



# **GHIT R&D Forum**

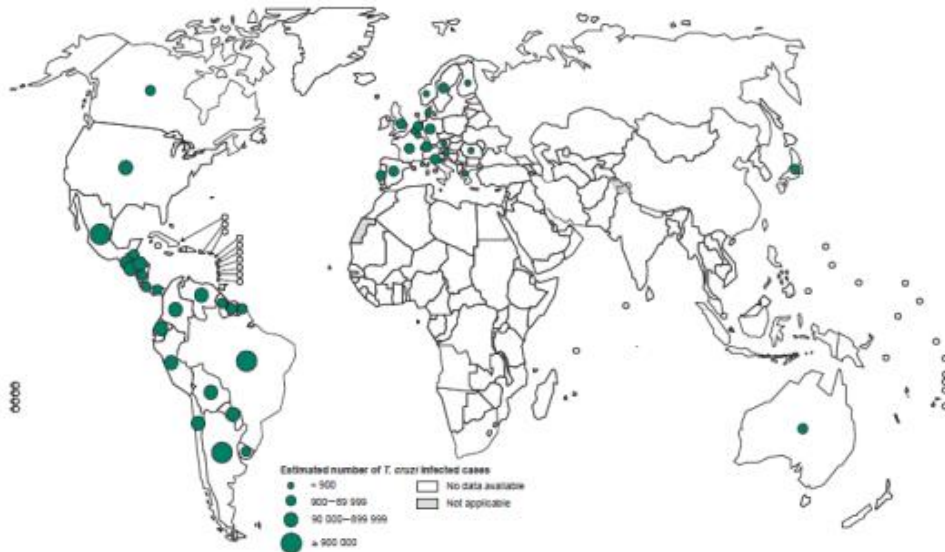
**Session 4: Propelling R&D for late-stage projects**

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

**Daisuke Imoto  
Head of Office  
DNDi Japan**

# Chagas Disease – Unmet Medical Need

Distribution of cases of *T. cruzi* infection, based on official estimates, worldwide, 2010–2013 (WHO, 3<sup>rd</sup> 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

## 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

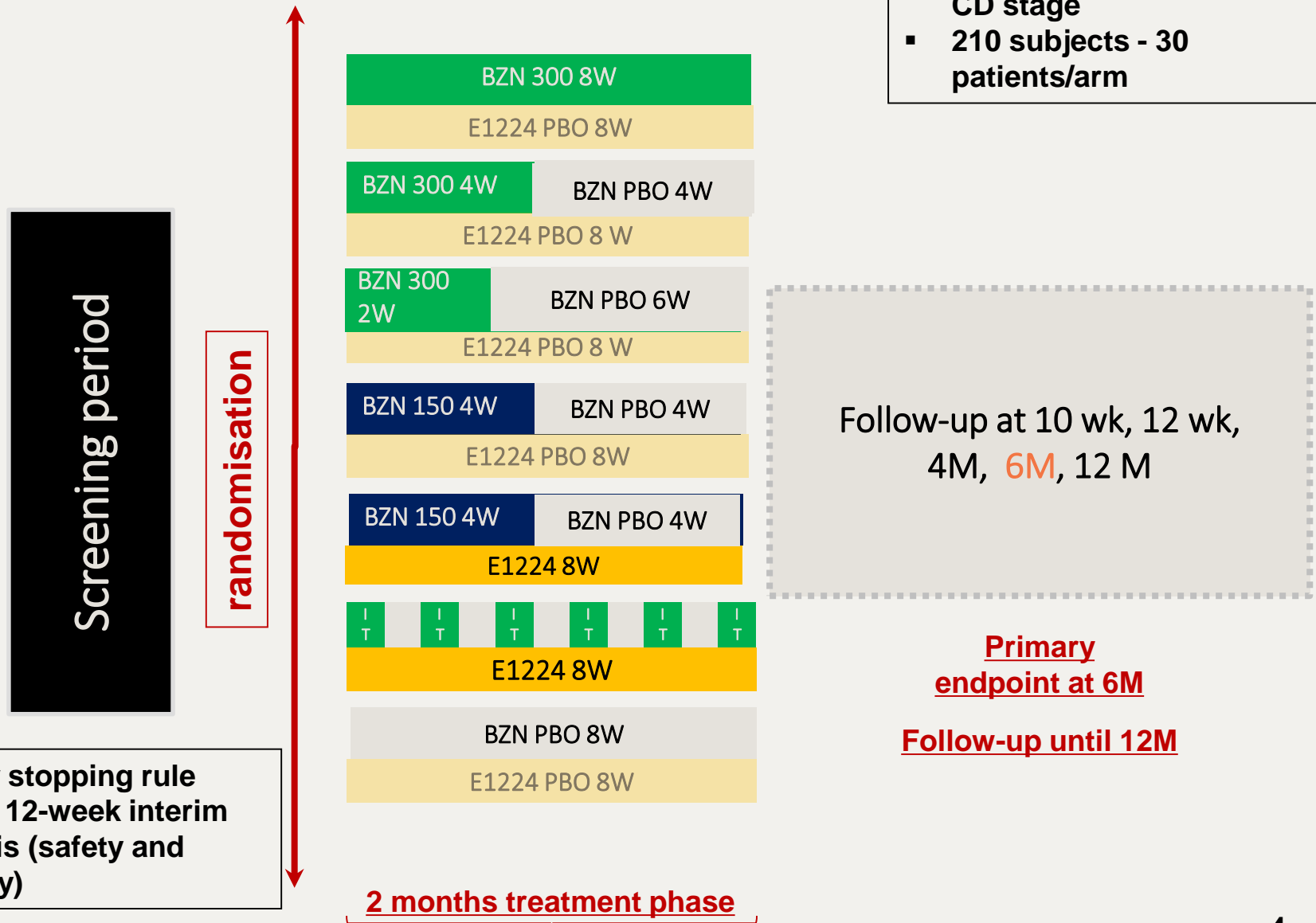
Eisai Co., Ltd. (Japan), Collective of Applied Studies and Social Development (CEADES) (Spain/Bolivia), Platform of Integral Care for Patients with Chagas Disease, (Bolivia), Universidad Mayor de San Simon, Bolivia; Universidad Autónoma Juan Misael Saracho, (Bolivia)

- ❖ 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 1<sup>st</sup> drug in 40 years of a new drug for this disease”**

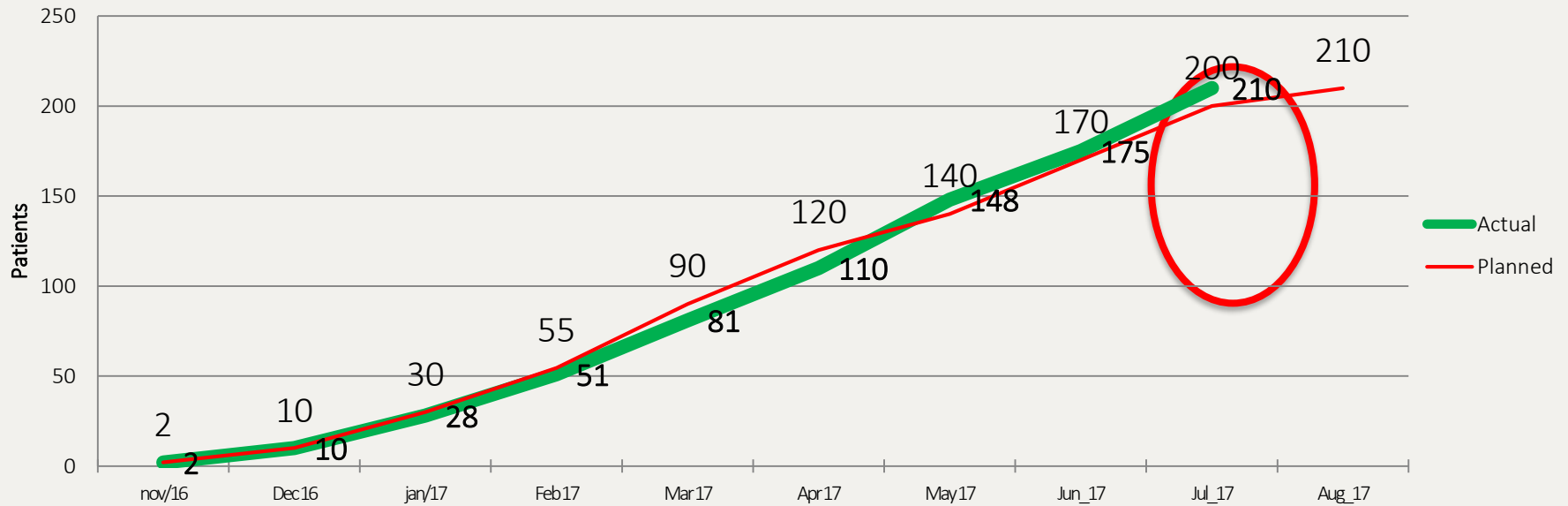
# BENDITA overall design

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



# Recruitment Finalized

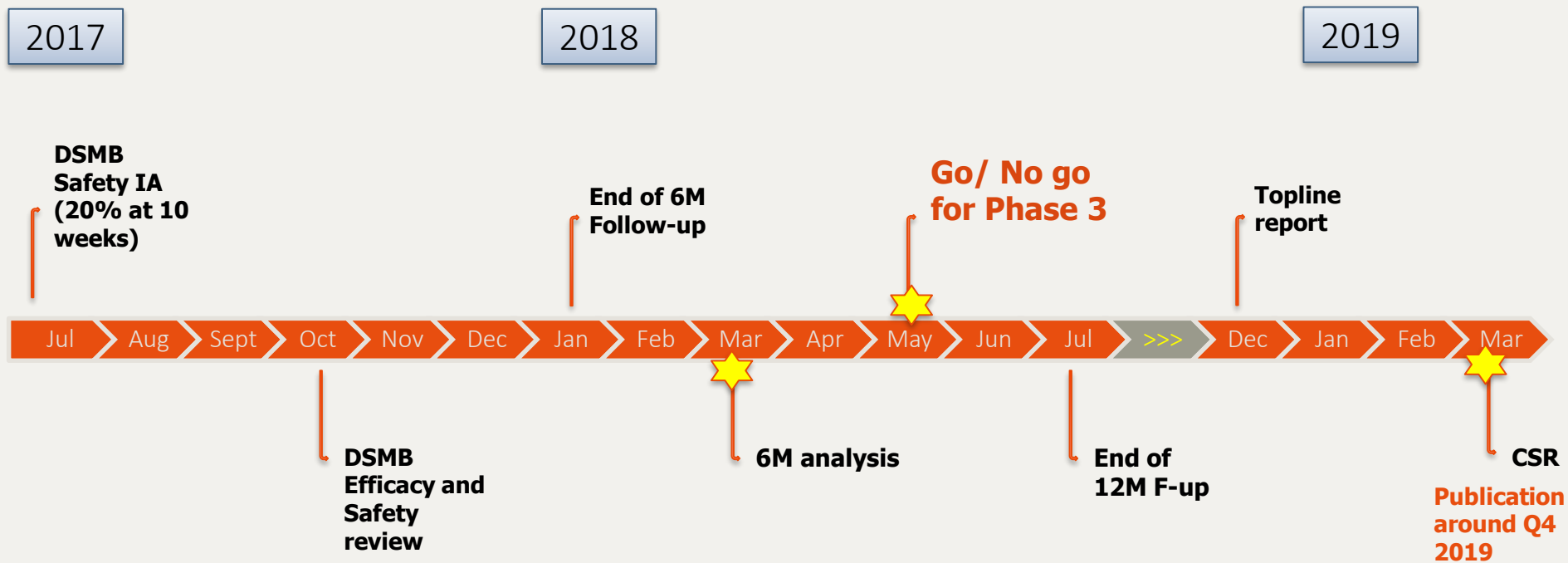
Bendita - Recruitment



**All Patients finalized treatment**

**Patients in follow-up: 208 (treatment completed)**

# Next steps





# 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 18<sup>th</sup> disease of the WHO list of NTDs**

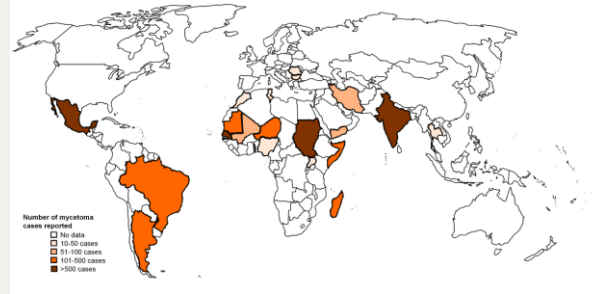
**DNDi strongly advocated for Mycetoma to be included in the list**



# 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

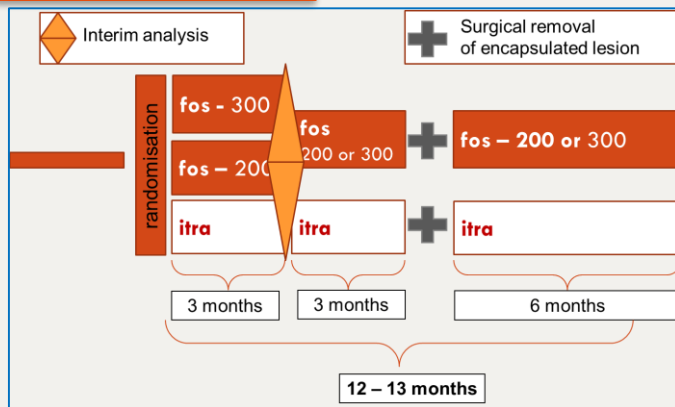
# On-going Project: Mycetoma Treatment, Fosravuconazole Clinical Trial (in Sudan)

## 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



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

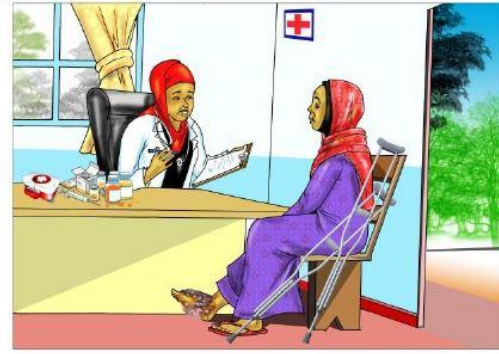
### Conduct

- Mycetoma Research Centre Khartoum, a WHO Collaborative Centre
- Subjects 18 years or older
- Single eumycetoma lesion  $\geq 2$  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

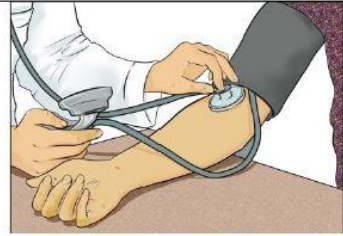
- Eisai intends to continue supporting the development of E1224 including the drug product supply (clinical trials) needed for regulatory approval
- Continuing to engage with endemic countries NRAs and Policy makers for most appropriate approval strategy /unmet medical need

اسمي----- و أود أن أشرح لك عن مرض الميسيتوما (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.



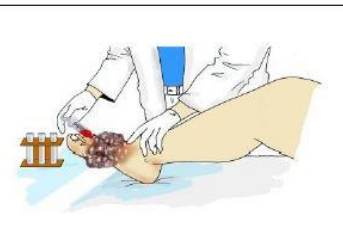
يوجد مرض الميسيتوما بصورة منتشرة في السودان، الاسم المحلي لهذا المرض هو المادورا أو النبت. يمكن أن يتسبب المرض في تشوه الجسم، الإعاقة أو الموت إذا لم يتم علاجه. يصعب علاج النوع الفطري من مرض الميسيتوما. نقوم الآن بإجراء دراسة لمقارنة دواء يسمى إيتراكانازول (Itracanzole) مع فوسرافونازول (Fosravuconazole) المستخدم حاليا في علاج الميسيتوما بالسودان المسمى

إذا وافقت أن تكون بهذه الدراسة، سيقوم الطبيب بتسجيل معلوماتك و إجراء بعض الفحوصات. معظم الفحوصات روتينية مثل أخذ عينة (نسيج) والجراحة. بعد توقيعك على الإقرار المفصل، سيسألك الطبيب عن أصابتك (أو طفلك) بأي مرض مع توضيح أخذك (أو طفلك) لأي علاج.



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

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



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

سنقوم 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

# Comments to GHIT Fund

- 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





Best  
science  
for the **most**  
neglected

**Thank you to all  
our Donors and  
Partners**

[www.dndi.org](http://www.dndi.org)  
[www.dndijapan.org](http://www.dndijapan.org)