E1224 – RESULTS OF PROOF OF CONCEPT CLINICAL TRIAL IN PATIENTS WITH CHRONIC INDETERMINATE CHAGAS DISEASE

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Major Partners:

Eisai Ltd., Japan; Plataforma de Atención Integral a los Pacientes con Enfermedad de Chagas (**CEADES Bolivia/CRESIB Barcelona**); Universidad Mayor de San Simon, Cochabamba, Universidad Autonoma Juan Misael Saracho de Tarija; INGEBI/CONICET, Buenos Aires, Argentina; NUDFAC, Brazil; University of Georgia, US; Wellcome Trust, UK

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E1224

Plataforma Chagas

Plataforma de Atención Integral a los Pacientes con Enfermedad de Chagas

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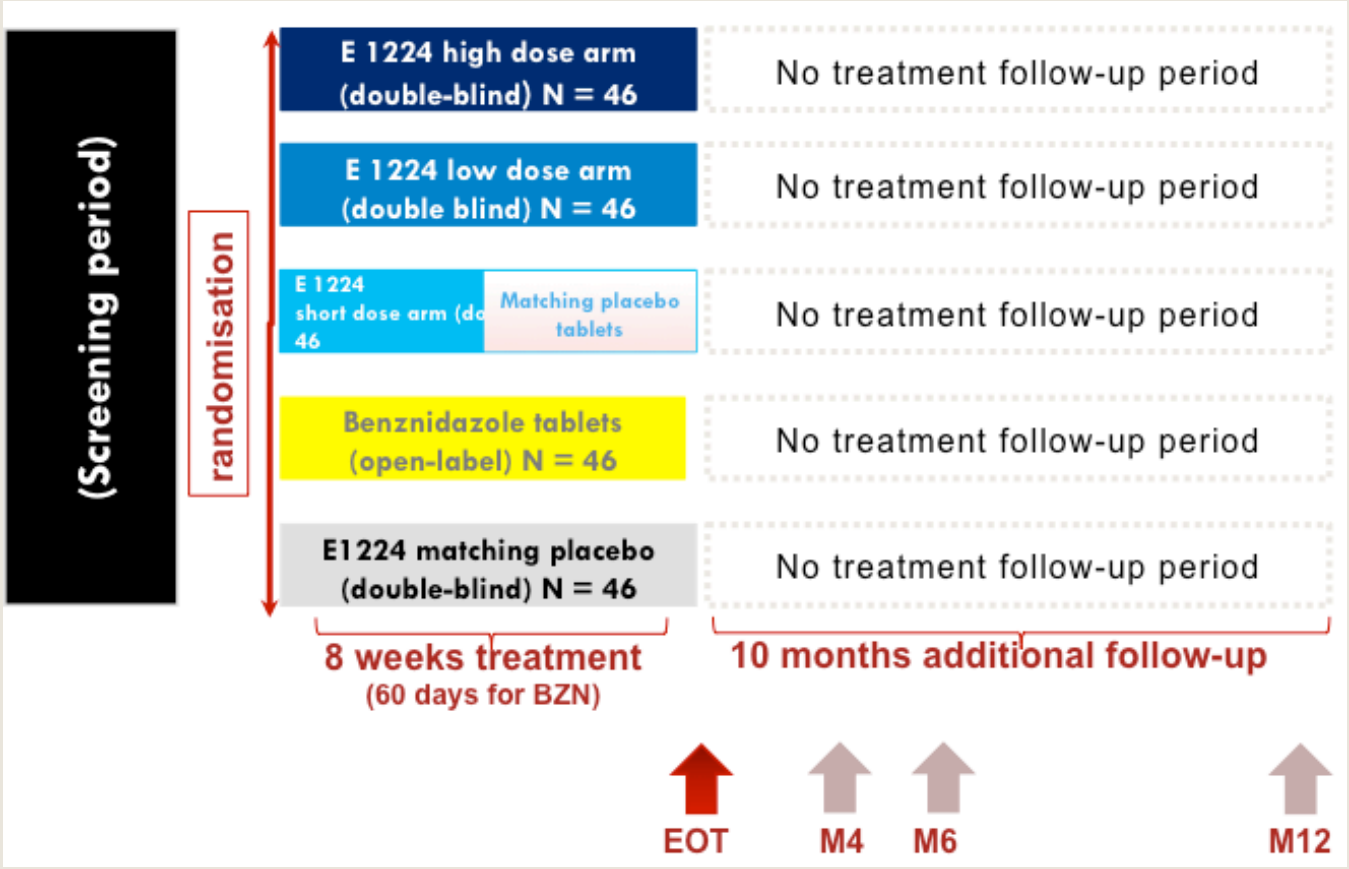
Phase 2 Study design

DNDi-CH-E1224-001
NCT01489228

- **Efficacy based on serial qualitative and quantitaive PCR and other candidate biomarker assessments**
- **Parasite assessment before and after treatment**
- **PKPD for both E1224 and BZN**



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Study Assays

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Biomarkers CRESIB– BCN

- BNP
- Troponin
- APO A1
- Protrombotic markers (ETP, F1+2)
- Lytic Antibodies

Conventional Serology UMSS-Cochabamba

- Elisa C
- Elisa R

Biomarkers UGA, Georgia-US

- Multiplex serodiagnostic assay

PCR qualitative and quantitative UMSS - Cochabamba

Genotyping Conicet-Buenos Aires

PK NUDFAC- Brazil Ricardo Gutierrez - Argentina

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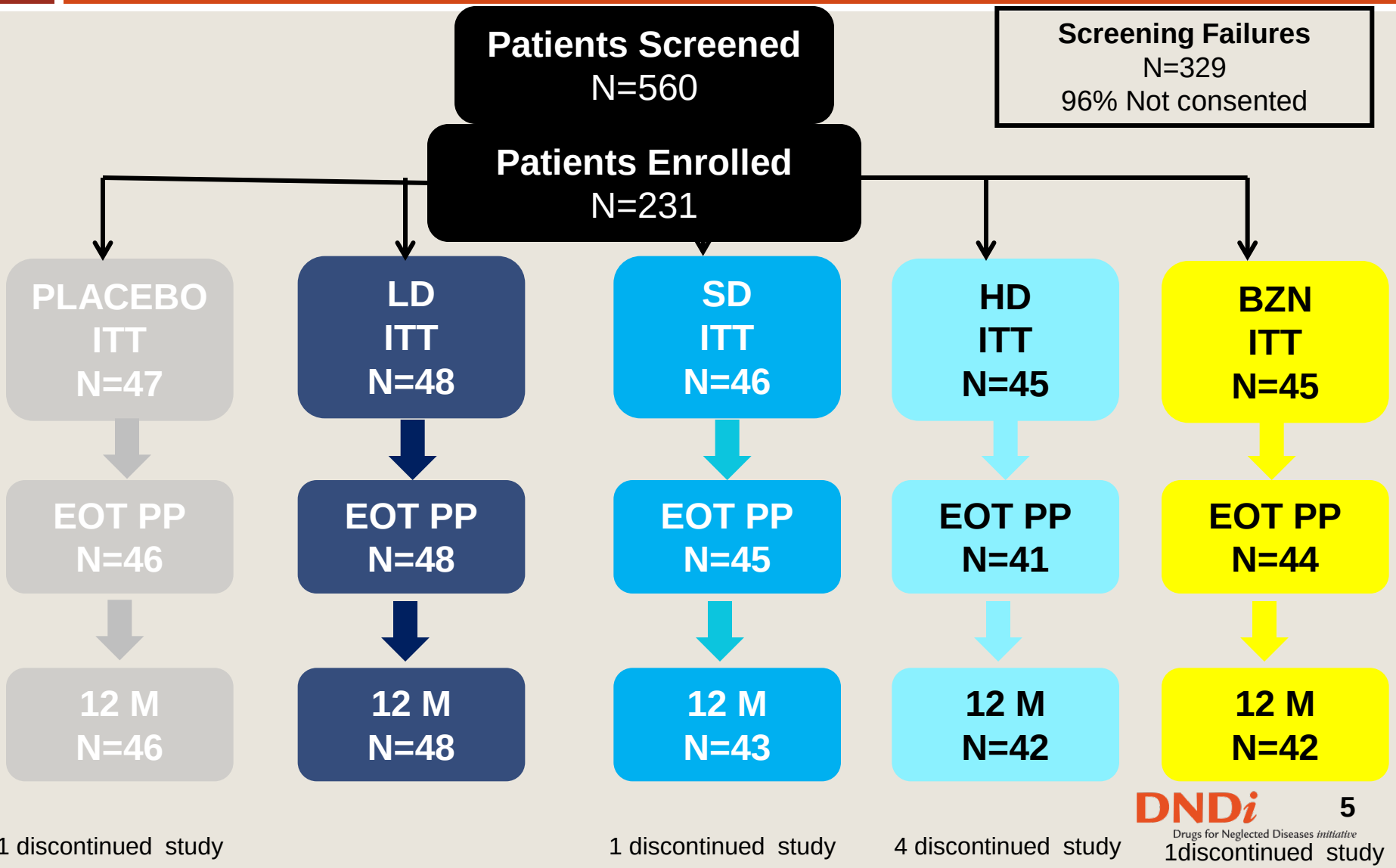
Study Disposition



Efficacy Results

Assessment by PCR at D65 and 12 months

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)**

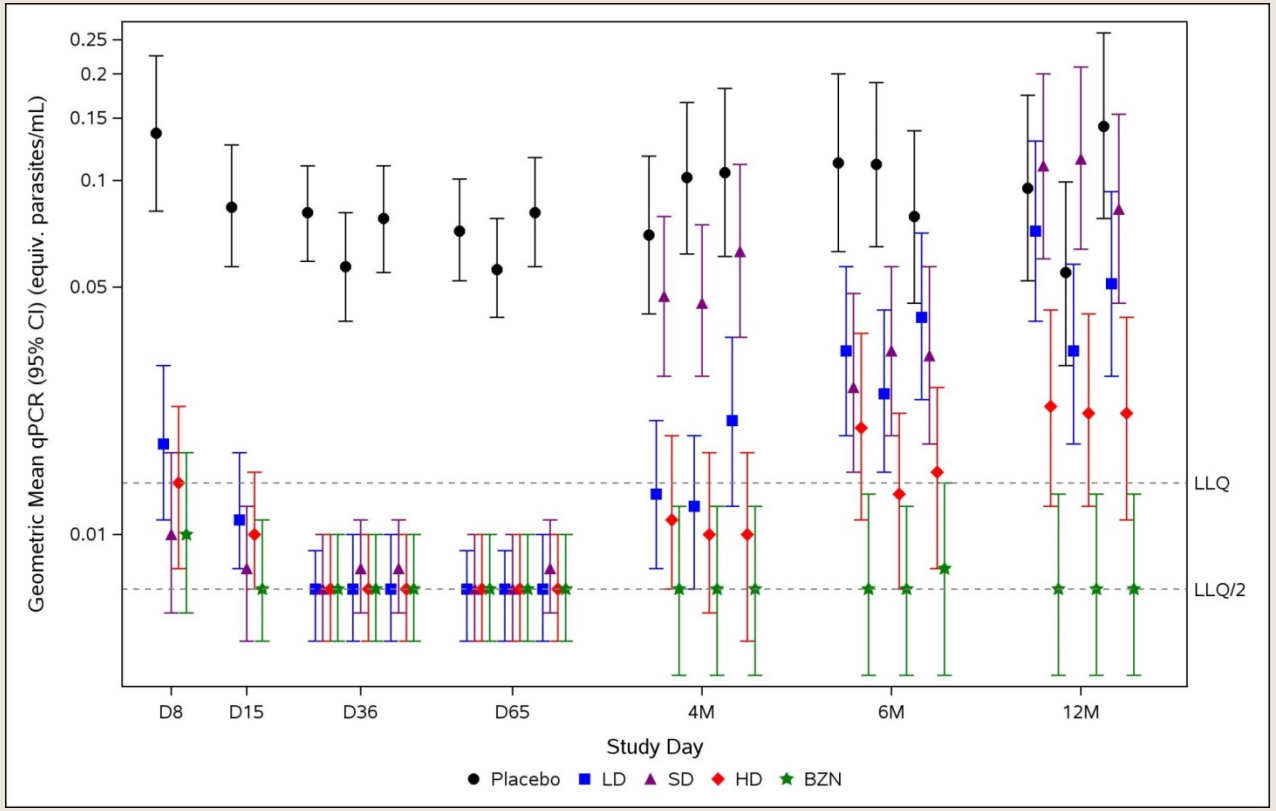
12 Month Follow-up

			(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)**

- Significant difference at EOT for all comparisons vs. placebo (<.001)
- Significant difference (one-sided) $p < 0.025$ for the comparison of HD arm vs. placebo and BZN arm vs. placebo for sustained response at 12 months

qPCR Repeated Measure Analysis:

Estimated Values (Population: ITT/Safety)



Stepwise Cox model - time to first relapse

- Increased hazard of relapse with treatment group (placebo vs. LD and SD) and higher quantitative PCR at baseline (1.10 (1.03, 1.16))
- Decreased hazard of relapse with HD E1224 (0.60 (0.26, 1.37)) and BZN (0.06 (0.02, 0.21))

Safety Results

TEAE / SAEs (Population: Safety)

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- **TEAE leading to drug discontinuation, highest proportion in the HD E1224 and BZN arms**
  - **5 (11.1%) HD E1224 –elevated transaminases**
  - **4 (8.9%) BZN – elevated transaminases and drug hypersensitivity reactions**
- **6 (2.6 %) SAEs were identified. All recovered completely.**
  - **4 (6.7%) E1224 – appendicitis (SD), 2 abortions (HD), cholecystitis (HD)**
  - **2 (3.3%) BZN – anembryonic pregnancy and bronchitis**

Safety Results

Most common AEs(Population: Safety)

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- **Most common BZN related AEs: nausea (20%), dermatologic AEs (14%), hypersensitivity (24.4%) reactions, and neuropathy (13%)**
- **HD E1224 group: higher incidence of dose proportional ALT, AST and GGT increases**
- **ECG results comparable across treatment groups**
- **BZN patients had a slightly increased incidence of QTc F prolongation.**

PK Profile - E1224/BZN

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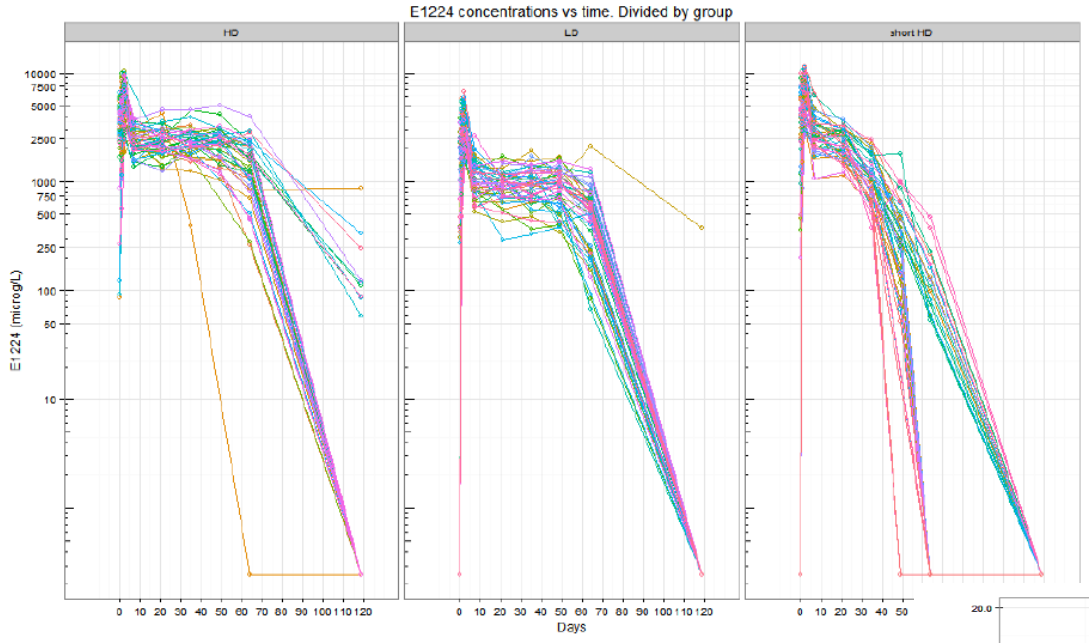
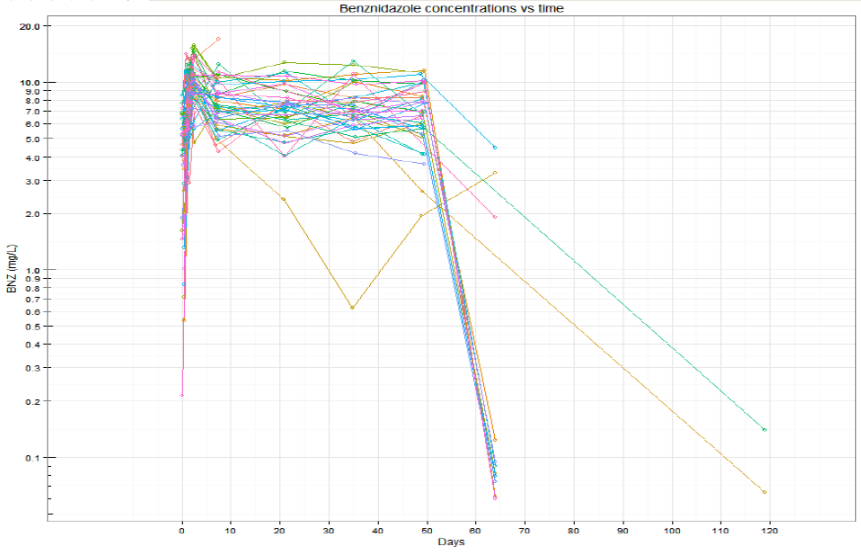


Figure2. E1224 divided by treatment group (HD, LD and SD) – log scale. Each color represents a different patient.

- **The E1224 loading dose schedule reach steady state and provide stable trough concentrations**
- **E1224 concentrations proportional to dose**
- **No evidence of accumulation**

- **Benznidazole results:**
  - **Comparable to earlier PK studies**
  - **Good compliance**



Project Investigators and Collaborators

Dr. Faustino Torrico, Cristina Alonso-Vega, Lineth Garcia, Rudy Parrado (Universidad Mayor de San Simon, Cochabamba, Bolivia), Dr. Lourdes Ortiz (Tarija, Bolivia); Dr. Joaquin Gascón, Maria Jesus Pinazo (CRESIB, Barcelona, Spain); Dr. Sergio Sosa-Estani ("Vector-borne infectious diseases" department, Ministry of Health, Argentina); Dr. Alejandro Schijman, Margarida Bisio, Tomás Duffy, Carolina Cura, Natalia Juiz (INGEBI/ CONICET, Buenos Aires, Argentina); Facundo Garcia Bournissen, (CONICET, Buenos Aires, Argentina) | DNDi team: Glaucia Santina, Jayme Fernandes, Bethania Blum, Erika Correia, Isabela Ribeiro

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MUCHAS GRACIAS