Update on Clinical Trials on Chagas Disease

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DIAGNOSIS AND TREATMENT

CURE INFECTION

PREVENT MORBIMORTALITY

PERSONAL AND FAMILY WELLBEING

AVOID CONGENITAL TRANSMISSION

REDUCE DISEASE BURDEN
<table>
<thead>
<tr>
<th></th>
<th>Acceptable</th>
<th>Ideal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target population</td>
<td>Chronic indeterminate</td>
<td>Chronic indeterminate and Acute</td>
</tr>
<tr>
<td>Geographic Distribution</td>
<td>All regions</td>
<td>All regions</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Non-inferior to benznidazole standard dose* in all parasitological areas</td>
<td>Superior to benznidazole standard dose in different phases of disease (acute and chronic) (parasitological)</td>
</tr>
<tr>
<td>Safety</td>
<td>Superior to benznidazole* in the frequency of definitive treatment discontinuations due to medical indication (clinical and laboratory)**</td>
<td>Superior to benznidazole* in the frequency of definitive treatment discontinuations due to medical indication (clinical and laboratory)**</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Pregnancy</td>
<td>No contraindications</td>
</tr>
<tr>
<td>Precautions</td>
<td>No genotoxicity**; no pro-arrythmic potential</td>
<td>No genotoxicity; no teratogenicity; no pro-arrythmic potential</td>
</tr>
<tr>
<td>Interactions</td>
<td>No clinically significant interaction with anti-arrythmic and anticoagulant drugs</td>
<td>No clinically significant interaction with other drugs</td>
</tr>
<tr>
<td>Presentation</td>
<td>Oral/Parenteral (short POC)*** Age-adapted</td>
<td>Oral Age-adapted</td>
</tr>
<tr>
<td>Stability</td>
<td>3 years, climatic zone IV</td>
<td>5 years, climatic zone IV</td>
</tr>
<tr>
<td>Dosing regimen</td>
<td>Oral - any duration Parenteral - &lt;7 days</td>
<td>&lt;30days</td>
</tr>
<tr>
<td>Cost</td>
<td>Lowest possible</td>
<td>≤ current treatment cost</td>
</tr>
</tbody>
</table>

* As per WHO recommendation; ** No genotoxicity is a condition only for NCEs; *** Need for parenteral treatment for severe disease
## Phase II Clinical Trials

<table>
<thead>
<tr>
<th></th>
<th>CHAGASAZOL</th>
<th>STOP-CHAGAS</th>
<th>PROOF-OF-CONCEPT of E1224</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>78 (3 groups of 26 patients)</td>
<td>120 (4 groups of 30 patients)</td>
<td>230 (5 groups of 46 patients)</td>
</tr>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td>Age ≥ 18; two positive serologic tests; positive rt-PCR</td>
<td>Age 18-50; ≥ 2 positive serologic tests; positive rt-PCR; normal ECG &amp; echo</td>
<td>Age 18-50; ≥ 2 positive serologic tests; positive rt-PCR; normal ECG</td>
</tr>
</tbody>
</table>
| **Study treatments** | -BZN: 150 mg BID  
-POS: 100 mg BID (low dose)  
-POS: 400 mg BID (high dose) | -PCBpos: 10 ml BID  
-POS: 400 mg (10 ml) BID  
-BZN 200 mg + PCBpos 10 ml BID  
-BZN 200 mg + POS 400 mg (10 ml) BID | -PCB (8w)  
-E1224 low dose (8w)  
-E1224 high dose (8w)  
-E1224 (4w) followed by PCB (4w): short dose  
-BZN (5mg/kg/d/60d) |
| **Primary end point** | Consistently negative results of rt-PCR over the entire FU period (8, 16, 24, and 40 weeks after EOT) | Consistently negative results of rt-PCR over the entire FU period (4, 8, 12, and 16 weeks after EOT) | Consistently negative results of rt-PCR at EOT and until 12 months of FU (4, 6 and 12 months) |
| **Population**       | Patients from Bolivia living in Spain | Patients from ARG (77%), CHILE or LA living in Spain | Patients from Bolivia (Tarija & Cochabamba) |
**CHAGASAZOL & STOP-CHAGAS**

**Randomized Trial of Posaconazole and Benznidazole for Chronic Chagas’ Disease**

Israel Molina, M.D., Jordi Gómez i Prat, M.D., Fernando Salvador, M.D., Begoña Treviño, M.D., Elena Sulleiro, M.D., Núria Serre, M.D., Diara Pou, M.D., Silvia Roure, M.D., Juan Cabezoz, M.D., Lluís Valerio, Ph.D., Albert Blanco-Grau, M.D., Adrián Sánchez-Montalvá, M.D., Xavier Vidal, Ph.D., and Albert Pahissa, Ph.D.

**Benznidazole and Posaconazole in Eliminating Parasites in Asymptomatic T. Cruzi Carriers**

The STOP-CHAGAS Trial

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**CHAGASAZOL**

Sustained negativization of PCR

- **Analysis**
  - Intention-to-treat
  - Per-Protocol

- **BZN**
  - 62
  - 19

- **POS high**
  - 20

- **POS low**
  - 8
  - 10

- **STOP-CHAGAS**

Sustained negativization of PCR

- **Analysis**
  - Intention-to-treat
  - Per-Protocol

- **BZN**
  - 100

- **BZN+POS**
  - 80

- **POS**
  - 13
  - 13

- **PCB**
  - 10
  - 7

*only patients who completed treatment and FU

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Molina I et al. NEJM 2014;370:1893

Merlio C et al. Deseret at ACC 2016
E1224-001

• E1224, Phase 2, Proof of concept

E1224: DNDi
Proof of Concept for a Safe, Effective and Affordable New Therapy for Chagas Disease

- **E1224 high dose arm** (double-blind) N = 46
- **E1224 low dose arm** (double blind) N = 46
- **E1224 short dose arm** N = 46
- **Matching placebo tablets**
- **Benznidazole tablets** (open-label) N = 46
- **E1224 matching placebo** (double-blind) N = 46

- **Screening period**: 8 weeks treatment (60 days for BZN)
- **Randomisation**

  - **EOT**
  - **M12**
  - **M6**
  - **M4**

- **No treatment follow-up period**

- **10 months additional follow-up**
FEXINIDAZOL

- Phase 2, Proof of concept:

**Fexnidazole Phase II**

DNDi

Proof-of-Concept Dose Ranging Study
Evaluation of Dose and duration

8 weeks treatment 4 months additional follow-up

20 patients/arm
Stopping rules: futility and safety
Cardiac and liver safety surveillance
Randomized Trial of Benznidazole for Chronic Chagas’ Cardiomyopathy


2854 randomized

1431 BNZ
84% took ≥75% of target dose

Discontinuation 192
(13.4%)

Lost to follow-up (n=8)

99.5% Complete Follow-up

Mean FU 5.4 yrs.

1423 Placebo
90% took ≥75% of target dose

Discontinuation 51
(3.6%)

Lost to follow-up (n=7)

99.5% Complete Follow-up
NEW SCHEME INTERMITTENT BZN

- Pilot study to assess an intermittent scheme of BZN
- 5mg/kg/day, two daily doses every 5 days, 60 days

New Scheme of Intermittent Benznidazole Administration in Patients Chronically Infected with *Trypanosoma cruzi*: a Pilot Short-Term Follow-Up Study with Adult Patients

María Gabriela Álvarez, a Yolanda Hernández, b Graciela Bertocchi, a Marisa Fernández, b Bruno Lococo, a Juan Carlos Ramírez, c Carolina Cura, b Constanza Lopez Albizu, b Alejandro Schijman, c Marcelo Abril, d Sergio Sosa-Estani, b Rodolfo Viotti a

Hospital Interzonal General de Agudos Eva Perón, San Martín, Buenos Aires, Argentina a; Instituto Nacional de Parasitología Dr. Mario Fatale Chaben, Buenos Aires, Argentina b; Instituto de Ingeniería Genética y Biología Molecular (INGEBI), Buenos Aires, Argentina c; Fundación Mundo Sano, Buenos Aires, Argentina d
BERENICE

BERENICE is a European research network (Collaborative Project) coordinated by Vall d’Hebron University Hospital and its Research Institute (VHC-HUVH, Barcelona, Spain). Our Consortium brings together 8 European and Latin American partners. Starting in September 2012, this 5-year project is supported by the European Commission Under the Health Innovation Work Programme of the 7th Framework Programme.

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SUMMARY OF RECENT RCTs

• Posaconazole (monotherapy or in combination) and E1224 (monotherapy) were effective during treatment and relapsed after EOT (demonstrated by PCR Positive)

• Fexinidazole (suspended for safety issues) was effective during treatment with sustained response (100%) at 12 months FUP

• Benznidazole was effective during treatment with sustained response (~ 80%) at 12 months FUP

• PCR proved useful for assessing treatment response to anti-trypanosomal drugs