Titles: “A new treatment for Chagas disease” and “Mycetoma Treatment, Fosravuconazole Clinical Trial”
Eisai declared to supply DEC tablets until LF elimination.

The majority of all the listed projects are funded by GHIT.
Fosravuconazole Development History

• Developed rauconazole in 1995
  – Demonstrated potent in vitro antifungal activity against various fungal species and in vivo efficacy in animal models of infection
  – Initially available only in an oral formulation
  – Clinically effective in three Phase 2 efficacy studies and one Phase 2 prophylaxis study
    • Oropharyngeal Candidiasis, Esophageal Candidiasis, Onychomycosis, Prophylaxis against fungal infections

• Developed fosravuconazole in 2007
  – A water-soluble prodrug of rauconazole
  – Increased dramatically solubility in water and oral bioavailability

• DNDi and Eisai signed a collaboration and license agreement for the clinical development of fosravuconazole for the treatment of Chagas disease and eumycetoma in 2009 and 2015.
Features of fosravuconazole: New Azole Antifungals
-Ergosterol biosynthesis inhibitor-

- High solubility in water
- High oral bioavailability
- Rapidly converting to ravuconazole, providing high plasma concentration of ravuconazole after administration
- Long half-life 7.7 to 10.5 days allowing once a week administration

Both IV and oral formulation

Fosravuconazole (E1224) (pro-drug)

Ravuconazole (active moiety)
Triazoles show promise for the treatment of Chagas Disease:

- *Leishmania* and *Trypanosoma* parasites produce ergosterol-related sterols by a biosynthetic pathway similar to that in pathogenic fungi.
- They have been shown to be susceptible to sterol biosynthesis inhibitors in vitro.
- Potent *in vitro* inhibitors of *T. cruzi* growth
  - Ravuconazole caused amastigote growth inhibition at 1 nM concentration
- Efficacy demonstrated in *in vivo* mouse and dog models of infection
- Potential companion drugs for combination therapy
  - Potential to minimize the toxicity of benznidazole and nifurtimox

*In vitro* activity against amastigote proliferation in Vero cells

*In vivo* activity in a murine model of acute Chagas disease

Project Goals and Background
A new treatment for Chagas Disease

- Objectives:
  - Conduct of a phase II proof-of-concept study for evaluation of efficacy and safety of the E1224
  - Implement development activities to support registration:
    - CTM preparation; In-kind contribution with Eisai
      - Manufacturing, Stability testing, Process validation
    - pre-clinical distribution, metabolism, pharmacokinetics studies;
    - as well as, toxicology studies

Molecular formula: \( C_{23}H_{20}F_2N_4O_8PS \cdot C_6H_{14}N_2O_2 \cdot C_2H_6O \)
Molecular weight: 739.73 (the molecular weight of free acid is 547.47)
Phase 2 Monotherapy data


**Graph:**
- X-axis: Time (days)
- Y-axis: Mean qPCR
- Lines represent different treatment groups:
  - **Plc**: placebo
  - **BNZ**: benznidazole (300 mg/day for 8W)
  - **LD**: low dose of E1224 (200 mg/week for 8W)
  - **HD**: high dose of E1224 (400 mg/week for 8W)
  - **SD**: short dose of E1224 (400 mg/week for 4W)

**Recurrence**
BENDITA - BEznidazole New Doses Improved Treatment and Associations

- 210 subjects - 30 patients/arm
- Futility stopping rule
- 12-week interim analysis

Proof-of-Concept BZN New Regimen and BZN / E1224 Combination

Follow-up at 10 wk, 12 wk, 4M, 6M, 12 M

Primary endpoint at 6M

Global Health Innovative Technology Fund
Ravuconazole showed ≥16-fold higher activity (MIC$_{50}$ and MIC$_{90}$) than those of other antifungal compounds against Madurella mycetomatis which is the most common etiologic agent of eumycetoma worldwide.
### Fosravuconazole vs Itraconazole

**Similar MOA:** inhibition of ergosterol biosynthesis

<table>
<thead>
<tr>
<th>Fosravuconazole</th>
<th>Itraconazole</th>
</tr>
</thead>
</table>
| **In vitro Antifungal Activity** | • In vitro Antifungal Activity  
  – 16-fold stronger than itraconazole |
| **Human PK** | • In vitro Antifungal Activity  
  – 16-fold weaker than ravuconazole |
|  
  – Long half-life 7.7 to 10.5 days allowing once a week dosing  
  – no food effect  
  – moderate inhibitor of CYP3A4 |  
  – Half life 1.5-2 days  
  – after meal  
  – strong inhibitor of CYP3A4 |
| **Skin levels (rat, monkey): ≥1.2 x blood level** |  
  – Skin levels (humans): 0.5-2.0 x plasma level |
| **Clinical data** | **Clinical data** |
|  
  – No data in Eumycetoma |  
  – very limited data in eumycetoma  
  ✓ One publication N=13 patients:  
    Efficacy; 1 cured, 9 partial response  
    • 400 mg 12 months  
    • low cure rate: < 5%  
    • no major difference in improvement between Month 6 and Month 12 |

The most potent and promising candidate
Close Relationship with DNDi

✔ Very hard to conduct the clinical studies by a Japanese pharmaceutical company alone in the Neglected Tropical Diseases fields.

✔ Clearly needed to collaborate with PDP, such as Drugs for Neglected Diseases initiative (DNDi) etc.

➢ Advantages for activities in collaboration with DNDi

– Open the door to conduct clinical studies in endemic regions
  • Chagas disease: South America (Bolivia)
  • Mycetoma: Africa (Sudan)

– Open the door for building a network with experts in clinical sites
  • Professor Fahal in MRC (Sudan) etc
Lessons learned & Comments to GHIT Fund

Lessons learned

• The critical issue of CTM supply will be warranty expiration of CTM due to the lengthy delays of clinical studies in developing country. The information exchange frequently and deeply between supply site and clinical site would be essential.

• The clinical trials for Chagas disease was delayed because the supply of BZN was unsteady in some situations.

Comments to GHIT Fund

• We are grateful that GHIT Fund decided to offer the grants to Phase III projects up to a ceiling of half of all budget, and expect further grant funding of GHIT Fund.

• We hope GHIT to continuously makes efforts to mitigate funding gap. For example, 1) could GHIT shorten the review period for proposals?, or 2) could GHIT retroactively cover costs in the funding gap period when next proposal is approved?
Thank you for your attention!

We have a lot of opportunities to collaborate with all scientists and researchers all of the world in Global Health field.

Eisai Co., Ltd.