Once-weekly repurposed fosravuconazole versus daily itraconazole, with surgery, in patients with eumycetoma in Sudan: a randomised, double-blind, phase 2, proof-of-concept superiority trial

***Ahmed H. Fahal**[1], Eiman S. Ahmed[1], Sahar M. Bakhiet[1,2], Osama E. Bakheet[1], Lamis A. Fahal[1], Abubaker A. Mohamed[1], El Semani W. Mohammedelamin[1], Mustafa E. Bahar[1], Hadil Y. Attalla[1], Emmanuel E. Siddig[1,3], Najwa A. Mahmoud[1], Ahmed M. Musa[1,2], Wendy W. J. van de Sande[3], Bruno Scherrer[4], Peelen Oyieko[5], Thaddaeus W. Egondi[5], Kevin O. Onyango[5], Katsura Hata[6], Wan-Yu Chu (MSc)[7], Thomas P. C.Dorlo (PhD)[7], Borna A. Nyaoke (MD)[5], Nathalie Strub-Wourgaft (MD)[8], Eduard E. Zijlstra (MD)[8]

[1]Mycetoma Research Center, Khartoum, Sudan; [2]Institute of Endemic Diseases, University of Khartoum, Sudan; [3]Erasmus MC, University Medical Center Rotterdam, Netherlands; [4]Bruno Scherrer Conseil, Saint Arnoult en Yvelines, France; [5]Drugs for Neglected Diseases initiative, Nairobi, Kenya; [6]Global Health Research Section, Eisai Co., Ltd., Japan; [7]Department of Pharmacy, Uppsala University, Sweden; [8]Drugs for Neglected Diseases initiative, Geneva, Switzerland

Conflict of Interest:
The author has declared no conflict of interest.

MYCETOMA

The disease

Mycetoma is a chronic disabling disease, characterized by massive deformities and destruction, leading to loss of function.

Facts

Only 35%

Estimated cure rate for fungal mycetoma with current treatments

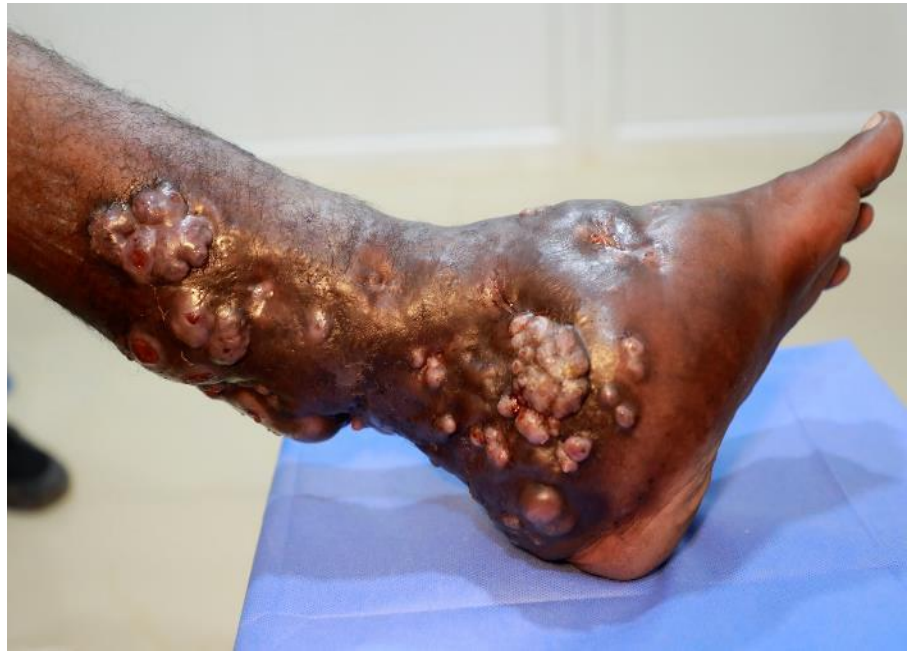
Occurs most often in the so-called

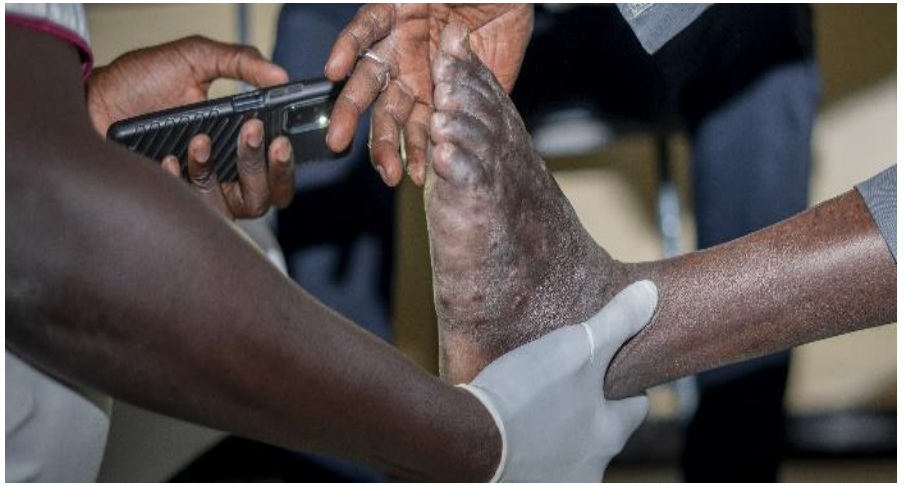
‘Mycetoma Belt’

between latitudes 15°S and 30°N

Unknown

Global burden





Mechanism of action: inhibition of ergosterol biosynthesis

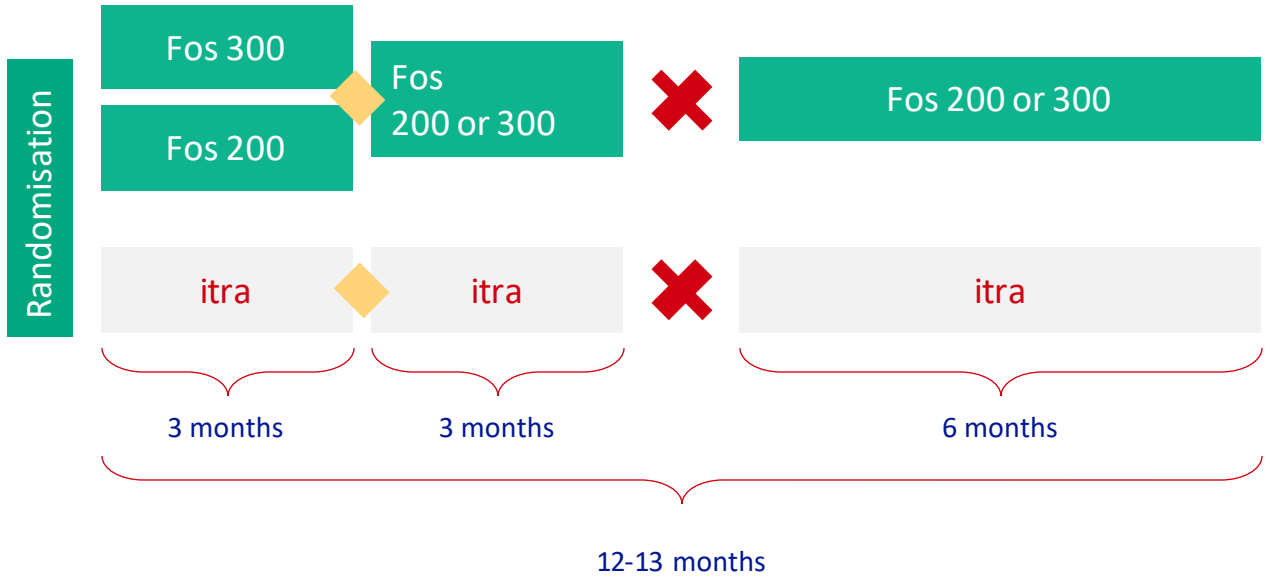
FOSRAVUCONAZOLE	ITRACONAZOLE
***In vitro* antifungal activity (ravuconazole)** • MIC_{90}: 0.016 mg/ml • **16-fold stronger than itraconazole**	***In vitro* antifungal activity** MIC_{90}: 0.25 mg/ml
Physicochemical property ✓ **Solubility: high, allowing PO & IV formulation**	**Physicochemical property** ⊗ **Solubility: low, causing variation in absorption**
Human PK • **The half-life of ravuconazole = 8 – 11 days (GIB edition 7, 2016)** ✓ **Dosing: once a week, no food effect**	**Human PK** • Half-life = 1.5 – 2 days (mycoses 32, Suppl. 1, 67-87, 1989) • Dosing: b.i.d. • To be taken after meal
DDI risk • Moderate inhibitor of CYP3A4 • **No. of contraindicated drugs = 0**	**DDI risk** ⊗ Strong inhibitor of CYP3A4 ⊗ No. of contraindicated drugs >20

- Thus, in real clinical settings, itraconazole is not easy to use, mainly due to a high risk of drug-drug interactions, low solubility and a food effect that causes variable absorption.
- **Fosravuconazole is a highly mature antifungal agent that has high solubility, potent antifungal activity, high safety, long plasma half-life and minimal drug-drug interactions.**

PROTOCOL

A randomized, double-blind phase II proof-of-concept superiority trial of fosravuconazole 200 mg or 300 mg weekly dose versus itraconazole 400 mg daily all three arms combined with surgery, in patients with eumycetoma in Sudan

Study design



Interim analysis

Surgical removal of encapsulated lesion

- **138** patients - 2017
- **20 women** only (initially)
- **Single lesions** in one anatomical site
- Lesions caused by *Madurella mycetomatis* confirmed by PCR
- MRI and US for lesion size confirmation
- No bone involvement

Two Interim Analyses

DSMB Decision at Interim Analysis #1 (84 patients, 3 months)

- No fosravuconazole arm to be dropped (no-loser)
- Recruitment target increased from 138 to 165
- Restriction of number of females (max 20) lifted

DSMB Decision at Interim Analysis #2 (104 patients)

- **Recommendation: Stop for futility**
- Overall blinded cure rate was approx. 65%
- Slow recruitment, COVID-19, other local issues
- Superiority of Fos over Itra could not be demonstrated
- No safety issues
- Pharmacokinetics as expected

TREATMENT GROUPS

Population Analysed

Population	Fos 300mg (n=34)	Fos 200mg (n=34)	Itra 400mg (n=36)
Randomized	34	34	36
Intention-to-Treat (ITT)	34	34	36
Modified Intention-to-Treat (mITT)	34	34	36
Per Protocol (PP) Population	26	26	30
Safety Population	34	34	36

Reasons for exclusion from the per protocol set

- Inclusion/exclusion criteria not met (multiple lesions)
- Missed visit M6 and/or M12
- Missed MRI and ultrasound at M12
- Missed surgery at M6
- Poor compliance <90%

SUMMARY

Baseline history, signs and symptoms of eumycetoma patients by treatment group

Most frequent signs and symptoms of eumycetoma were:

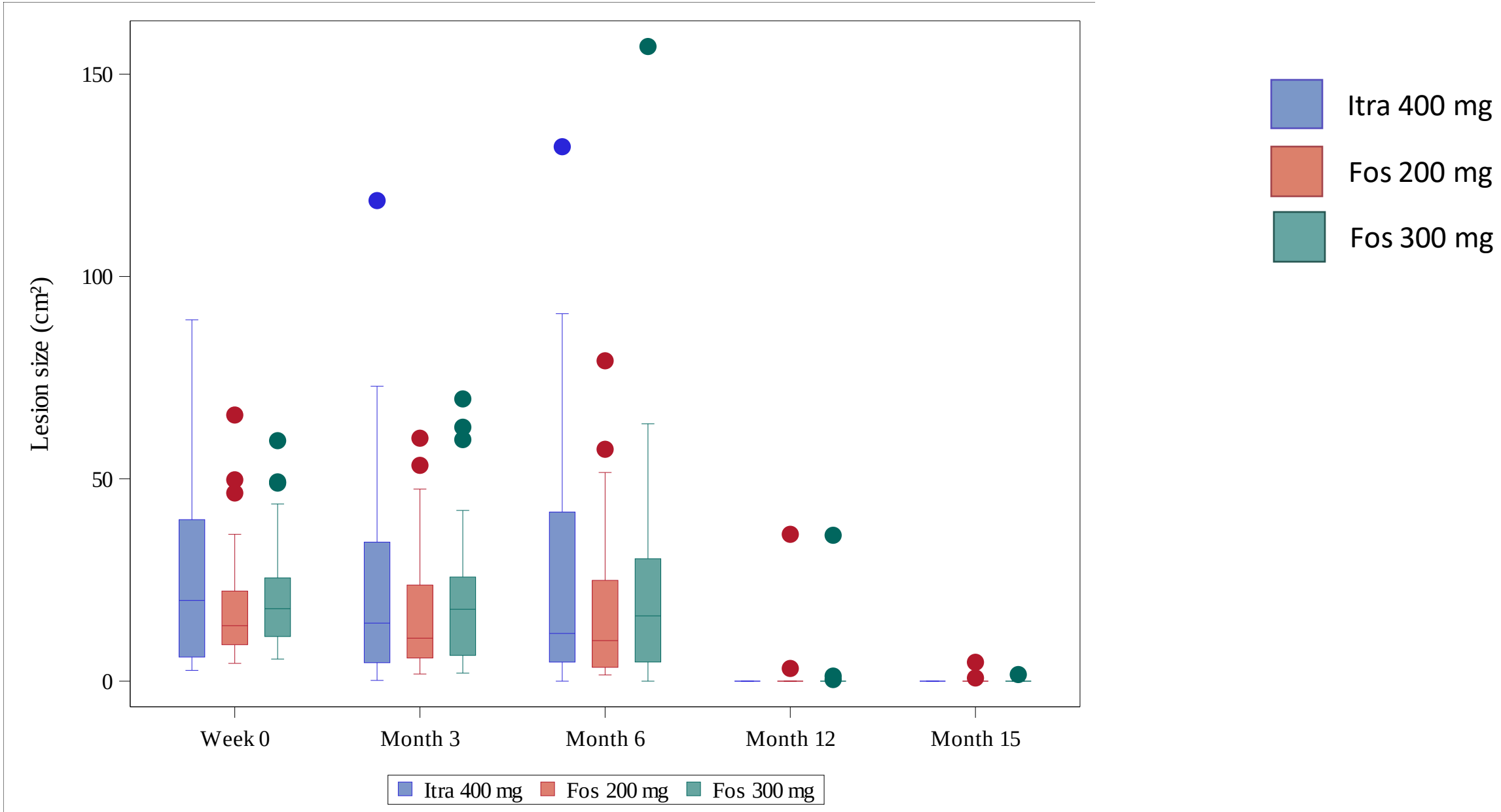
- Local swelling
- Sinuses
- Discharge
- Pain

No major differences in the medical history, signs and symptoms of eumycetoma among the treatment groups.

Even in small lesions, treatment duration may be long

- The role of immune response?
- Response to treatment?

No significant change in mean lesion size at six months from baseline



EFFICACY OUTCOME

Primary efficacy outcome after 12 months (EOT) – mITT population

	Fos 300 mg (n=34)	Fos 200 mg (n=34)	Itra 400 mg (n=36)
Complete cure (n)	17	22	27
Cure rate (efficacy) (%)	50.0	64.7	75.0
95% C.I (efficacy)	32.4,67.6	46.5,80.3	57.8, 87.9
Difference in efficacy	-25.0	-16.0	NA
95% C.I (difference)	-47.0, -30	-31.7, 11.1	NA
P-value[1]	0.030	0.347	NA

EFFICACY OUTCOME

Primary efficacy outcome after 12 months (EOT) – per protocol population

	Fos 300 mg (n=26)	Fos 200 mg (n=26)	Itra 400 mg (n=30)
Complete cure (n)	17	22	24
Cure rate (efficacy) (%)	65.4	84.6	80.0
95% C.I (efficacy)	44.3, 82.8	65.1, 95.6	61.4, 92.3
Difference in efficacy	-14.6	4.6	NA
95% C.I (difference)	-37.8, 8.6	-15.3, 24.5	NA
P-value[1]	0.218	0.652	NA

- Note 1: P value, testing the difference in efficacy between each of the fosravuconazole regimen arms and itraconazole
- Note 2: The overall target significance level (alpha) was set at 0.022 after adjusting for three analysis (2 interim and the final analyses).
- Note 3: Complete cure is defined by
  - (i) Absence of mycetoma mass, sinuses and discharge
  - (ii) Normal ultrasonic examination or normal MRI of the mycetoma site and
  - (iii) Negative fungal culture from a surgical biopsy if a mass is present

Efficacy conclusion

- mITT and PP analyses
- No superiority in efficacy of fosravuconazole over itraconazole
- Similar efficacy rates for all treatment arms

**not statistically significant*

Secondary efficacy endpoints

Time to complete cure was not significantly different between treatment arms (log rank = 0.3518)

- Age, duration of symptoms, baseline size lesion and change of lesion at 6 months were not significantly associated with outcome at 12 months

Overall summary of treatment-emergent adverse events at 12 months (end of treatment) and at 15 months follow-up: safety population

	Fos 300 mg (n=34)	Fos 200 mg (n=34)	Itra 400 mg (n=36)
Subjects with at least one TEAE	25 (73.5) [58]	28 (82.4) [71]	28 (77.8) [61]
Intensity			
Mild	18 (52.9) [35]	20 (58.8) [33]	19 (52.8) [32]
Moderate	17 (50.0) [21]	18 (52.9) [34]	17 (47.2) [26]
Severe	2 (5.9) [2]	1 (2.9) [1]	2 (5.6) [3]
Death	0 (0.0) [0]	1 (2.9) [3]	0 (0.0) [0]
Drug relatedness			
Related to study drug	0 (0.0) [0]	1 (2.9) [2]	3 (8.3) [3]
Not related to study drug	25 (73.5) [56]	28 (82.4) [67]	27 (75.0) [58]
Related to study participation (in - screening)	0 (0.0) [0]	1 (2.9) [1]	0 (0.0) [0]
Not related to study participation (in - screening)	2 (5.9) [2]	1 (2.9) [1]	0 (0.0) [0]
Adverse Event of Special Interest (AESI)	0 (0.0) [0]	0 (0.0) [0]	2 (5.6) [2]
Serious Adverse Events (SAEs)			
Not related to study drug	1 (2.9) [1]	1 (2.9) [4]	0 (0.0) [0]

Safety

- The treatments were overall **well tolerated**
- There were **no severe or serious treatment-related adverse events**.

Limitations

- Small to moderate – < 16 cm lesions
- Single anatomical lesions
- No bone involvement
- *Madurella mycetomatis* only
- Patients restricted to Sudan

Outstanding issues

- Different patient populations may need adapted regimens
- Larger and multiple lesions with bone involvement, lymph node metastasis
- Other fungi
- Paediatric <15 years – no data
- Long duration (adherence, cost)
- Timing and need for surgery

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Confederaziun svizra

Swiss Agency for Development and Cooperation SDC

DNDi
Best Science for the Most Neglected
20 years

Reference slides

MEDECINS SANS FRONTIERES

Eumycetoma treatment challenges: current drugs in use

Eumycetoma as a priority for new treatments:

Cure rates for bacterial mycetoma (actinomycetoma) >90%

Cure rates for fungal mycetoma (eumycetoma) <40%

Ketoconazole

- Severely restricted to certain indications by several national regulatory agencies because of toxicity (liver and adrenal).

Itraconazole

- Limited availability in low- & middle-income countries
- Expensive

Voriconazole, posaconazole, isavuconazole

- Limitations for use in low- & middle-income countries

	Organism (number of cases)	Dose	Outcome	Country
Ketoconazole[129]	*Madurella mycetomatis* (13 [8 from Sudan and 5 from Saudi Arabia])	200–400 mg once a day; median treatment duration is 13 months (range 3–36 months)	5 cured and 4 improved	Sudan and Saudi Arabia
Ketoconazole[130]	*M mycetomatis* (50)	200 mg twice a day for 3–36 months	36 (72%) were cured or had notable improvement; 10 (20%) had some improvement; 4 (8%) had no response or deteriorated	Sudan
Ketoconazole[131]	*M mycetomatis* (4), other (4)	400 mg once a day for 8–24 months	6 cured, no recurrence after 3 months (2 years follow-up); 2 improved	India
Itraconazole[132]	*M mycetomatis* (13)	200 mg twice a day for 3 months, then 200 mg once for 9 months	1 cured; [illegible] oved and cured after [illegible] nce	Sudan
Terbinafine[133]	*M mycetomatis* (10), *Falciformispora senegalensis* (3), other (3), not known (7)	500 mg twice a day for 24–48 weeks	[illegible] oved	Senegal
Voriconazole[134]	*Scedosporium apiospermium* (1)	400 mg once [illegible]	Cured	Côte d'Ivoire
Voriconazole[135]	*S apiospermium* (1)	Dos[illegible] duration	Cured	India
Voriconazole[135]	*Trematosphaeria grisea* (1)	[illegible] months duration	Little change	India
Voriconazole[136]	*M mycetomatis* (1)	[illegible] ice dailyfor 3 months, then [illegible] mg twice daily for 13 months	Cured	Mali
Voriconazole[137]	*Madurella* spp (1)	200 mg twice daily for 12 months	Cured	Senegal
Voriconazole[138]	*S apiospermum* (1)	200 mg twice a day; unknown duration	Cured (after 3 years follow-up)	Brazil
Posaconazole[139]	*M mycetomatis* (2), *T grisea* (3), *S apiospermum* (1)*	400 mg twice daily for a maximum of 34 months	Initially 5 were cured and 1 had no improvement; 2 were successfully retreated after interval of >10 months	Brazil
Liposomal amphotericin B[130]	*T grisea* (2), *Fusarium* spp (1)	Total dose 3·4 g and 2·8 g (*T grisea* cases), and 4·2 g (*Fusarium* spp case); maximum daily dose is 3 mg/kg	All showed temporary improvement but relapsed within 6 months	Not specified

*All refractory cases.

Table 3: **Treatment of eumycetoma in endemic cases and immunocompetent patients**

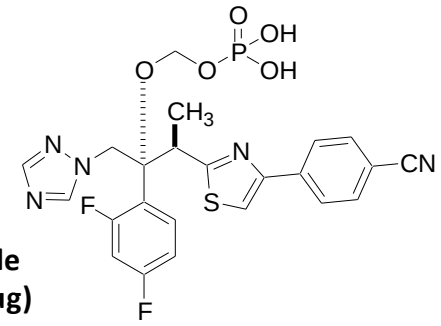
No randomized studies

Zijlstra et al. Lancet ID 2016

Features of fosravuconazole: a new azole antifungal - ergosterol biosynthesis inhibitor

- High solubility in water
- High oral bioavailability
- Rapidly converts to ravuconazole after administration
- Long 8-11-day half-life of ravuconazole allows once-a-week dosing

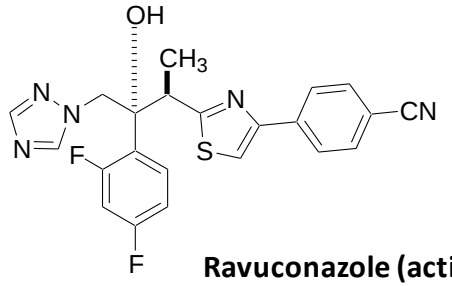
Both IV and oral formulation



Fosravuconazole (E1224) (pro-drug)

Alkaline phosphatase

in the body



Ravuconazole (active moiety)

Application of compound

Treatment of Chagas disease and mycetoma

Roles & responsibilities:

- **DNDi and MRC: Conducted phase II studies of E1224**
- **Eisai: Implemented drug development activities**
  - **E1224 capsules preparation: in-kind contribution by Eisai**
  - **pre-clinical ADMET studies**

Demographics

Parameter	Statistic	Fos 300 mg (n=34)	Fos 200 mg (n=34)	Itra 400 mg (n=36)
Age (years)				
	n	34	34	36
	Range (min-max)	15.0-77.0	16.0-44.0	15.0-58.0
	Mean (SD)	30.5 (12.9)	25.0 (7.3)	28.5 (12.5)
	Median (IQR)	29.0 (22.0-33.0)	23.0 (20.0-29.0)	24.5 (19.5-33.0)
Sex, n(%)				
	Female	3(8.8)	6(17.6)	9(25.0)
	Male	31(91.2)	28(82.4)	27(75.0)
Weight (Kg)				
	n	34	34	36
	Range (min-max)	36.0-95.5	38.9-88.5	36.0-85.5
	Mean (SD)	60.1 (12.0)	60.2 (13.2)	60.5 (11.4)
	Median (IQR)	60.5 (52.0-67.0)	57.3 (52.0-70.0)	60.0 (53.5-68.8)
Height (m)				
	n	34	34	36
	Range (min-max)	1.2-1.9	1.5-1.9	1.5-1.9
	Mean (SD)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
	Median (IQR)	1.7 (1.7-1.8)	1.7 (1.6-1.8)	1.7 (1.6-1.8)
BMI (Kg/M^2)				
	n	34	34	36
	Range (min-max)	16.0-31.2	16.0-28.7	16.1-31.0
	Mean (SD)	20.9 (3.5)	20.9 (3.6)	20.9 (3.8)
	Median (IQR)	20.8 (18.2-23.0)	20.7 (18.5-22.5)	19.9 (18.4-22.2)

Mycetoma medical history

Characteristic	Fos 300mg (n=34)	Fos 200mg (n=34)	Itra 400mg (n=36)
Duration of illness (months), mean (SD)	44.7 (38.0)	47.1 (49.6)	41.7 (44.1)
range (min, max)	2.0 ,168	2.0 ,240	0.0 ,180
History of trauma, n (%)	14 (41.2)	13 (38.2)	12 (33.3)
Family history of eumycetoma, n (%)	6 (17.6)	9 (26.5)	13 (36.1)
Local swelling, n (%)	34 (100)	34 (100)	36 (100)
Openings on the skin (sinuses), n (%)	25 (73.5)	27 (79.4)	23 (63.9)
Discharge from the eumycetoma lesion, n (%)	20 (58.8)	14 (41.2)	19 (52.8)
Pain, n (%)	7 (20.6)	5 (14.7)	5 (13.9)
Other symptoms, n (%)	0 (0.0)	0 (0.0)	1 (2.8)
Previous treatment of eumycetoma, n (%)	0 (0.0)	0 (0.0)	0 (0.0)

Signs and symptoms

	Fos 300mg (n=34)	Fos 200mg (n=34)	Itra 400mg (n=36)
Site of eumycetoma n (%)			
Foot	25 (73.5)	26 (76.5)	30 (83.3)
Lower limb (except foot)	3 (8.8)	1 (2.9)	5 (13.9)
Other (left hand, right hand, thigh)	6 (17.6)	7 (20.6)	1 (2.8)
Single lesion n (%)	34 (100)	34 (100)	36 (100)
Size of the lesion (cm^2)			
Mean (SD)	21.4 (14.3)	18.6 (14.3)	26.6 (23.7)
Median (Q1, Q3)	17.9 (11.0,25.5)	13.7 (9.0,22.3)	19.9 (6.0,39.9)
Note: Size of the lesion is given by the area of an ellipse,	calculated as [π*0.25*length*width].		
Sinus findings related to primary eumycetoma lesion			
Active sinuses			
Mean (SD)	1.1 (2.1)	0.7 (1.5)	1.4 (3.6)
Median (Q1, Q3)	0.0 (0.0,1.0)	0.0 (0.0,1.0)	0.0 (0.0,1.0)
Non-active sinuses			
Mean (SD)	1.0 (2.0)	0.9 (1.4)	1.1 (3.4)
Median (Q1, Q3)	0.0 (0.0,2.0)	0.0 (0.0,1.0)	0.0 (0.0,1.0)
Healed sinuses			
Mean (SD)	0.7 (1.2)	1.0 (2.0)	1.3 (3.5)
Median (Q1, Q3)	0.0 (0.0,2.0)	0.0 (0.0,2.0)	0.0 (0.0,0.0)

Signs and symptoms

	Fos 300mg (n=34)	Fos 200mg (n=34)	Itra 400mg (n=36)
Findings related to presence of eumycetoma, n (%)			
Presence of discharge grains	13 (38.2)	10 (29.4)	16 (44.4)
Enlarged lymph nodes	0 (0.0)	0 (0.0)	0 (0.0)
Varicose veins	0 (0.0)	0 (0.0)	0 (0.0)
Sweating	0 (0.0)	0 (0.0)	1 (2.8)

Medical history summary by PT and treatment group – ITT

Preferred Term (PT)	Fos 300 mg (n=34)	Fos 200 mg (n=34)	Itra 400 mg (n=36)
Subjects with at least one medical history	6 (17.6) [7]	6 (17.6) [6]	5 (13.9) [6]
Appendicectomy	2 (5.9) [2]	0 (0.0) [0]	0 (0.0) [0]
Blindness	1 (2.9) [1]	0 (0.0) [0]	0 (0.0) [0]
Bradycardia	1 (2.9) [1]	1 (2.9) [1]	1 (2.8) [1]
Dermatitis Contact	0 (0.0) [0]	1 (2.9) [1]	0 (0.0) [0]
Headache	1 (2.9) [1]	0 (0.0) [0]	0 (0.0) [0]
Hepatic Cyst	1 (2.9) [1]	0 (0.0) [0]	0 (0.0) [0]
Intervertebral Disc Protrusion	0 (0.0) [0]	1 (2.9) [1]	0 (0.0) [0]
Jaundice	0 (0.0) [0]	0 (0.0) [0]	1 (2.8) [1]
Migraine	0 (0.0) [0]	0 (0.0) [0]	2 (5.6) [2]
Scar	0 (0.0) [0]	1 (2.9) [1]	0 (0.0) [0]
Tinea Versicolor	0 (0.0) [0]	1 (2.9) [1]	1 (2.8) [1]
Urinary Tract Infection	1 (2.9) [1]	1 (2.9) [1]	1 (2.8) [1]

Note: Data are presented as n (%) [N] where n is the number of patients and N is the [Number of events].

SAFETY RESULTS

Liver toxicity

Many patients had lower than normal ALT with no increase during treatment