Chagas Disease Portfolio

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DNDi
Drugs for Neglected Diseases initiative
Chagas Disease: an unmet medical need

- Parasitic disease with greater disease burden in the New World
- Leading cause of infectious myocarditis worldwide

- Only two drugs available: nifurtimox and benznidazole
  - Safety and tolerability issues
  - Long treatment period (1-2 months)
  - No pediatric formulations available
Chagas Disease: knowledge gaps

- PK/PD relationship for Chagas disease largely unknown
- Limited knowledge on the relevance of animal models
- Limited information on the importance of the different parasite lineages to human disease, coexistence of infection and mechanisms of resistance
- Lack of early test of cure in Chagas disease
- Limited sensitivity of parasitological methods, PCR
DNDi’s Chagas Strategy

**Short-term objectives:**
Better use of existing treatments through new formulations, therapeutic switching, and combinations

- Pediatric dosage form of benznidazole
- Azoles
- Combination treatment

**Long-term objectives:**
New drugs and improved R & D capacity

- Nitroimidazoles, fenarimol series, K777
- Improved screening methodologies
- Lead optimisation consortium
- Biological markers of treatment response: validated and qualified
## Target Product Profile 2011

<table>
<thead>
<tr>
<th></th>
<th>Acceptable</th>
<th>Ideal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target population</strong></td>
<td>Chronic</td>
<td>Chronic and Acute (Reactivations)</td>
</tr>
<tr>
<td><strong>Strains</strong></td>
<td>Tcl, TcII, TcV and TcVI (according to new 2009 classification)</td>
<td>All according to new classification (2009)*</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>All areas</td>
<td>All areas</td>
</tr>
<tr>
<td><strong>Adult/children</strong></td>
<td>Adult</td>
<td>All</td>
</tr>
<tr>
<td><strong>Clinical efficacy</strong></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><strong>Safety</strong></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><strong>Activity against resistant strains</strong></td>
<td>Not necessary</td>
<td>Active against nitrofuran- and nitroimidazole-resistant <em>T. cruzi</em> strains</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Pregnancy/lactation</td>
<td>None</td>
</tr>
<tr>
<td><strong>Precautions</strong></td>
<td>No genotoxicity; No prolongation of QTc interval</td>
<td>No genotoxicity; No teratogenicity; No negative inotropic effect; No prolongation of QTc interval</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>No clinically significant interaction with anti-hypertensive, anti-arrythmic and anticoagulants drugs</td>
<td>None</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td>Oral</td>
<td>Oral</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>Comparable to systemic antifungal treatments</td>
<td>Once daily/ 30days</td>
</tr>
</tbody>
</table>
Balancing knowledge gaps and the urgent medical need

- Clinical development and generation of scientific information that would help fill existing gaps and inform future drug development

- PCR - selected primary endpoint for clinical trials following extensive expert consultation

- Early regulatory consultation and agreement on endpoints, trial design and development strategy

- Generation of data in support of PCR ($T.cruzi$ DNA) and other biological markers of therapeutic response

- Generation of PK/PD data in humans (with different markers and parasite genotyping) for E1224 and benznidazole
Chagas Portfolio – June 2011

**Discovery**
- Screening Activities
  - Compound mining
  - Chemical classes
  - Target-based
  - HTS
- LO Consortium
  - CDCO
  - Epichem
  - Murdoch U.
  - UFOP
- Drug combination (Chagas)
- K777 (Chagas)
- Azoles E1224
- Biomarker (Chagas)

**Pre-clinical**
- Benznidazole Paediatric dosage form (Chagas)
- Exploratory

**Clinical**
- 2 Posaconazole (ICS – Spain, Merck)
- Bz BENEFIT Trial
  - Hamilton Health Sciences et al
- Bz TRAENA study
  - Instituto Fatala Chalben
- Exploratory

**Implementation**
- Others
  - Benznidazole
  - LAFEPE
  - Nifurtimox
  - Bayer
- Genzyme/Fiocruz Target identification and screening
- Chagas Drug Discovery Consortium
  - Tarleton/Ana Rodriguez /NIH
  - screen @ Broad
- Genomic Institute of the Novartis Research Foundation (GNF) / UCSF
**Pediatric Benznidazole**

**Overall Objective:**
An affordable, age-adapted, easy to use, pediatric dosage form for Chagas disease

**Definition of Tablet Strength and Formulation:**
12.5 mg dispersible tablets for <20 kg children

Partner: LAFEPE (sole Bz producer)
DNDi-LAFEPE signed agreement in 2008 for the development of a Bz pediatric formulation
Selection of Dosage Form

Pediatric Formulation
Pediatric Benznidazole 2011-2012

- Submission to Brazil DRA: March 2011
  - Feedback awaited 10/2011
- Implementation of access plan: interaction with different stakeholders to ensure the product availability, affordability, and adoption in key endemic countries
- Population PK study of Pediatric Benznidazole in children with Chagas disease (Argentina, PI: Jayme Altcheh)
  - Recruitment initiated in May 2011 – 30 children recruited, so far
- Comparative Bioavailability Study of Pediatric Benznidazole in Healthy Normal Volunteers (Brazil, CRO: NUDFAC).
E1224: A Drug Candidate in a Promising Class

Pharmacological characteristics

- Water-soluble monolysine salt of a phosphonoxyethyl ether of ravuconazole
- Rapid conversion to ravuconazole
- Good bioavailability and long terminal half-life
- Completed preclinical studies and Phase I studies
- Encouraging safety and tolerability profile

Rationale for Chagas disease

- Ergosterol synthesis inhibitor
- Ravuconazole: extremely potent \textit{in vitro} inhibitor of \textit{T. cruzi} growth
- Activity of ravuconazole documented in all \textit{T. cruzi} lineages tested
- Differences in performance ascribed to PK parameters in animal models (AUC, T1/2 and Vd)
E1224 - Phase II trial

• **Target population:** Adult patients (18-50y) with chronic indeterminate CD

• **General Objective:** To determine whether each of three different dosing regimens of E1224 are **efficacious and safe** in eradicating *T. cruzi* parasitemia in individuals with the chronic indeterminate form of CD, in comparison to placebo

• **Study sites:** “Plataforma de Atención al Paciente con Enfermedad de Chagas” in Cochabamba and Tarija, Bolivia

• **PI:** Drs. Faustino Torrico and Joaquim Gascón

**Study initiated in July 2011**

**Scope of current assessment:**
Early development, proof-of-concept evaluation
PCR Study
Optimization of sampling procedure for PCR technique to assess parasitological response for patients with Chronic Chagas Disease treated with benznidazole in Aiquile, Bolivia

- PCR - selected primary endpoint for clinical trials following extensive expert consultation
- Improvements in PCR sensitivity through sampling procedures vs logistics and feasibility for implementation in the field
- Collaboration with MSF Spain, Bolivia Mission (MSF-OCBA) and UMSS

Primary objective: To estimate the gain in sensitivity of several multiple-sample strategies of PCR with respect to the current standard (single sample of 10 ml) to detect Chagas chronic stage at baseline assessment.
Study Design

Target recruitment n=220
Study initiation – April 13th (185 patients recruited)

Baseline

Day 70

6 months

12 months

Primary endpoint:
+ or – PCR in sero+ patients

Secondary endpoint
Definition of optimal sampling
+ or – PCR in PCR +(10 or 5+10 ml)

Current Strategy = 1 sample of 10 ml
Reinforcement Strategy = adding other sample: RS1: 10+5; RS2: 10+10 at D7; RS3: 10+5+10 at D7
Substitution Strategy = SS1: 5 ml; SS2: 5+10 at D7
Biomarkers in Chagas

- RT-PCR lab optimization and validation for clinical studies
- NHEPACHA network for long term evaluation of candidate biomarkers
- Proteomic platforms: collaboration with HUG and McGill University
- Non-human primate study: collaboration with Univ. of Georgia and TBRI
- TRAENA – qualification of *T. cruzi* DNA and selected markers
- Coordination of activities with different partners
  - Work towards the integration of data on candidate markers
  - Collaboration in PAHO/TDR PCR
  - CRESIB
Chagas Clinical Research Platform

Objectives:

- Facilitate effective and efficient trials to deliver improved treatment for Chagas disease
- Strengthen institutional research capacity
- Support an environment conducive to quality research
- Develop a critical mass of expertise
- Define priority areas for clinical evaluation of new treatments in Chagas disease
- Conduct periodic review and update of Target Product Profile in Chagas Disease
- Facilitate access to new tools
- Articulate with other initiatives
Thank you to our partners and donors!