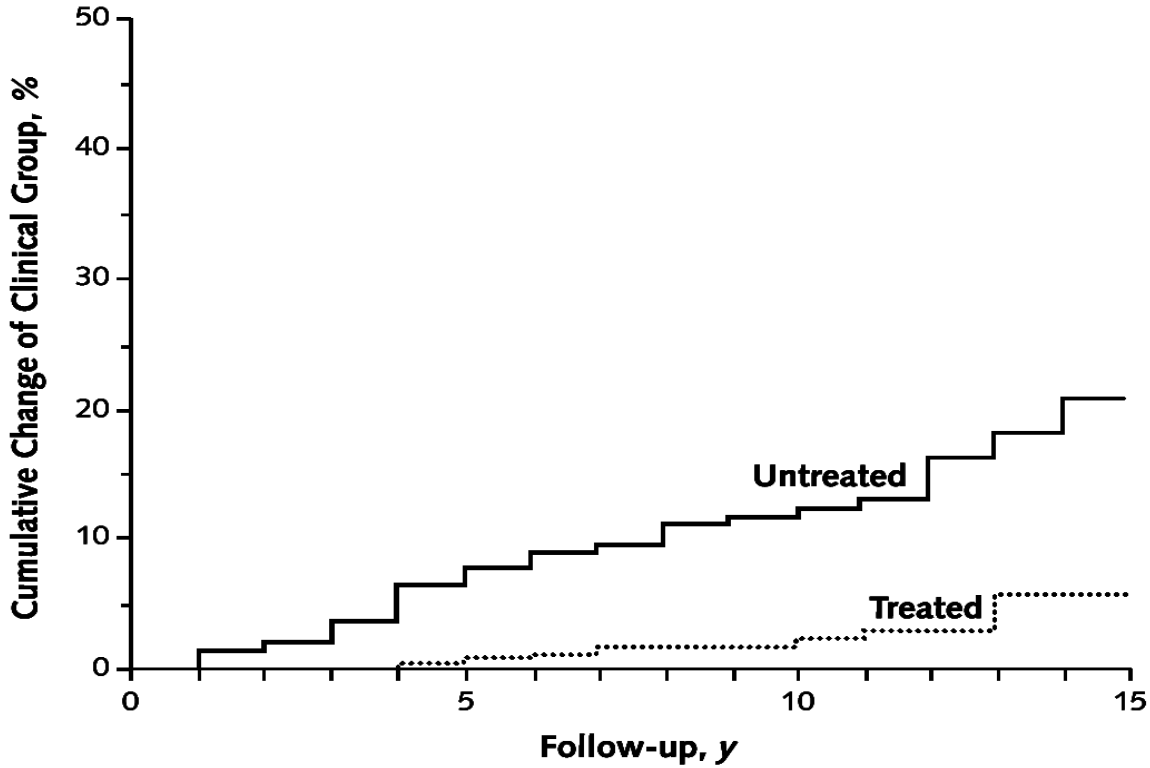
A Nonrandomized Trial

Ann Intern Med 2006;144:724-734

Rodolfo Viotti, MD; Carlos Vigliano, MD; Bruno Lococo, MD; Graciela Bertocchi, MD; Marcos Petti, MD; María Gabriela Alvarez, MD; Miriam Postan, MD, PhD; and Alejandro Armenti, MD

- 556 pts
- Age : 30-50 yrs
- 283 pts: BZN- 30 days
- 283 : controls

Folow-up: 9,8 y



	Treated	Controls	HR (CI 95%)	p
Progression of disease	4%	14%	0,24 (0,10-0,59)	0,002
New ECG alterations	5%	16%	0,27 (0,13-0,57)	0,001
Seroconversion	15%	6%	2,10 (1,06-4,06)	0,034

Revista da Sociedade Brasileira de Medicina Tropical 40(1):1-10, jan-fev, 2007

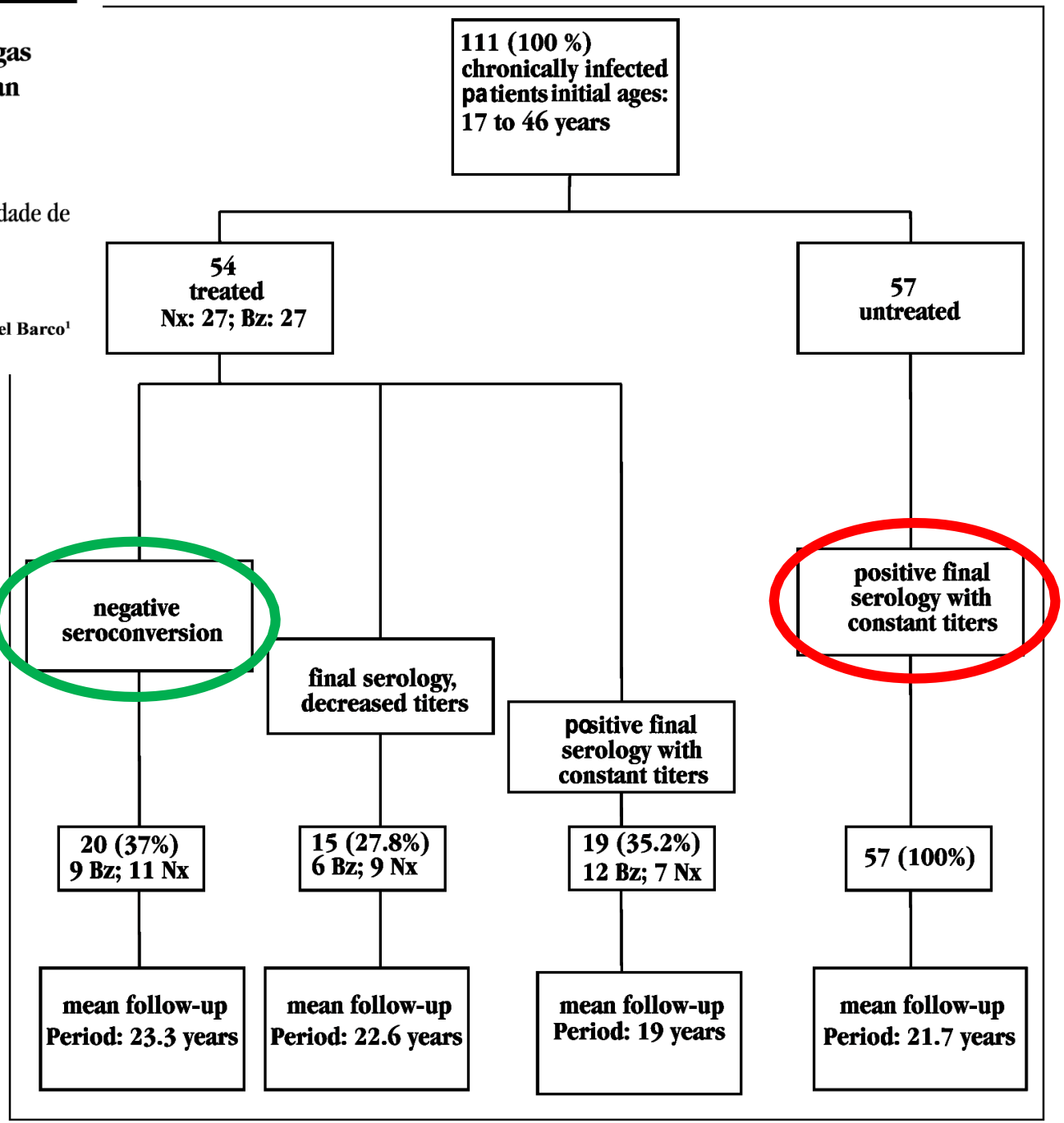
ARTIGO/ARTICLE

Trypanocide treatment among adults with chronic Chagas disease living in Santa Fe City (Argentina), over a mean follow-up of 21 years: parasitological, serological and clinical evolution

Tratamento tripanocida em adultos chagásicos crônicos, residentes na Cidade de Santa Fé (Argentina), com seguimento de 21 anos em média: evolução parasitológica, sorológica e clínica

Diana L. Fabbro[1], Mirtha L. Streiger[1], Enrique D. Arias[1], María L. Bizai[1], Mónica del Barco[1] and Norberto A. Amicone[1]

Seguimiento serológico



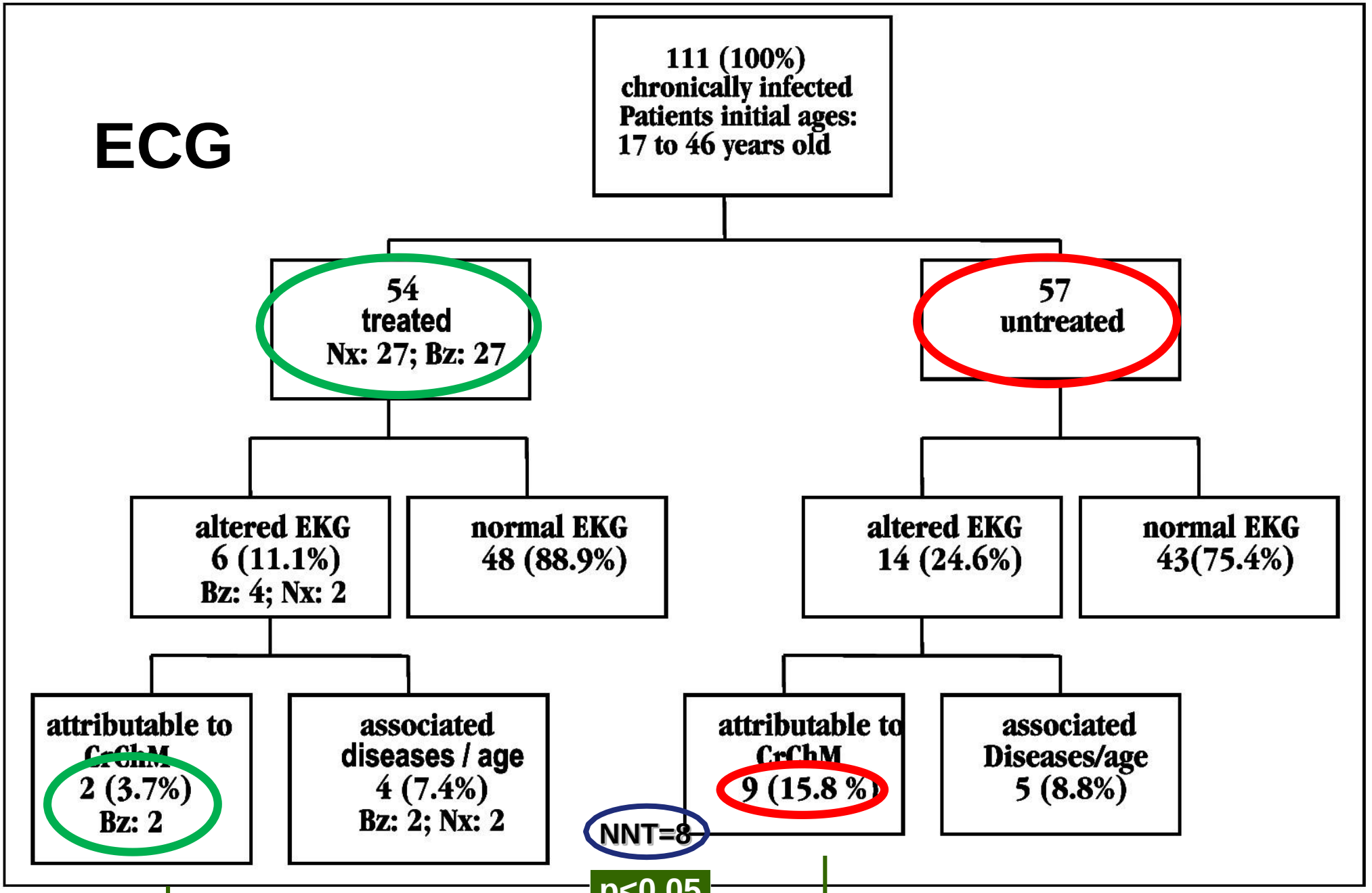


Figure 3 - Electrocardiographic evolution of chronic chagasic infected patients, treated and untreated, who had no initial electrical disturbances, in an average 21 years follow-up period.

Towards a Paradigm Shift in the Treatment of Chronic Chagas Disease

R. Viotti,[a] B. Alarcón de Noya,[b] T. Araujo-Jorge,[c] M. J. Grijalva,[d] F. Guhl,[e] M. C. López,[f] J. M. Ramsey,[g] I. Ribeiro,[h] A. G. Schijman,[i] S. Sosa-Estani,[j] F. Torrico,[k] J. Gascon,[l] on behalf of the Latin American Network for Chagas Disease, NHEPACHA

Antimicrob Agents Chemother 2014;58:635-9

TABLE 1 Results of nonrandomized studies with etiological treatment for patients with chronic Chagas disease, showing the relationship between clinical and serological evolution[a]

	No. of patients:		No. of patients (treated/not treated) that had:		% of patients:		
						Negative for seroconversion	
1st author, yr (reference)	Treated	Not treated	EKG changes	Progression of cardiomyopathy	With reduction of risk progression	Treated	Not treated
Viotti, 1994 (33)	131	70	0/4	2/17	88	19	6
Gallerano, 2000 (35)	535	668	14/34	4/18	78	5	Data not available
Viotti, 2006 (37)	283	283	5/16	4/14	71	15	6
Fabbro De Suasnábar, 2000 (34)	54	57	4/16		75	37	Data not available
Avg			6/17	3/16	78	19	6

[a] Treatment was with benznidazole except for reference 35, which reports on 309 patients treated with alopurinol, 130 treated with benznidazole, and 96 treated with nifurtimox.

Chagas Disease Public Meeting on Patient-Focused Drug Development

April 28, 2015

No registration fees;

Orphan drug status

granted in 2010

Chagas Disease Fact Sheet PDF

Enfermedad de Chagas PDF

On April 28, 2015, FDA met with patients during one of FDA's Patient-Focused Drug Development meetings to discuss patients' concerns regarding their symptoms and treatment options for Chagas disease. These meetings are important as patients have the opportunity to convey their concerns about current medications and the types of medications they would like to see in the future.

No drugs have yet been shown to meet standards of safety and efficacy for FDA approval for the treatment of Chagas' disease, but several potential treatments are in various stages of clinical investigation. Two investigational drugs are available through the Center for Disease Control and Prevention (CDC), at a doctor's request.

- Benznidazole
- Nifurtimox

112 studies found for: chagas

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Rank	Status	Study
1	Completed Has Results	Abbott ESA Chagas Assay Post-Market Study **Condition:** Chagas Disease **Intervention:** Device: Testing Donor Specimens with ESA Chagas
2	Completed	Population Pharmacokinetics of Benznidazole in Children With Chagas Disease **Condition:** Chagas Disease **Intervention:** Drug: Benznidazole
3	Completed	Galectin-3 as a Biomarker in Patients With Chagas Disease **Condition:** Chagas Disease. **Intervention:**
4	Completed	Assessment of Speckle Tracking Strain Predictive Value for Myocardial Fibrosis in Chagas Disease **Condition:** Chagas Disease **Intervention:** Other: No intervention was performed.
5	Completed Has Results	A Study of the Use of Oral Posaconazole (POS) in the Treatment of Asymptomatic Chronic Chagas Disease (P05267) **Condition:** Chagas Disease **Interventions:** Drug: Posaconazole; Drug: Placebo for posaconazole; Drug: Benznidazole
6	Completed	MicroRNAs as Biomarkers in Patients With Chagas Disease **Condition:** Chagas Disease **Intervention:**
7	Completed	Syndecan-4 as a Biomarker in Patients With Chagas Disease **Condition:** Chagas Disease **Intervention:**
8	Completed	Effects of Omega-3 Supplementation on the Cytokine and Lipid Profiles in Patients With Chronic Chagas Cardiomyopathy

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35 studies found for: chagas children

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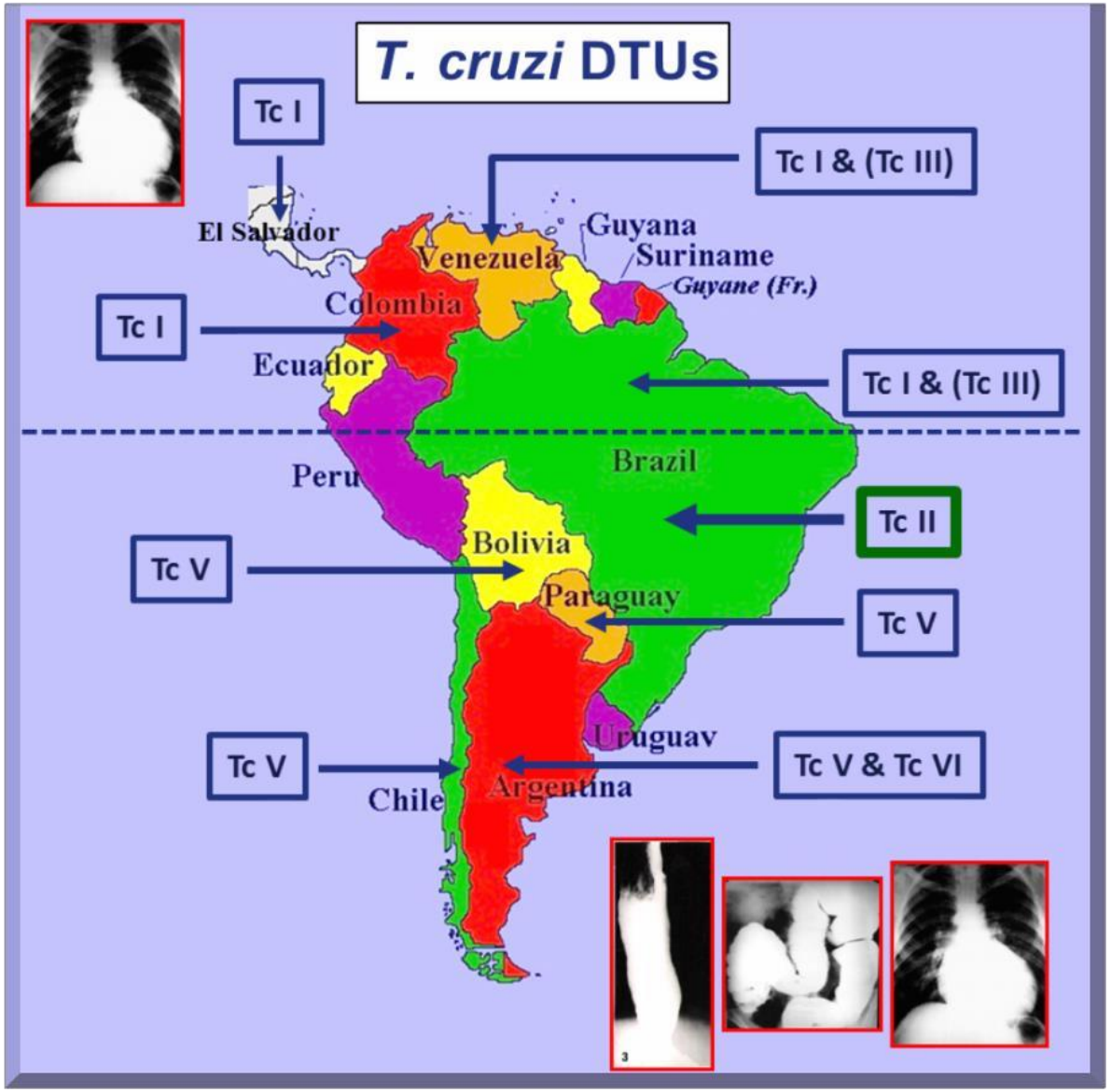
Rank	Status	Study
1	Completed	Population Pharmacokinetics of Benznidazole in Children With Chagas Disease **Condition:** Chagas Disease **Intervention:** Drug: Benznidazole
2	Unknown †	Population Pharmacokinetics Study of Benznidazole in Children With Chagas'Disease **Condition:** Chagas' Disease **Intervention:** Drug: Benznidazole 12,5mg or 100mg
3	Recruiting	Prospective Study of a Pediatric Nifurtimox Formulation for Chagas' Disease **Condition:** Chagas Disease **Interventions:** Drug: Nifurtimox (BAYA2502); Drug: Nifurtimox (BAYA2502) followed by Placebo
4	Completed	Study of Benznidazole Transfer Into Breastmilk in Lactating Women With Chagas Disease

T.CRUZI STRAINS AND DTUS



Feasibility, Drug Safety, and Effectiveness of Etiological Treatment Programs for Chagas Disease in Honduras, Guatemala, and Bolivia: 10-Year Experience of Médecins Sans Frontières

PLoS NEGLECTED TROPICAL DISEASES

BZN: 5-7.5 mg/kg/day(*2-3 times*) x 60d Maximum: 300 mg/day	T. cruzi I Yoro (Honduras)	T. cruzi I Olopa (Guatemala)	T. cruzi V Entre Rios (Bolivia)	T. cruzi V Sucre (Bolivia)
Program duration	1999-2002	2003-2006	2002-2006	2005-2008
Age group (years)	<12	<15	<15	<18
N of patients tested	24,771	8,927	7,613	19,400
N of patients +tive at initial screening	256	124	1,475	1,179
N of patients confirmed +tive	232	124	1,475	1,145
Seroprevalence	0.9%	1.4%	19.4%	5.9%
N of patients treated 2804	231	124	1,409	1,040
Completed treatment	99%	95%	91%	88%
Seroconversion rate*	87.1%	58.1%	5.4%	0%
Time of post-Tx evaluation	18 mo	18 mo	18m-60mo	9m-27mo
Patients evaluated	100%	26%	78%	27%

Yun O et al. PLoS Negl Trop Dis 2009; 3: e488

*conventional ELISA and recombinant ELISA negatives

Rápida negativización serológica después del tratamiento etiológico para enfermedad de Chagas en un grupo de escolares colombianos.

BZN: 5.0mg kg/day during 60 days	Boyacá (Colombia)
Program duration	2002-2003
Age group (years)	4-15
N of children tested	1,643
N of children +tive (ELISA & IIF)	92
Seroprevalence	5.6%
N of children treated	48
Completed treatment	100%
Seroconversion rate*	94.4%
Time of post-Tx evaluation	5 m
Children evaluated	75%

T. cruzi I

Guhl F, Nichols RS, Montoya R, Rosas F, Velasco VM, Mora E, Herrera C, Santa Cruz MM, Pinto N, Aguilera G, Salcedo P, Zipa NY, Florez J, Olarte A, Castillo G. Curso de Diagnóstico, Manejo y Tratamiento de la enfermedad de Chagas OPS/MSF/SSA, p. 205-212.

*negative IIF

RESEARCH ARTICLE

Electrocardiographic Abnormalities and Treatment with Benznidazole among Children with Chronic Infection by *Trypanosoma cruzi*: A Retrospective Cohort Study

PLoS Negl Trop Dis 2016 May 9;10(5):e0004651

Lisandro D. Colantonio[1,2], Nilda Prado[3], Elsa L. Segura[3], Sergio Sosa-Estani[3]*

1 Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, Birmingham, Alabama, United States of America, **2** Department of Public Health, School of Medicine, University of Buenos Aires, Buenos Aires, Argentina, **3** National Institute of Parasitology "Dr. Mario Fatala Chaben"-CONICET-ANLIS, Ministry of Health, Buenos Aires, Argentina

Electrocardiographic items	No treatment with benznidazole (n = 38) n (%)	Treatment with benznidazole (n = 48) n (%)
Overall assessment		
Abnormal	8 (21)	8 (17)
Rhythm		
Atrial ectopic	1 (3)	0 (0)
Supraventricular arrhythmias		
Supraventricular extrasystoles	1 (3)	0 (0)
Other atrial arrhythmias	0 (0)	1 (2)
Abnormal initial QRS complex		
Present	1 (3)	0 (0)
Miscellaneous		
Right ventricular hypertrophy	1 (3)	1 (2)
P wave	1 (3)	0 (0)

Median FU: 8.6 yrs

Conclusions/Significance

Electrocardiographic abnormalities are frequent among children with chronic *T. cruzi* infection. Treatment with benznidazole for 60 days may not be associated with less electrocardiographic abnormalities.

The multivariable adjusted HR for incident ECG abnormalities comparing children treated with BZ vs those not treated was 0.68 (95%CI: 0.25, 1.88)

310 adult pts
Chronic CD
Normal ECG

Characteristics of the untreated and treated with BZ groups.	UNTREATED (47p – 15.16%)	TREATED (263p – 84.84%)	p
AGE (last visit) years	68.89 (± 6.81)	56.07 (± 9.59)	< 0.0001
FOLLOW- UP years	19.68 (± 8.51)	17.97 (± 5.99)	0.486
MALE	10 (21.30%)	97 (36.9%)	0.045
WHITE	37 (78.70%)	194 (73.80%)	0.586
OEA **(Out of endemic area)**	19.65 (± 8.69)	16.77 (± 7.49)	0.012
DM **(Diab. mellitus occurrence)**	3 (6.40%)	21 (8.00%)	>0.999
DLP **(Dyslipidemia occurrence)**	8 (17.00%)	77 (29.30%)	0.109
CAD **(Coronary artery disease)**	2 (4.30%)	5 (1.90%)	0.288
HR bpm	68.32 (± 9.74)	70.32 (± 8.84)	0.198
SBP mmhg	134.32 (± 20.05)	130.07 (± 18.12)	0.202
DBP mmhg	81.36 (± 12.50)	81.30 (± 10.39)	0.716
NL ECG	22 (46.81%)	208 (79.08%)	< 0.0001

NNT=3

RESEARCH ARTICLE

PLOS | NEGLECTED TROPICAL DISEASES

CONCLUSION:

These data suggest that treatment with BZ prevents the occurrence of ECG alterations. On the other hand, patients who develop ECG abnormalities present with more significant clinical events.

Patients untreated and treated with BZ and events occurrence.	UNTREATED (47p – 15.16%)	TREATED (263p – 84.84%)	p
HEART FAILURE	2 (4.26%)	6 (2.29%)	0.348
STROKE	0	4 (1.50%)	>0.999
DEATHS	5 (10.60%)	7 (2.70%)	0.022
HEART DEATHS	3 (6.40%)	3 (1.10%)	0.047
COMBINED OUTCOMES	7 (14.89%)	17 (6.46%)	0.096

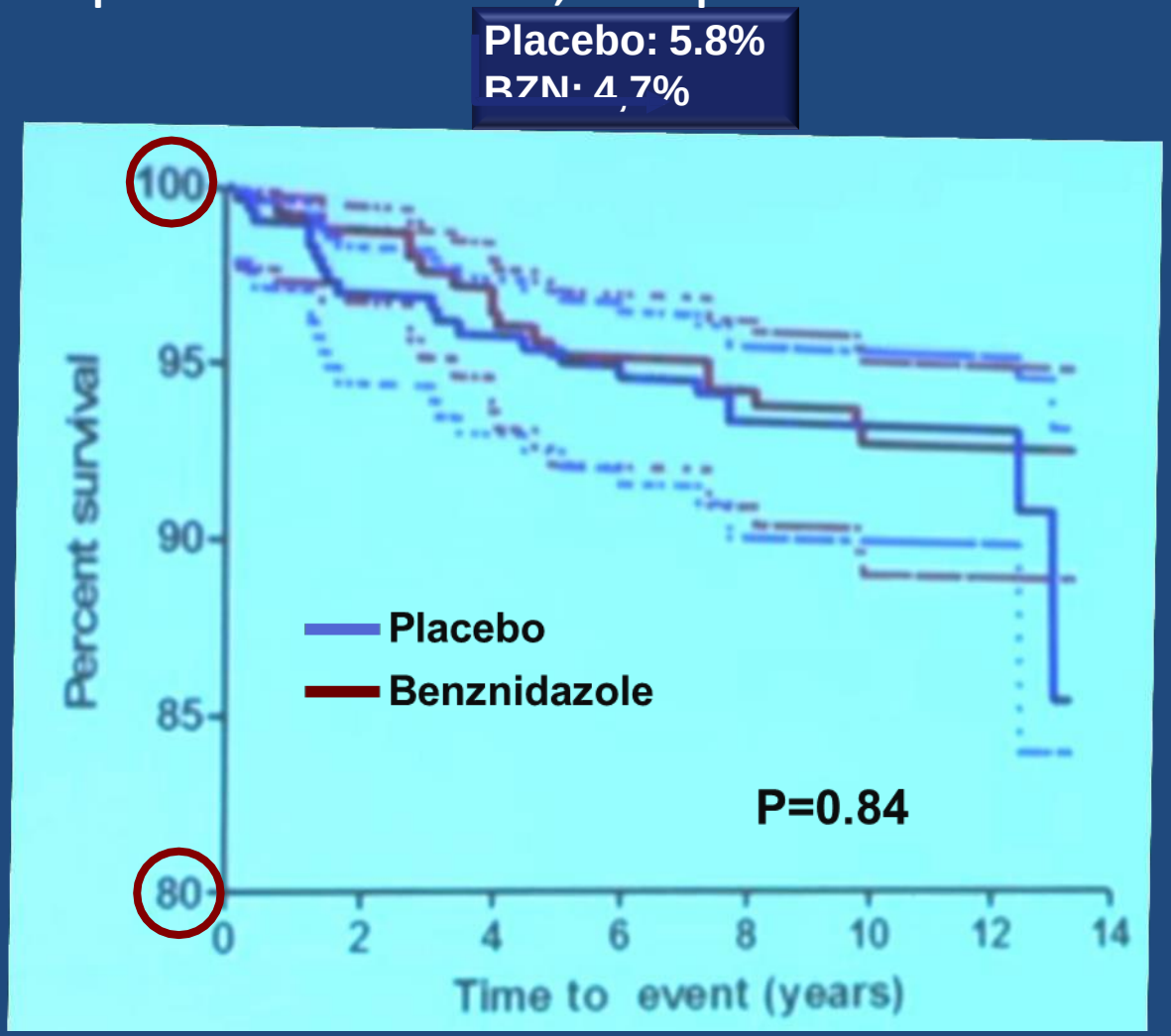
PLoS Negl Trop Dis 2016 Mar 14;10(3):e0004508.

TRAENA

Endpoint: muerte, fallo cardiaco, alt ECG con compromiso hemodinámico, marcapasos.

Objetivo: BZN vs Placebo previene la progresión del compromiso cardiaco.

- 763 sujetos (Placebo: 381; BZN: 382)
- Edad: 20-55 a (x= 38 a)
- 25% alt ECG
- Seguimiento: 8 yrs; Mediana: 10 yrs



From: Adelina Riarte, Plataforma Chagas 2015 You Tube video

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Randomized Trial of Benznidazole for Chronic Chagas' Cardiomyopathy

C.A. Morillo, J.A. Marin-Neto, A. Avezum, S. Sosa-Estani, A. Rassi, Jr., F. Rosas, E. Villena, R. Quiroz, R. Bonilla, C. Britto, F. Guhl, E. Velazquez, L. Bonilla, B. Meeks, P. Rao-Melacini, J. Pogue, A. Mattos, J. Lazdins, A. Rassi, S.J. Connolly, and S. Yusuf, for the BENEFIT Investigators*

ABSTRACT

BACKGROUND

The role of trypanocidal therapy in patients with established Chagas' cardiomyopathy is unproven.

METHODS

We conducted a prospective, multicenter, randomized study involving 2854 patients with Chagas' cardiomyopathy who received benznidazole or placebo for up to 80 days and were followed for a mean of 5.4 years. The primary outcome in the time-to-event analysis was the first event of any of the components of the composite outcome of death, resuscitated cardiac arrest, sustained ventricular tachycardia, insertion of a pacemaker or implantable cardioverter–defibrillator, cardiac transplantation, new heart failure, stroke, or other thromboembolic event.

RESULTS

The primary outcome occurred in 394 patients (27.5%) in the benznidazole group and in 414 (29.1%) in the placebo group (hazard ratio, 0.93; 95% confidence interval [CI], 0.81 to 1.07; P=0.31). At baseline, a polymerase-chain-reaction (PCR) assay was performed on blood samples obtained from 1896 patients; 60.5% had positive results for *Trypanosoma cruzi* on PCR. The rates of conversion to negative PCR results (PCR conversion) were 66.2% in the benznidazole group and 33.5% in the placebo group at the end of treatment, 55.4% and 35.3%, respectively, at 2 years, and 46.7% and 33.1%, respectively, at 5 years or more (P<0.001 for all comparisons). The effect of treatment on PCR conversion varied according to geographic region: in Brazil, the odds ratio for PCR conversion was 3.03 (95% CI, 2.12 to 4.34) at 2 years and 1.87 (95% CI, 1.33 to 2.63) at 5 or more years; in Colombia and El Salvador, the odds ratio was 1.33 (95% CI, 0.90 to 1.98) at 2 years and 0.96 (95% CI, 0.63 to 1.45) at 5 or more years; and in Argentina and Bolivia, the odds ratio was 2.63 (95% CI, 1.89 to 3.66) at 2 years and 2.79 (95% CI, 1.99 to 3.92) at 5 or more years (P<0.001 for interaction). However, the rates of PCR conversion did not correspond to effects on clinical outcome (P=0.16 for interaction).

CONCLUSIONS

Trypanocidal therapy with benznidazole in patients with established Chagas' cardiomyopathy significantly reduced serum parasite detection but did not significantly reduce cardiac clinical deterioration through 5 years of follow-up. (Funded by the Population Health Research Institute and others; ClinicalTrials.gov number, NCT00123916; Current Controlled Trials number, ISRCTN13967269.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Morillo at the Population Health Research Institute, Hamilton Health Sciences and McMaster University, David Braley CVSRI Rm. 3C-120, Hamilton, ON L8L 2X2, Canada, or at morillo@hhsc.ca.

*A complete list of investigators in the Benznidazole Evaluation for Interrupting Trypanosomiasis (BENEFIT) trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Morillo and Marin-Neto contributed equally to this article.

This article was published on September 1, 2015, and updated on September 10, 2015, at NEJM.org.

DOI: 10.1056/NEJMoa1507574

BENEFIT trial

"BENznidazole Evaluation For Interrupting Trypanosomiasis"

Brazil N=1358
Argentina N=559
Colombia N=502
Bolivia N=357
El Salvador N=78

Chagas Heart Disease

≥2 positive serological tests
Abnormal ECG (≥2 alterations)
Age: 18-75 years
No advanced cardiomyopathy (NYHA IV)

Nov 2004-Oct 2011 (N=2854)

R

BZN
1431

PCB
1423

Primary end point

- *Death*
- *Resuscitation from cardiac arrest*
- *Documented sustained ventricular tachycardia*
- *New development of symptomatic CHF*
- *Heart Transplant*
- *Need for Pacemaker or ICD*
- *Stroke or any other thromboembolic event*

Mean FU: 5.4 years

300 mg/d during 40 to 80 days (period adjusted according to patient's body weight)

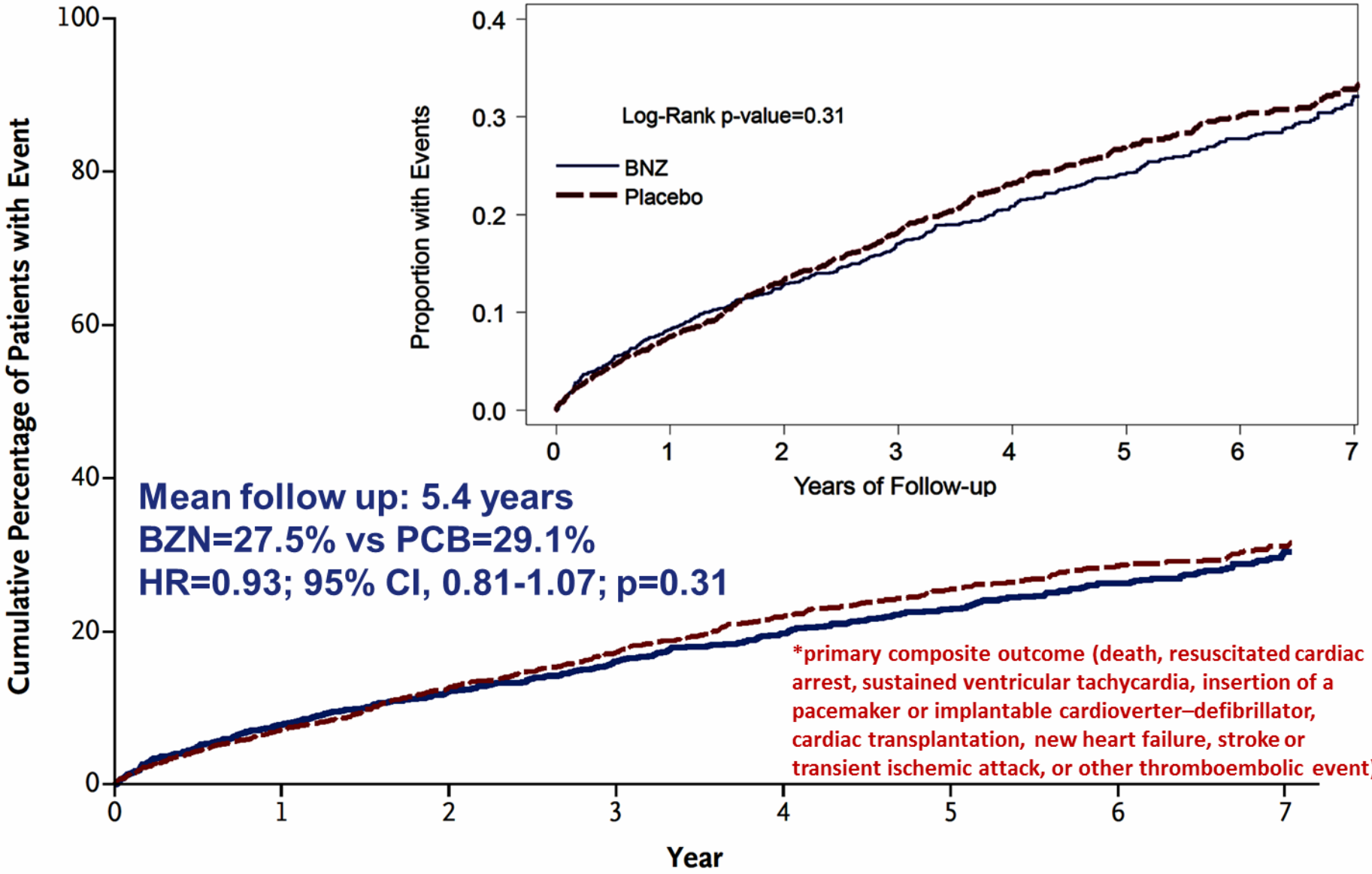
Rassi A jr, 2016

Safety: Adverse Events Leading to Drug Interruption

	BNZ	Placebo	P
Any adverse event	23.9%	9.5%	<0.001
Permanent treatment discontinuation	13.4%	3.6%	< 0.001
Cutaneous rash	9.6%	1.3%	<0.001
Gastrointestinal	7.8%	2.9%	<0.001
Nervous system	3.6%	1.3%	<0.001
Leukopenia < 1.9 $10^3/mm^3$ neutrophil	0.1%	0.1%	1
Alanine aminotransferase >2X ULN	4.9%	1.6%	<0.001

Primary Composite Outcome* during 7 Years of Follow-up

BENEFIT trial



*primary composite outcome (death, resuscitated cardiac arrest, sustained ventricular tachycardia, insertion of a pacemaker or implantable cardioverter–defibrillator, cardiac transplantation, new heart failure, stroke or transient ischemic attack, or other thromboembolic event)

No. at Risk								
Benznidazole	1431	1312	1246	1178	936	695	484	323
Placebo	1423	1316	1233	1155	881	649	459	294

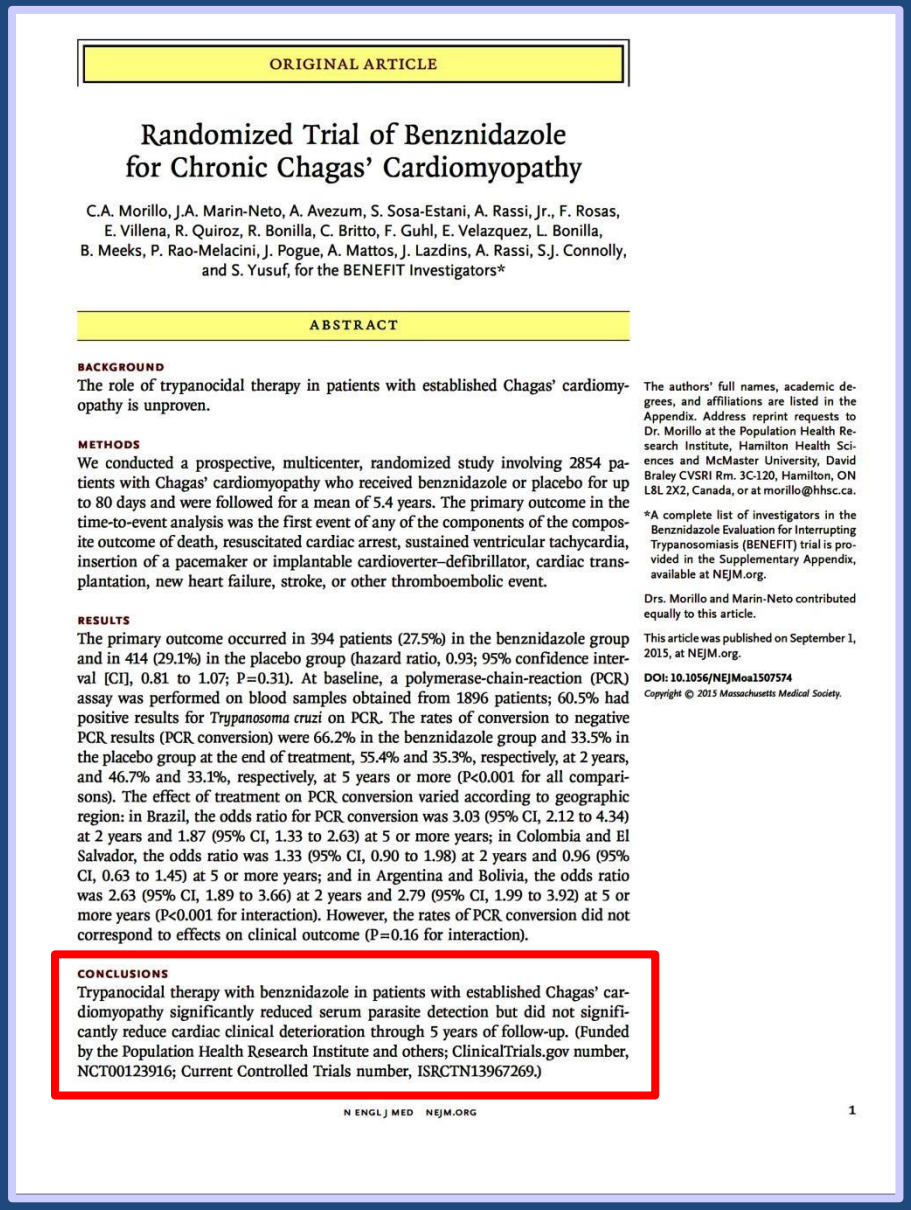
PCR negativization after treatment

Overall population	BENZNIDAZOLE	PLACEBO	P value
End of treatment	66.2%	33.5%	p<0.001
2 years after therapy	55.4%	35.3%	p<0.001
≥ 5 years after therapy N=918	46.7%	33.1%	p<0.001

BZN: 59.5% with positive PCR at baseline
PCB: 61.7% with positive PCR at baseline

BENEFIT trial

El tratamiento con benznidazol en sujetos con cardiopatía por enfermedad de Chagas reduce significativamente la parasitemia pero no reduce el compromiso cardiológico a 5 años de seguimiento.



ORIGINAL ARTICLE

Randomized Trial of Benznidazole for Chronic Chagas' Cardiomyopathy

C.A. Morillo, J.A. Marin-Neto, A. Avezum, S. Sosa-Estani, A. Rassi, Jr., F. Rosas, E. Villena, R. Quiroz, R. Bonilla, C. Britto, F. Guhl, E. Velazquez, L. Bonilla, B. Meeks, P. Rao-Melacini, J. Pogue, A. Mattos, J. Lazdins, A. Rassi, S.J. Connolly, and S. Yusuf, for the BENEFIT Investigators*

ABSTRACT

BACKGROUND

The role of trypanocidal therapy in patients with established Chagas' cardiomyopathy is unproven.

METHODS

We conducted a prospective, multicenter, randomized study involving 2854 patients with Chagas' cardiomyopathy who received benznidazole or placebo for up to 80 days and were followed for a mean of 5.4 years. The primary outcome in the time-to-event analysis was the first event of any of the components of the composite outcome of death, resuscitated cardiac arrest, sustained ventricular tachycardia, insertion of a pacemaker or implantable cardioverter–defibrillator, cardiac transplantation, new heart failure, stroke, or other thromboembolic event.

RESULTS

The primary outcome occurred in 394 patients (27.5%) in the benznidazole group and in 414 (29.1%) in the placebo group (hazard ratio, 0.93; 95% confidence interval [CI], 0.81 to 1.07; P=0.31). At baseline, a polymerase-chain-reaction (PCR) assay was performed on blood samples obtained from 1896 patients; 60.5% had positive results for *Trypanosoma cruzi* on PCR. The rates of conversion to negative PCR results (PCR conversion) were 66.2% in the benznidazole group and 33.5% in the placebo group at the end of treatment, 55.4% and 35.3%, respectively, at 2 years, and 46.7% and 33.1%, respectively, at 5 years or more (P<0.001 for all comparisons). The effect of treatment on PCR conversion varied according to geographic region: in Brazil, the odds ratio for PCR conversion was 3.03 (95% CI, 2.12 to 4.34) at 2 years and 1.87 (95% CI, 1.33 to 2.63) at 5 or more years; in Colombia and El Salvador, the odds ratio was 1.33 (95% CI, 0.90 to 1.98) at 2 years and 0.96 (95% CI, 0.63 to 1.45) at 5 or more years; and in Argentina and Bolivia, the odds ratio was 2.63 (95% CI, 1.89 to 3.66) at 2 years and 2.79 (95% CI, 1.99 to 3.92) at 5 or more years (P<0.001 for interaction). However, the rates of PCR conversion did not correspond to effects on clinical outcome (P=0.16 for interaction).

CONCLUSIONS

Trypanocidal therapy with benznidazole in patients with established Chagas' cardiomyopathy significantly reduced serum parasite detection but did not significantly reduce cardiac clinical deterioration through 5 years of follow-up. (Funded by the Population Health Research Institute and others; ClinicalTrials.gov number, NCT00123916; Current Controlled Trials number, ISRCTN13967269.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Morillo at the Population Health Research Institute, Hamilton Health Sciences and McMaster University, David Braley CVSRI Rm. 3C-120, Hamilton, ON L8L 2X2, Canada, or at morillo@hhsc.ca.

*A complete list of investigators in the Benznidazole Evaluation for Interrupting Trypanosomiasis (BENEFIT) trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Morillo and Marin-Neto contributed equally to this article.

This article was published on September 1, 2015, at NEJM.org.

DOI: 10.1056/NEJMoa1507574

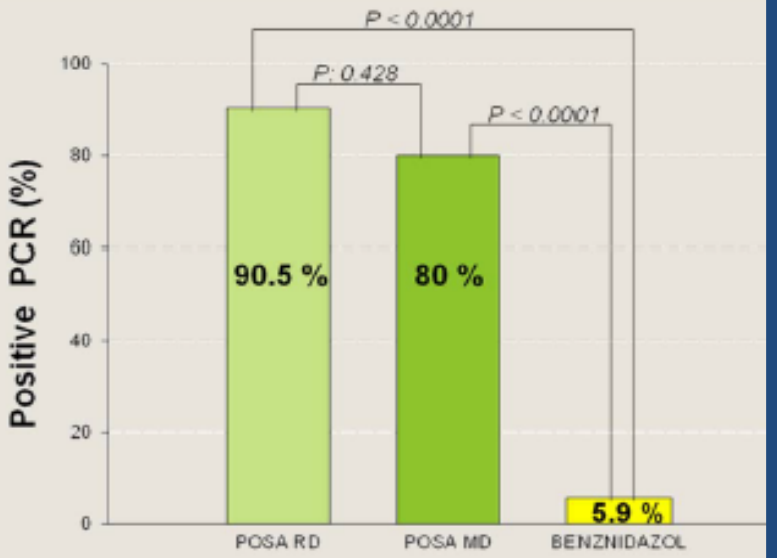
Azole Class Clinical Trial Results - ICTMM

Molina *et al.*
NCT01162967

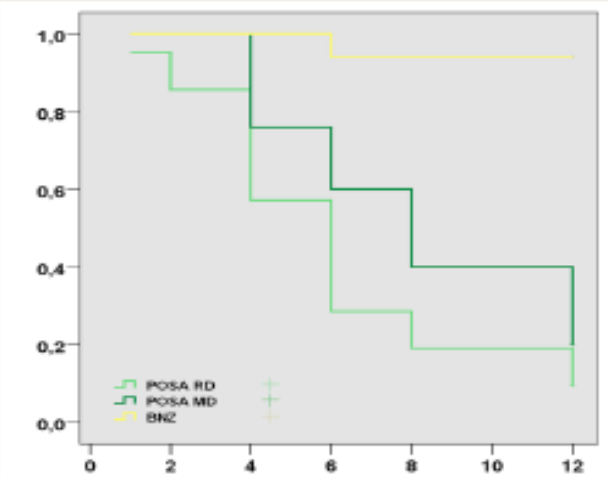
CHAGASAZOL

Proportion 1:1:1

Benznidazol 300mg/dia	Posaconazol 200mg/dia	Posaconazol 800mg/dia
26 patients	27 patients	25 patients
5 Treatment Stopped	3 Lost pre-treatment	0 Treatment Stopped
4 Lost to follow up	0 Treatment Stopped	0 Lost to follow up
	3 Lost to follow up	
17 patients	21 patients	25 patients



Cumulative probability of failure



PCR TREATMENT: D0 D7 D14 D28 D45 D60

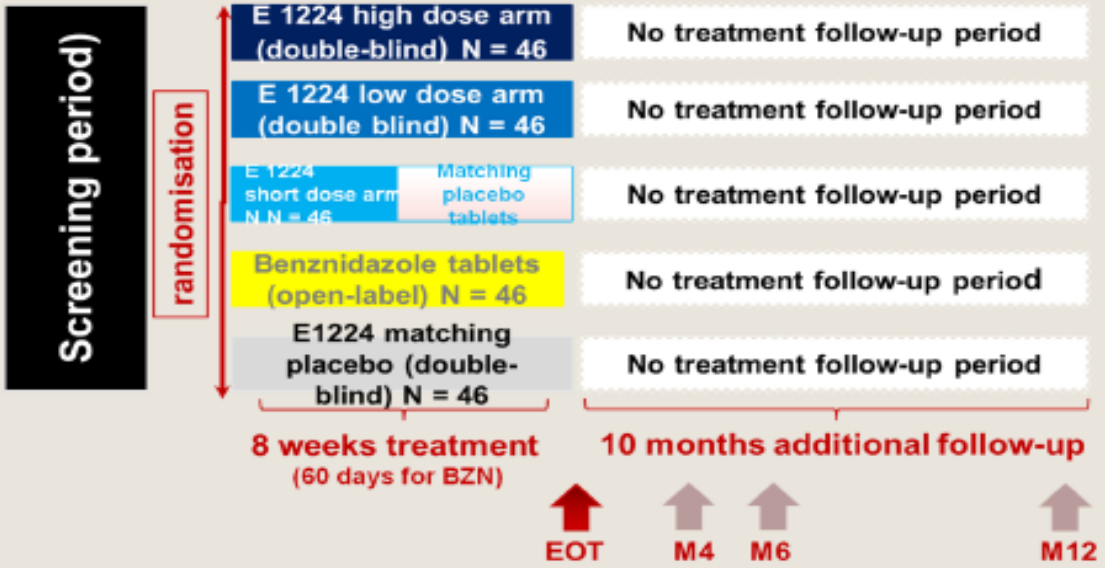
FOLLOW UP: M4 M6 M8 M12

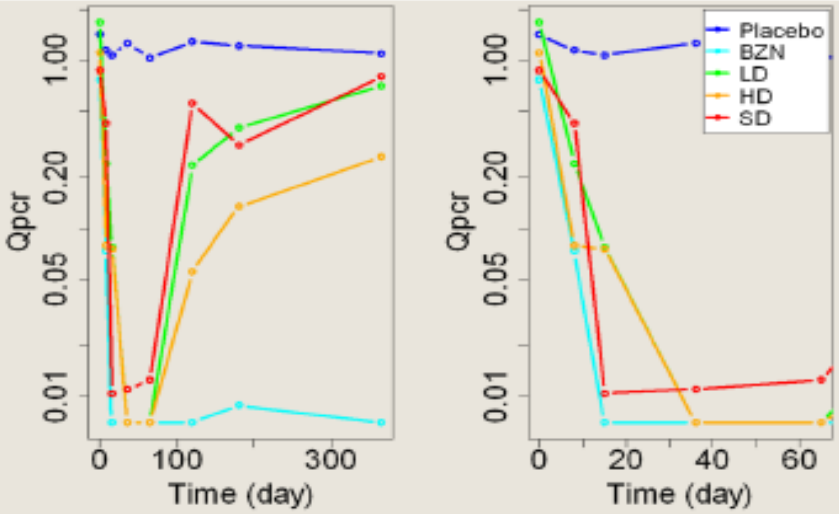
TWICE / 10ML

<40: Positive

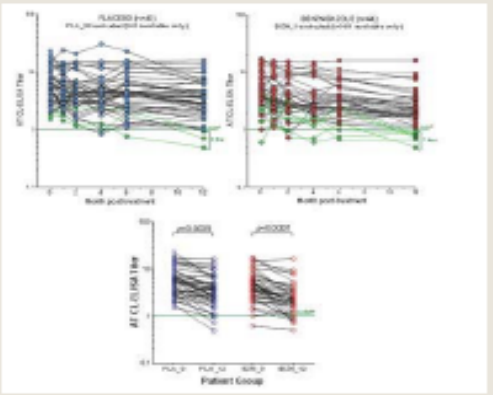
E1224 - Phase II PoC Study

DNDi-CH-E1224-001
NCT01489228





Efficacy based on repeated PCR and candidate biomarkers, parallel evaluation of serology



Day 65 (EOT)

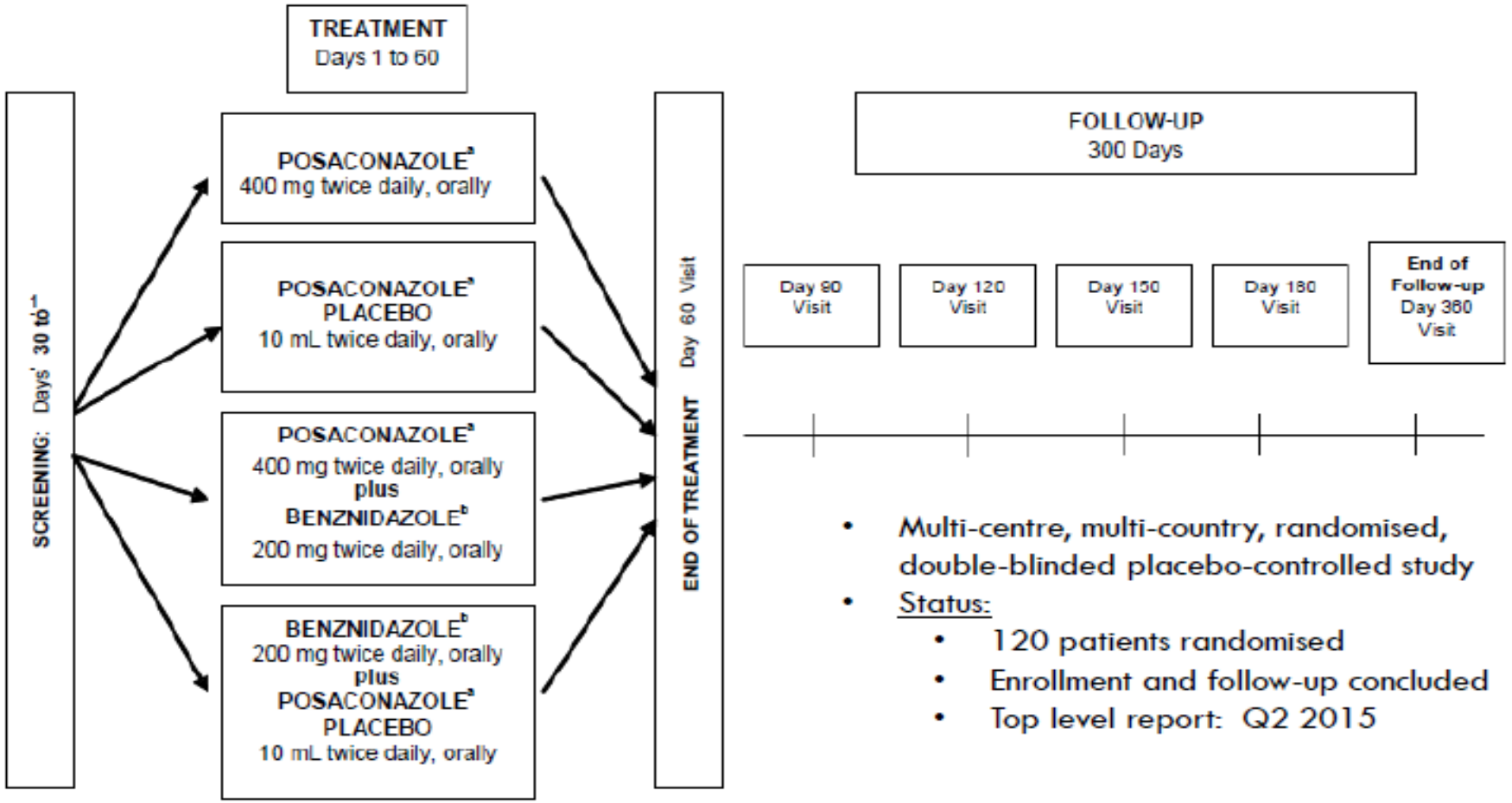
			Placebo (N=47)	LD (N=48)	SD (N=46)	HD (N=45)	BZN (N=45)	All (N=231)
Parasite clearance at D65		N	47	48	46	45	45	231
		Missing	0	0	0	0	0	0
	No	n (%)	35 (74.5)	5 (10.4)	5 (10.9)	11 (24.4)	4 (8.9)	60 (26.0)
	Yes	n (%)	12 (25.5)	43 (89.6)	41 (89.1)	34 (75.6)	41 (91.1)	171 (74.0)

12 Month Follow-up

			(N=47)	(N=48)	(N=46)	(N=45)	(N=45)	(N=231)
Sustained clearance At 12 months	No	n (%)	43 (91.5)	44 (91.7)	41 (89.1)	32 (71.1)	8 (19.0)	168 (72.7)
	Yes	n (%)	4 (8.5)	4 (8.3)	5 (10.9)	13 (28.9)	37 (81.0)	63 (27.3)

ISGlobal Institut de Salut Global Barcelona
CEADES
DNDi Drugs for Neglected Diseases initiative

STOP-CHAGAS - A Study of the Use of Oral Posaconazole (POS) in the Treatment of Asymptomatic Chronic Chagas Disease - NCT01377480

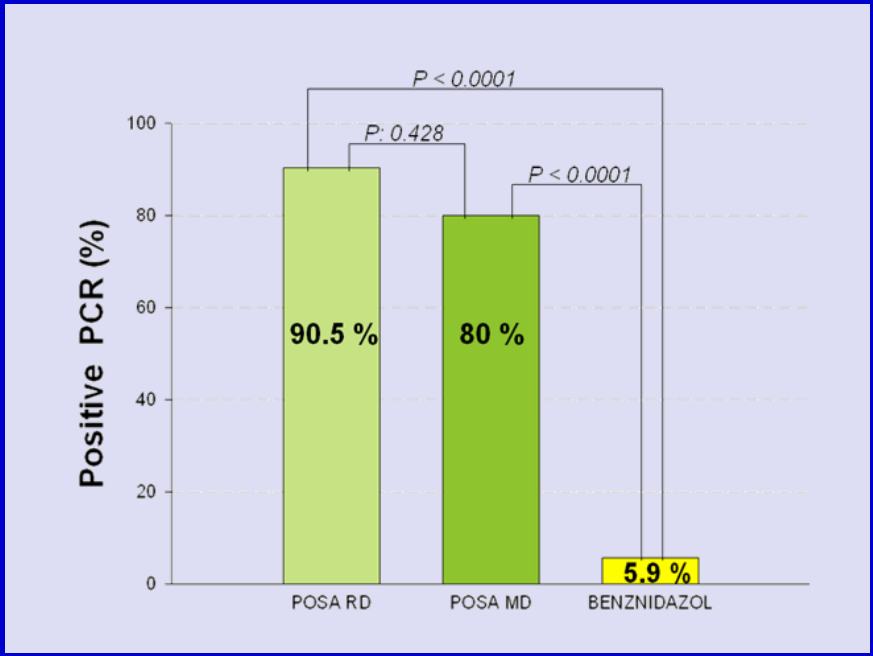


- Multi-centre, multi-country, randomised, double-blinded placebo-controlled study
- Status:
  - 120 patients randomised
  - Enrollment and follow-up concluded
  - Top level report: Q2 2015

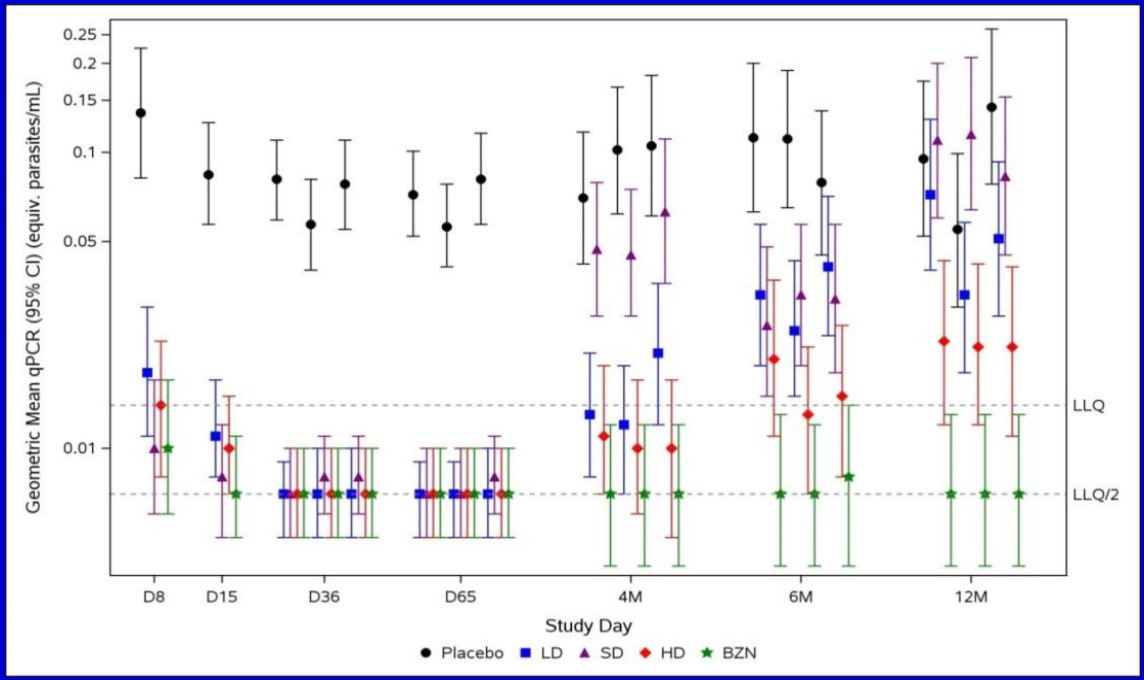
PI : Morillo CA

Steering Committee: S Sosa-Estani, A Avezum, S Yusuf, S Chrolavicious.

CHAGAZASOL (NCT01162967), Posaconazol vs Benznidazol Efectividad a 12 meses



DNDi-CH-E1224-001 (NCT01489228), Ravuconazol, benznidazol y placebo Efectividad a 12 meses



Los azoles no son efectivos para el tratamiento de la enfermedad de Chagas

Fexinidazole
Proof-of-Concept Dose Ranging Study

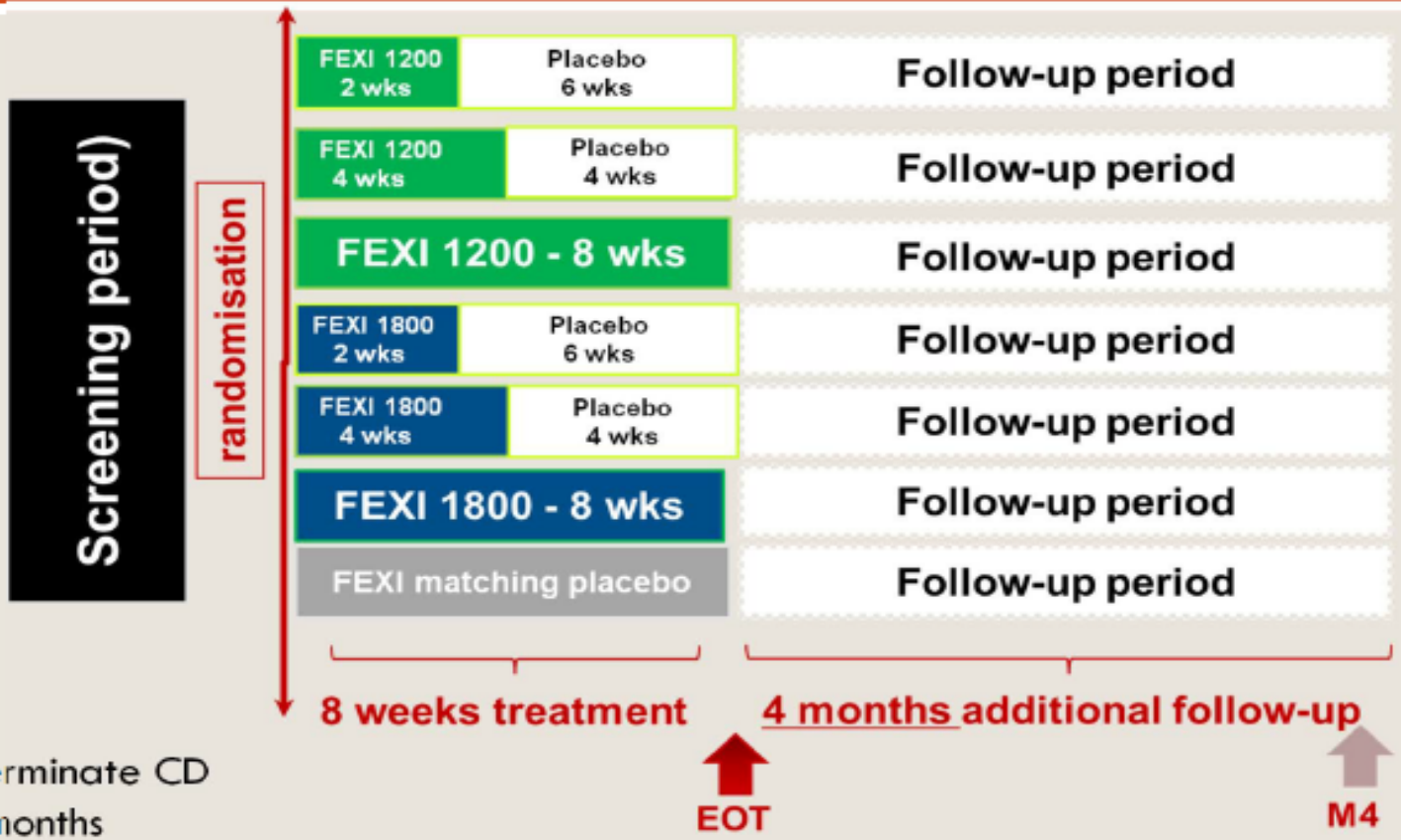
Study initiated:
July 2014

Study recruitment temporary interruption: Oct 17, 2014

Study recruitment interruption:
December 11, 2014

Target for Top Line Report (TLR):
August 2015

180 ICF signed
47 patients randomised
LVLP planned April 2015



- 140 adults with chronic indeterminate CD
- PCR sustained response at 6 months
- Stopping rules: futility and safety

Risk Management:

- Timelines for recruitment
- Safety monitoring

ISGlobal Instituto de Salud Global Barcelona
CEADES
cooperación española
DNDi Drugs for Neglected Diseases initiative

Adverse Events After the Use of Benznidazole in Infants and Children With Chagas Disease

WHAT'S KNOWN ON THIS SUBJECT: Treatment of Chagas disease with benznidazole in adults leads to a high incidence of severe drug reactions. However, benznidazole seems to lead to less frequent (and less severe) ADRs in children, but there are scarce data on the subject.

WHAT THIS STUDY ADDS: We describe a cohort of children with Chagas disease treated with benznidazole. A lower incidence of ADRs was observed in smaller children compared with older children and adults. All ADRs observed were mild, and treatment response was excellent.

Los niños menores toleran mejor la medicación

AUTHORS: Jaime Altcheh, MD,[a] Guillermo Moscatelli, MD,[a] Samanta Moroni, MD,[a] Facundo Garcia-Bournissen, MD,[b] and Hector Freilij, MD[a]

[a]Servicio de Parasitologia y Enfermedad de Chagas, Hospital de Niños R Gutierrez, Buenos Aires, Argentina; and [b]Division of Clinical Pharmacology and Toxicology, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

KEY WORDS
infant, children, Chagas disease, congenital, benznidazole, adverse events, pediatric pharmacology

ABBREVIATIONS
ADR—adverse drug reaction
CI—confidence interval
IQR—interquartile range
CNS—central nervous system

www.pediatrics.org/cgi/doi/10.1542/peds.2010-1172

doi:10.1542/peds.2010-1172

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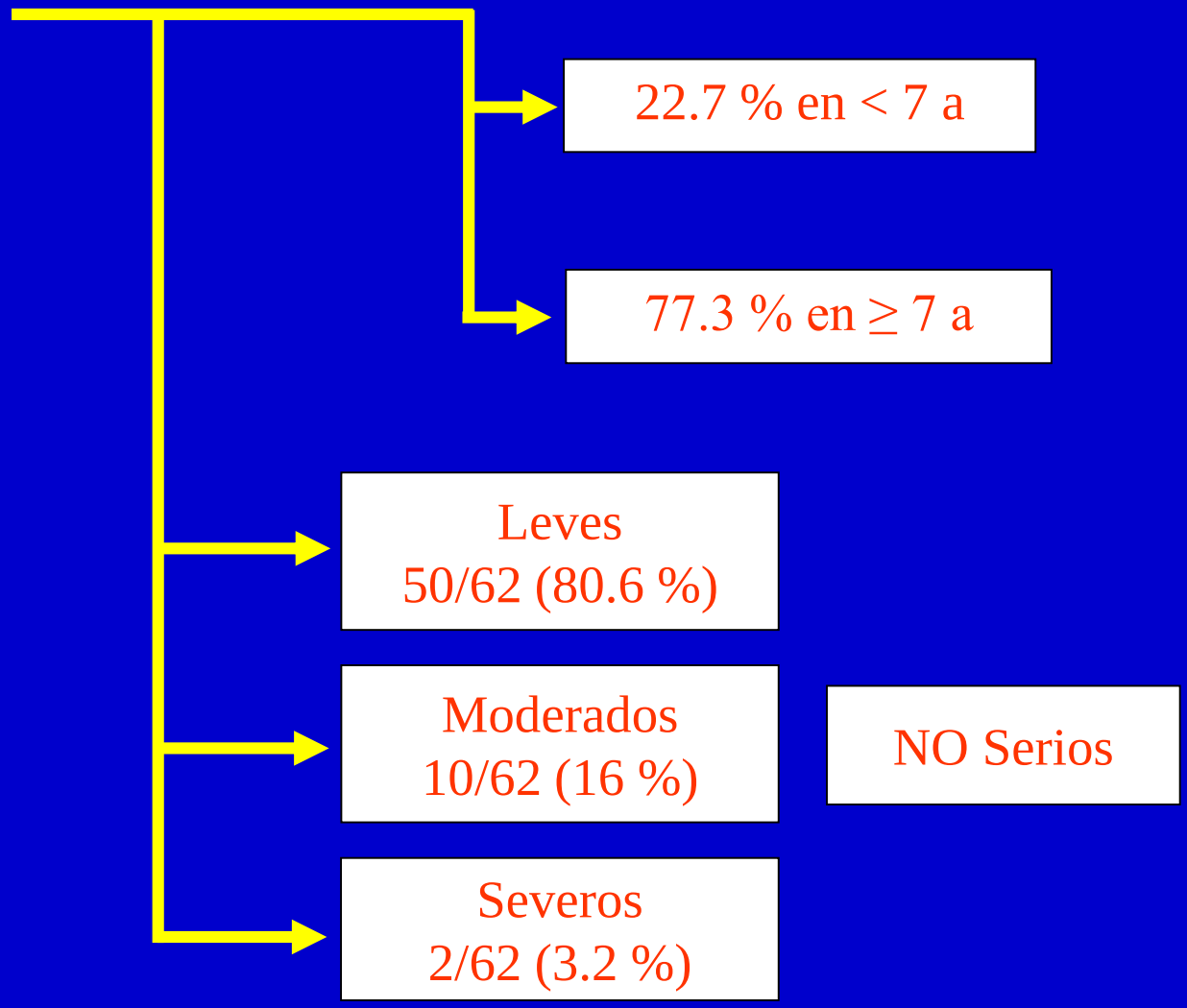
EVENTOS ADVERSOS (107 pacientes)

- 41% presentaron EA
- 21% en piel
- 9% SNC
- 8.5% GI
- 28% Alt. Bioquímicas
- Edad media 9.9 años
- 73% en los 1^{ros} 10 días



Adverse Events After the Use of Benznidazole in Infants and Children With Chagas Disease
Jaime Altcheh, Guillermo Moscatelli, Samanta Moroni, Facundo Garcia-Bournissen and Hector Freilij
Pediatrics published online Dec 20, 2010;
DOI: 10.1542/peds.2010-1172

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Nifurtimox

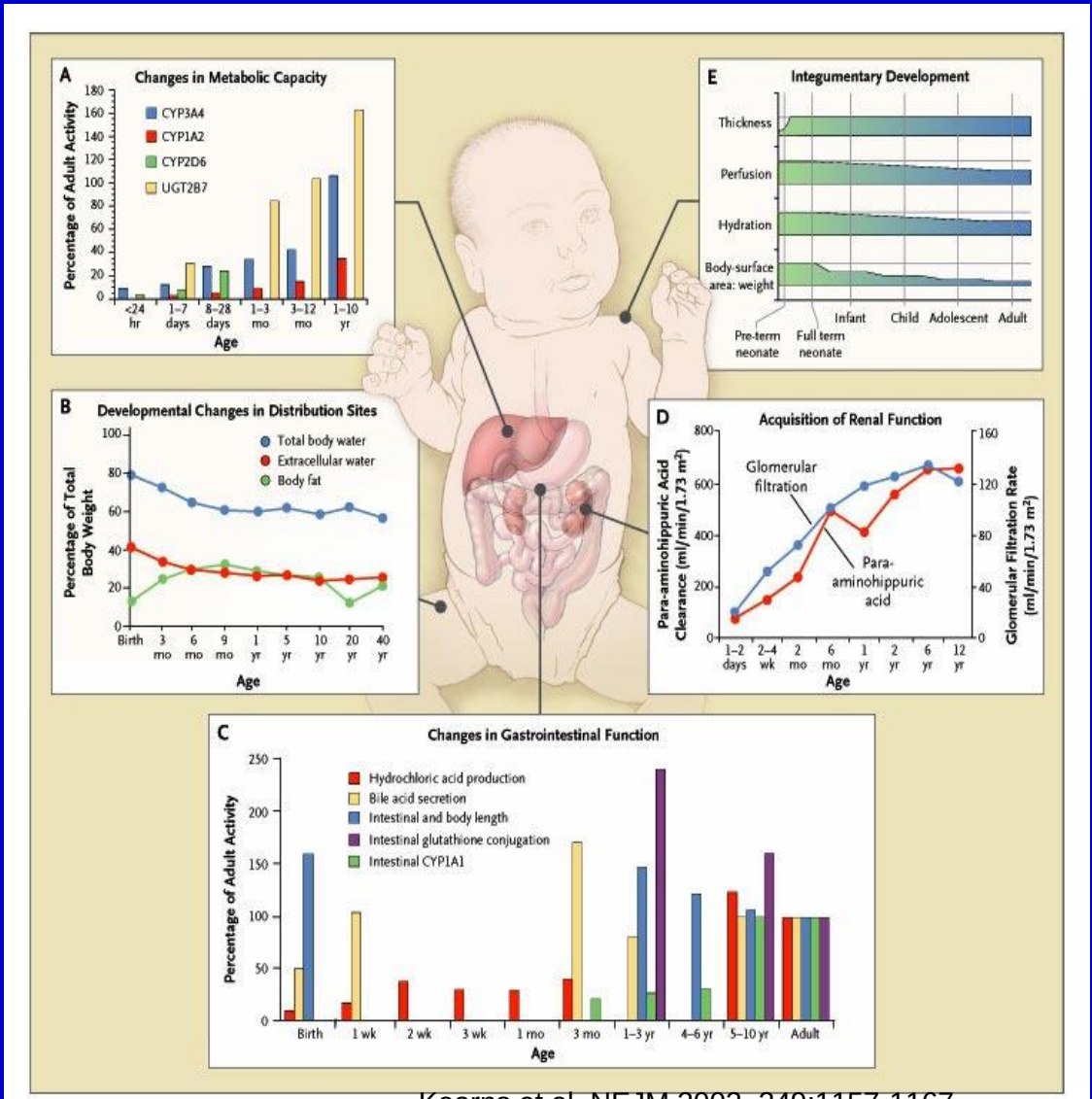
Lead Author	Country year	Phase	Age	N	Doses mg/kg/d	Duration Treatment	Efficacy	Safety
Altcheh	Argentina 2005	Acute	15d-10y	168	10-15	60d	Sero-conversion: 87-100%	Irritability,anorexia, vomiting
Bianchi	Colombia 2015	Asymp. Chronic	9-19y	62	8-12	60d	Sero-conversion: 13.5% of pts @ 12m vs BL 42% of pts @ 30m vs. BL 88% decrease in qPCR @ 30m vs BL	ECG abnormality, hyperexia, headache, abdominal pain, asthenia
Bocca Tourres	Argentina 1969	Acute	various	88	12-30	30-90d	Deacreased fever, irritability, chagoma, lymphadenopathy 59-79% sero-conversion + neg. xenodiagnosis	Anorexia, loss appetite
Lugones	Argentina 1969	Acute	0- >14y	407	15-25	90d	Resolution of fever, headache, local edema, erythema, adenopathy Decreased cardiomegaly resolution	Anorexia, nausea, excitation, vomiting, gastralgia
Wegner	Arg, Braz, S.Salv 1972	Acute	0 -16y	439	12.5-20	90d	Decreaesd hepatomegaly, splenomegaly, edema, chagoma Sero-conversion: 81% NFX vs 0% placebo at 20m	Anorexia, nausea, vomiting, nervous-ness, gastric pain, skin conditions


Un niño NO es un adulto pequeño...
un adulto pequeño, es un señor bajito
¡¡Haz llegar tu mensaje!!
AEP

Los niños son diferentes

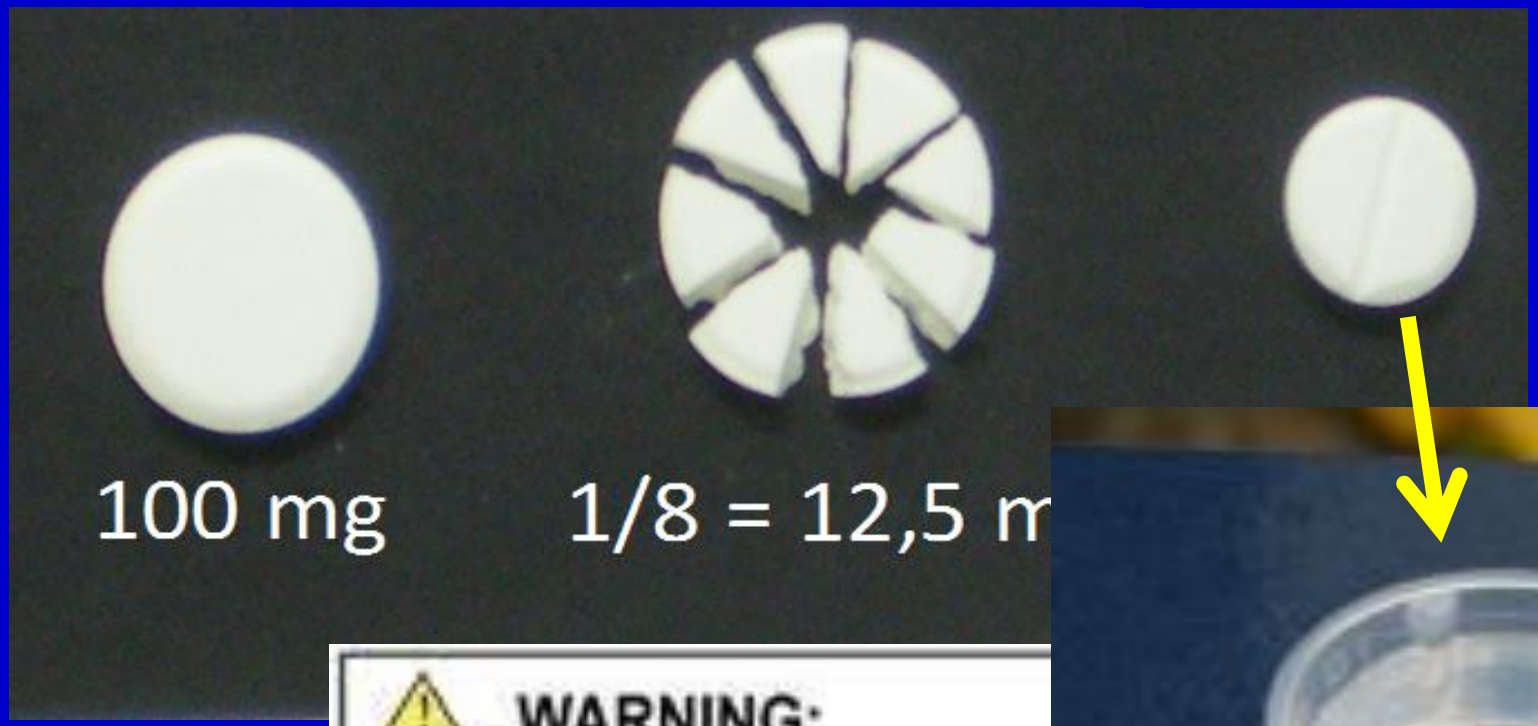
Los niños son diferentes en:
- Absorción
- Distribución
- Función renal (excresión)
- Función hepatica (metabolismo)
- Farmacodinamia:

Respuesta terapeutica
Eventos adversos



Kearns et al. NEJM 2003. 349:1157-1167

BNZ formulation problem



Formulaciones pediátricas
Plan de desarrollo

Comp de 100 mg BZ, 120 mg NFTX	12,5 mg BZ, 30 mg NFTX dispersables
Tratamiento 60- 90 - 120 dias	Tratamientos de 30-60 días
Escasos datos de eficacia y seguridad	Ensayos clínicos
Farmacocinetica escasa información en adultos, NO en niños	Ensayos clínicos PK/PD en niños y adultos
Registro en pocos paises de LatAm	Registro FDA, EMEA

OPEN ACCESS Freely available online

PLOS | NEGLECTED TROPICAL DISEASES

Population Pharmacokinetic Study of Benznidazole in Pediatric Chagas Disease Suggests Efficacy despite Lower Plasma Concentrations than in Adults

Jaime Altcheh[1], Guillermo Moscatelli[1], Guido Mastrantonio[2], Samanta Moroni[1], Norberto Giglio[1], Maria Elena Marson[2], Griselda Ballering[1], Margarita Bisio[1], Gideon Koren[3], Facundo García-Bournissen[1,3]*

1 Servicio de Parasitología y Chagas, Hospital de Niños Ricardo Gutiérrez, Ciudad de Buenos Aires, Argentina, 2 Área de Toxicología, Departamento de Ciencias Biológicas, Facultad de Ciencias Exactas, Universidad Nacional de La Plata, La Plata, Provincia de Buenos Aires, Argentina, 3 Division of Clinical Pharmacology & Toxicology, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

Clinicaltrials.gov registry # NCT00699387

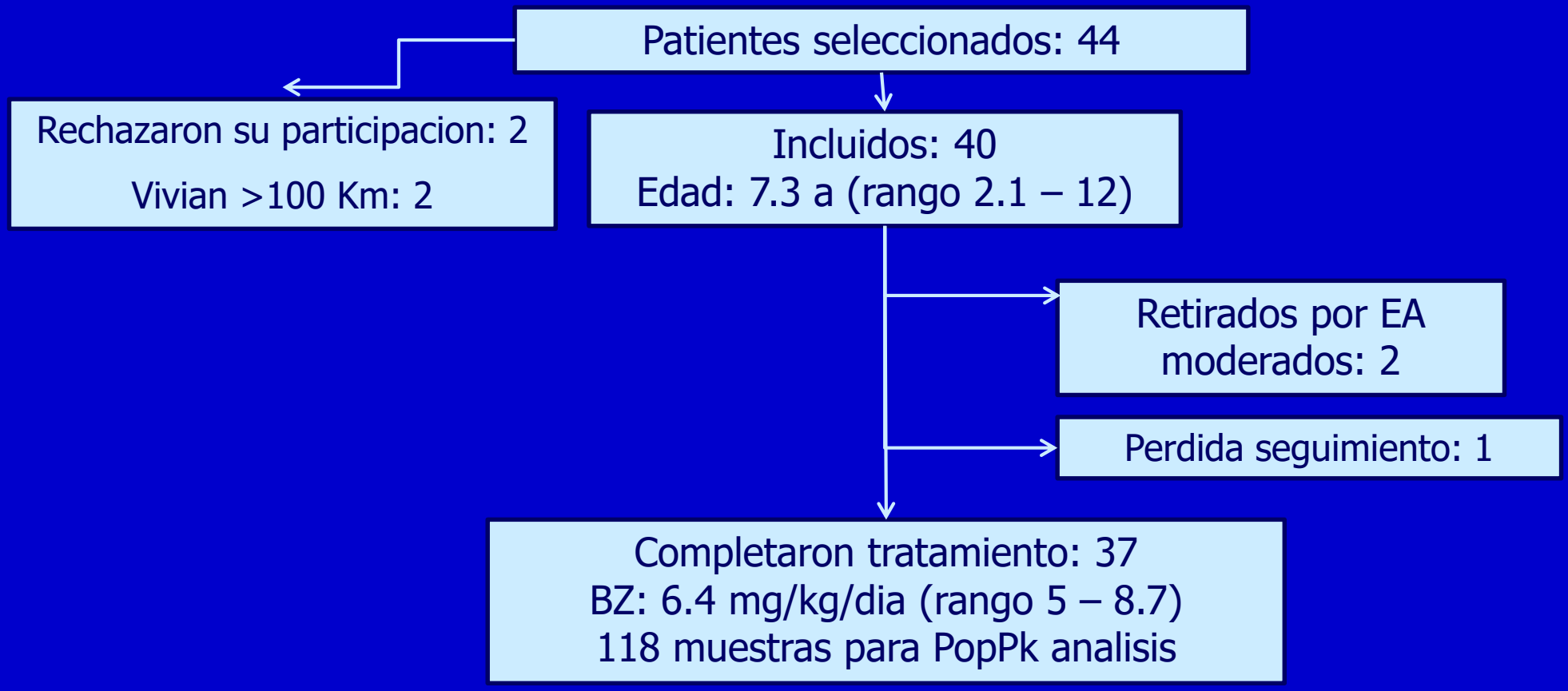
HOSPITAL DE NIÑOS H N R G Dr. RICARDO GUTIERREZ

Parasitología y Chagas * Hospital de Niños R. Gutiérrez *

SickKids

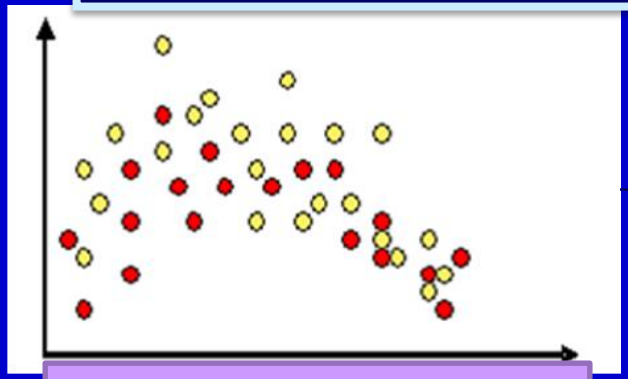
UNIVERSITY OF TORONTO

Flujograma estudio



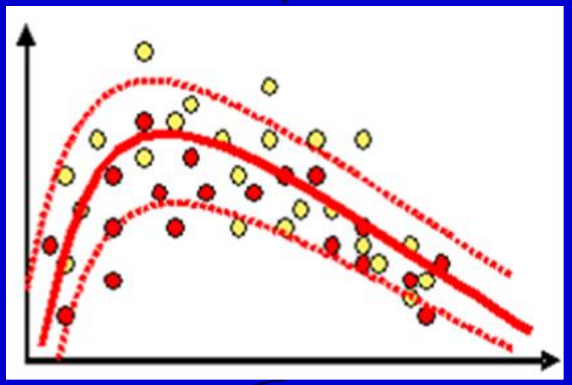
Todos los niños tratados presentaron negativizacion de qPCR *T. cruzi* , y mostraron caida en el titulo de anticuerpos.

¿Que es la farmacocinetica poblacional?



Informacion de concentraciones sanguineas provenientes de distintos pacientes en diferentes ocasiones

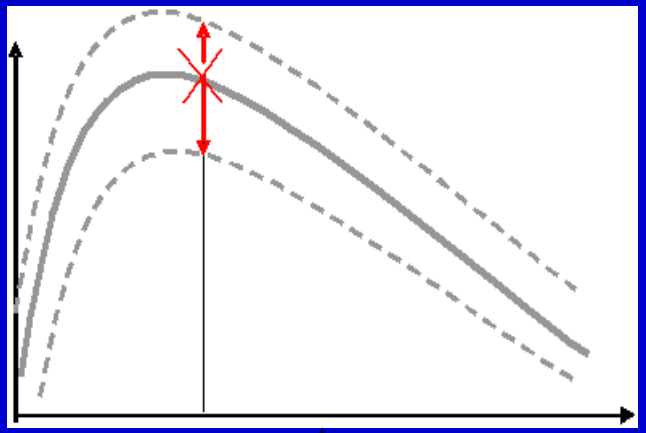
Seleccion de un modelo farmacocinetico poblacional



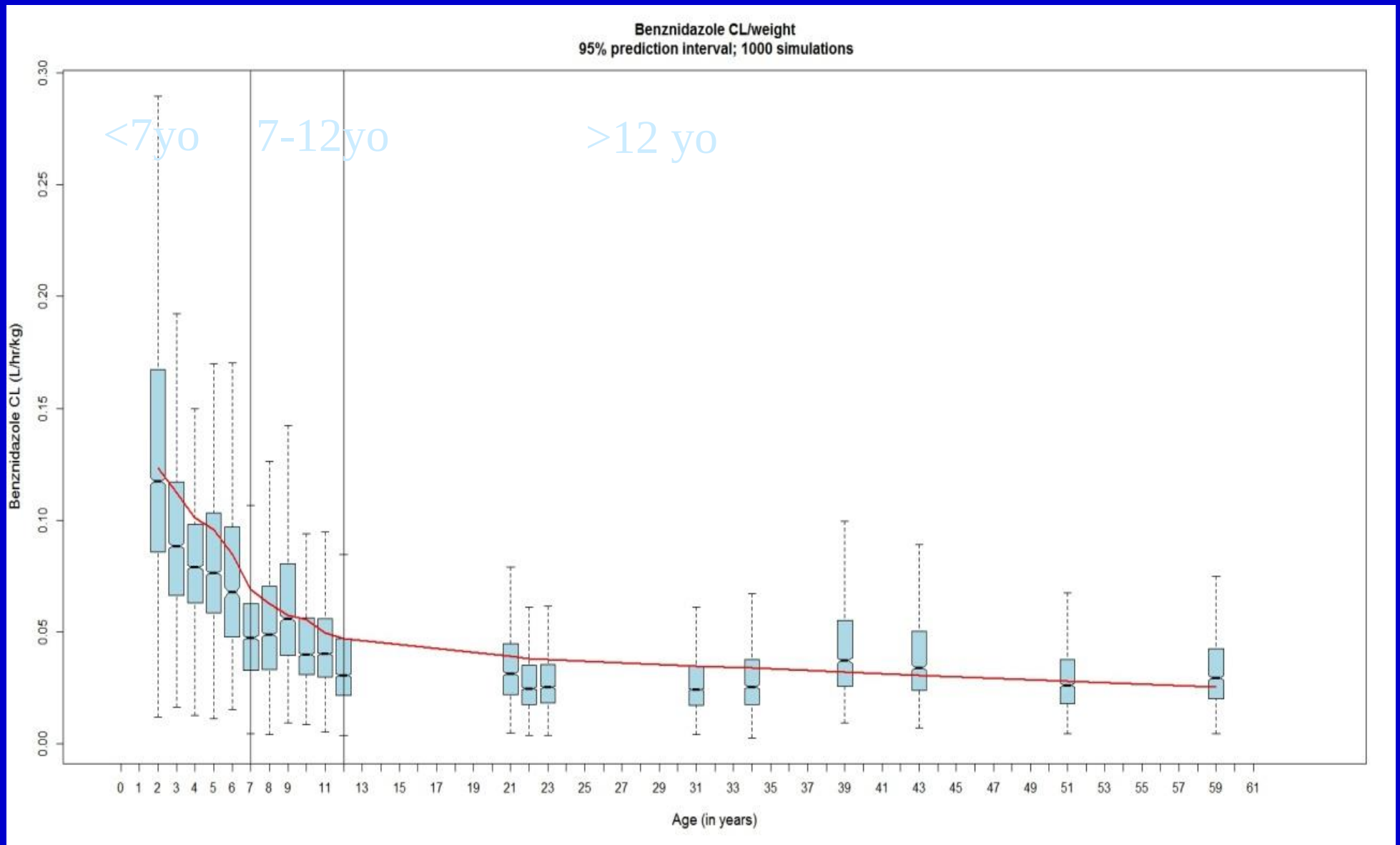
Estimacion de valores tipicos para los parametros farmacocineticos en la poblacion, y de la variabilidad inter e intra-individual

Evaluacion del rol de co-variables (por ej. Funcion renal, peso, edad, etc) en la variabilidad observada

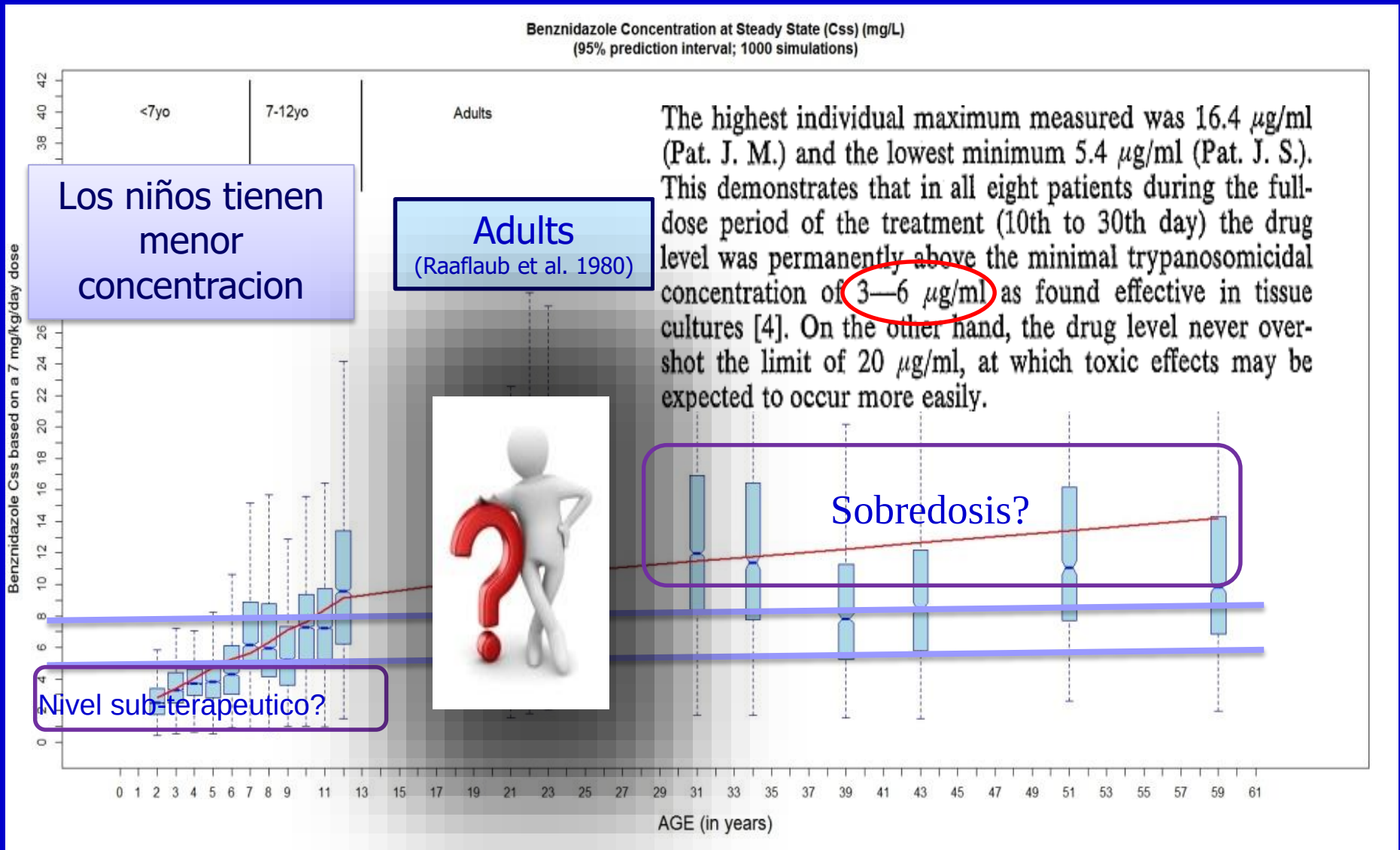
Obtencion de un modelo farmacocinetico que permita prediccion de concentraciones sanguineas en sub-grupos de pacientes de interes (por ej, insuficiencia renal, neonatos, etc)



Weight-corrected clearance (popPK)

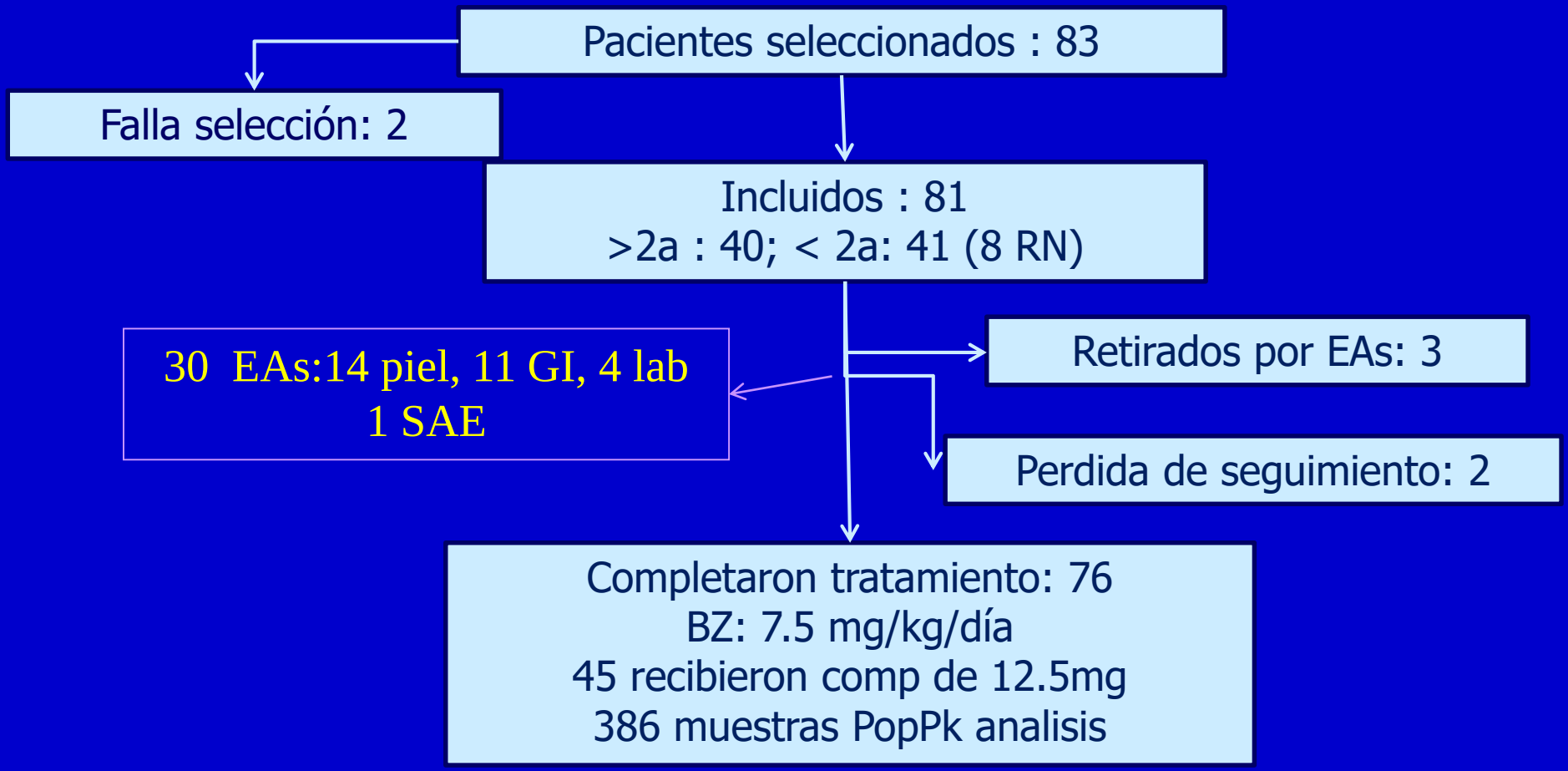


Concentracion en estado estacionario (popPK)



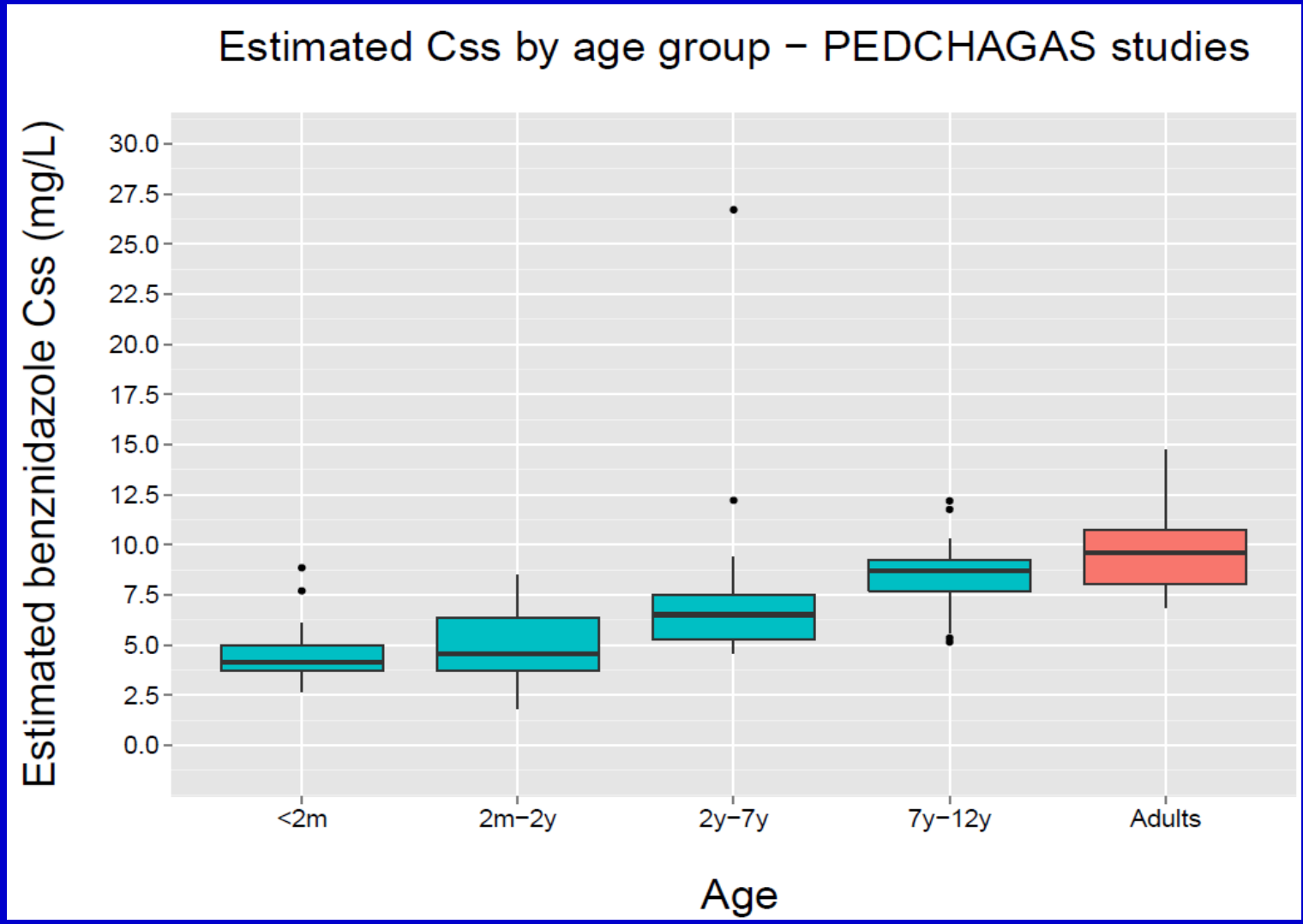
Resultados

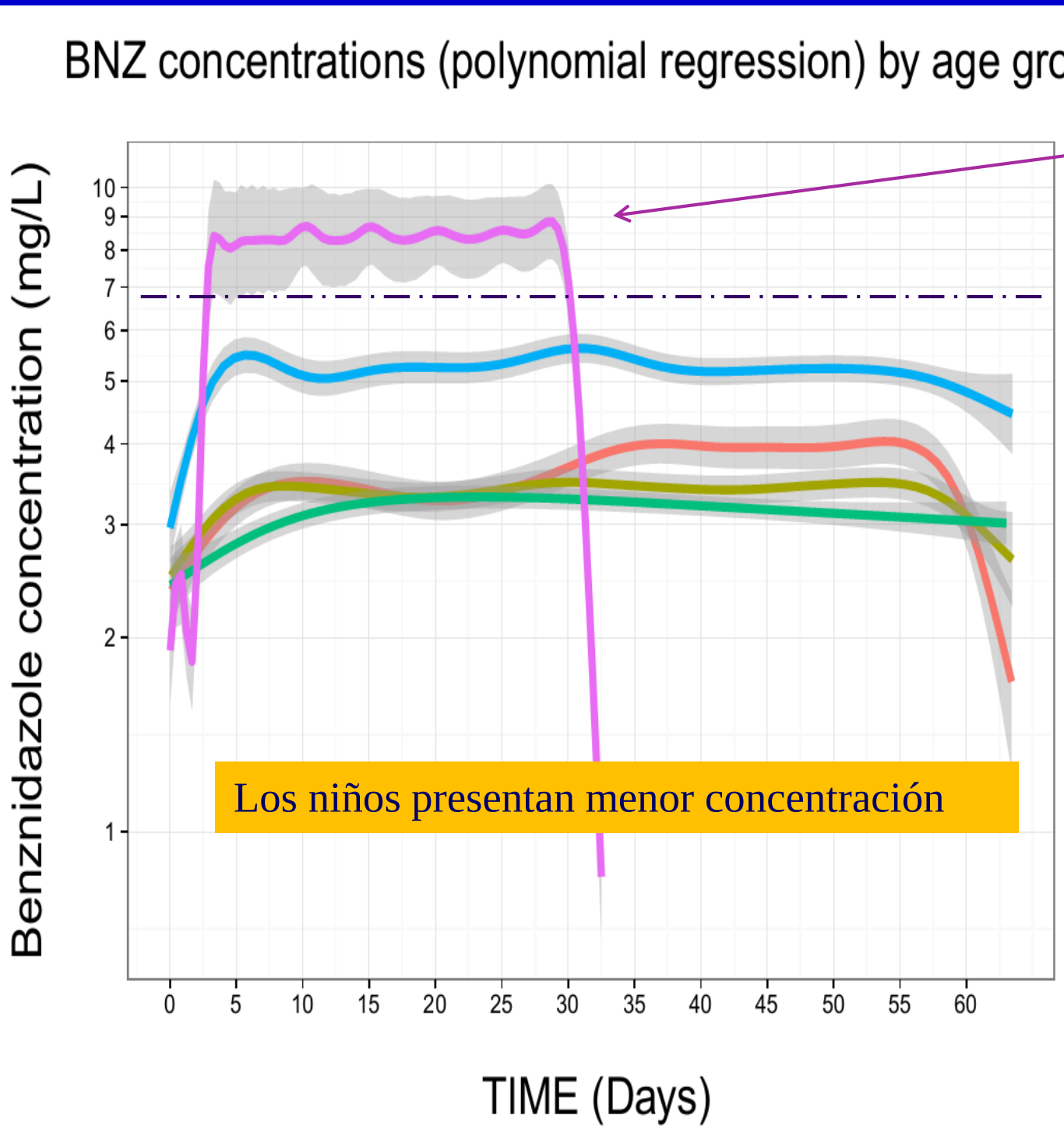
Pediatric network
PEDCHAGAS



Todos los niños presentaron qPCR negativa al final del tratamiento

Concentración





Adultos, Raaflaub 1980

The highest individual maximum measured was 16.4 μg/ml (Pat. J. M.) and the lowest minimum 5.4 μg/ml (Pat. J. S.). This demonstrates that in all eight patients during the full-dose period of the treatment (10th to 30th day) the drug level was permanently above the minimal trypanosomicidal concentration of 3—6 μg/ml as found effective in tissue cultures [4]. On the other hand, the drug level never overshot the limit of 20 μg/ml, at which toxic effects may be expected to occur more easily.

Los niños presentan menor concentración

Nifurtimox

Fundamentos para el desarrollo.

- Desarrollo de una formulacion pediatrica Development of pediatric formulations with unchanged biopharmaceutical characteristics (30mg & 120mg tablets)
  - Dispersable para ser administrada en niños
  - Comprimidos ranurados para una adecuada dosificacion
- Evaluar tratamientos cortos (60 vs 30 días)
- Evaluar parametros poblacionales PK/PD
- Evaluar seguridad en niños
- Registro en FDA y otros paises

1. **Bioequivalence Study NCT 01927224**
2. **Food Effect Study NCT 02606864**
3. **Phase III Study in Pediatric CD Patients (CHICO Study) NCT 02625974**

Nifurtimox Clinical Studies

Bioequivalence Study NCT01927224 (1)

Objectives

- Assess bioequivalence (BE) between the existing oral formulation of 120 mg NFX tablet and 4 x 30 mg NFX tablets (new pediatric formulation) administered after a high calorie/high fat meal
- Determine the Pop PK of NFX tablets administered as slurry after disintegration in small amounts of tap water

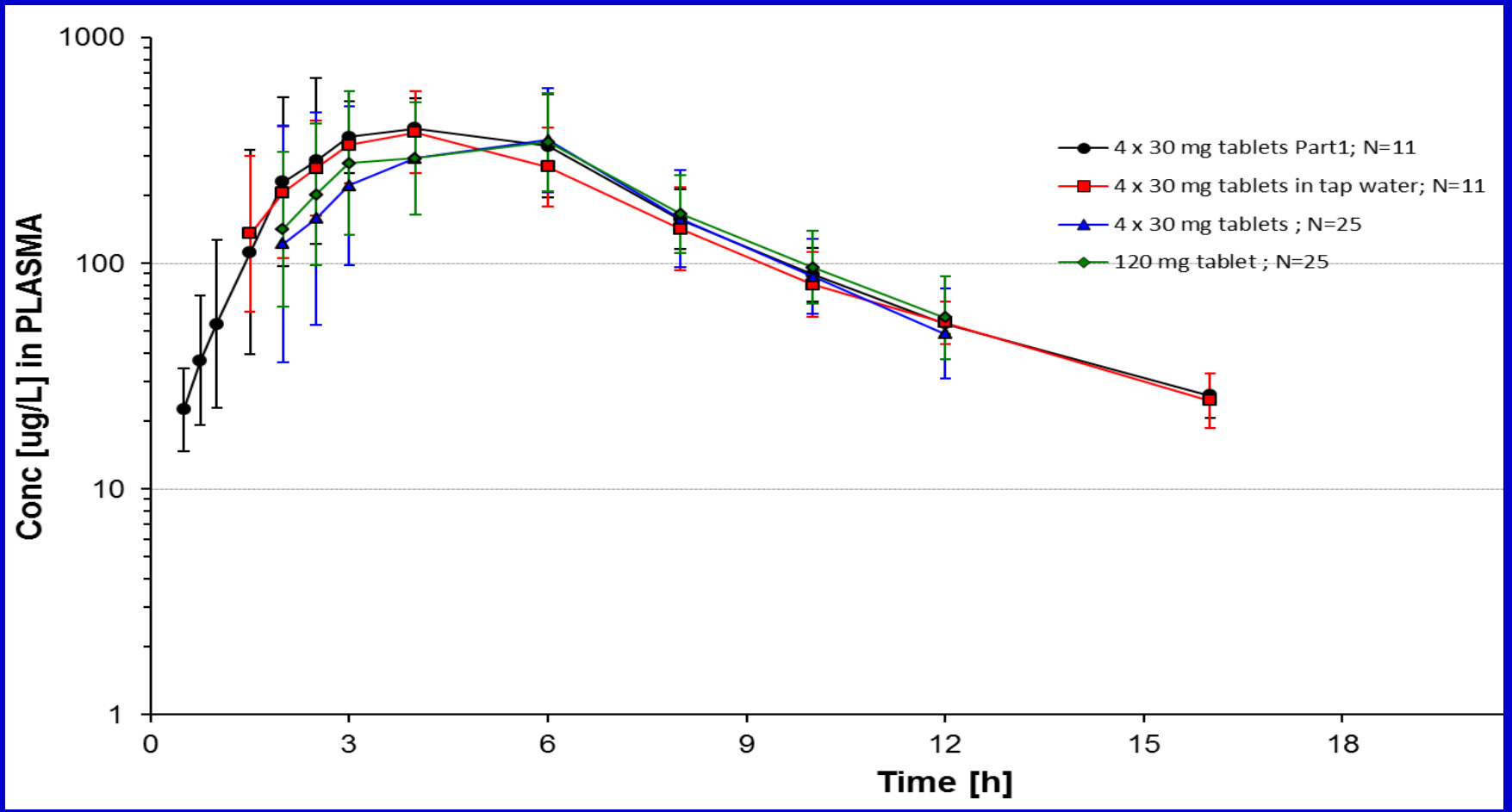
Design

- Non-blinded, randomized, single dose cross-over study

Subjects

- Adult male and female patients diagnosed with chronic Chagas' disease;
  age 18 – 45 years (N = 36)

Bioequivalence Study NCT01927224 (2)



Comparable PK for the 120 and 30 mg tablet application

Nifurtimox Clinical Studies

Bioequivalence Study NCT01927224 (3)

Final Results

- 4 x 30mg tablets are bioequivalent to 1 x 120mg
- Exposure after intake of 30mg slurry (disintegrated in water) or a 30 mg tablet is comparable
- Well known AE profile of NFX confirmed (headache, nausea, abdominal pain, vomiting); no SAEs were reported

Nifurtimox Clinical Studies

Food Effect Study NCT02606864 (1)

Objectives

- Quantify the food effect of oral Nifurtimox
  - Primary PK variables: AUC(0-tlast), Cmax and tmax
  - Bioequivalence criteria applied to quantify the food effect
- Safety after fasted administration
- Renal excretion of Nifurtimox

Design

- 4x30 mg single dose, cross over study
- Fasted vs after a high fat, high calorie meal

Nifurtimox Clinical Studies

Food Effect Study NCT02606864 (2)

Subjects

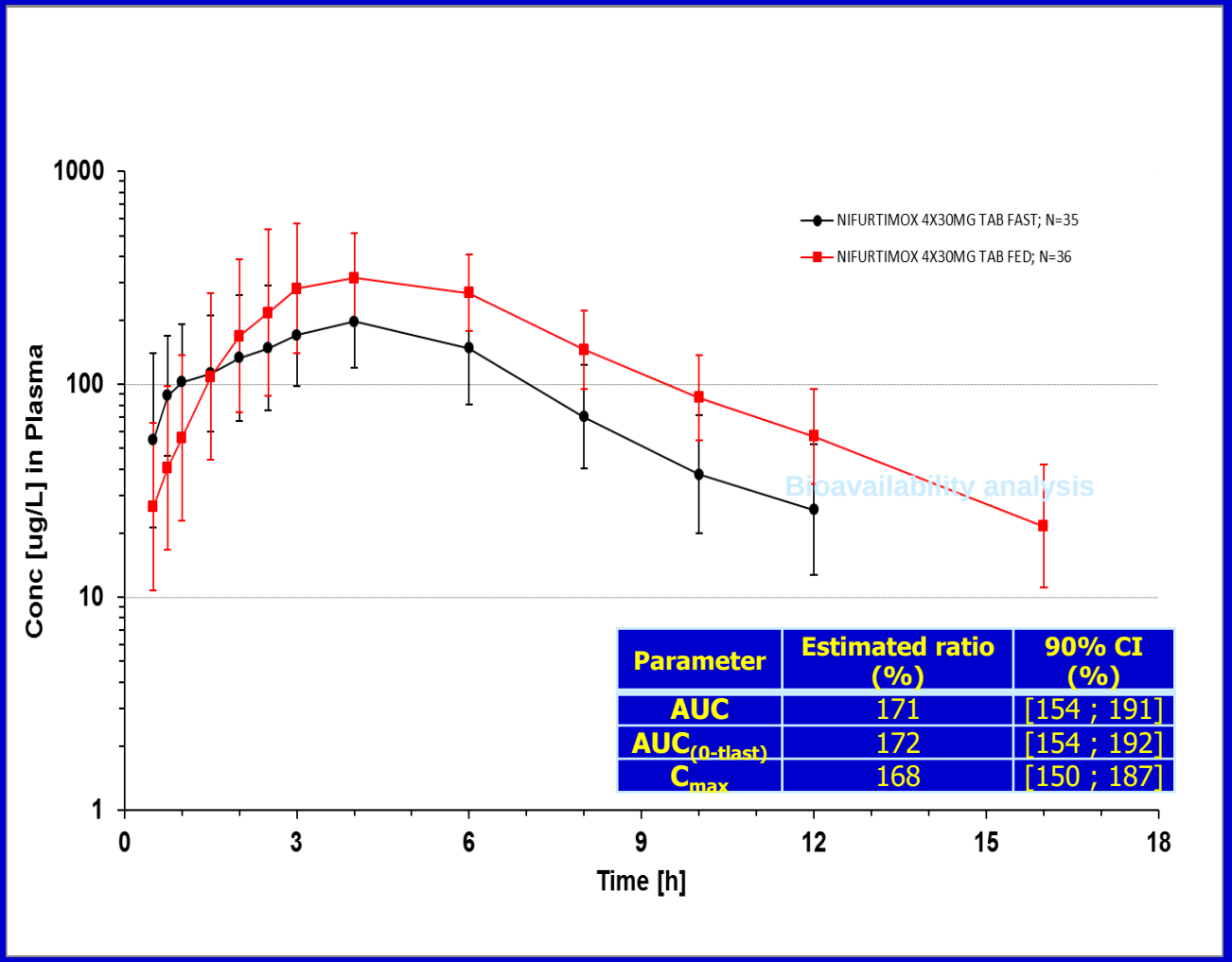
- Adult male and female patients diagnosed with chronic Chagas' disease; age 18 – 45 years (N = 36)

Status

- Clinical phase completed
- PK analysis completed,
- Preliminary data indicate significant increase of oral bioavailability when given with food

Food Effect Study NCT02606864 (2)

Pharmacokinetic parameters (geo. mean, %C.V.)		
Parameter	**Fasted**	**Fed**
AUC [µg·h/L]	1480 / 40.4 (675 – 2900)	2530 / 21.3 (1510 – 4000)
AUC(0-t_{last}) [µg·h/L]	1390 / 40.6 (619 – 2770)	2390 / 21.7 (1370 – 3830)
AUC(0-24) [µg·h/L]	1460 / 39.7 (674 – 2870)	2500 / 21.4 (1460 – 3970)
CL/F[L/h]	81.2 / 40.4 (41.4 – 178)	47.4 / 21.3 (30.0 – 79.6)
C_{max} [µg/L]	277 / 36.7 (145 – 604)	465 / 33.4 (218 – 905)
MRT [h]	5.83 / 22.7 (3.65 – 10.1)	6.56 / 21.5 (4.73 – 10.6)
$t_{1/2}$ [h]	3.07 / 34.6 (1.59 – 7.16)	3.13 / 27.4 (1.77 – 6.23)
t_{max} [h]	3.00 (0.50 – 6.05)	4.00 (1.00 – 8.00)
V_z/F [L]	359 / 36.5 (196 – 792)	214 / 37.4 (99.2 – 574)



Parameter	Estimated ratio (%)	90% CI (%)
AUC	171	[154 ; 191]
$AUC_{(0\text{-}tlast)}$	172	[154 ; 192]
C_{max}	168	[150 ; 187]

PK Nifurtimox en niños???

Información sobre la farmacología en niños y lactantes es vital para un adecuado tratamiento.

Comp de adultos…….
NO !!!!

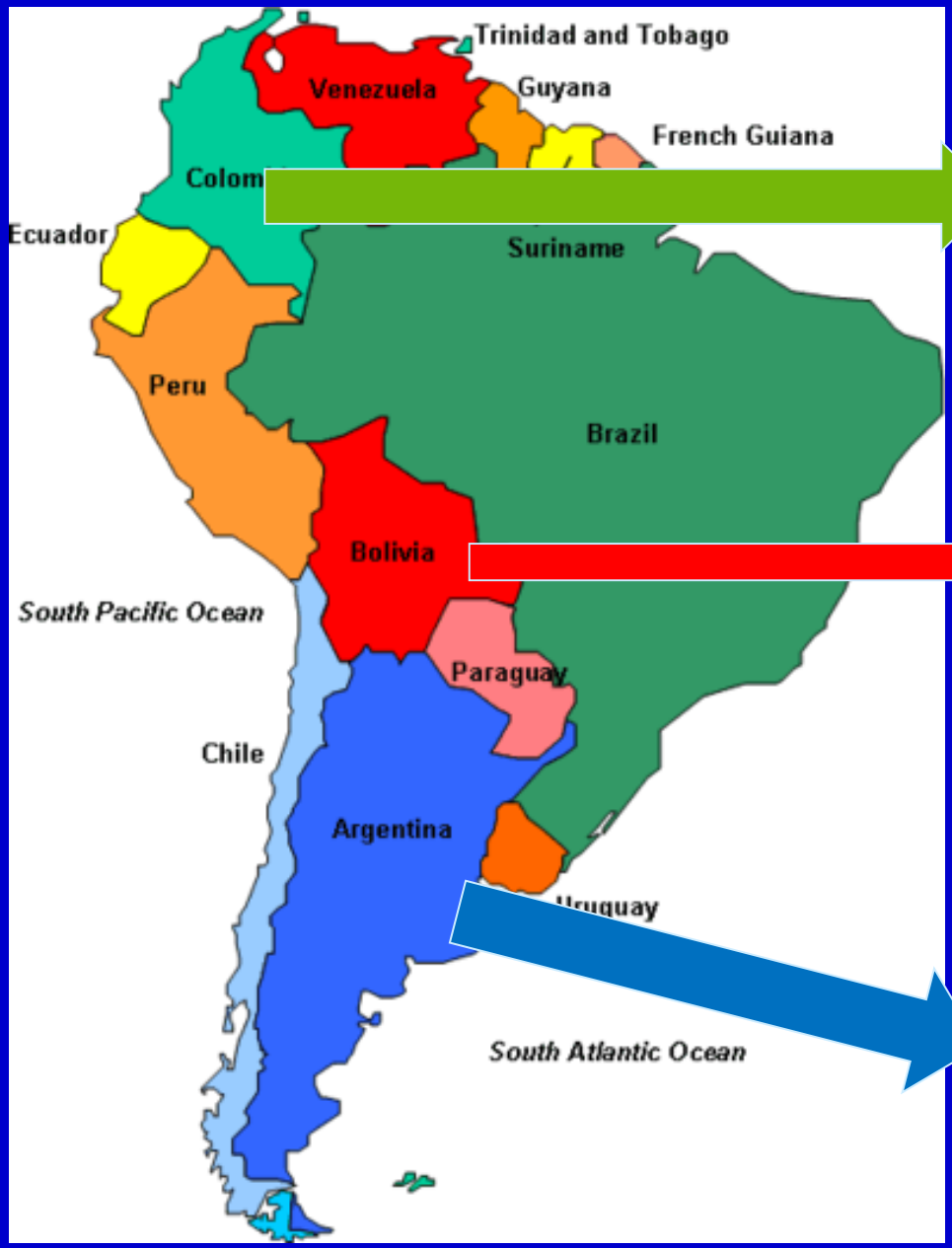
Nifurtimox Chagas Pediatric Study
CHICO study - NCT02625974

El camino hacia la formulación pediátrica

Estudio prospectivo con control retrospectivo para evaluar la eficacia y la seguridad de una nueva formulación pediátrica de nifurtimox en pacientes de 0 a 17 años con enfermedad de Chagas

Nifurtimox Chagas Pediatric Study
CHICO study - NCT02625974

Bayer HealthCare



PEDCHAGAS

Colombia
3 centros

Bolivia
3 centros

Argentina
15 centros
PEDCHAGAS group

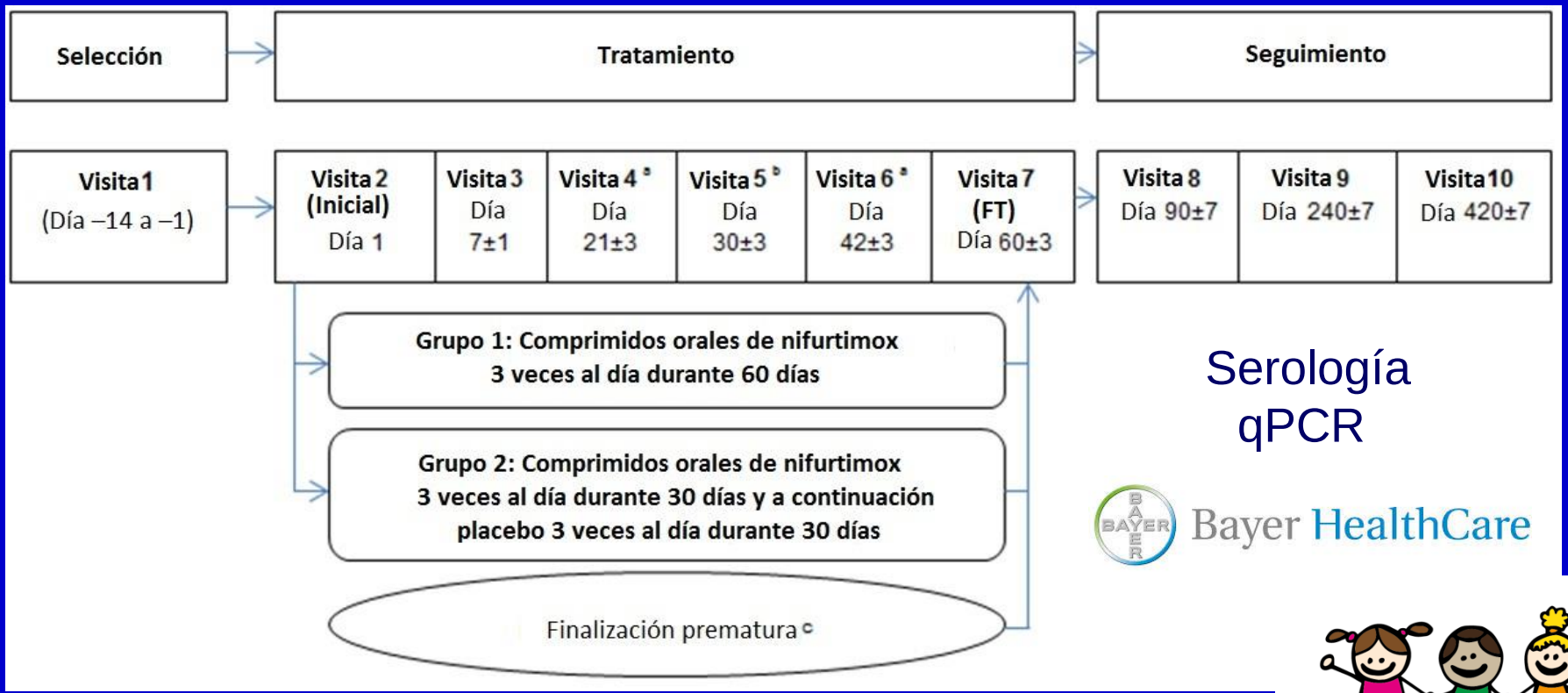
BAY16027

Nifurtimox CHICO study - NCT02625974

Nifurtimox en comprimidos de 30 mg y 120 mg

Grupo 1: 60 días de nifurtimox.

Grupo 2: 30 días de nifurtimox - 30 días de placebo.



Serología
qPCR

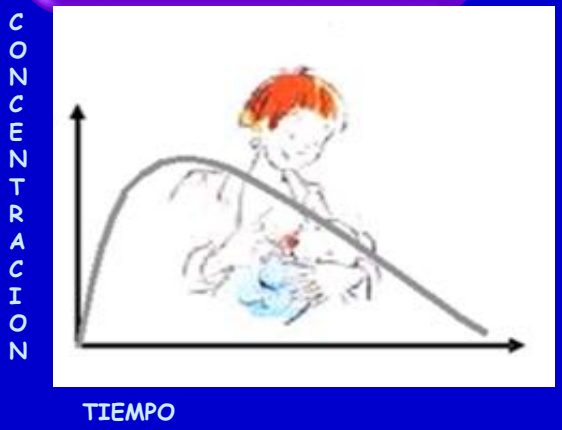
Bayer HealthCare

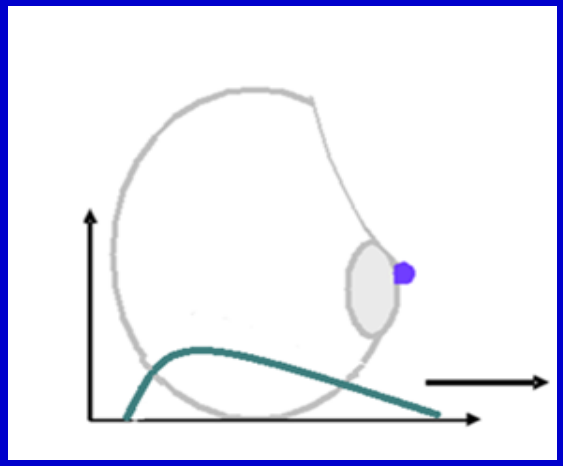
PEDCHAGAS

BENZNIDAZOL

Lactancia

Dosis media de BZ: 5.66 mg/kg/día (3.6-6.7) máx. 400 mg





Asumiendo una ingesta diaria de leche de 150ml/kg la dosis de BZ es de 0.6 mg/kg

Conc. Media BZ: 4.5 mg/l (SD 4.11, rango 1.3-12.57)

Conc. Media BZ: 3.8 mg/l (SD 1.06, rango 2.4-5.9)

RID = Dosis materna /kg / Dosis niño / kg

10.9 , SD 3.2 (rango 5.4-16.8)

Relación leche/plasma:

X 0.99 (SD 0.7)

El niño recibe un 10% de la dosis materna

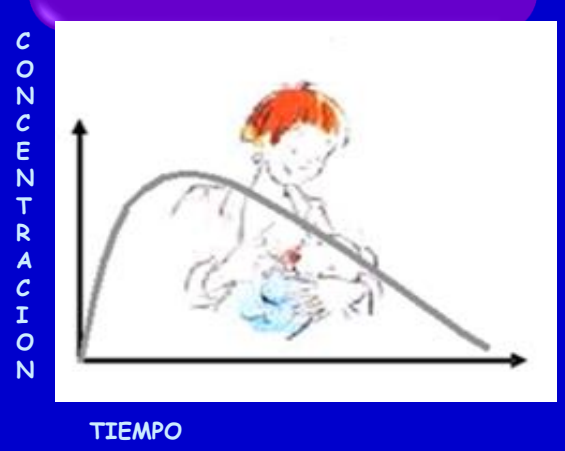
García-Bournissen F, Moroni S, Marson ME, Moscatelli G, Mastrantonio G, Bisio M, Cornou L, Ballering G, Altcheh J. Limited infant exposure to benznidazole through breast milk during maternal treatment for Chagas disease. Arch Dis Child. 2014 Sep 10. pii: archdischild-2014-306358. doi: 10.1136/archdischild-2014-306358.

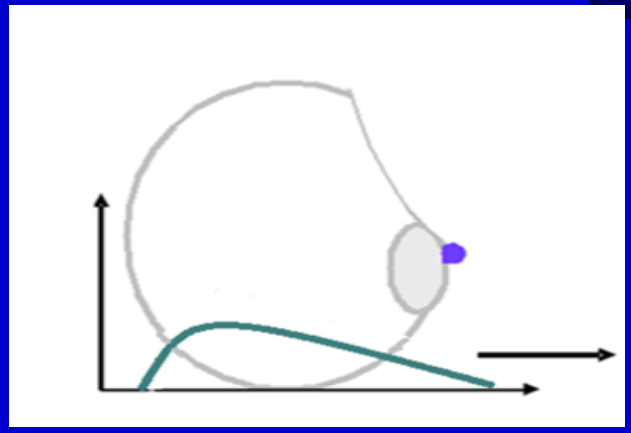
NIFURTIMOX

Lactancia

Dosis media de NFT: 9,82 mg/kg/día (8,3-12) máx. 720 mg

Asumiendo una ingesta diaria de leche de 150ml/kg la dosis de BZ es de 0.36 mg/kg





Conc. Media NFT: 0,56 mg/l (SD:0,4; x: 0,3; IQR 0,2-1,1))

Conc. Media NFT: 0,39 mg/l (IQR 0,34-0,40)

RID = Dosis materna /kg / Dosis niño / kg

3,6% , SD 4.35 (IQR 1.98-6.82)

Relación leche/plasma:

El niño recibe un 4% de la dosis materna

Mem Inst Oswaldo Cruz, Rio de Janeiro: 1-3, 2015

Prevention of congenital Chagas through treatment of girls and women of childbearing age

Guillermo Moscatelli/+, Samanta Moroni, Facundo García-Bournissen, Griselda Ballering, Margarita Bisio, Héctor Freilij, Jaime Altcheh

Department of Parasitology and Chagas, Ricardo Gutiérrez Children's Hospital, Buenos Aires, Argentina

Serology and mother real-time quantitative polymerase chain reaction (qPCR) results throughout follow-up before treatment and three years after treatment - Children study

Mothers [age at treatment (years)]	Serology (day 0)		Serology (3 years)		qPCR	
	EIA	IHA	EIA	IHA	Day 0	3 years
9	3.5	256	UN	UN	P	N
11	10.6	64	4.1	64	P	N
11	6.4	64	6.7	64	P	N
12	8.9	256	6.2	512	P	N
13	11	128	2.8	UN	P	N
13	10.5	256	5.4	16	P	N
14	8.1	128	4.3	16	N	N
14	7.4	64	5.1	UN	P	N
14	3.1	16	2.5	32	N	N
16	11.7	1,024	11.3	1,024	P	N
20	12.4	1,024	7.2	64	P	N
20	10.6	128	6.6	64	P	N
21	12	512	10.2	128	P	N
29	11.6	1,024	6.6	256	P	N
34	12.1	2,048	9.5	128	P	N

EIA: enzymatic immunoassay; IHA: indirect haemagglutination assay; N: negative; P: positive; UN: unreactive.

2017: N: 23;
8/23 recibieron 30 días de tratamiento

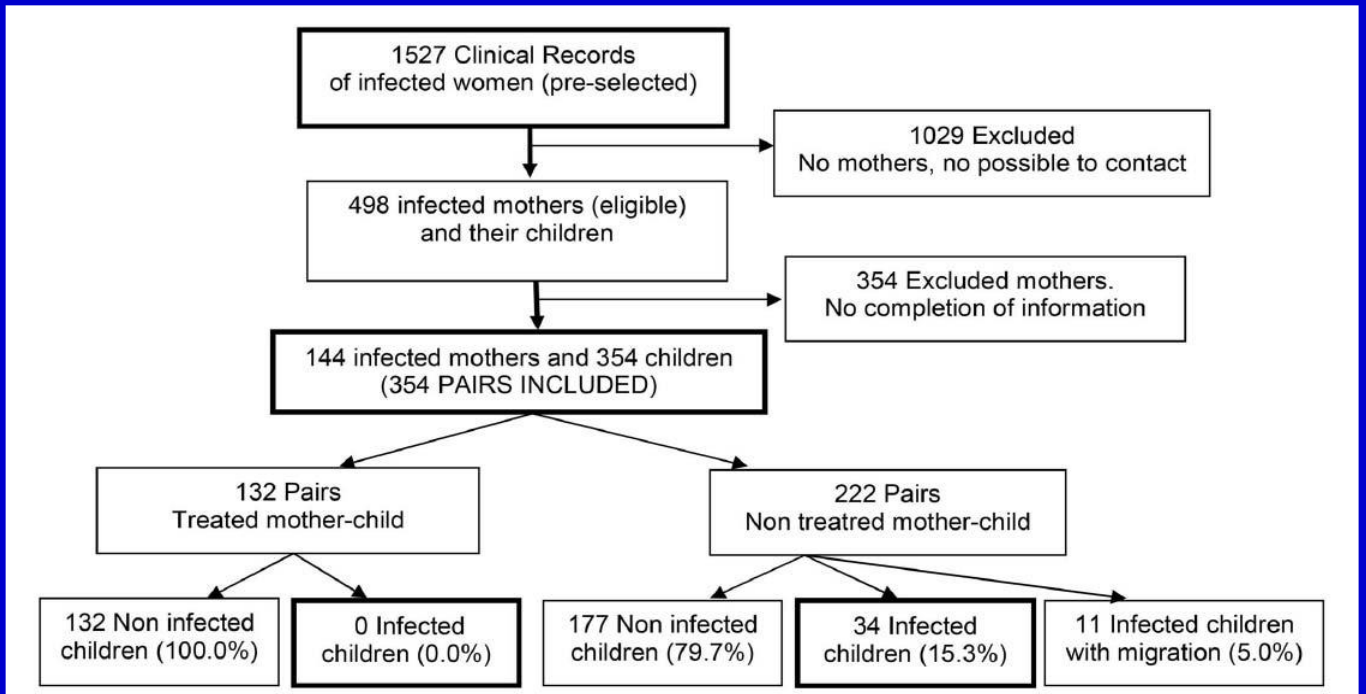
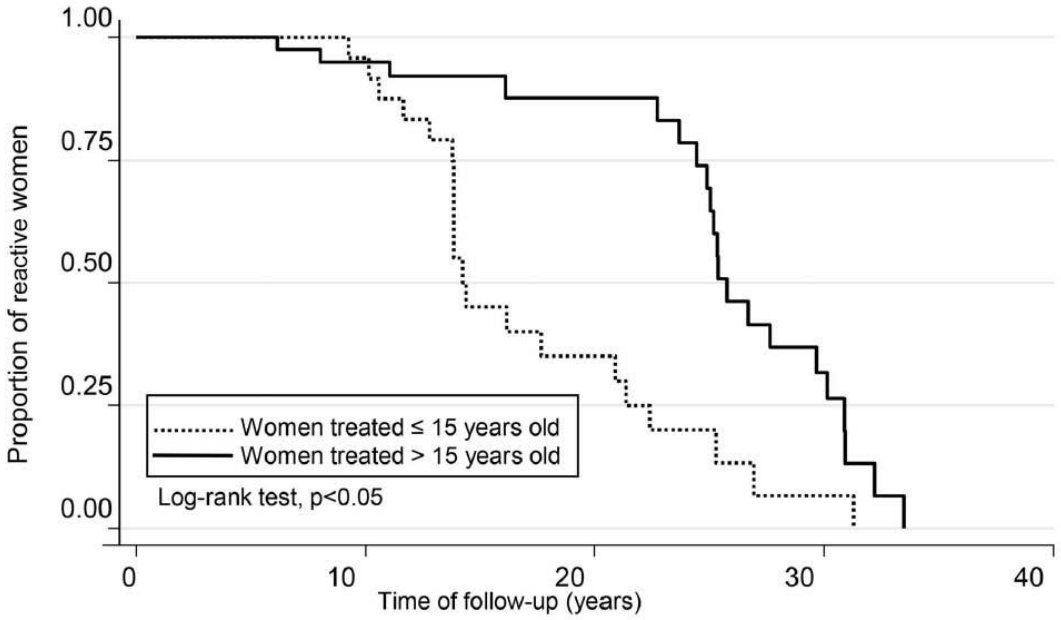


Figure 1. Flowchart of the study.
doi:10.1371/journal.pntd.0003312.g001

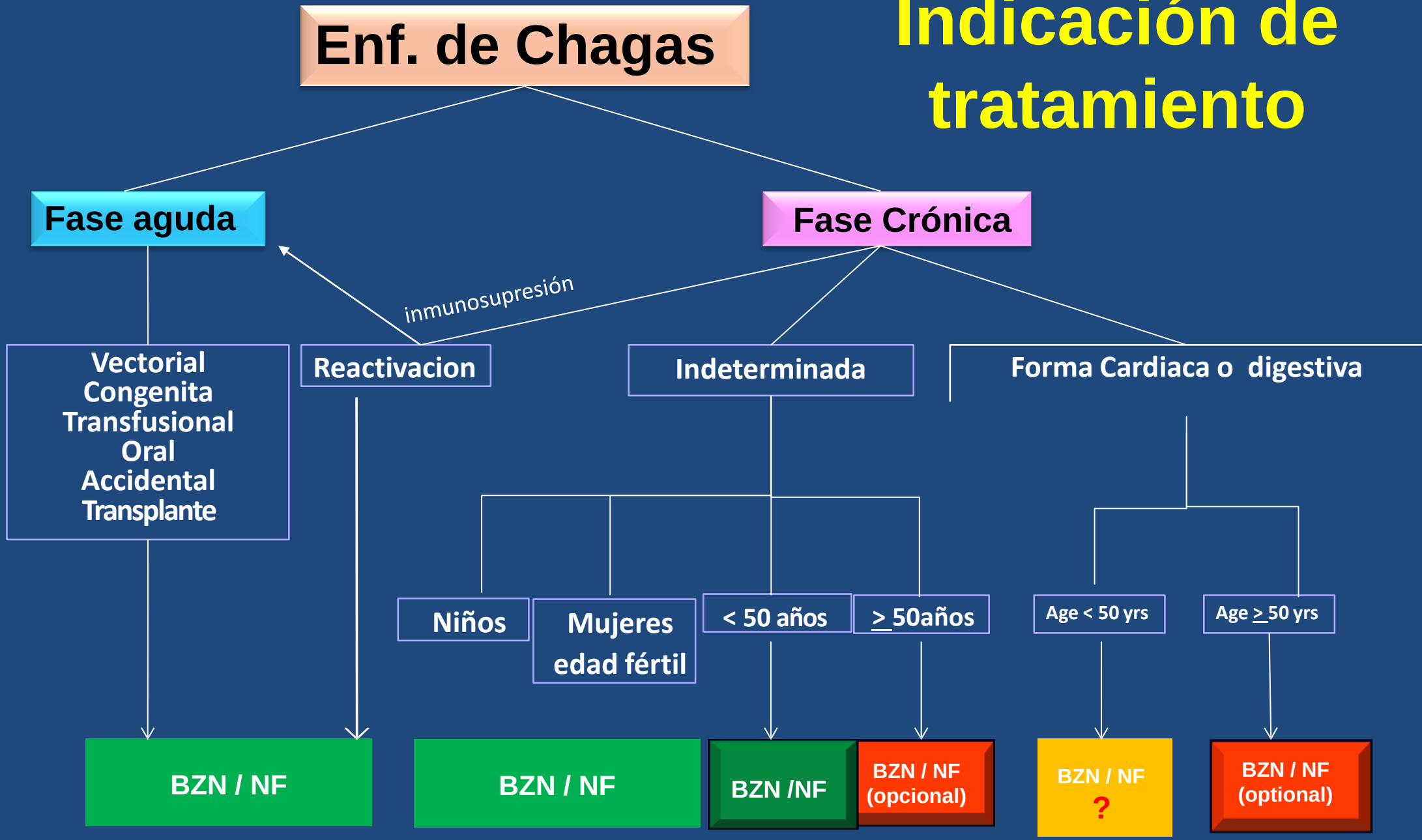
RR 0.04 [95% CI 0.012, 0.166]



4. Kaplan-Meier curve showing serological reactivity rate by age during follow-up in 71 treated women.
371/journal.pntd.0003312.g004

Fabbro et al PLoS NTD 2014

Indicación de tratamiento



NF=nifurtimox BZN=benznidazol

Perspectivas futuras
Lo que planteamos 2012

- Nueva formulación BZ pediátrica y estudio de PopPK en menores de 2 años.

- PopPK nifurtimox en niños, formulación pediatrica.

- Transferencia de nifurtimox y benznidazol a la leche materna

- Estudios de PopPK de benznidazol en adultos

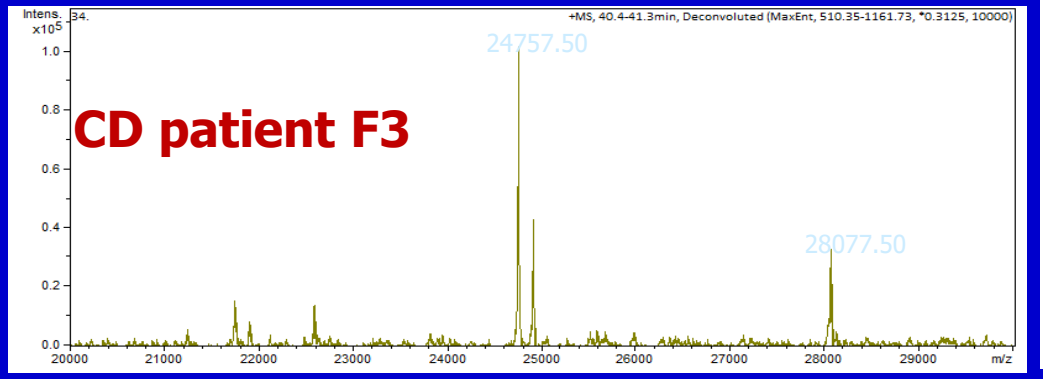
- Tiempo: 30 vs 60 días y dosis < en adultos

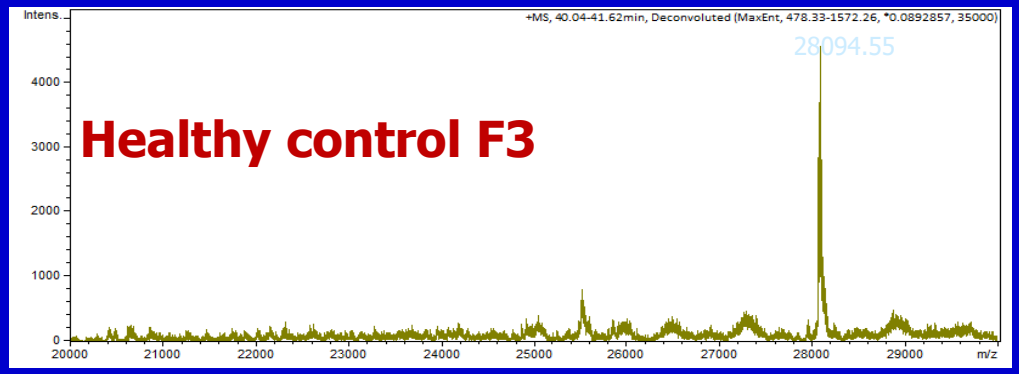
- Identificacion de los metabolitos de benznidazol, y las enzimas responsables del metabolismo (CYP, etc)

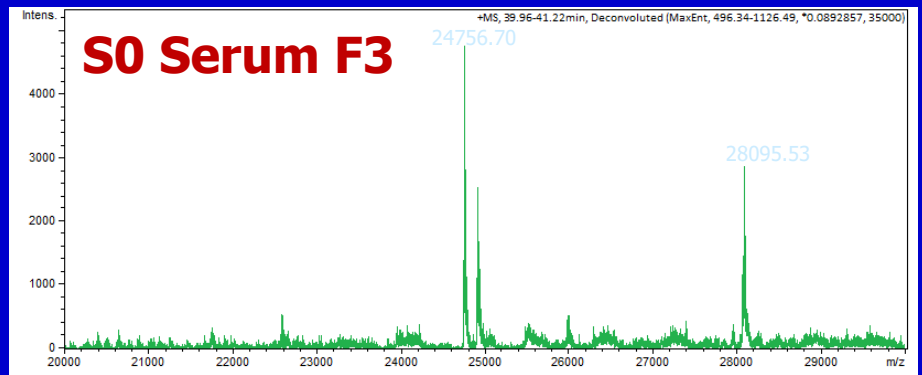
- Estudios de nuevas drogas para el Chagas.

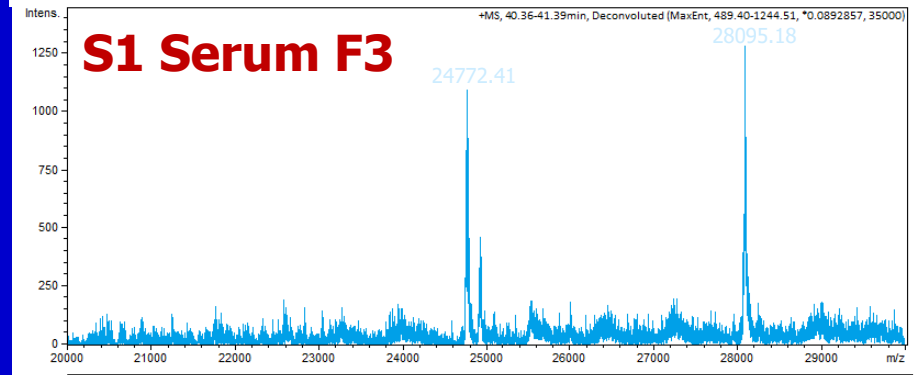
DNDi
Drugs for Neglected Diseases *initiative*

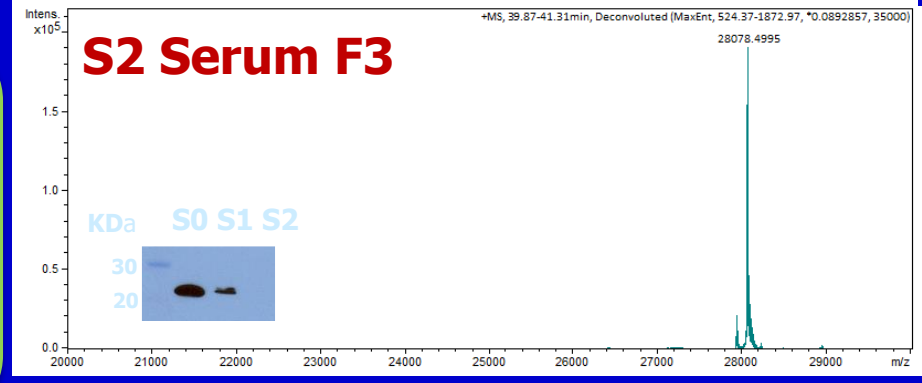
ApoA1 24.7 kDa fragment MS analysis





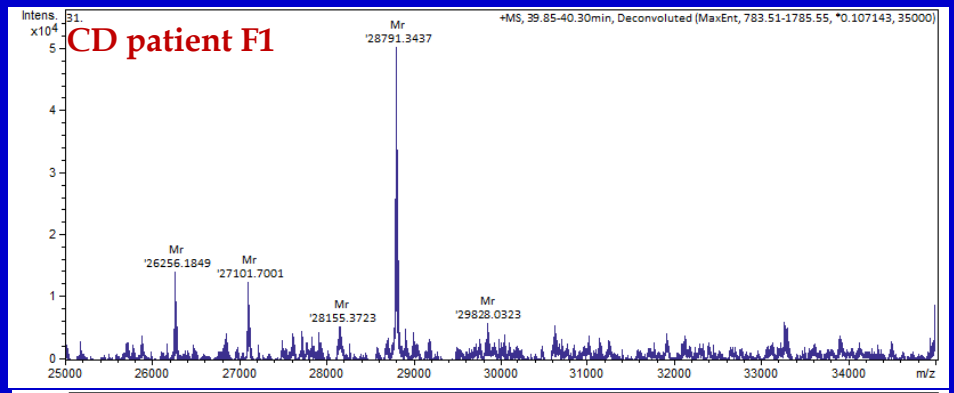


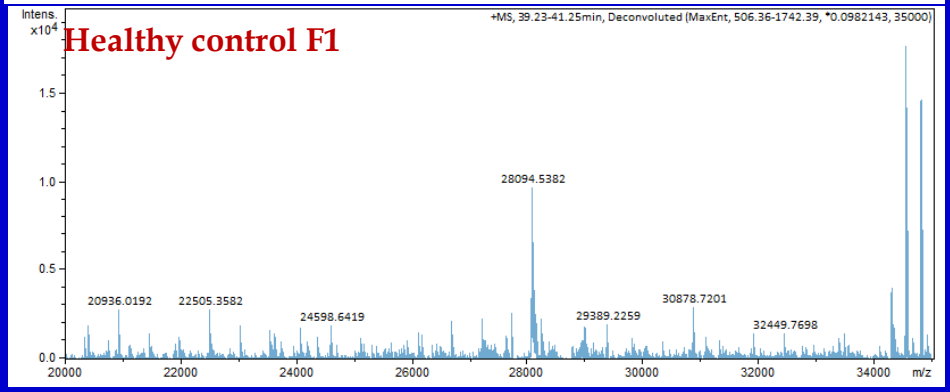




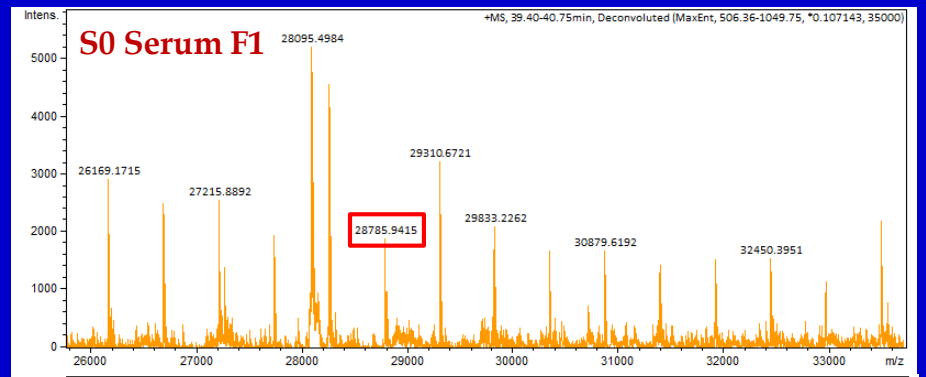
- ✓ ApoA1 24.7 KDa fragment is not present in HC but upregulated in CD
- ✓ Fragment is upregulated at diagnosis and end of treatment but not present at seroconversion where only the full length protein is detected

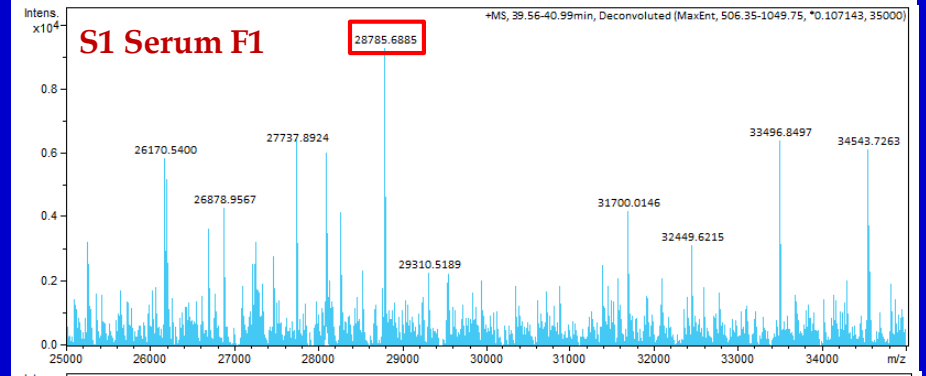
FBN 28.9 kDa fragment MS analysis

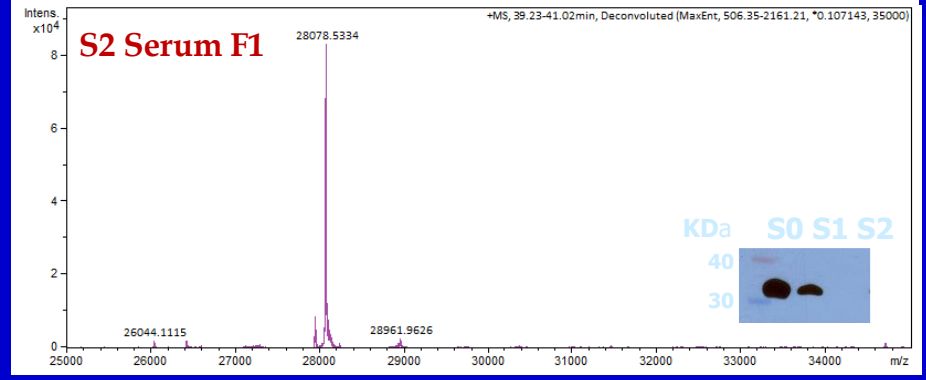




- ✓ FBN fragment is upregulated in CD but absent in HC
- ✓ Fragment is present at diagnosis and end of treatment but not at seroconversion. Only ApoA1 full length is detected at the same retention







Enfermedad de Chagas

- La enfermedad de Chagas es curable.
- Control del vector + busqueda de infectados !!!!!
- La mayor parte de los pacientes son asintomáticos.
- Sistema de salud sobrecargado con enfermos, no preparado para buscar asintomáticos.
- Requiere de un manejo infectológico.
- No es solamente una enfermedad cardiaca ó gastrointestinal.
- El tratamiento requiere de una cercana supervisión.
- Si tratamos niños no habrá secuelas.
- Nuevas drogas: las ensayos clínicos de eficacia deben ser evaluadas en niños.

Un adulto con enfermedad de Chagas es un niño no tratado

PEDCHAGAS

El Chagas se cura

PEDCHAGAS

PEDCHAGAS

IMIPP (Instituto Multidisciplinario de Investigaciones en Patologías Pediátricas)

CONICET

Centro Colaborador OPS / OMS en Enfermedad de Chagas Pediátrica (2016)

Organización Panamericana de la Salud

Organización Mundial de la Salud Américas