Research and development landscape in Chagas disease

Isabela Ribeiro
Eric Chatelain

ECTMIH, Basel September 1st 2015
New Era for Chagas Disease
Drug Development
Why?
Results Clinical Trials
NCT0116967 and NCT01489228

Parasitological Success with BZN

Efficacy based on repeated PCR and candidate biomarkers, parallel evaluation of serology

<table>
<thead>
<tr>
<th>Sustained clearance At 12 months</th>
<th>(N=47)</th>
<th>(N=48)</th>
<th>(N=46)</th>
<th>(N=45)</th>
<th>(N=45)</th>
<th>(N=231)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>43 (91.5)</td>
<td>44 (91.7)</td>
<td>41 (89.1)</td>
<td>32 (71.1)</td>
<td>8 (19.0)</td>
<td>168 (72.7)</td>
</tr>
<tr>
<td>Yes</td>
<td>4 (8.5)</td>
<td>4 (8.3)</td>
<td>5 (10.9)</td>
<td>13 (28.9)</td>
<td>37 (81.0)</td>
<td>63 (27.3)</td>
</tr>
</tbody>
</table>
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
    Age: 7.3 years (range 2.1 – 12)
  - NCT00699387: 81 Children 1d – 12 years old
    Age: >2a: 40; < 2a: 41 (8 newborn)

Adults, Raaflaub 1980
Implications for Delivery of Future Chagas Candidate

- Highlighted Major Translational Challenges
  - Need to translate research data to assays compatible with Drug Discovery & Development process
  - Better translation in vitro/in vivo models and the clinic
  - Address the right questions in our models
  - Better understanding of PK/PD relationships
- Break dogma and test hypothesis
- Integrate when available or generate MoA data: helpful to predict potential safety issues and monitor specific parameters during development (Toxicology studies, clinical trials)
New Developments in the Non-Clinical Area of Chagas Disease R&D
A New Era for Chagas Disease Drug Discovery?

New Compound Sets Identified from High Throughput Phenotypic Screening Against Three Kinetoplastid Parasites: An Open Resource Imaging

Anti-Trypanosomal Treatment with Benznidazole is Superior to Posaconazole Regimens in Models of Chagas Disease (AAC, 2015)
Chagas Disease Drug Discovery: A Very Dynamic Landscape

- New research tools (Azoles)
- New technologies (Imaging, BLI, ...)
- New HTS assays for *T. cruzi* (*High content*)
- New secondary screening assays
  - Tc Strains specific assays
  - Time-kill/Reversibility assay
  - Parasite stage-specific assay
- *In vivo* models translating
- Hypothesis testing
New Screening Cascade
Acceptance criteria for a new chemical series

**New series profiling**

- **Screening on T. cruzi Tulahuen WT strain (TcVI)**
  - IC₅₀ < 5 µM
  - Max. activity > 90%

- **Cytotoxicity on host cell 3T3**
  - SI > 10

**Panel of T. cruzi strains**

- Potency against all genotypes (priority to TcI, TcII, TcV and TcVI) or NO GO

- CYP51 > 10 µM, or DE-PRIORITY ISATION

- Trypomastigotes
  - Potency or DE-PRIORITY ISATION

- Time to kill
  - Fast-acting preferred

- Intellectual Property assessment → FTO

**Towards PoP**

**Primary ADME characterisation**

- *In silico* predictions of Phys/Chem properties → no predicted absorption liabilities

- Kinetic solubility (pH 2 & 6.5) > 50 µg/ml

- gLog D < 4

- CYP 3A4 inhibition (1 & 10 µM) > 10 µM

- *In vitro* metabolism (mouse LMs) 
  - $E_H < 0.5$

**PK in Balb/c mice**

- (PO 20 mg/kg and IV 1 mg/kg)

**Pre-formulation (if needed)**

**Tolerability in Balb/c**

- *In vitro* validation against *T. Cruzi* CL Brener (TcVI)

**PoP efficacy in vivo – 5 days**

- Balb/c mice infected with CL Brener (at the highest dose)
Further profiling for a successful PoP

**ADME**
- Plasma stability (mouse, rat & human)
- Plasma protein binding (mouse, rat & human)
- Permeability (Caco-2)

**Safety & Toxicology**
- Panel of mammalian cells for cytotoxicity
  - CYP screening $> 10 \mu M$
  - hERG $> 30 \mu M$
  - Mini AMES negative
  - *In vitro* Micronucleus negative
  - CEREP profiling negative
- Preliminary CV test in rat negative

**Potency**
- Reversibility in *T. cruzi* Tulahuen assay

**In vitro ADME**
- *In silico* predictions
  - KS $> 100 \mu g/mL$
  - $g\log D < 3$
  - *In vitro* metabolism $E_H < 0.3$
  - CYP 3A4 inhibition $< 50%$
  - PPB (mouse)

**In vivo efficacy**
- In vitro validation against *T. cruzi* CL Brener
  - Acute model
  - Chronic model
  - Dose – response in chronic model

**In vivo ADME**
- PO exposure in Balb/c

**In vitro efficacy – *T. cruzi* Tulahuen WT strain in 3T3**
- IC$_{50}$ $< 1 \mu M$
- Max. activity $> 95%$
- SI $> 100$

Entrance in LO
New Target Product Profile
## Chagas Disease – TPP 2015

<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</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 regions (parasitological)</td>
<td>Superiority to benznidazole standard dose to different phases of disease (acute and chronic) (parasitological)</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Superiority to benznidazole* in the frequency of definitive treatment discontinuations for medical indication (clinical and laboratory)**</td>
<td>Superiority to benznidazole* in the frequency of definitive treatment discontinuations for 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 anticoagulants drugs</td>
<td>No clinically significant interaction</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td>Oral/Parenteral (short POC)*** Age-adapted</td>
<td>Oral Age-adapted</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;30days</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>Lowest possible</td>
<td>Current treatments</td>
</tr>
</tbody>
</table>

* As per WHO recommendation; ** No genotoxicity is a condition only for NCEs; *** Need for parenteral treatment for severe disease
The Current R&D Landscape
Chagas Landscape 2015

Research » Translational » Development

Screen | Hit to Lead | Lead Opt. | Pre-clinical | Phase I | Phase IIa / PoC | Phase IIb / III | Registration | Implem

EU-FP7 Consortia
- KINDRED
- NMTryp
- PDE4NP
- A-ParaDDisE

Various Groups Worldwide
- GNF
- Eisai / Broad
- GSK / DDU
- GSK
- Anacor / UGA
- DDU
- UCSD SAR114137
- Celgene

Chagas DD Consortium

GSK Tres Cantos

LSHTM STPH LMPH

IPK Dundee Eskitis

Series from various partners and sources ongoing
- Broad
- GSK “Chagas” Box
- Sanofi
- Celgene
- others

DNDi Activities

BERENICE

DNDi only
- Pediatric Nifurtimox (Bayer)
- Adult Benznidazole (ELEA)
- BENEFIT
- STOPCHAGAS
- BENEFIT
- Fexinidazole
- Benznidazole Regimen
- Pediatric Benznidazole Pharmacovigilance
- GAP

Biomarkers

DNDi

Drugs for Neglected Diseases initiative
Initiatives Medicamentos para Enfermedades Olvidadas
Fexinidazole
A Clinical Candidate (1)

- «Nitros» are a validated compound class for their potential for Chagas Disease but have drawbacks
  - Current drugs: Benznidazole, Nifurtimox

- Reports for Fexinidazole potential for Chagas Disease
  - 2012: Very good efficacy in acute and chronic mouse in vivo models, multiple strains

- Non-genotoxic 5-Nitroimidazole
- Pre-clinical safety data available (tox, safety pharmacology)
- Well tolerated in human (Phase I)
- Currently in clinical trial (Phase II/III) for HAT
Fexinidazole
Proof-of-Concept Dose Ranging Study

Principal Investigators:
Faustino Torrico, Joaquim Gascón, Lourdes Ortiz

Sites: Bolivia and Argentina:
Plataforma de Atención Integral a los Pacientes con Enfermedad de Chagas
CEADES Bolivia/IS Global/CRESIB

INGEBI/CONICET, Buenos Aires, Argentina

Study Initiation Date: July 2014

FEXI 1200 2 wks Placebo 6 wks
FEXI 1200 4 wks Placebo 4 wks
FEXI 1200 - 8 wks
FEXI 1800 2 wks Placebo 6 wks
FEXI 1800 4 wks Placebo 4 wks
FEXI 1800 - 8 wks
FEXI matching placebo

Follow-up period
Follow-up period
Follow-up period
Follow-up period
Follow-up period
Follow-up period
Follow-up period
Follow-up period

Screening period
randomisation

8 weeks treatment
4 months additional follow-up
EOT
M4
New Treatment BNZ Regimens
Aiming to Maintain or Improve Efficacy and Increase Tolerability

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

**CURRENT BNZ THERAPY**

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Tolerability</th>
</tr>
</thead>
<tbody>
<tr>
<td>80%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Opportunities

**CURRENT BNZ THERAPY**

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Tolerability</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

- 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
**Improved Treatment Regimens of Benznidazole**

**BZN New Regimen and BZN / E1224 Combination**

**Investigators** - Dr. Sergio Sosa-Estani, Nilda Prado (ANLIS, Instituto Nacional de Parasitología “Fatala Chabén”); Dr. Faustino Torrico (Platform of Integral Care for Patients with Chagas Disease, Cochabamba, Bolivia), Dr. Lourdes Ortiz (Platform of Integral Care for Patients with Chagas Disease, Tarija, Bolivia); Dr. Joaquim Gascón (Centre de Recerca en Salut Internacional de Barcelona; CRESIB, Barcelona, Spain); Alejandro Schijman (INGEBI/ CONICET, Buenos Aires, Argentina); Dr. Rosmiro Javier Fernandez ( Hosp Independencia-Santiago del Estero).

**Sites:** Bolivia, Spain and Argentina:

Plataforma de Atención Integral a los Pacientes con Enfermedad de Chagas
CEADES Bolivia/IS Global/CRESIB

Hospital Eva Peron, Buenos Aires
INP Fatala-Chaben, Buenos Aires
Centro de Chagas, Santiago del Estero

INGEBI/CONICET, Buenos Aires, Argentina

Collaboration with Eisai, ELEA and Mundo Sano Foundation
Improved Treatment Regimens of Benznidazole
BZN New Regimen and BZN / E1224 Combination

• Double-blind, double-dummy, randomised, prospective, comparative, placebo-controlled, pharmacokinetic-pharmacodynamic and proof-of-concept study design, with nine-parallel groups.

• Adults with chronic Chagas disease, indeterminate
• Target enrolment 270 patients

• Multi-centre, multi-country study
• Sustained Parasitological Response, by PCR (3 PCRs in triplicate at each timepoint)
• 12 months of follow-up
Future Clinical Trials
Chronic Chagas Disease

- Multi-centre RCT of Nifurtimox in children
  - Bayer –sponsored
  - Assessment of efficacy and safety of Nifurtimox in children
  - 30 versus 60 days treatment
  - Historical placebo-control

- New chemotherapy regimens and biomarkers for Chagas disease - NIH project – Faustino Torrico, Joaquim Gascon, Igor Almeida

- CHICAMOCHA 3 - Equivalence of Usual Interventions for Trypanosomiasis (EQUITY) (CHICAMOCHA-3) -NCT02369978

- BERENICE project
Conclusions

Discovery
Pre-clinical Research

Close The Circle!
Hypothesis Testing
Data Generation
Clinical Validation
Access

Clinical Research
Conclusions

- Significant impact of recent clinical trial data (adults and children) on the overall Chagas disease R&D landscape.

- Moving towards a better understanding of the characteristics needed for a compound to bring forward.

- Translational Challenges are being tackled both in vitro and in vivo; Need for other compounds in clinical trial for validation.

- Recent major change/shaking of the Chagas drug discovery landscape:
  - Scientific impact
  - New «players»: GNF, GSK/DDU, Broad/Eisai, numerous academic groups and EU/FP7 consortia.
Conclusions

- Moving towards new treatments for the chronic form of Chagas Disease
  - POC studies for fexinidazole and reduced doses and duration of BNZ and Nifurtimox, in monotherapy and combination with E1224

- Support for scaling up and diagnosis of current treatment options
Thank You to All Our Partners & Donors

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