Update on Clinical Trials on Chagas Disease

Fabiana Barreira
Clinical Manager
DIAGNOSIS AND TREATMENT

CURE INFECTION

PREVENT MORBIMORTALITY

PERSONAL AND FAMILY WELLBEING

AVOID CONGENITAL TRANSMISSION

REDUCE DISEASE BURDEN
# Chagas Disease – Target Product Profile 2015

<table>
<thead>
<tr>
<th></th>
<th>Acceptable</th>
<th>Ideal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target population</strong></td>
<td>Chronic indeterminate</td>
<td>Chronic indeterminate and Acute</td>
</tr>
<tr>
<td><strong>Geographic Distribution</strong></td>
<td>All regions</td>
<td>All regions</td>
</tr>
<tr>
<td><strong>Efficacy</strong></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><strong>Safety</strong></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><strong>Contraindications</strong></td>
<td>Pregnancy</td>
<td>No contraindications</td>
</tr>
<tr>
<td><strong>Precautions</strong></td>
<td>No genotoxicity**; no pro-arrythmic potential</td>
<td>No genotoxicity; no teratogenicity; no pro-arrythmic potential</td>
</tr>
<tr>
<td><strong>Interactions</strong></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><strong>Presentation</strong></td>
<td>Oral/Parenteral (short POC)***</td>
<td>Oral Age-adapted</td>
</tr>
<tr>
<td></td>
<td>Age-adapted</td>
<td></td>
</tr>
<tr>
<td><strong>Stability</strong></td>
<td>3 years, climatic zone IV</td>
<td>5 years, climatic zone IV</td>
</tr>
<tr>
<td><strong>Dosing regimen</strong></td>
<td>Oral - any duration Parenteral - &lt;7 days</td>
<td>&lt;30 days</td>
</tr>
<tr>
<td><strong>Cost</strong></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
<table>
<thead>
<tr>
<th>Phase II Clinical Trials</th>
<th>CHAGASAZOL</th>
<th>STOP-CHAGAS</th>
<th>PROOF-OF-CONCEPT of E1224</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</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>Inclusion criteria</td>
<td>Age &gt; 18; two positive serologic tests; positive rt-PCR</td>
<td>Age 18-50; &gt; 2 positive serologic tests; positive rt-PCR; normal ECG &amp; echo</td>
<td>Age 18-50; &gt; 2 positive serologic tests; positive rt-PCR; normal ECG</td>
</tr>
<tr>
<td>Study treatments</td>
<td>-BZN: 150 mg BID</td>
<td>-PCBpos: 10 ml BID</td>
<td>-PCB (8w)</td>
</tr>
<tr>
<td></td>
<td>-POS: 100 mg BID (low dose)</td>
<td>-POS: 400 mg (10 ml) BID</td>
<td>-E1224 low dose (8w)</td>
</tr>
<tr>
<td></td>
<td>-POS: 400 mg BID (high dose)</td>
<td>-BZN 200 mg + PCBpos 10 ml BID</td>
<td>-E1224 high dose (8w)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-BZN 200 mg + POS 400 mg (10 ml) BID</td>
<td>-E1224 (4w) followed by PCB (4w): short dose</td>
</tr>
<tr>
<td>Primary end point</td>
<td>Consistently negative results of rt-PCR over the entirely FU period (8, 16, 24, and 40 weeks after EOT)</td>
<td>Consistently negative results of rt-PCR over the entirely FU period (4, 8, 12, and 16 weeks after EOT)</td>
<td>Consistently negative results of rt-PCR at EOT and until 12 months of FU (4, 6 and 12 months)</td>
</tr>
<tr>
<td>Population</td>
<td>Patients from Bolivia living in Spain</td>
<td>Patients from ARG (77%), CHILE or LA living in Spain</td>
<td>Patients from Bolivia (Tarija &amp; Cochabamba)</td>
</tr>
</tbody>
</table>
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., Diana Pou, M.D., Silvia Roure, M.D., Juan Cabezos, M.D., Lluís Valero, 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

**CHAGASAZOL**

Sustained negativization of PCR

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Intention-to-treat</th>
<th>Per-Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>BZN</td>
<td>62</td>
<td>94</td>
</tr>
<tr>
<td>POS high</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>POS low</td>
<td>8</td>
<td>10</td>
</tr>
</tbody>
</table>

**STOP-CHAGAS**

Sustained negativization of PCR

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<tr>
<th>Analysis</th>
<th>Intention-to-treat</th>
<th>Per-Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>BZN</td>
<td>87</td>
<td>100</td>
</tr>
<tr>
<td>BZN+POS</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>POS</td>
<td>13.13</td>
<td>7</td>
</tr>
<tr>
<td>PCB</td>
<td>10</td>
<td>7</td>
</tr>
</tbody>
</table>

*only patients who completed treatment and FU

**END of treatment**

Molina I et al, *NEJM* 2014;370:1193

Moliné C et al, Dissected 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

8 weeks treatment (60 days for BZN)
10 months additional follow-up

Screening period
Randomisation

EOT M12 M6 M4
FEXINIDAZOL

- Phase 2, Proof of concept:

Fexnidazole Phase II
DNDi

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

20 patients/arm
Stopping rules: futility and safety
Cardiac and liver safety surveillance

EOT

M4 13
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

1423 Placebo
90% took ≥75% of target dose

Discontinuation 51 (3.6%)
Lost to follow-up (n=7)

Mean FU 5.4 yrs.

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
BERENICE

BERENICE is a European research network (Collaborative Project) coordinated by Vall d’Hebron University Hospital and its Research Institute (VH-UVH, 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.

For further information, please visit our website at: www.berenice-project.eu

Project Coordinator
Isaac Molina
P. de la Vall d’Hebron, 119-129
08035 Barcelona, SPAIN
Phone: +34 93 274 22 51
Email: imolina@vhebron.net

Project Manager
Esperanza Esteban
P. de la Vall d’Hebron, 119-129
08035 Barcelona, SPAIN
Phone: +34 93 274 22 00 (Ext. 64 73)
Email: esperanza.esteban@vhebron.org
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
THANK YOU

https://www.dndi.org/