NEW TREATMENT OPPORTUNITIES IN CHAGAS DISEASE

ICOPA Mexico - August 12, 2014
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.
- New challenges for 2011: Initiation of several clinical studies.
- CCRP Meeting 2013, Cochabamba, April 2013.
<table>
<thead>
<tr>
<th><strong>Target population</strong></th>
<th><strong>Acceptable</strong></th>
<th><strong>Ideal</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Strains</td>
<td>TcI, TcII, TcV and TcVI (according to new 2009 classification)</td>
<td>All according to new classification (2009)*</td>
</tr>
<tr>
<td>Distribution</td>
<td>All areas</td>
<td>All areas</td>
</tr>
<tr>
<td>Adult/children</td>
<td>Adult</td>
<td>All</td>
</tr>
<tr>
<td>Clinical efficacy</td>
<td>Non inferior to benznidazole in all endemic regions (parasitological)</td>
<td>Superiority to benznidazole to different phases of disease (acute and chronic) (parasitological)</td>
</tr>
<tr>
<td>Safety</td>
<td>Superiority to benznidazole ** 3 CE plus 2 standard LE or ECG during treatment</td>
<td>Superiority to benznidazole or nifurtimox No CE or LE or ECG needed during treatment</td>
</tr>
<tr>
<td>Activity against resistant strains</td>
<td>Not necessary</td>
<td>Active against nitrofuran- and nitroimidazole-resistant <em>T. cruzi</em> strains</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Pregnancy/lactation</td>
<td>None</td>
</tr>
<tr>
<td>Precautions</td>
<td>No genotoxicity; No pro-arrythmic potential</td>
<td>No genotoxicity; No teratogenicity; No negative inotropic effect; No pro-arrythmic potential</td>
</tr>
<tr>
<td>Interactions</td>
<td>No clinically significant interaction with anti-hypertensive, anti-arrythmic and anticoagulants drugs</td>
<td>None</td>
</tr>
<tr>
<td>Presentation</td>
<td>Oral</td>
<td>Oral</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>Comparable to systemic antifungal treatments</td>
<td>Once daily/ 30days</td>
</tr>
</tbody>
</table>
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
Parasitological Response with Benznidazole
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)
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)

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

Percentage of positive PCR at follow-up
Chagas Disease
Clinical Trial Results and Impact on Strategy

- Efficacy and safety information on theazole 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 theazole class and ergosterol biosynthesis inhibitors as a target for Chagas disease
Fexinidazole
A new nitroimidazole clinical candidate

- Non-genotoxic 5-Nitroimidazole
- Reports for Fexinidazole potential for Chagas Disease
  - 1983:
  - 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 (Phase II/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
### Fexinidazole Proof-of-Concept Dose Ranging Study

- **Study initiated:** July 2014
- **Target for Study:**
- **Conclusion:** August 2015

<table>
<thead>
<tr>
<th>Dose Range</th>
<th>Duration</th>
<th>Treatment Code</th>
</tr>
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<tbody>
<tr>
<td>FEXI 1200 2 wks</td>
<td>8 wks</td>
<td>FEXI 1200 - 8 wks</td>
</tr>
<tr>
<td>FEXI 1200 4 wks</td>
<td>4 wks</td>
<td>FEXI 1800 - 8 wks</td>
</tr>
<tr>
<td>FEXI 1800 2 wks</td>
<td>6 wks</td>
<td>FEXI matching placebo</td>
</tr>
<tr>
<td>FEXI 1800 4 wks</td>
<td>4 wks</td>
<td>No treatment follow-up period</td>
</tr>
</tbody>
</table>

- **Screening period:** 8 weeks treatment
- **Randomisation:**
- **4 months additional follow-up**
- **EOT**
- **M4**

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

- 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

Current situation

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
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

- **Current regimen**
  - Dose: 5mg/kg
  - Frequency of dosing: bid
  - Treatment duration: 60d
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
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