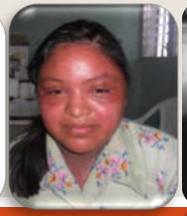
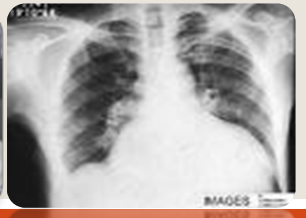
NEW TREATMENT OPPORTUNITIES IN CHAGAS DISEASE

DNDi
Drugs for Neglected Diseases *initiative*

ICOPA Mexico - August 12, 2014

Chagas Disease



An Unmet Medical Need

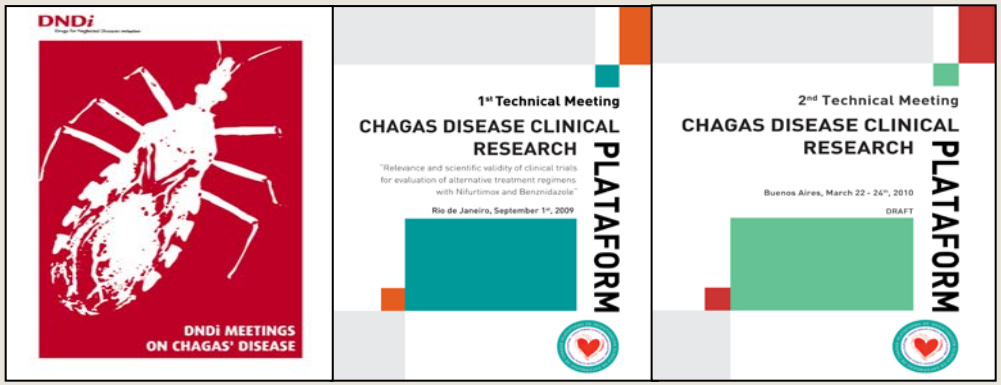
- Most common parasitic disease in the Americas
- Leading cause of infectious myocarditis worldwide
- Two drugs available: nifurtimox and benznidazole
- < 1% of those infected receive treatment
  - Safety and tolerability issues
  - Long treatment period (1-2 months)

Knowledge Gaps

- Limited knowledge on the relevance of animal models
- Limited data on the importance of
  - Relation of parasite strains to human disease
  - Coexistence of infection
  - Mechanisms of resistance
- PK/PD in Chagas largely unknown
- No consensus and limited information for a reference treatment
- Lack of early test of cure
- Limited sensitivity of PCR test

Chagas Clinical Research Platform

- Understanding the needs and gaps: First expert meeting in 2005.
- Developing the first TPP for Chagas Disease: Meetings in 2006.
- “Wake-up, time to treat!”, DNDi global campaign, 2009.
- Launch of the Chagas Disease Clinical Research Platform, Uberaba, Brazil. October 2009.
- CCRP 1st Technical Meeting. Rio de Janeiro, Set. 2009.
- CCRP 2nd Technical Meeting, TPP review. Buenos Aires, March 2010.
- New challenges for 2011: Initiation of several clinical studies.
- CCRP Meeting 2011, Rio de Janeiro, Dec. 2011.
- CCRP Meeting 2012, Rio de Janeiro, Sept. 2012.
- CCRP Meeting 2013, Cochabamba, April 2013.



Chagas Disease – The TPP

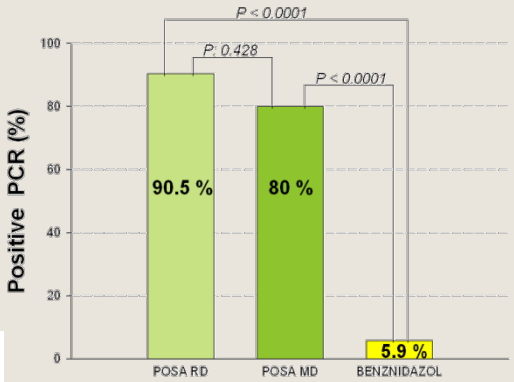
	Acceptable	Ideal
Target population	Chronic	Chronic and Acute (Reactivations)
Strains	TcI, TcII, TcV and TcVI (according to new 2009 classification)	All according to new classification (2009)*
Distribution	All areas	All areas
Adult/children	Adult	All
Clinical efficacy	Non inferior to benznidazole in all endemic regions (parasitological)	Superiority to benznidazole to different phases of disease (acute and chronic) (parasitological)
Safety	Superiority to benznidazole ** 3 CE plus 2 standard LE or ECG during treatment	Superiority to benznidazole or nifurtimox No CE or LE or ECG needed during treatment
Activity against resistant strains	Not necessary	Active against nitrofuran- and nitroimidazole-resistant *T. cruzi* strains
Contraindications	Pregnancy/lactation	None
Precautions	No genotoxicity; No pro-arrythmic potential	No genotoxicity; No teratogenicity; No negative inotropic effect; ; No pro-arrythmic potential
Interactions	No clinically significant interaction with anti-hypertensive, anti-arrythmic and anticoagulants drugs	None
Presentation	Oral	Oral
Stability	3 years, climatic zone IV	5 years, climatic zone IV
Dosing regimen	Comparable to systemic antifungal treatments	Once daily/ 30days

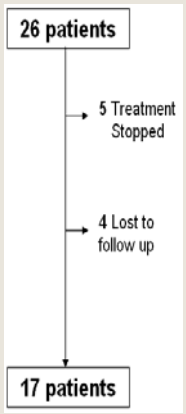
DNDi
Drugs for Neglected Diseases *initiative*

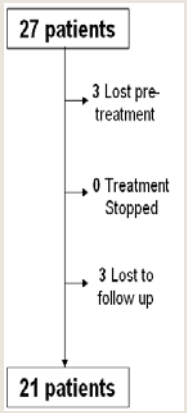
Azole and Benznidazole Clinical Trials Chronic Chagas Disease

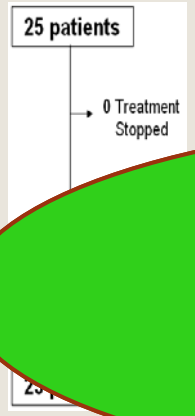
- **Benznidazole in adults**
  - **TRAENA (started in 03/1999 – 12/2012)**
  - **BENEFIT (11/2004 – ongoing)**
- **Posaconazole and Benznidazole**
  - **CHAGASAZOL - Hospital Val Hebron – Barcelona**
  - **STOP-CHAGAS – Merck-sponsored, multi-country clinical trial**
- **E1224 and Benznidazole**
  - **Phase 2, PoC E1224 - Bolivia**
- **Benznidazole in children**
  - **Pop PK study in children 0-12 years**

Chagasazol - NCT0116967
E1224 PoC – NCT01489228

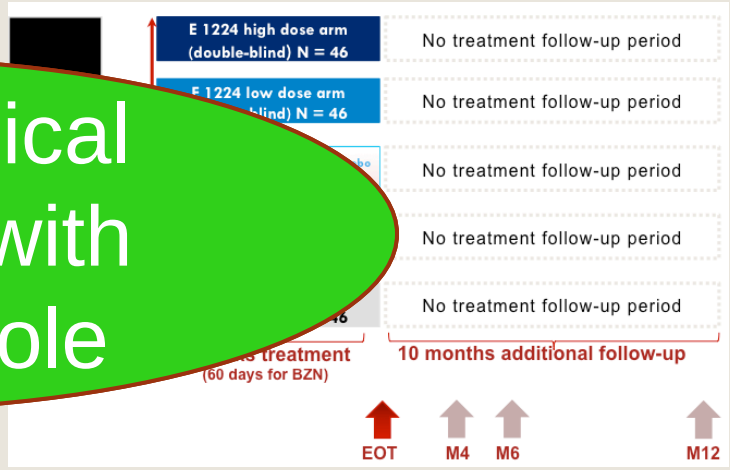






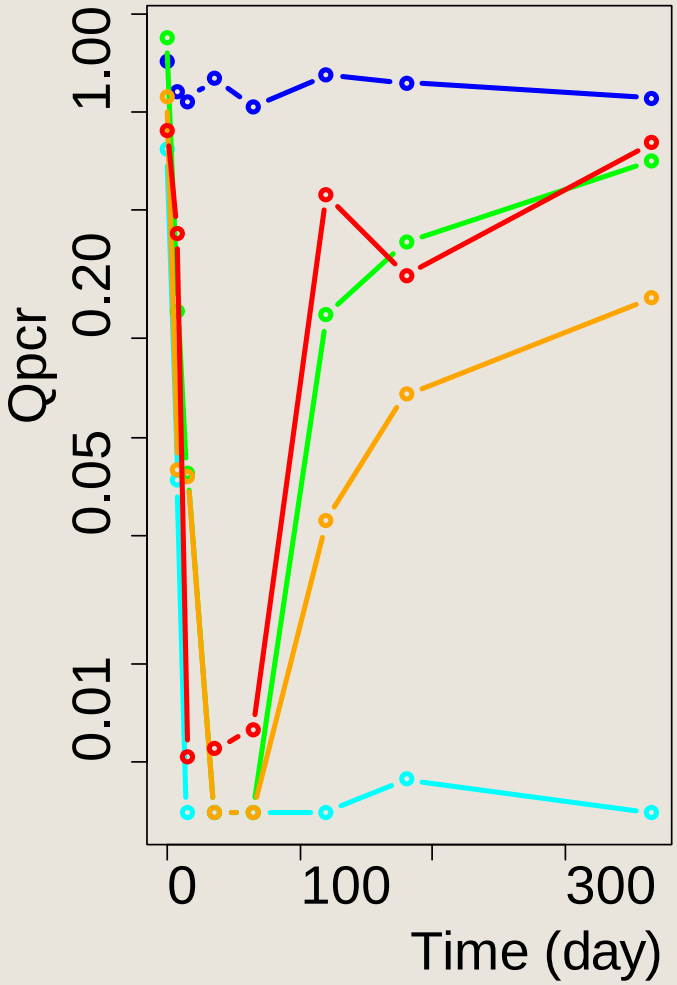


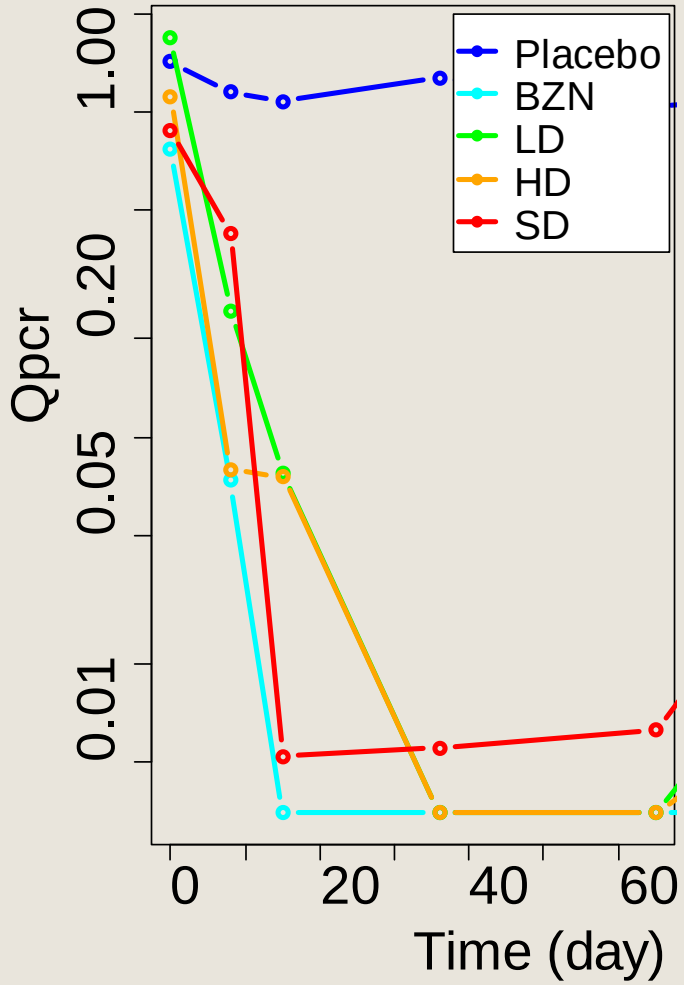
Parasitological Response with Benznidazole



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

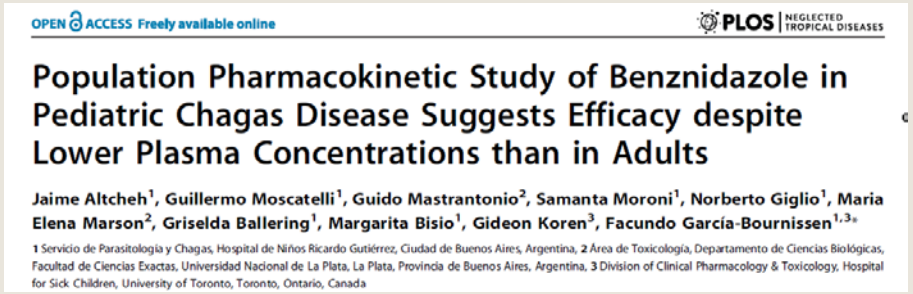
E1224 PoC – NCT01489228
qPCR: mean observed data vs time





Population Pharmacokinetics of Benznidazole in Children With Chagas Disease

- **2 open-label, single-arm, prospective Pop PK studies**
  # NCT01549236 40 Children 2 – 12 years old 40
  Age: 7.3 years (range 2.1 – 12)
  # NCT00699387 81 **Children 1d – 12 years old**
  Age: >2a : 40; < 2a: 41 (8 newborn)
- **Samples for PK were obtained at randomly pre-assigned times**
- **Benznidazole in plasma was measured by HPLC, HPLC-MS-MS**
- **PopPK modeling was performed with NONMEM software (non linear mixed effects analysis)**



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

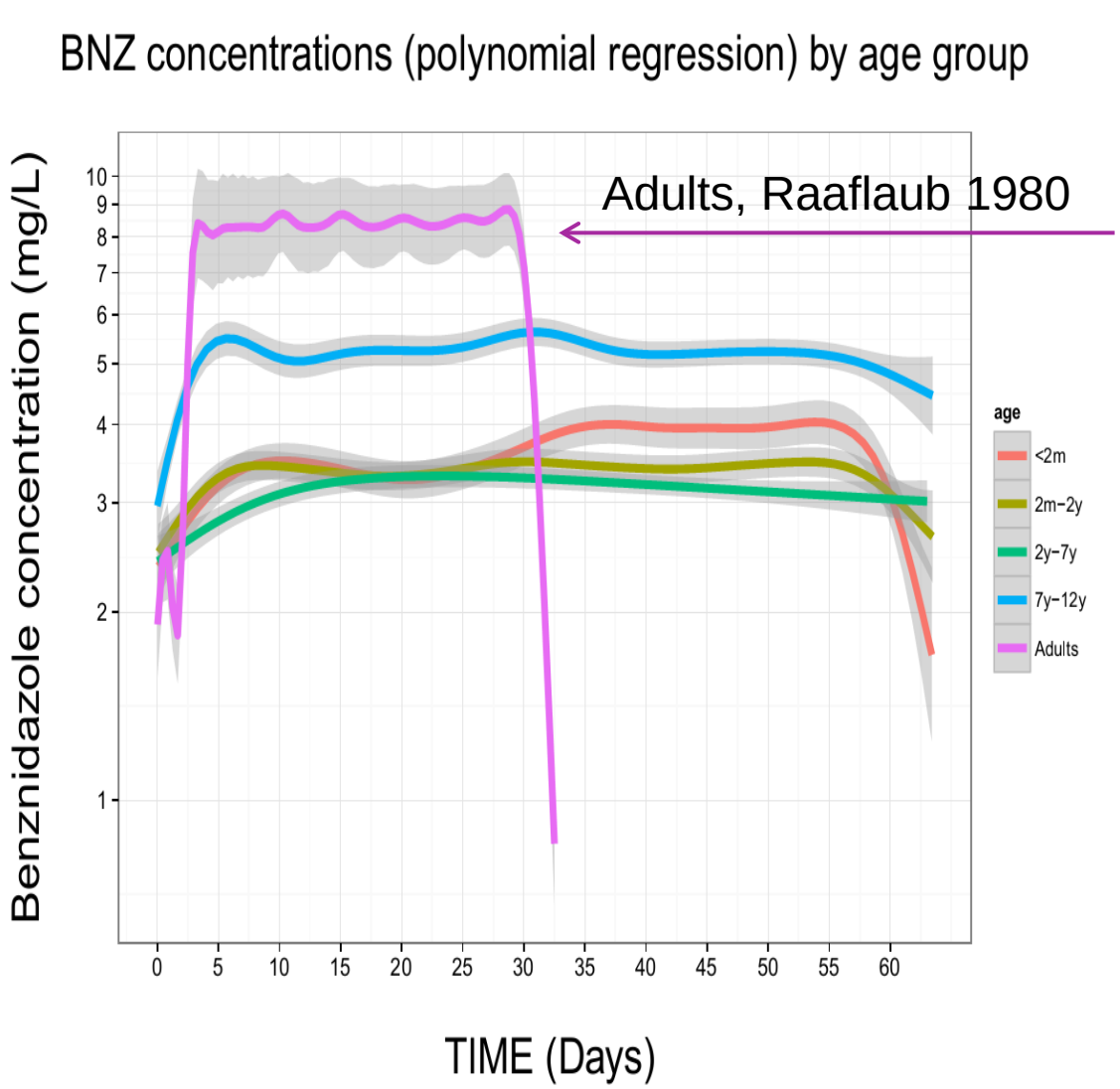
Jaime Altcheh[1], Guillermo Moscatelli[1], Guido Mastrantonio[2], Samanta Moroni[1], Norberto Giglio[1], Maria Elena Marson[2], Griselda Ballering[1], Margarita Bisio[1], Gideon Koren[3], Facundo García-Bournissen[1,3]*

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

Pediatric network
PEDCHAGAS

DNDi
Drugs for Neglected Diseases *initiative*

Population Pharmacokinetics of Benznidazole in Children With Chagas Disease



- 100% PCR negative at EOT
- Have we been overdosing adults?...

Pediatric network
PEDCHAGAS

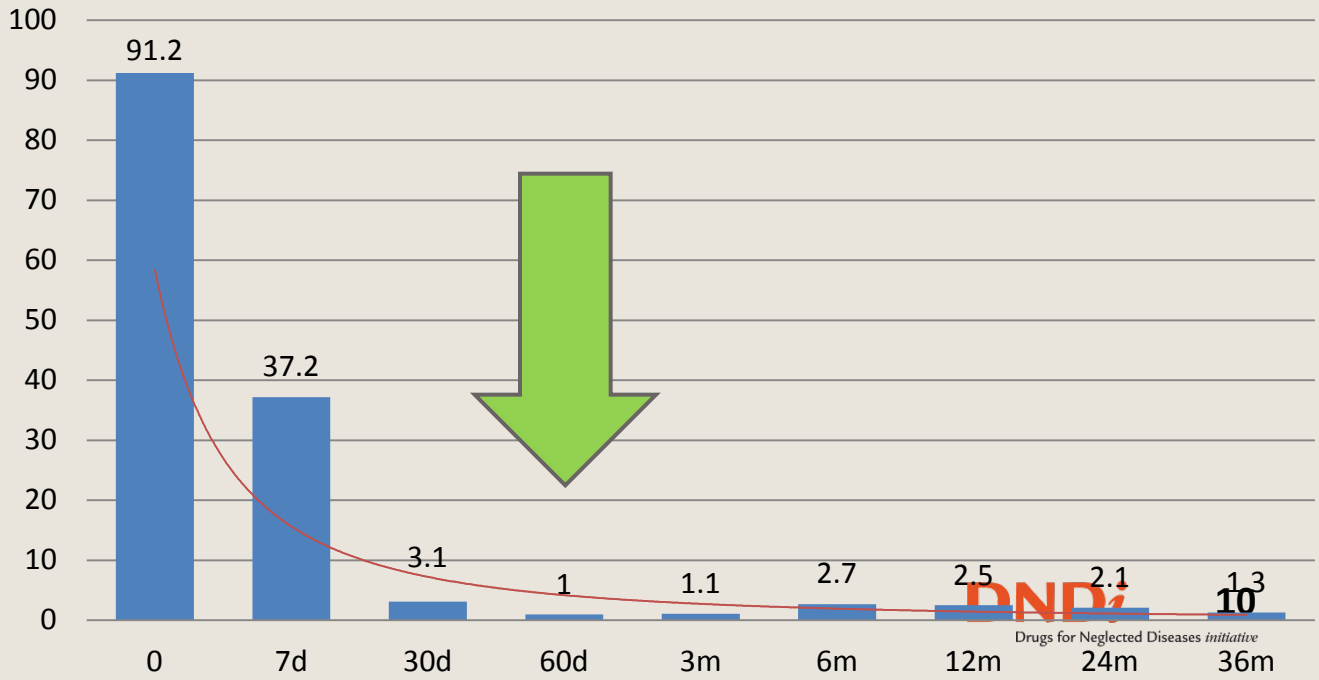
PCR in a cohort of 206 BZN- treated children (101 by conventional PCR and 105 by qPCR)

Time	n	+	%	95 IC
0	206	188	91,2	86,6-94,4
7d	102	38	37,2	28,4-46,9
30d	96	3	3,1	1-8,7
60d	183	2	1	0,3-3,9
3m	84	1	1,1	0,2-6,4
6m	72	2	2,7	0,7-9,5
12m	79	2	2,5	0,7-8,7
24m	46	1	2,1	0,3- 11,3
36m	76	1	1,3	0,2-7

Parasitología y Chagas * Hospital de Niños R. Gutiérrez *

HOSPITAL DE NIÑOS H N R G Dr. RICARDO GUTIERREZ

Percentage of positive PCR at follow-up



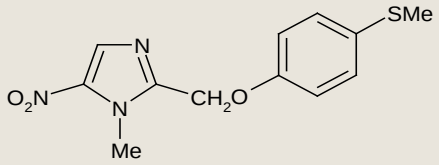
DNDi Drugs for Neglected Diseases *initiative*

Chagas Disease
Clinical Trial Results and Impact on Strategy

- **Efficacy and safety information on the azole and benznidazole to support further clinical development and access**
  - Though not well tolerated, nitroimidazoles are potent and efficacious agents in Chagas disease (at least in selected epidemiological settings)
  - Benznidazole had a rapid and sustained effect, with significant drop in parasite counts after just one week of treatment
    - Data support increased access to current treatment, and
    - Evaluation of alternative regimens of BZN treatment
  - There is significant risk with the azole class and ergosterol biosynthesis inhibitors as a target for Chagas disease

DNDi
Drugs for Neglected Diseases *initiative*

Fexinidazole
A new nitroimidazole clinical candidate



- Non-genotoxic 5-Nitroimidazole
- Reports for Fexinidazole potential for Chagas Disease
  - 1983:

OPEN ACCESS Freely available online
PLOS | NEGLECTED TROPICAL DISEASES

Fexinidazole: A Potential New Drug Candidate for Chagas Disease

Maria Terezinha Bahia[1]*, Isabel Mayer de Andrade[1], Tassiane Assíria Fontes Martins[1], Álvaro Fernando da Silva do Nascimento[1], Livia de Figueiredo Diniz[1], Ivo Santana Caldas[1], André Talvani[1], Bernadette Bourdin Trunz[2], Els Torreele[2], Isabela Ribeiro[2]

1 Laboratório de Doença de Chagas, Departamento de Ciências Biológicas & Núcleo de Pesquisas em Ciências Biológicas, Universidade Federal de Ouro Preto, Campus Universitário, Morro do Cruzeiro, Ouro Preto, Brazil, 2 Drugs for Neglected Disease initiative (DND), Geneva, Switzerland

  - 2012:
- Very good efficacy in acute and chronic mouse in vivo models
  - Cure in BNZ-»resistant» strains
  - Pre-clinical data available (28-day toxicity studies, Safety Pharmacology, 90-day tox data from Hoechst)
- Well tolerated in human (Phase I)
- Currently in clinical trial (PhaseII/III) for HAT (and Leish)
- Clinical candidate nomination – June 2013

Fexinidazole
Proof-of-Concept Dose Ranging Study

Principal Investigators: Faustino Torrico, Joaquim Gascón, Lourdes Ortiz

Coordinator:
Jimy Pinto

DNDi Team:
Fabiana Barreira
Cristina Alonso
Erika Correia
Isabela Ribeiro

Plataforma de Atención Integral a los Pacientes con Enfermedad de Chagas
CEADES Bolivia/IS Global/CRESIB

Universidad Mayor de San Simon, Cochabamba, Universidad Autonoma Juan Misael Saracho de Tarija

INGEBI/CONICET, Buenos Aires, Argentina

ISGlobal Instituto de Salud Global Barcelona
CEADES Salud y Medio Ambiente
cooperación española

DNDi Drugs for Neglected Diseases *initiative*

Fexinidazole
Proof-of-Concept Dose Ranging Study

Study initiated:
July 2014

Target for Study Conclusion:
August 2015

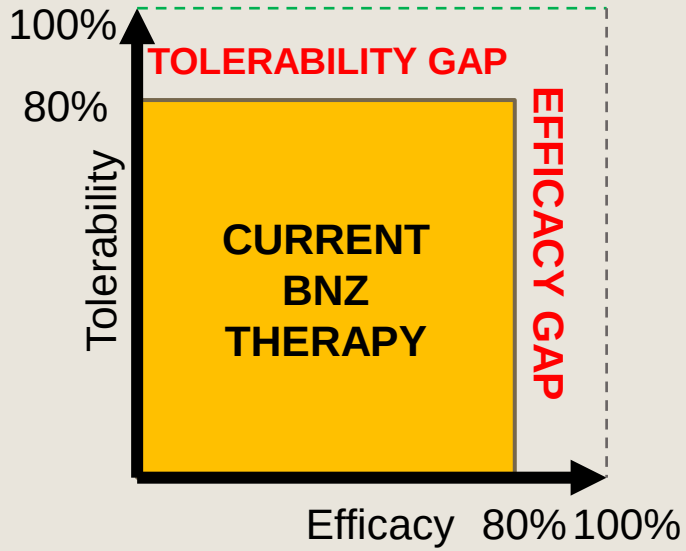
- 140 adults with chronic indeterminate CD
- PCR sustained response at 6 months
- Stopping rules: futility and safety
- Cardiac and liver safety surveillance

ISGlobal Instituto de Salud Global Barcelona
CEADES
cooperación española

DNDi Drugs for Neglected Diseases *initiative*

Benznidazole
Current Status and Opportunities

Current situation

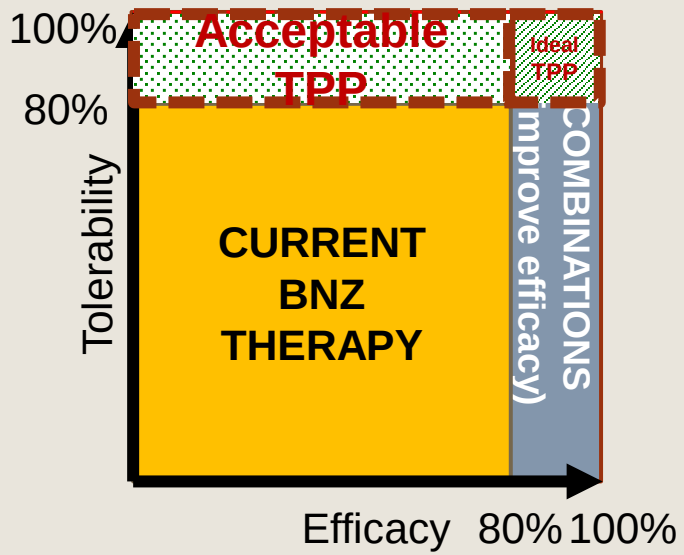


- BNZ is an effective drug

… but

- Efficacy gap
  - About 80% sustained response at 12 months
- Tolerability gap
  - 15-20% do not complete treatment
    - Majority due to ADRs

Opportunities



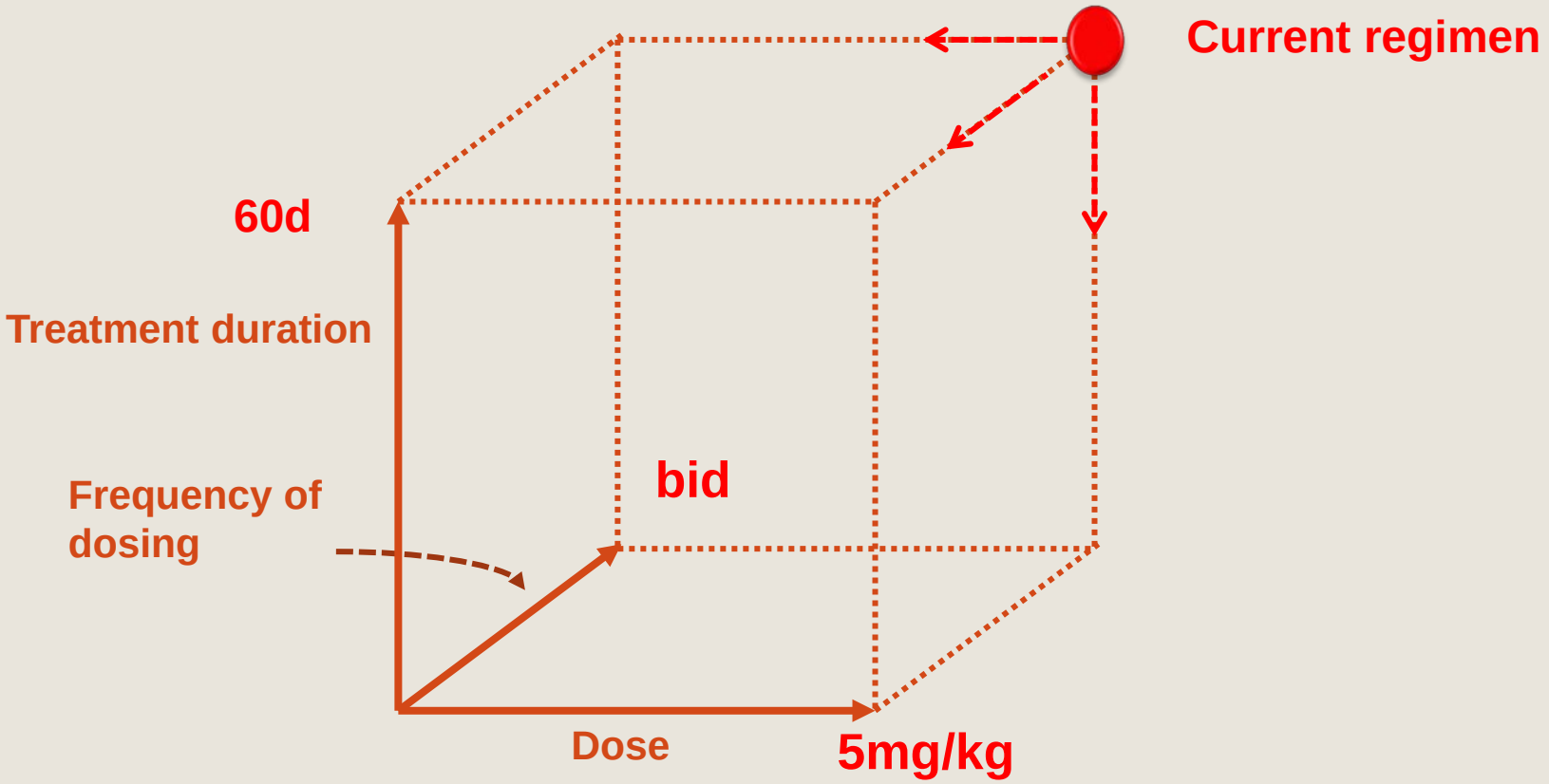
- Reduce BNZ exposure
  - Aim to improve tolerability and maintain efficacy
  - Does not address efficacy gap
- Combination therapy
  - Aim to improve efficacy and maintain or improve tolerability
  - May not address tolerability gap

DNDi
Drugs for Neglected Diseases *initiative*

Benznidazole New Treatment Regimens

- New treatment benznidazole asap, earlier than 2018
  - Goal: Improve safety, tolerability and compliance
  - At a minimum, maintain current efficacy rates
- Evaluation of BNZ monotherapy and combination treatment
- Need to select the optimum combination of BZN dose, dosing frequency and treatment duration
  - Use small, focused study to assess range of options and eliminate non-viable approaches quickly and cheaply
- Will eventually need a large multi-centre trial for final guidelines change
  - Design based on the dose selection study

Benznidazole New Treatment Regimens

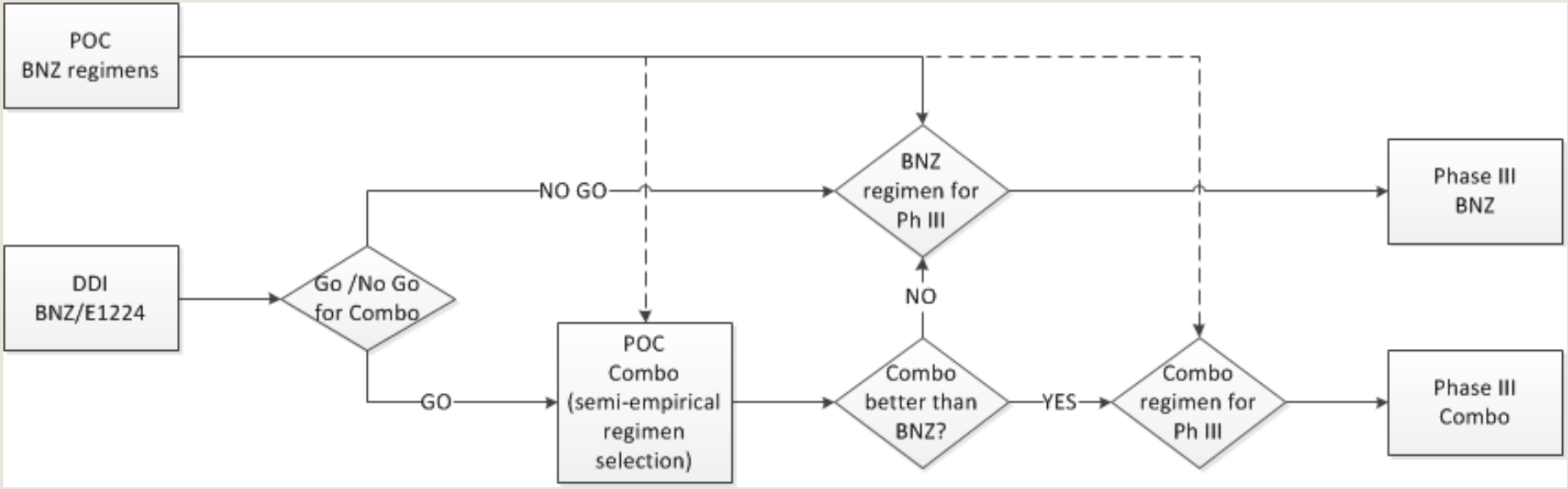


Benznidazole - Dose Selection Study

- Adult patients with chronic indeterminate CD
- Bolivia and Argentina, multi-centre study
- Design: prospective, randomized, double-blind, POC, dose selection, historically-controlled, PKPD study
- Serology and PCR confirmed CD diagnosis
- Evaluation of 2, 4 and 8 weeks treatment, with different daily doses of BNZ
- Efficacy Endpoint: 6 M sustained PCR negativisation, compared to placebo-treated historical controls
  - Interim analysis: 10 week PCR readout (inform combo dose selection)
- PKPD and Safety evaluation

Benznidazole New Treatment Regimens Development Strategy

Program design



- BNZ POC and E1224/BZN Drug-drug interaction (DDI) evaluation in parallel
- Use interim analysis of BNZ POC to help select regimens for E1224Combo POC
- Multi-country, multi-centre Phase III evaluation

DNDi
Drugs for Neglected Diseases *initiative*

Conclusions

- **Significant impact of recent clinical trial data on the overall Chagas disease R&D landscape**
  - **Additional push for scaling up diagnosis and treatment of Chagas disease, improved access to available drugs and formulations**
- **Work towards 1 new treatment by 2018 for the chronic form of Chagas Disease**
  - **POC studies for reduced BNZ, combination and Fexinidazole**
  - **Phase 3 evaluation**
- **Continued activities to stimulate development of Biomarkers of therapeutic response**

DNDi
Drugs for Neglected Diseases *initiative*