GHIT R&D Forum

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

Clinical Development of E1224 "A New Treatment for Chagas Disease" & "Mycetoma Treatment, Fosravuconazole Clinical Trial"

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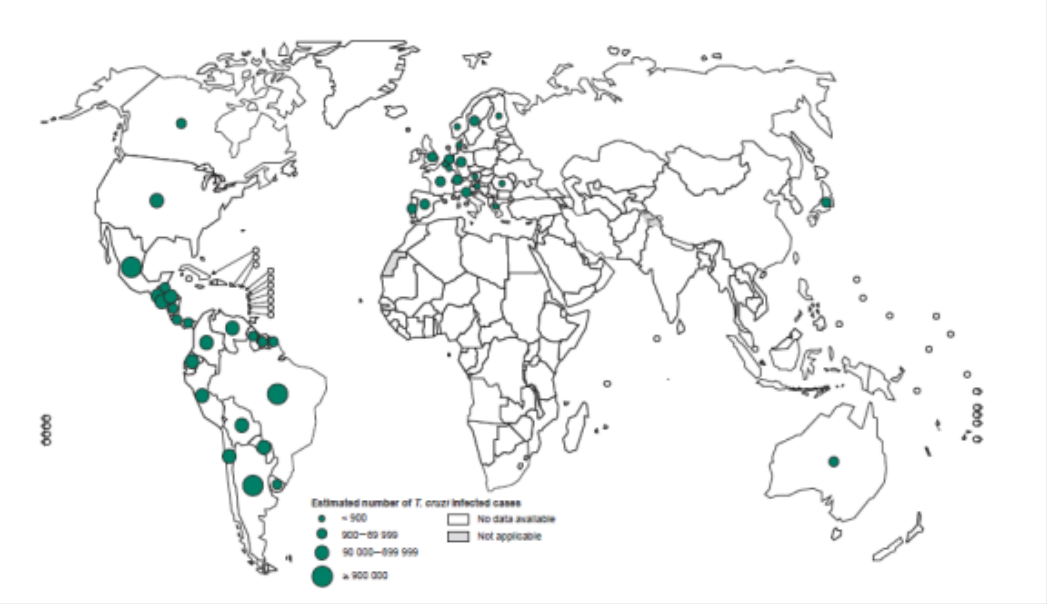
Chagas Disease – Unmet Medical Need

Distribution of cases of *T. cruzi* infection, based on official estimates, worldwide, *2010–2013 (WHO, 3rd NTD report, 2015)*



- 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		
Region	**Age group**	2010
Endemic Area	< 1 year	10,584
	1 to 5 years	113,424
	5 to 15 years	420,801
	15 to 20 years	331,607
	Adults	2,643,920
Total Endemic Area		3,520,337
Non-endemic	< 1 year	6,099
	1 to 5 years	82,072
	5 to 15 years	429,058
	15 to 20 years	397,059
	Adults	2,988,189
Total Non-Endemic Area		**3,902,477**
Endemic + non-endemic	< 1 year	16,683
	1 to 5 years	195,496
	5 to 15 years	849,859
	15 to 20 years	728,667
	Adults	5,632,109
Total Endemic + Non-endemic Area		**7,422,814**

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

DND*i* 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 DND*i* 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**

Screening period

randomisation

BZN 300 8W
E1224 PBO 8W

BZN 300 4W | BZN PBO 4W
E1224 PBO 8 W

BZN 300 2W | BZN PBO 6W
E1224 PBO 8 W

BZN 150 4W | BZN PBO 4W
E1224 PBO 8W

BZN 150 4W | BZN PBO 4W
E1224 8W

I T | I T | I T | I T | I T | I T
E1224 8W

BZN PBO 8W
E1224 PBO 8W

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

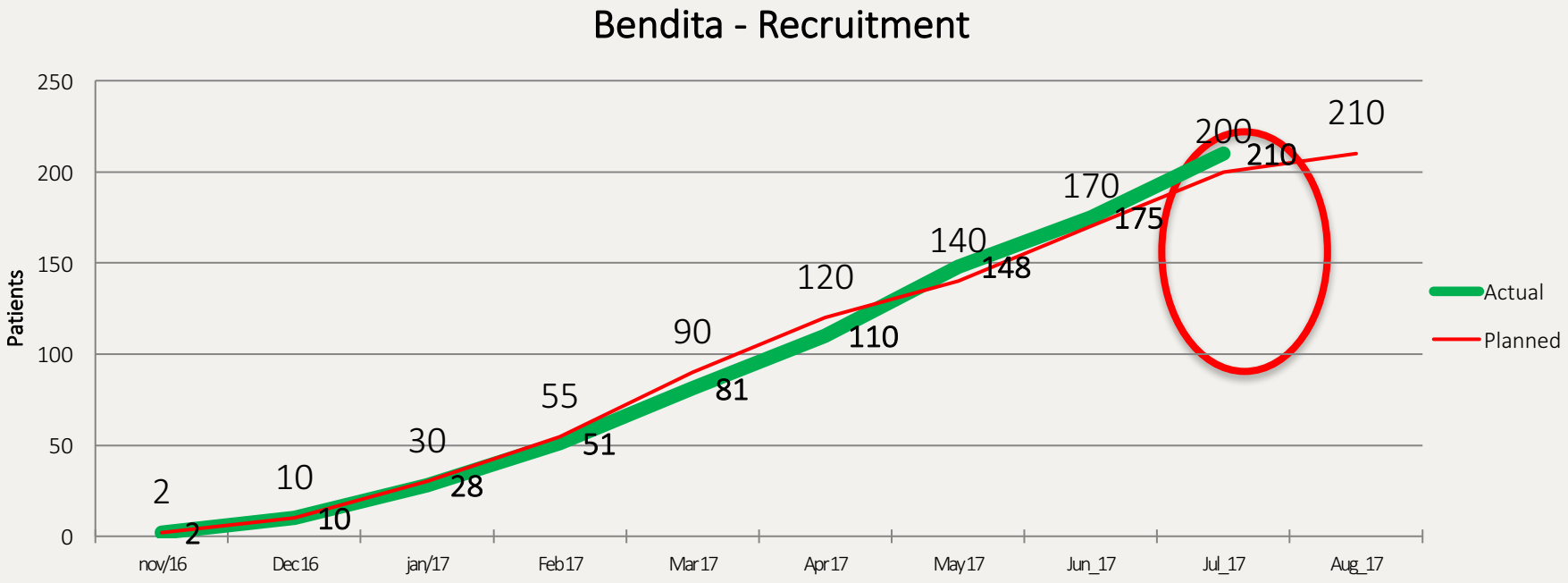
Primary endpoint at 6M

Follow-up until 12M

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

2 months treatment phase

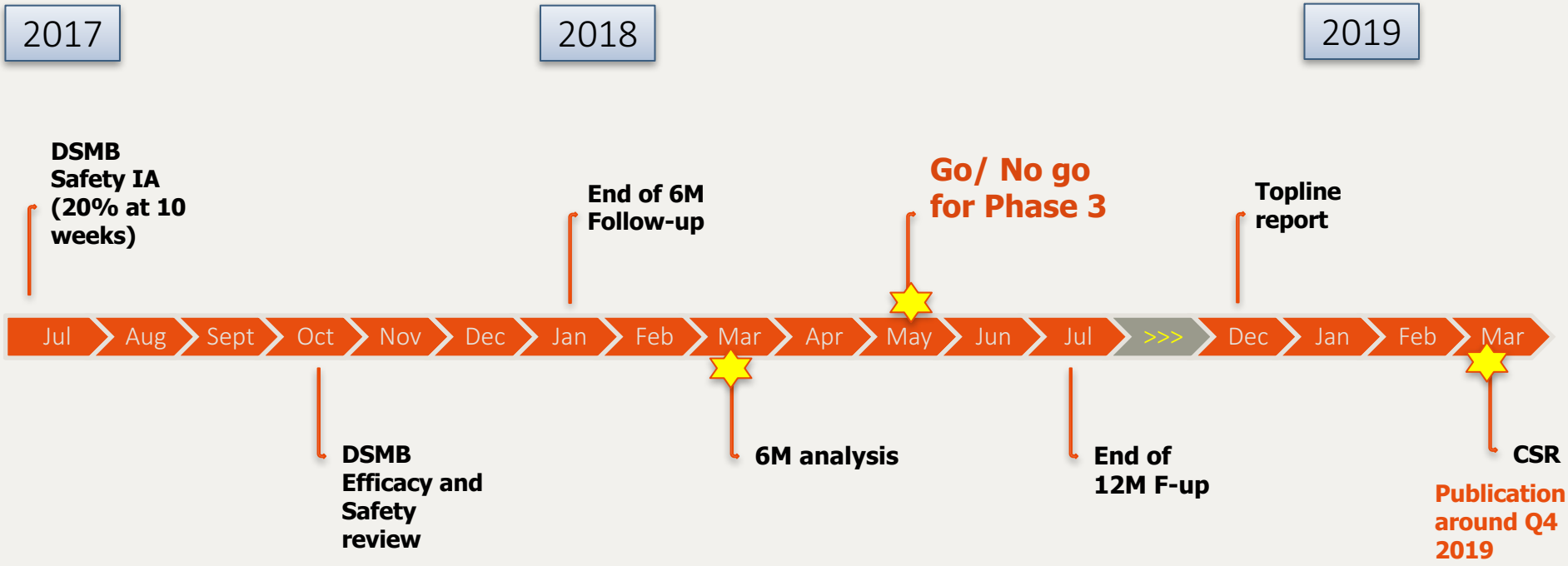
Recruitment Finalized



All Patients finalized treatment

Patients in follow-up: 208 (treatment completed)

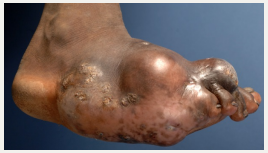
Next steps


2017
2018
2019
DSMB Safety IA (20% at 10 weeks)
End of 6M Follow-up
Go/ No go for Phase 3
Topline report
Jul
Aug
Sept
Oct
Nov
Dec
Jan
Feb
Mar
Apr
May
Jun
Jul
>>>
Dec
Jan
Feb
Mar
DSMB Efficacy and Safety review
6M analysis
End of 12M F-up
CSR
Publication around Q4 2019

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

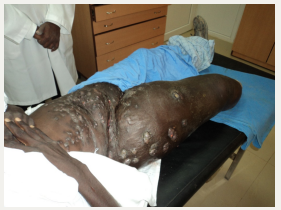


[Symptoms]

- 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]

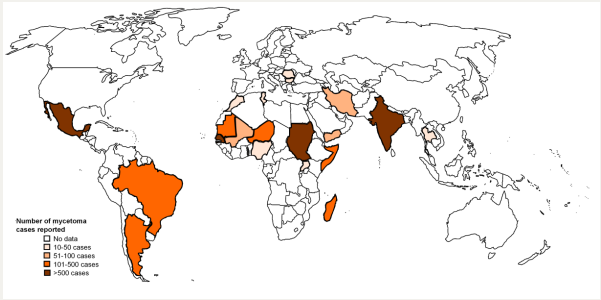
- Basic epidemiological information is lacking, global burden remains unknown
- The Mycetoma Research Centre (MRC) in Khartoum, Sudan, has recorded around 6,500 patients since 1991 – most patients are young and poor
- Actinomycetoma (bacterial form) has a 90% cure rate while the **eumycetoma (fungal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

DND*i* 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)

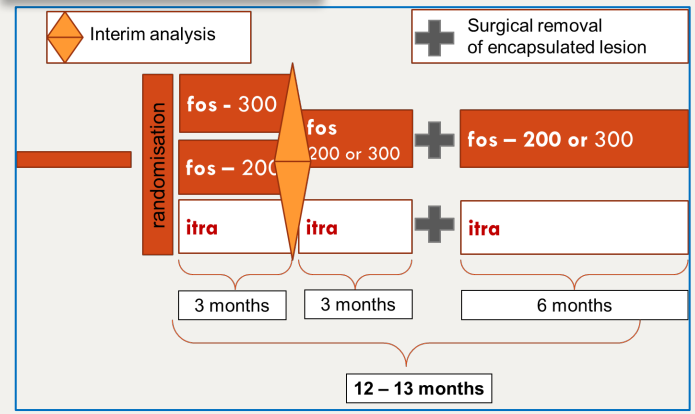
Objective & Goal

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* acitivity against *Madurella mycetomatis*
- *Its pharmacokinetic properties are favorable and its toxicity is low*

Study design

N total = 138



Additional 12 months follow-up if success / maintenance of response

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

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

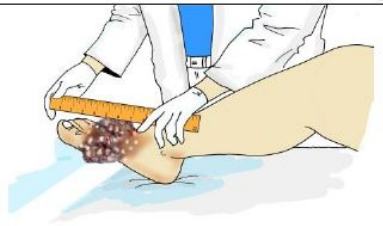
Next steps

- 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

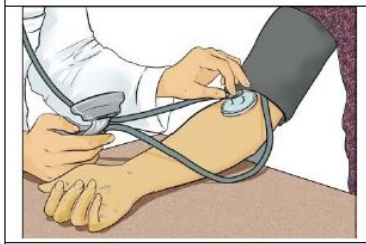
اسمي---------- و أودّ أن أشرح لك عن مرض الميستوما (النبت) والبحث الذي نقوم به هنا.قبل موافقتك على المشاركة،من المهم أن تعرف بقدر المستطاع عن الدراسة.لا تتردد بطرح أي أسئلة تجول بخاطرك.يسرنا الأجابة على كل الأسئلة المطروحة من جانبك.

اذا وافقت أن تكون بهذه الدراسة،سيقوم الطبيب بتسجيل معلوماتك و اجراء بعض الفحوصات.معظم الفحوصات روتينيه مثل أخذ عينة (نسيج)و الجراحة.بعد توقيعك على الاقرار المفصّل،سيسألك الطبيب عن اصابتك(أو طفلك) بأي مرض مع توضيح أخذك (أو طفلك) لأي علاج.

يوجد مرض الميستوما بصورة منتشرة في السودان،الاسم المحلي لهذا المرض هوالمادورا أو النبت.يمكن أن يتسبب المرض في تشوّه الجسم،الاعاقة أو الموت اذا لم يتم علاجه.يصعب علاج النوع الفطري من مرض الميستوما.نقوم الأن باجراء دراسة لمقارنة دواء يسمىبالدواء المستخدم حاليا في علاج الميستوما بالسودان المسمى Fosravuconazole.Itracanazole

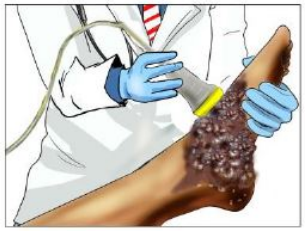


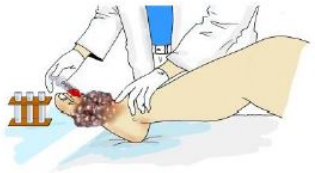
سنقوم كذلك بقياس حجم الميستوما و أخذ عدة صور فوتوغرافية لها.



سيتم الكشف عليك(أوطفلك) وذلك يشمل حساب عدد ضربات القلب،ضغط الدم،الطول و الوزن.

سنقوم بأخذ 23 مل من الدم (حوالي ملعقتين طعام) لفحص





سيتم أخذ عينة للمعمل لتأكيد الميستوما.سيتبع ذلك أخذ صورة أشعة،موجات صوتية و رنين

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 DND*i* 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

Comments to GHIT Fund

- DND*i* 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

Best science for the most neglected

Thank you to all our Donors and Partners

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