GHIT R&D Forum

December 8th, 2017 at Tokyo Garden Terrace Kioi Conference

Titles: “A new treatment for Chagas disease” and “Mycetoma Treatment, Fosravuconazole Clinical Trial”

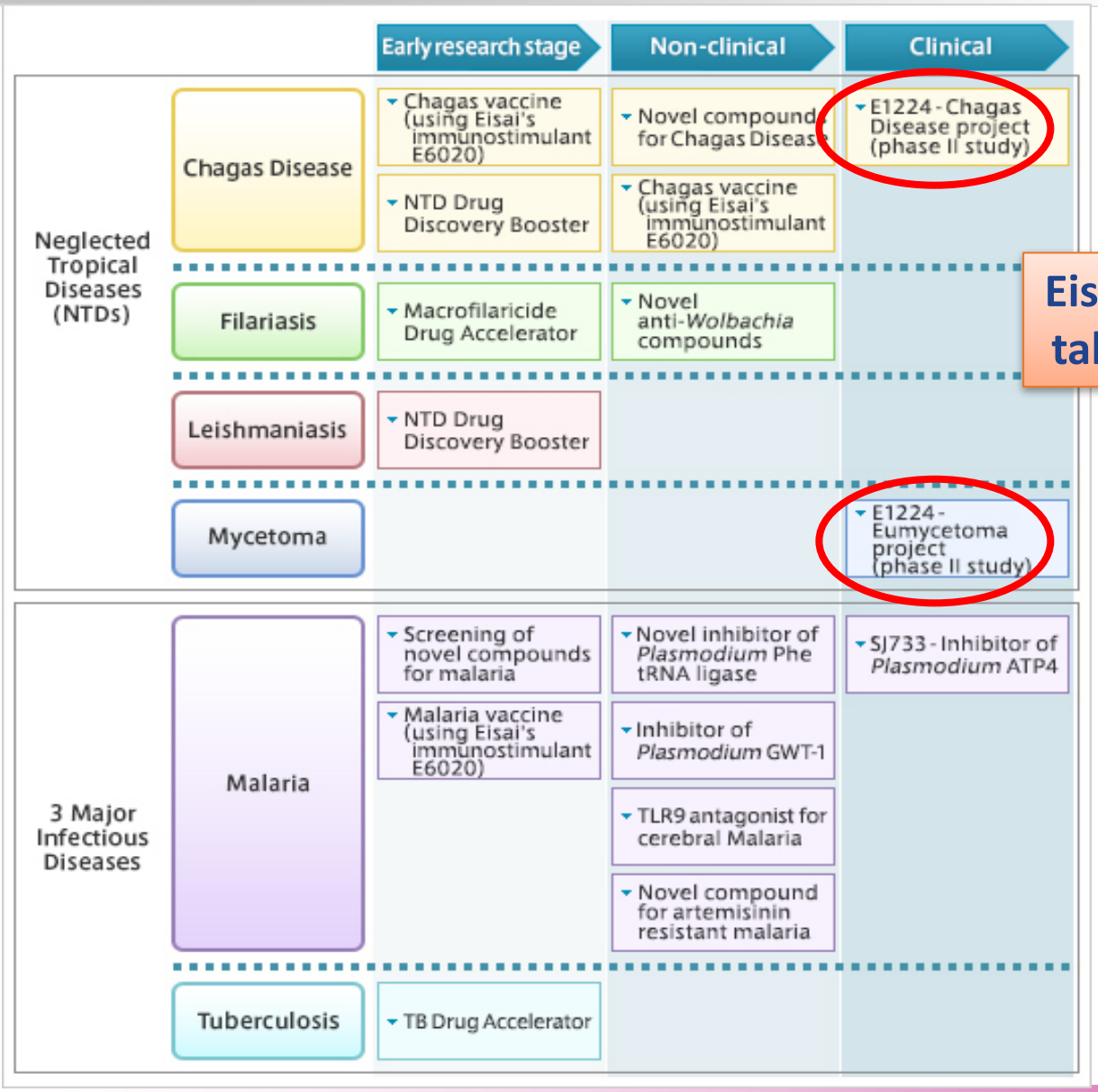
Eisai Co., Ltd.

December 8, 2017

Katsura Hata

Global Health Research Section

NTDs/Three Major Infectious Diseases Research Project Portfolio in Eisai



Eisai declared to supply DEC tablets until LF elimination.

The majority of all the listed projects are **funded by GHIT**.

Fosravuconazole Development History

- **Developed ravuconazole 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 ravuconazole
  - 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.**

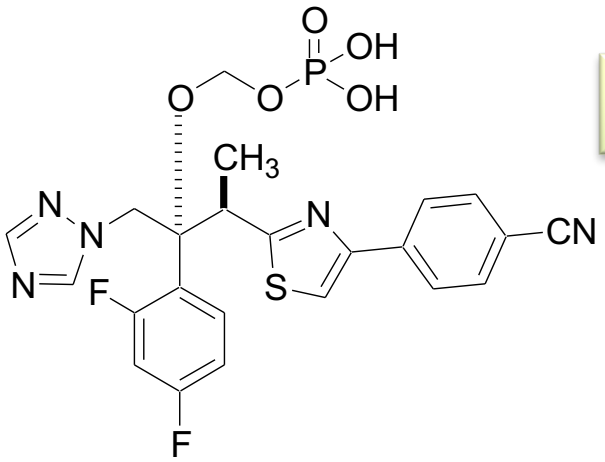
Features of fosravuconazole: New Azole Antifungals

-Ergosterol biosynthesis inhibitor-

- High solubility in water
- High oral bioavailability

→ Both IV and oral formulation

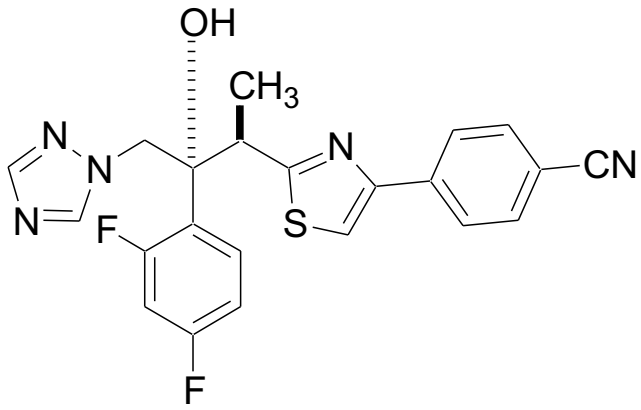
- Rapidly converting to ravuconazole, providing high plasma concentration of ravuconazole after administration
- Long half-life 7.7 to 10.5 days allowing once a week administration



Fosravuconazole (E1224)
(pro-drug)

Alkaline phosphatase

in the body

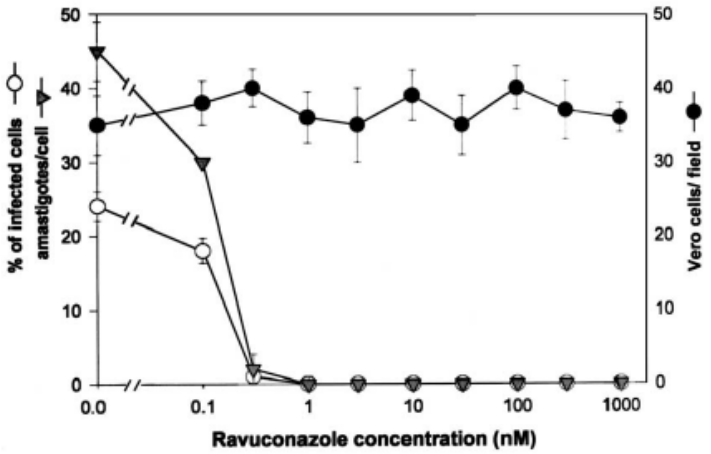


Ravuconazole
(active moiety)

Fosravuconazole as Antiprotozoal Agents

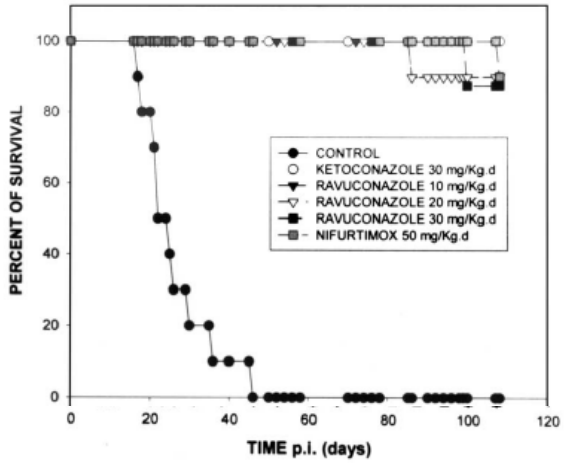
Triazoles show promise for the treatment of Chagas Disease:

- ✓ *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**

.A. Urbina et al. / International Journal of Antimicrobial Agents 21 (2003) 27–38



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

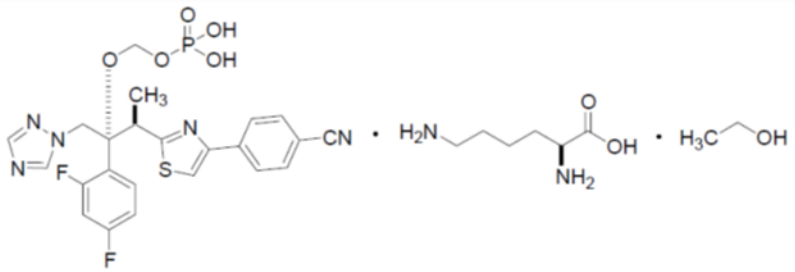
J. A. Urbina et.al.,
Int. J. Antimicrob. Agents
21: 21-38, 2003

Project Goals and Background
A new treatment for Chagas Disease

DND*i*

- **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

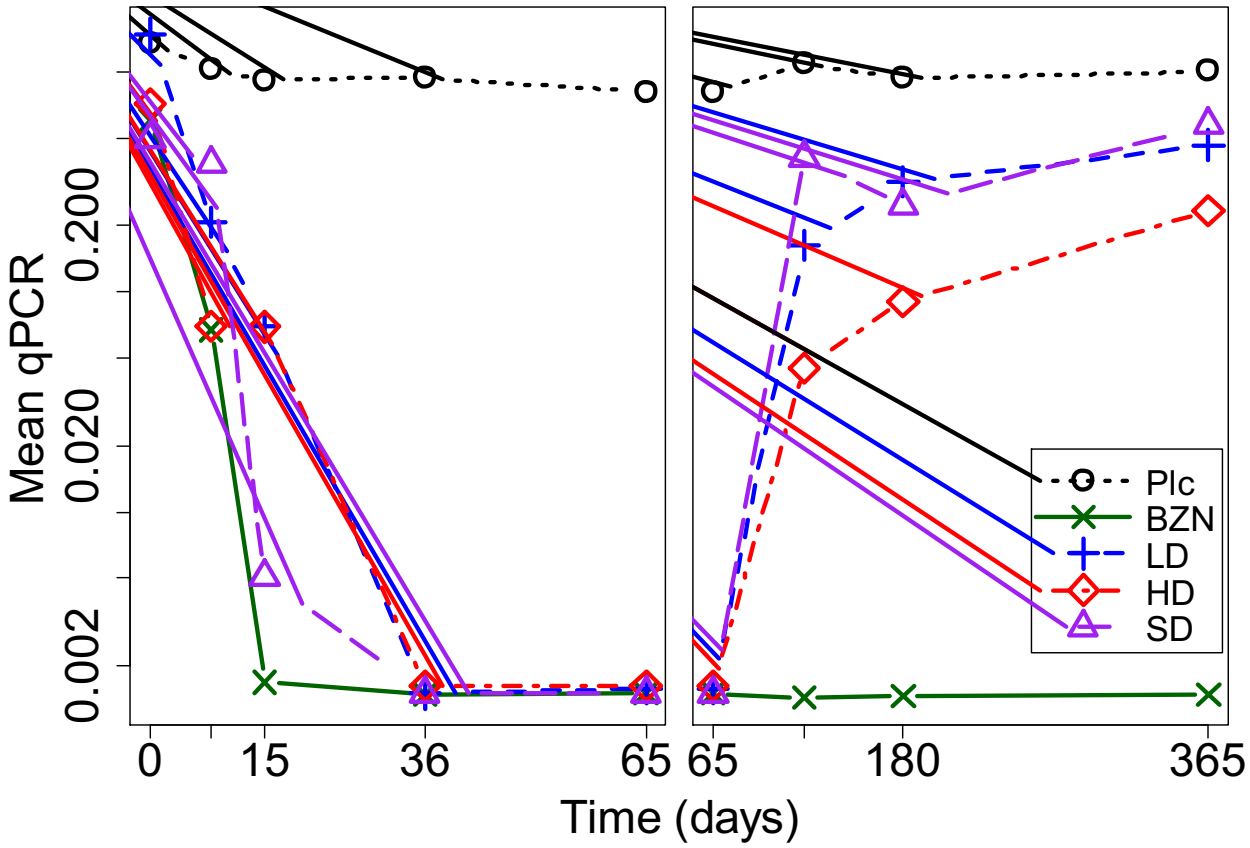
Eisai



Molecular formula: $C_{23}H_{20}F_2N_5O_5PS \cdot C_6H_{14}N_2O_2 \cdot C_2H_6O$
Molecular weight: 739.73 (the molecular weight of free acid is 547.47)

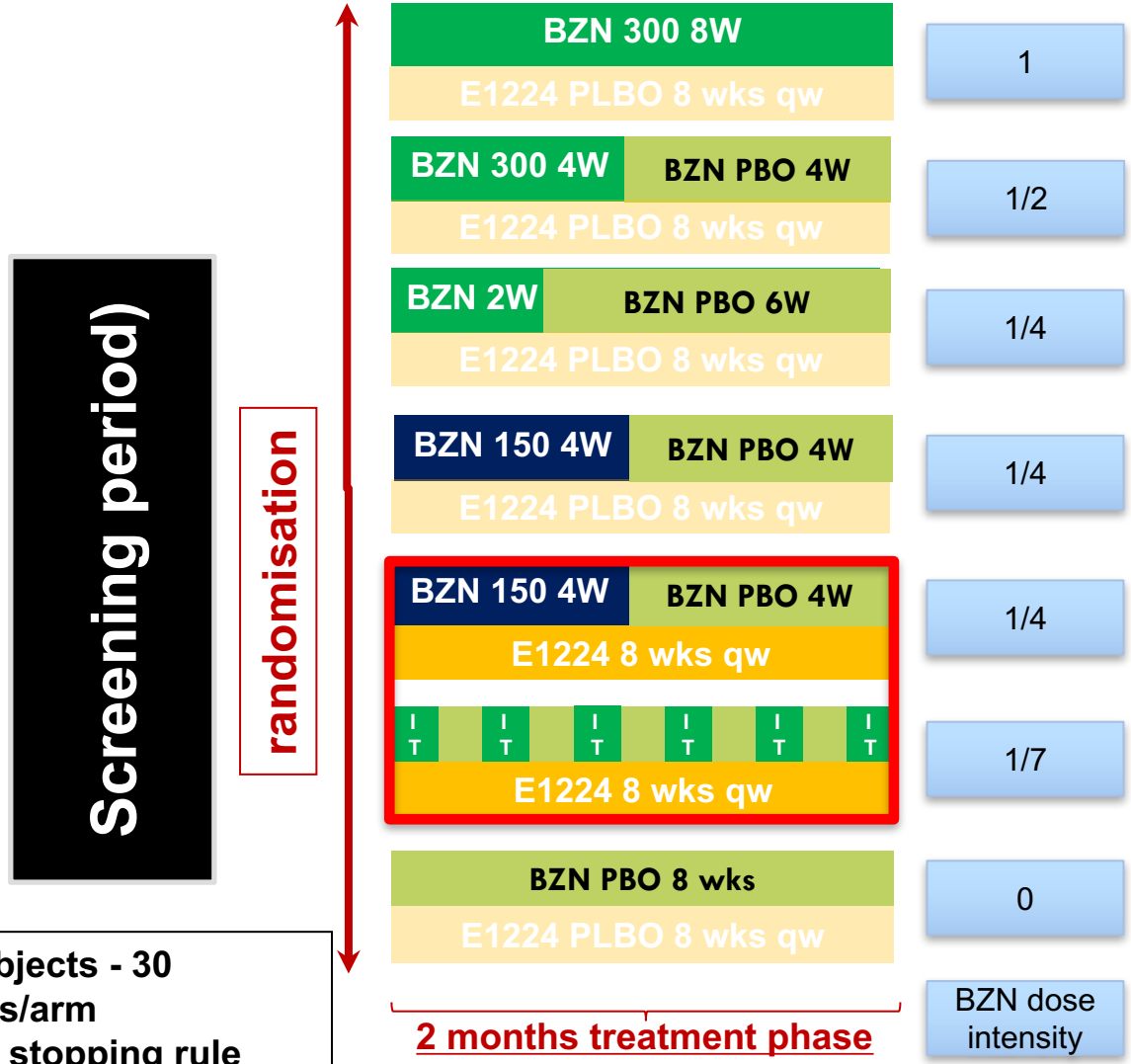
Phase 2 Monotherapy data

- F. Torrico et al. Treatment of adult chronic indeterminate Chagas disease: proof-of-concept randomized placebo-controlled study of benznidazole and three E1224 dosing regimens. *Lancet Infect Dis* 2017: in print



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

BENDITA - BEnznidazole 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

GHIT Fund
Global Health Innovative Technology Fund

In vitro Activity of ravuconazole against *M. mycetomatis*

Table 1. *In vitro* susceptibility of *Madurella mycetomatis* to ketoconazole, itraconazole, and ravuconazole.

Antifungal agent	GM[a] MIC (μg/ml)	MIC Range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
Ketoconazole	0.072	0.031–0.25	0.063	0.25
Itraconazole	0.063	≤0.016–0.5	0.063	0.25
Ravuconazole	0.005	≤0.002–0.031	0.004	0.016

[a]GM, geometric mean.
doi:10.1371/journal.pntd.0002942.t001

PLOS Neglected Tropical Diseases. 2014. 8:1-4
Antimicrob. Agents Chemother. 2012. 56:6054–6056
Antimicrob. Agents Chemother. 2004. 48:2742–2746
Antimicrob. Agents Chemother. 2005. 49:1364–1368
Antimicrob. Agents Chemother. 2010. 54:2738–2740
Antimicrob. Agents Chemother. 2011. 55:1771–1773

Antifungal susceptibility

Antifungal	MIC_{50} (range) μg/ml	Antifungal	MIC_{50} (range) μg/ml
Ketoconazole	0.125 (<0.01-1)	Amphotericin B	2 (<0.01-4)
Itraconazole	0.06 (<0.01-0.5)	Terbinafin	8 (1->16)
Posaconazole	0.06 (<0.03-0.125)	5-flucytosine	>128 (<128)
Fluconazole	16 (0.25->128)	Caspofungin	128 (16->128)
Voriconazole	0.125 (<0.01-1)	Anidulafungin	>128 (0.5->128)
Isavuconazole	0.06 (<0.01-0.125)	Micafungin	>128 (8->128)
Ravuconazole	0.004 (<0.002-0.03)		

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

Fosravuconazole

- **In vitro Antifungal Activity**
  - 16-fold stronger than itraconazole
- **Human PK**
  - Long half-life 7.7 to 10.5 days allowing once a week dosing
  - no food effect
  - moderate inhibitor of CYP3A4
- Skin levels (rat, monkey): ≥1.2 x blood level
- **Clinical data**
  - No data in Eumycetoma

The most potent and promising candidate

Itraconazole

- **In vitro Antifungal Activity**
  - 16-fold weaker than ravuconazole
- **Human PK**
  - Half life 1.5-2 days
  - after meal
  - strong inhibitor of CYP3A4
- Skin levels (humans): 0.5-2.0 x plasma level
- **Clinical data**
  - 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

Close Relationship with DND*i*

- ✓ 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* (DND*i*) *etc*.

➢ Advantages for activities in collaboration with DND*i*

- 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.