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

Faustino Torrico
Joaquim Gascon
Isabela Ribeiro

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
Phase 2 Study design

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

DNDi-CH-E1224-001
NCT01489228
Study Assays

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

- Conventional Serology
  - UMSS-Cochabamba
    - Elisa C
    - Elisa R

- PCR
  - UMSS-Cochabamba
    - Qualitative and quantitative

- Genotyping
  - Conicet-Buenos Aires

- Biomarkers
  - UGA, Georgia-US
    - Multiplex serodiagnostic assay

- PK
  - NUDFAC- Brazil
  - Ricardo Gutierrez - Argentina

DNDi-CH-E1224-001
NCT01489228
Study Disposition

Patients Screened
N=560

Patients Enrolled
N=231

Screening Failures
N=329
96% Not consented

PLACEBO
ITT
N=47

EOT PP
N=46

12 M
N=46

1 discontinued study

LD
ITT
N=48

EOT PP
N=48

12 M
N=48

1 discontinued study

SD
ITT
N=46

EOT PP
N=45

12 M
N=43

4 discontinued study

HD
ITT
N=45

EOT PP
N=41

12 M
N=42

BZN
ITT
N=45

EOT PP
N=44

12 M
N=42

DNDi-CH-E1224-001
NCT01489228
# Efficacy Results

Assessment by PCR at D65 and 12 months

## Day 65 (EOT)

<table>
<thead>
<tr>
<th>Parasite clearance at D65</th>
<th>Placebo (N=47)</th>
<th>LD (N=48)</th>
<th>SD (N=46)</th>
<th>HD (N=45)</th>
<th>BZN (N=45)</th>
<th>All (N=231)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>47</td>
<td>48</td>
<td>46</td>
<td>45</td>
<td>45</td>
<td>231</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>35 (74.5)</td>
<td>5 (10.4)</td>
<td>5 (10.9)</td>
<td>11 (24.4)</td>
<td>4 (8.9)</td>
<td>60 (26.0)</td>
</tr>
</tbody>
</table>

## 12 Month Follow-up

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

- 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
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)

☐ 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
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

- 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
Thank You to All Our Partners & Donors

www.dndi.org
www.dndi.org.br

www.connect2fightneglect.org
MUCHAS GRACIAS

TEAM TARIJA

TEAM COCHABAMBA