Chagas Disease: an unmet medical need

- Parasitic disease with greatest 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
Azoles and Chagas disease

Azole class of compounds: Itraconazole, Posaconazole, Ravuconazole/E1224, others
Mechanism of action: C14-demethylase inhibition

E.G. Hankins et al. / Molecular & Biochemical Parasitology 144 (2005) 68–75
E1224 (ravuconazole prodrug) Product Profile

- Water-soluble monolysine salt of a phosphonoxymethyl ether of ravuconazole
- Rapid conversion to ravuconazole (within seconds)
- Ravuconazole is the active moiety
- Broad-spectrum triazole antifungal
- Available in parenteral and oral formulations (50 and 100 mg tablets, now capsules)
- Stable product, 5 years shelf-life for tablet formulation
E1224 (ravuconazole prodrug)  
Product Profile

- Phase 2 trials of ravuconazole showed efficacy in treating mucosal Candida infections and onychomycosis in humans
  - Proof of concept for invasive aspergillosis and systemic candidiasis demonstrated in animal models
- Available in both IV and PO formulations
- Linear dose proportional increase in ravuconazole $C_{\text{max}}$ and AUC following E1224 IV and PO administration
- Little effect of food intake on ravuconazole PK parameters after E1224 PO administration
- Long plasma half life of ravuconazole (about 7 to 10 days)
- Once weekly dosing after a 3-day loading dose regimen
- Good safety profile: consistent with azole class; no visual disturbances or hallucinations
Phase 1 Key Findings

Safety

- Safety profile of oral E1224 consistent with azole class

- Liver enzyme elevations
  - Dose-related
  - Most elevations less than 3X upper limit of normal
  - Onset after Day 7 of treatment, typically between Days 10-14
  - Reversible: Resolution began upon discontinuation of drug
  - At the target dose for IFI (400 mg bid X 3 d, then 200 mg qd), elevation incidence is comparable to other triazoles
Phase I Key Findings

Safety

- **QT**
  - No QTc prolongation
  - No arrhythmias or significant, clinically relevant adverse events reported during thorough QT study

- **Other**
  - Only minor adverse events (mild or moderate in severity) occurred in all Phase 1 studies (pruritus, headache, nausea, etc.). Frequency was similar to that seen with other azoles
# Liver Enzymes: E1224 versus Placebo

<table>
<thead>
<tr>
<th></th>
<th>PLACEBO</th>
<th>E1224</th>
<th>400 mg BID X 3 days then 200 mg QD X 6-11 days</th>
<th>200 mg QD X 14 days</th>
<th>400 mg X 14 days or &gt;400 mg for &gt;3 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>19</td>
<td>105</td>
<td>46</td>
<td>8</td>
<td>51</td>
</tr>
<tr>
<td>AST/ALT/BILIRUBIN:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;ULN</td>
<td>5 (26.3%)</td>
<td>40 (38.1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1.5 X ULN</td>
<td>4 (21%)</td>
<td>20 (19%)</td>
<td>8 (17%)</td>
<td>0</td>
<td>12 (24%)</td>
</tr>
<tr>
<td>AST/ALT:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2 X ULN</td>
<td>1 (5%)</td>
<td>15 (14%)</td>
<td>5 (11%)</td>
<td>0</td>
<td>10 (20%)</td>
</tr>
<tr>
<td>&gt;3 X ULN</td>
<td>1 (5%)</td>
<td>7 (7%)</td>
<td>1 (2%)</td>
<td>0</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>&gt;5 X ULN</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Highest incidence of ALT elevations seen only with 400 mg maintenance dose – lower doses were planned for subsequent studies*
Phase 1 Key Findings

Pharmacokinetics

- E1224 PO formulation
  - High Bioavailability
  - No food effect
  - No effect on cytochrome P450 isoenzymes
- Both PO E1224 $C_{\text{max}}$ and AUC are several-fold higher than PO RAVU
- PO loading dose strategy is feasible
- Steady state reached in 3 days

![Graph showing comparison of E1224 and RAVU Cmax over time]

- E1224 400 BID/200 QD PO
- E1224 400 QD PO
- RAVU 400 QD PO

~6x
Phase 1 Key Findings

**Pharmacokinetics**

- **PO loading dose strategy is feasible**
- **3-day, daily loading dose**
- **Steady state reached in 3 days**
## Effect of Food on Ravuconazole PK

<table>
<thead>
<tr>
<th></th>
<th>E1224 600mg N=9</th>
<th>E1224 600mg N=8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fasted</td>
<td>Fed</td>
</tr>
<tr>
<td>$C_{\text{max}}$ ($\mu g/mL$)</td>
<td>Mean (SD) 8.83 (3.31)</td>
<td>8.70 (2.57)</td>
</tr>
<tr>
<td>$\text{AUC}_{0-t}$ ($\mu g\cdot hr/mL$)</td>
<td>Mean (SD) 976 (305)</td>
<td>949 (308)</td>
</tr>
<tr>
<td>$T_{1/2}$ (hr)</td>
<td>Mean (SD) 215 (72)</td>
<td>209 (57)</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (hr)</td>
<td>Mean (SD) 3.11 (0.60)</td>
<td>6.00 (1.07)</td>
</tr>
</tbody>
</table>

- Standard FDA Meal comprised of 500-600 calories from fats
- No change in $C_{\text{max}}$ or AUC
- Two-fold increase in $T_{\text{max}}$ with food
Anti/protozoal activity

- **Ravuconazole**
  - MIC 300 nM (221 ng/ml) for epimastigote form
  - MIC 1 nM (7.4 ng/ml) IC\textsubscript{50} = 0.1 nM for amastigote form
  - No effect on cell viability and proliferation at concentrations 1000-fold higher than MIC
  - Parasite strain not specified (EP and Y strains mentioned in the cited ref.)

In vitro IC$_{50}$ Ravuconazole - IPK

<table>
<thead>
<tr>
<th>Strain</th>
<th>TC serotype</th>
<th>IC$_{50}$</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dm28c</td>
<td>I</td>
<td>0.9</td>
<td>3</td>
</tr>
<tr>
<td>Y</td>
<td>II</td>
<td>0.9</td>
<td>4</td>
</tr>
<tr>
<td>ERA</td>
<td>IV</td>
<td>1.4</td>
<td>3</td>
</tr>
<tr>
<td>92.80</td>
<td>V</td>
<td>1.9</td>
<td>3</td>
</tr>
</tbody>
</table>

In general, IC$_{50}$s for Ravuconazole are around 2-10 times lower than those obtained with Posaconazole.
Background

In vivo Activity – 20-d Acute Murine Model

<table>
<thead>
<tr>
<th>Strain</th>
<th>Control (untreated)</th>
<th>Benznidazole 100 mg/kg, daily</th>
<th>Ravuconazole 15 mg/kg, b.i.d.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL</td>
<td>S: 3/12 C: 0/3</td>
<td>S: 12/12</td>
<td>S: 12/12</td>
</tr>
<tr>
<td>Y</td>
<td>S: 2/11 C: 0/2</td>
<td>S: 12/12</td>
<td>C: 9/12</td>
</tr>
<tr>
<td>Colombiana</td>
<td>S: 1/11 C: 0/1</td>
<td>S: 12/12</td>
<td>C: 7/12</td>
</tr>
</tbody>
</table>

Survival (S, survivors/total number of animals) and parasitological cures (C, negative tests/survivors), 60 days p.i.

Efficacy of E1224 treatment for 20 days in *Trypanosoma cruzi* murine model¹

<table>
<thead>
<tr>
<th>Experimental groups²</th>
<th>Number of surviving/total number of animals</th>
<th>Number of negative FBE³/number of mice</th>
<th>Number of negative blood PCR⁴ sample/number of mice</th>
<th>Total of negative assays/number of mice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uninfected</td>
<td>7/7 (100%)</td>
<td>7/7</td>
<td>7/7</td>
<td>7/7 (100%)</td>
</tr>
<tr>
<td>Untreated</td>
<td>0/7 (0%)</td>
<td>0/7</td>
<td>-⁵</td>
<td>0/7 (0%)</td>
</tr>
<tr>
<td>Bz 100 mg/kg/day</td>
<td>7/7 (100%)</td>
<td>6/7</td>
<td>6/6</td>
<td>6/7 (85.7%)</td>
</tr>
<tr>
<td>E1224 10mg/kg</td>
<td>7/7 (100%)</td>
<td>7/7</td>
<td>7/7</td>
<td>7/7 (100%)</td>
</tr>
<tr>
<td>E1224 20mg/kg</td>
<td>7/7 (100%)</td>
<td>6/7</td>
<td>5/6</td>
<td>5/7 (71.5%)</td>
</tr>
<tr>
<td>E1224 30mg/kg</td>
<td>7/7 (100%)</td>
<td>7/7</td>
<td>6/7</td>
<td>6/7 (85.7%)</td>
</tr>
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<td>7/7 (100%)</td>
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</tr>
<tr>
<td>E1224 50mg/kg</td>
<td>7/7 (100%)</td>
<td>6/7</td>
<td>6/6</td>
<td>6/7 (85.7%)</td>
</tr>
</tbody>
</table>

¹Swiss female (7/group) weight 20 to 24 g were inoculated with 5x10³ trypomastigotes (Y strain)
²Treatment was initiated at 4 days after inoculation followed by 20 days and it was administered per oral route.
³FEB - fresh blood examination performed before and after cyclophosphamide immunosuppression
⁴PCR assay was performed in the 1st and 6th month after treatment
⁵All mice died before 30 days of infection
Focus on dosing regimens that would maximize the probability of parasite eradication while also being optimally safe for the subjects.

Phase 1 data: Liver enzyme elevations were not seen with total loading doses of less than 2400 mg or given as 400mg per week for 12 weeks.

Achieving high $C_{\text{max}}$ concentrations and reaching steady state rapidly leads to rapid killing and sustained parasite eradication.

Duration of treatment was based on the standard of care for chronic indeterminate Chagas disease treatment of eight weeks of benznidazole therapy.
Rationale for E1224 Dose Selection for Chagas Disease

E1224’s long half-life permits novel dosing regimens:
• PK models show that a 3-day loading dose followed by doses given 1 day per week (weekly therapy) provides favorable PK

CD PK/PD Driver Assumption:
-Free AUC/MIC is the key PD parameter

• Y strain amastigote
  Dose: 400 BID LD then 200 mg QD MD
  • AUC/MIC = 1,045,793
  • MIC = 7.4 ng/mL
  • Free AUC/MIC = 31,372

400 mg QD (Days 1-3), then start weekly 400 mg x 12 weeks

400 mg QD (Days 1-3), then start weekly 200 mg x 12 weeks
E1224 - Phase 2 trial
Early development, proof-of-concept evaluation

- **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 Integral al Paciente de Chagas, Instituto de Investigaciones Biomédicas, Facultad de Medicina, Universidad Mayor San Simón CEADES, Cochabamba; Universidad Autonoma Juan Misael Saracho, Tarija, Bolivia

- **PI:** Drs. Faustino Torrico and Joaquim Gascón
Phase 2 Study Design

- **Efficacy based on repeated PCR and candidate biomarkers**
- **Population PK Analysis included**

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**Screening period**

- **Randomisation**
  - E1224 high-dose arm (double-blind) N = 46
    - No treatment follow-up period
  - E1224 low dose arm (double-blind) N = 46
    - No treatment follow-up period
  - E1224 Short-dose arm N N = 46
    - No treatment follow-up period
  - Benznidazole tablets (open-label) N = 46
    - No treatment follow-up period
  - E1224 matching placebo (double-blind) N = 46
    - No treatment follow-up period

- **8 weeks treatment** (60 days for BZN)

- **10 months additional follow-up**

- **EOT**
  - M4
  - M6
  - M12
E1224 - Project Organisation

DNDi: Scientific Coordination & Project Management

Eisai, US Clinical Team, QA and PV

R. Tarleton
Univ Georgia, US
MultiplexSerodiagnostic

I. Almeida
Univ Texas, US
Lytic Abs

CoreLabPartnerR
Rockville, US
CRO Central
Holter and EKG

Cardinal CRO
Data Management; Statistics

CRESIB, Spain
Co-PI
BNP, Prothrombotic Agent Analysis

Eisai, Japan
Project Leader,
Manufacturing

Plataform CBBA-Barcelona, Bolivia
Co-PI, recruitment and Fup, PCR

NUDFAC, Recife
PK Sample Analysis

A. Schijman,
CONICET PCR QA
Genotyping

External QA: Sunnikan & others
- Number of patients offered study participation: 820
- Number of patients screened: 560 (53% in Cbba; 47% in Tarija)
- Number of patients included: 231 (June 26th LPI)
- Causes of screening failure: 20% biochemical alterations; 20% PCR negative; 16% other (EKG, positive pregnancy tests, abnormal labs).
Key Project Milestones

**Milestone 1**
- Completion of 50% Phase 2 POC study recruitment – total of 115 patients

**Milestone 2**
- Evaluation of primary efficacy and safety endpoint of Phase 2 POC clinical study (EOT) – Q4 2012
- Initiate preparatory activities for Phase 3 clinical trial – Q4 2012

**Decision point:** Preliminary analysis of primary efficacy and safety will be performed to determine the initiation of Phase 3 clinical trial preparations.

**Go decision:** if at least one regimen of E1224 shows superior efficacy in comparison to placebo and no significant safety concerns are identified.

**No go:** if no regimen of E1224 is superior to placebo and/or significant safety concerns are identified.
Key Project Milestones

**Milestone 3**

- End of 12 months follow-up in Phase 2 clinical trial – Q2 2013

**Decision point:**

- Analysis of sustained response and safety to determine the initiation of Phase 3 clinical trial, dose selection, and decisions regarding pediatric investigations and/or combination therapy.
- Results to be integrated with available information from other clinical trials on azole compounds.

**Go decision:** if at least one regimen of E1224 shows a favorable sustained treatment response in comparison to placebo and no significant safety concerns are identified.

**No go:** if no regimen of E1224 is superior to placebo and/or significant safety concerns are identified.

- Decision matrix adjusted based on availability of results of other azole clinical trials and success measurements developed in the context of this project.
Obrigada a todos os colaboradores, doadores e pacientes!

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