GHIT R&D Forum
Session 4: Propelling R&D for late-stage projects

Clinical Development of E1224
“A New Treatment for Chagas Disease” &
“Myctoma Treatment, Fosravuconazole Clinical Trial”

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Chagas Disease – Unmet Medical Need


- Most common parasitic disease in the Americas
- Endemic in 21 countries / 6-8M infected / 70M at risk
- Largest disease burden in chronic indeterminate patients
- 20-30% will evolve to cardiomyopathy with important morbidity and mortality
- Currently only 2 registered compounds: BZN and nifurtimox

< 18,000 patients treated/year

Estimated prevalence segmented by age group

<table>
<thead>
<tr>
<th>Region</th>
<th>Age group</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endemic Area</td>
<td>&lt; 1 year</td>
<td>10,584</td>
</tr>
<tr>
<td></td>
<td>1 to 5 years</td>
<td>113,424</td>
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<tr>
<td></td>
<td>5 to 15 years</td>
<td>420,801</td>
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<tr>
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<td>15 to 20 years</td>
<td>331,607</td>
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<tr>
<td></td>
<td>Adults</td>
<td>2,643,920</td>
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<tr>
<td>Total Endemic Area</td>
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<tr>
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<td>1 to 5 years</td>
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<tr>
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<td>5 to 15 years</td>
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<td>15 to 20 years</td>
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<td>Adults</td>
<td>2,988,189</td>
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<tr>
<td>Total Non-Endemic Area</td>
<td>&lt; 1 year</td>
<td>16,683</td>
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<tr>
<td></td>
<td>1 to 5 years</td>
<td>195,496</td>
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<tr>
<td></td>
<td>5 to 15 years</td>
<td>849,859</td>
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<tr>
<td></td>
<td>15 to 20 years</td>
<td>728,667</td>
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<tr>
<td></td>
<td>Adults</td>
<td>5,632,109</td>
</tr>
<tr>
<td>Endemic + non-endemic</td>
<td>&lt; 1 year</td>
<td>16,683</td>
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<td></td>
<td>Adults</td>
<td>5,632,109</td>
</tr>
<tr>
<td>Total Endemic + Non-endemic Area</td>
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<td>7,422,814</td>
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</table>
Improved Treatment Options are Needed for all Stages of Chagas Infection

- Current available treatments are more than 40 years old
  - Good efficacy in the acute phase, but need to be used in long regimens and cause significant side effects

→ The efficacy and safety of shorter treatment courses and/or at lower doses need to be explored
→ New drugs and new combinations are also needed

**DNDi aims to deliver:**

- **Alternative regimens of existing drugs** (lower doses, shorter duration, combinations)
- **A safe and efficacious new drug treatment** of chronic Chagas patients, ideally efficacious for acute Chagas patients, also safe to use during pregnancy
- **An early test of cure** and/or markers of therapeutic response
On-going Project:
A new treatment for Chagas Disease (in Bolivia)

Objective & Goal
Evaluate new therapeutic regimens of benznidazole, in monotherapy and in combination with fosravuconazole, for the treatment of adult patients with chronic indeterminate Chagas disease

Partnership
Eisai Co., Ltd. (Japan), Collective of Applied Studies and Social Development (CEADES) (Spain/Bolivia), Platform of Integral Care for Patients with Chagas Disease, (Bolivia), Universidad Mayor de San Simon, Bolivia; Universidad Autónoma Juan Misael Saracho, (Bolivia)

❖ Eisai and DNDi signed a collaboration and license agreement for the clinical development of Chagas Disease in 2009

→ The Lancet published in 2009 an article that announces the start of the clinical trial highlighting the partnership between Eisai and DNDi (Vol. 374, October 31. 2009)

“The 1st drug in 40 years of a new drug for this disease”
BENDITA overall design

- Adults (18 – 50 years old) at Chronic Indeterminate CD stage
- 210 subjects - 30 patients/arm

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

Primary endpoint at 6M

Follow-up until 12M

- Futility stopping rule
- 10 and 12-week interim analysis (safety and efficacy)

2 months treatment phase
Recruitment Finalized

All Patients finalized treatment

Patients in follow-up: 208 (treatment completed)
Next steps

- **2017**
  - DSMB Safety IA (20% at 10 weeks)

- **2018**
  - End of 6M Follow-up
  - DSMB Efficacy and Safety review
  - 6M analysis

- **2019**
  - Go/ No go for Phase 3
  - End of 12M F-up
  - Topline report
  - CSR Publication around Q4 2019

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DNDi | Drugs for Neglected Diseases initiative
Mycetoma – Neglected Unmet Medical Need

Definition: Chronic infection of subcutaneous tissues that has two different forms:

1) Actinomycetoma: bacterial infection with a >90% cure rate using antibiotics
2) Eumycetoma: fungal infection, endemic in Africa, is much more difficult to treat

[Symptoms]
- Feet become very swollen and disfigured. This slow-growing disease causes little pain and consequently people delay seeking treatment until the disease has reached the later stages, when amputation is often necessary - stigmatized
- If untreated, it gradually deteriorates into a serious condition, which can be fatal.

[Impact]
- Basic epidemiological information is lacking, global burden remains unknown
- The Mycetoma Research Centre (MRC) in Khartoum, Sudan, has recorded around 6,500 patients since 1991 – most patients are young and poor
- Actinomycetoma (bacterial form) has a 90% cure rate while the eumycetoma (fungal form) cure rate is only 25-35%

In 2016, Mycetoma was added to the 18th disease of the WHO list of NTDs

DNDi strongly advocated for Mycetoma to be included in the list
Mycetoma – Neglected Unmet Medical Need

[Geography]
- Endemic in tropical and subtropical regions – cases reported in 50 countries
- “Mycetoma Belt” between latitude 30° North and 15° South

[Transmission]
- Currently no definitive theory about the route of transmission
- The infection may come from the soil or animal dung, and it is thought that it enters the body after the skin has been pricked (e.g. by a thorn)

[Patient Needs]
- The current treatment is long, ineffective, expensive and have serious side effects (the median treatment duration is 12 months, and more than $2,000 /year)
- No point-of-care diagnostic test

DNDi aims to deliver:

A new safe, effective, and affordable treatment for patients with limited eumycetoma
On-going Project: Mycetoma Treatment, Fosravuconazole Clinical Trial (in Sudan)

Objective & Goal

Conduct a randomized controlled clinical trial (phase II study) to investigate the efficacy of Fosravuconazole (E1224) compared to the current treatment, Itraconazole

- Fosravuconazole, under development for Chagas disease, which has been shown to have potent in vitro activity against Madurella mycetomatis
- Its pharmacokinetic properties are favorable and its toxicity is low

Study design

N total = 138

Primary end-point will be complete cure at the 12-month as evidenced by:
- clinical assessment showing absence of mass, sinuses and discharge
- normal ultrasonic / MRI examination, or
- the presence of fibrosis only + negative fungal culture from a surgical biopsy

Measurements:

Clinical: diameter of the lesion, number of sinuses, presence of discharge

Imaging: 3D scanning with independent review

Radiological: MRI, ultrasound

Microbiology: demonstration of M. mycetomatis by PCR through fine needle aspiration and culture.

PK/PD

Additional 12 months follow-up if success / maintenance of response
Mycetoma Treatment, Fosravuconazole Clinical Trial
Conduct of Study and Next Steps

**Conduct**

- Mycetoma Research Centre Khartoum, a WHO Collaborative Centre
- Subjects 18 years or older
- Single eumycetoma lesion ≥ 2 cm and <10 cm in diameter caused by *Madurella mycetomatis* confirmed by PCR
- Target: 6-10 participants per month -> field visits by mobile teams / active screening
- Started enrolling patients in May 2017
- No surgical medical treatment before

**Next steps**

- Eisai intends to continue supporting the development of E1224 including the drug product supply (clinical trials) needed for regulatory approval
- Continuing to engage with endemic countries NRAs and Policy makers for most appropriate approval strategy /unmet medical need
يوجد مرض الميسوما بصورة منتشرة في السودان، الاسم المحلي لهذا المرض هو ميسوما أو الميد. يمكن أن يتسبب المرض في تهيج الجسم، الإعتداء، أو الموت إذا لم يتم علاجه. يصعب علاج النوع الفطري من مرض الميسوما. يقوم الآن بإجراء دراسة لمقترنة دواء يسمى "الدواء المستخدم حاليا في علاج الميسوما في السودان المسمى Fosravuconazole.itracanazole".

إذا وافقنا أن تكون هذه الدراسة، سيتم الطبخ بتسجيل معلوماتك وإجراء بعض الفحوصات. معظم الفحوصات وروتينية مثل أخذ عينة (بيضاء) أو (معلقة) عينك. إذا توقفت على الأدوات الم傀مة "سيسكات الطبيب أو طفلك". نأتي مرض مع توضيح أخذك (أو طفلك) في علاج.

سيتم الكشف عليه (أو طفلك) وذلك يشمل حساب عدد صورات القلب، ضغط الدم، الطول و الوزن.

سيتم إجراء عينة للمعل لتأكيد الميسوما. سيتطلب ذلك اخذ صورة أشعة سونائية و رنين.

سيقوم بأخذ 23 مل من الدم (حوالي ملعقتين طعام) لفحص.
Mycetoma Treatment, Fosravuconazole Clinical Trial

**Partnership**

Eisai Co., Ltd. (Japan), Mycetoma Research Centre (MRC) / Institute of Endemic Diseases (IEND), Khartoum University, Khartoum, Sudan, Erasmus Medical Center (The Netherlands)

- Eisai and DNDi signed a collaboration and license agreement for the clinical development of eumycetoma in 2015: Long-standing partnership with Eisai was essential
- The MRC has been collaborating with WHO (MRC is a WHO Centre) that gave the disease political prominence in 2016 by adding it to the list of NTDs
- Knowledge and insights relative to the disease and the affected population provided by the MRC are critical to have a better idea of what is actually needed in the field

**Challenges**

- Enrollment of patients has been slow due to various reasons including the rainy season, the inclusion criteria that are quite strict
- Informed consent form is difficult for local patients to understand (8 pages) we are examining a way to make it more patient-friendly
DNDi wishes to congratulate GHIT Fund for its brave decision to let us take the first step together toward finding a new treatment for patients with Mycetoma, for which no global surveillance systems exist and therefore very little is known currently.
Thank you to all our Donors and Partners

www.dndi.org
www.dndijapan.org