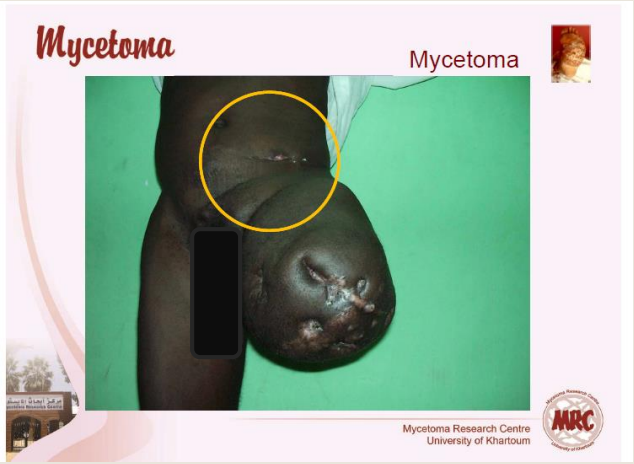
POTENTIAL R&D PATHWAYS FOR NEW TREATMENT OF EUMYCETOMA

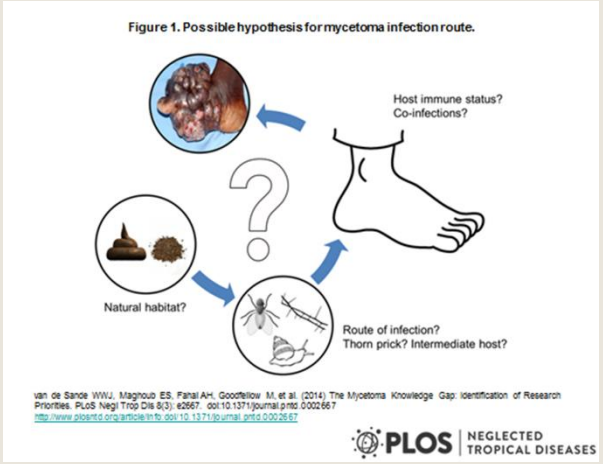
September 10, 2015

nathalie strub wourgaft

A very neglected condition with a single possible low hanging fruit treatment approach

- chronic infection of subcutaneous tissues, mainly foot - treatment failure results in progressive sequential amputations





- existing treatment options are failing

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Key characteristics of eu- and actino-mycetoma

	Eumycetoma	Actinomycetoma
Causative agent	Fungi	bacteria
Main endemic area	Africa	Middle- and South America
Treatment	Antifungal + surgery	antibiotics
Current regimen	Ketoconazole	amikacin (IV) + cotrim (PO)
	 FDA Drug Safety Communication: FDA limits usage of Nizoral (ketoconazole) oral tablets due to potentially fatal liver injury and risk of drug interactions and adrenal gland problems	
	or itraconazole 12 Months + mass removal	
Cure Rate	37% → 25.9%	> 90% (in Mexico)

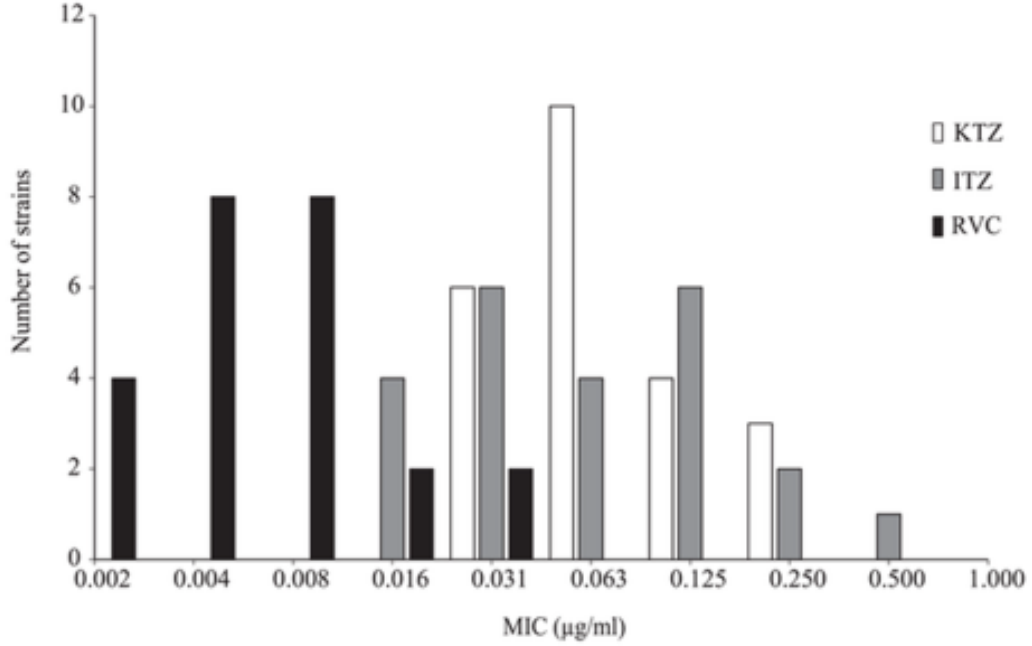
In vitro data: azoles the only class

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)		

Madurella mycetomatis highly susceptible to ravuconazole

Figure 1. In vitro activities of ketoconazole (KTC), itraconazole (ITC), and ravuconazole (RVC) against 23 isolates of Madurella mycetomatis represented by MICs.



Ahmed SA, Kloezen W, Duncanson F, Zijlstra EE, de Hoog GS, et al. (2014) Madurella mycetomatis Is Highly Susceptible to Ravuconazole. PLoS Negl Trop Dis 8(6): e2942. doi:10.1371/journal.pntd.0002942
http://127.0.0.1:8081/plosntds/article?id=info:doi/10.1371/journal.pntd.0002942

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In vitro antifungal activity of Sudanese Medicinal Plants

Table 1. In vitro antifungal activities of several extracts of seven locally plant species against 13 M. mycetomatis isolates.

Plant species	MIC 50[1] (range) in µg/ml Crude methanol extract	Hexane extract	Defatted methanol extract	Crude methanol fraction	Exhausted soluble methanol fraction	Souble hexane fraction	Soluble ethyl acetate fraction
Eugenia caryophillus	50 (ND[2])	ND (ND)	ND (ND)	ND (ND)	ND (ND)	ND (ND)	ND (ND)
Cinnamum verum	25 (ND)	ND (ND)	ND (ND)	ND (ND)	ND (ND)	ND (ND)	ND (ND)
Piper nigrum	25 (ND)	ND (ND)	ND (ND)	ND (ND)	ND (ND)	ND (ND)	ND (ND)
Zingiber officinalis	12.5 (ND)	ND (ND)	ND (ND)	ND (ND)	ND (ND)	ND (ND)	ND (ND)
Acacia nubica	1 (0.5–128)	2 (0.25–128)	4 (0.5–128)	ND (ND)	ND (ND)	ND (ND)	ND (ND)
Nigella sativa	1 (0.5–128)	2 (0.25–128)	4 (0.25–128)	ND (ND)	ND (ND)	ND (ND)	ND (ND)
Boswellia papyrifera	1 (0.5–128)	1 (0.25–128)	2 (0.25–128)	8 (8)	128 (128)	128 (128)	8 (8)
Ketoconazole	0.125 (0.03–0.25)						

[1]Minimal inhibitory concentrations (MIC) at which at least 50% of the *M. mycetomatis* isolates was inhibited (MIC50).

[2]ND: not done.

doi:10.1371/journal.pntd.0003488.t001

Elfadil H, Fahal A, Kloezen W, Ahmed EM, van de Sande W (2015) The In Vitro Antifungal Activity of Sudanese Medicinal Plants against Madurella mycetomatis, the Eumycetoma Major Causative Agent. PLoS Negl Trop Dis 9(3): e0003488. doi:10.1371/journal.pntd.0003488
http://127.0.0.1:8081/plosntds/article?id=info:doi/10.1371/journal.pntd.0003488

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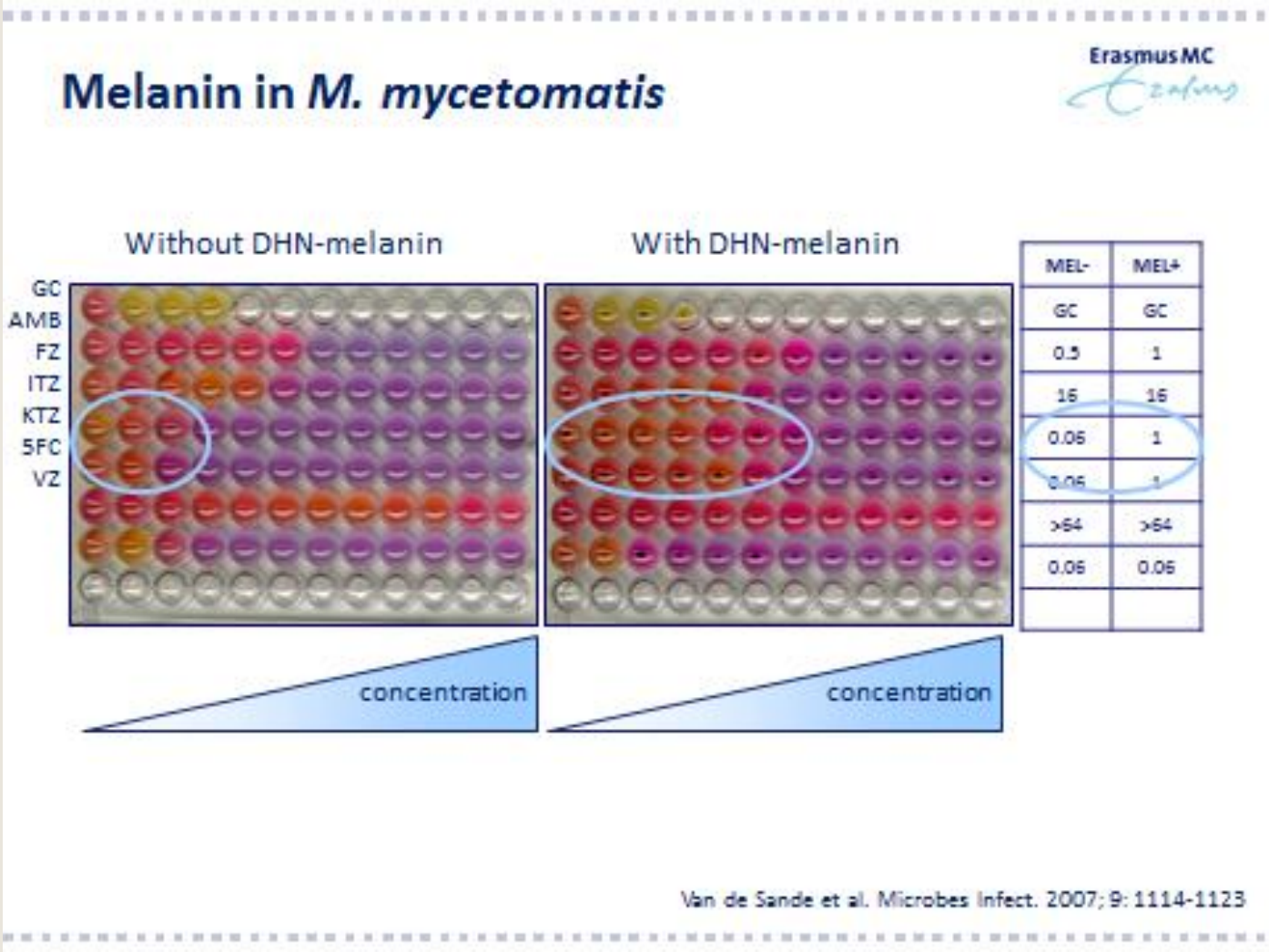
Rationale for poor direct in vitro/ in vivo translation with tested azoles



Ravuconazole less affected by melanin

(data to be provided)

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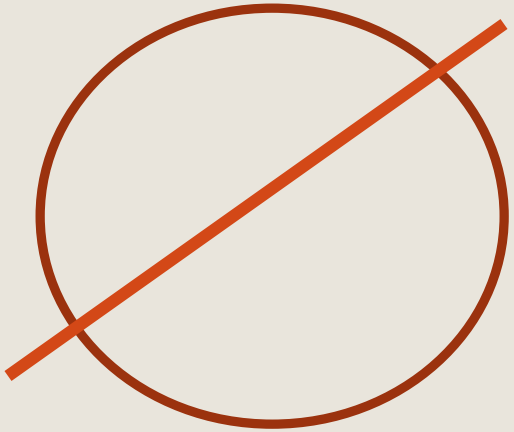
In vivo data



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Clinical data for eumycetoma treatment

Ed Zijlstra, submitted for publication

Drug	Organism	N	Dose	Outcome	Country	Reference
Ketoconazole	M. mycetomatis	13	200-400 mg OD Mean treatment 1 year	5 cured; 4 improved, 4 failed Combined with surgery in some	Sudan	Mahgoub ES, 1984
	M. mycetomatis	50	200 mg BD	72% cure or significant improvement; 20% some improvement; 8% no response or deteriorated	Sudan	Hay RJ, 1992
	M. mycetomatis (4) Other (4)	8	400 mg OD 8-24 months	6 cured, no recurrence after 3 months-2 years follow-up; 2 improved	India	Porte L, 2006
Itraconazole	M. mycetomatis	13	400 mg OD 3 months, then 200 mg 9 months	1 cured; 11 improved and cured after surgery; 1 recurrence	Sudan	Fahal AH
Terbinafine	M. mycetomatis (10) L. senegalensis (3) Other (3) Not known (7)	23	500 mg BD, 24-48 weeks	4 cured; 11 improved, 7 failed	Senegal	N'Diaye B , 2006
Voriconazole	S. apiospermium	1	400 mg OD, 18 months	Cured	Ivory Coast	Porte L, 2006
	S. apiospermium	1	Dose not specified, 6 months	Cured	India	Gulati , 2012
	M. grisea	1	Dose not specified, 6 months	Little change	India	Gulati , 2012
	M. mycetomatis	1	200 mg, 3 months, then 300 mg, 13 months	Cured	Mali	Lacroix C, 2005
	Madurella spp	1	200 mg, 12 months	Cured	Senegal	Loulergue P, 2006
	S. apiospermum	1	200 mg BD, unknown duration	Cured, after 3 years follow-up	Brazil	Oliveira F de M, 2013
Posaconazole	M. mycetomatis (2) M. grisea (3) S. apiospermum (1)	6*	800 mg OD	Initially: 5 cured, 1 no improvement; 2 successfully retreated after interval of >10 months	Brazil	Negroni R, 2005
Liposomal amphotericin B	M. grisea (2) Fusarium (1)	3	Total dose 3.4, 2.8, 4.2 grams; max. daily dose 3 mg/kg	All showed temporary improvement but relapsed within 6 months	Not specified	Hay RJ, 005

Draft Target Product Profile (nov 2013)

Profile	Ideal	Acceptable
Target population	Adults and children aged ≥5 Immnuocompetent or immunocompromised Pregnant and lactating All regions including India	Adults Immunocompetent West and East Africa
Regimen	< 6 without surgery	6 months with surgery 6-12 months without surgery
Route of administration	Oral Once a day	Oral or IM bid
Monitoring of efficacy	Clinical 6 weeks	clinical 6 weeks
Efficacy	Cure rate of > 90% No need for surgery (as in actinoM)	Cure defined a… appearance of mass, closure … return to normal. Acceptable = > keto and cure ≥75% Now itra
Tolerability/safety	No need for monitoring	Liver function monitoring (every 6 wks) – no more discontinuation due to liver enzyme increase than with keto (app 5%)
Drug-drug interaction	None	Adequate with ACTs or forgiveness and usual antibiotic treatments - contraception
Contra-indication	None	Pregnant % lactating -
Stability		
Cost	Not more than for actinoM or Buruli – Acceptable for EML	Cost 200 USD (based on actinoM cost in Sudan)

Identified R&D needs *(excluding diagnosis)*
Range from short to long-term

	Research needs
Short-term	Clinical PoC fosravuconazole
	Screening of existing libraries
	Ecological study
Medium-term	Clinical PoC isavuconazole
	Clinical PoC voriconazole
	Global epidemiology
Long-term	R&D for NCEs
	Clinical Combination
	PoC test , biomarker
	global collection of strains for typing and resistance

Proposed short-term project

- Pivotal study of fosravuconazole versus itraconazole in moderate mycetoma lesion caused by madurella mycetomatis in adult patients
- Design:
  - DB, randomised, monocentre superiority study
  - Interim analysis at month 3
  - One centre
- Primary objective:
  - Superiority of ravuconazole over itraconazole at 12 months follow-up

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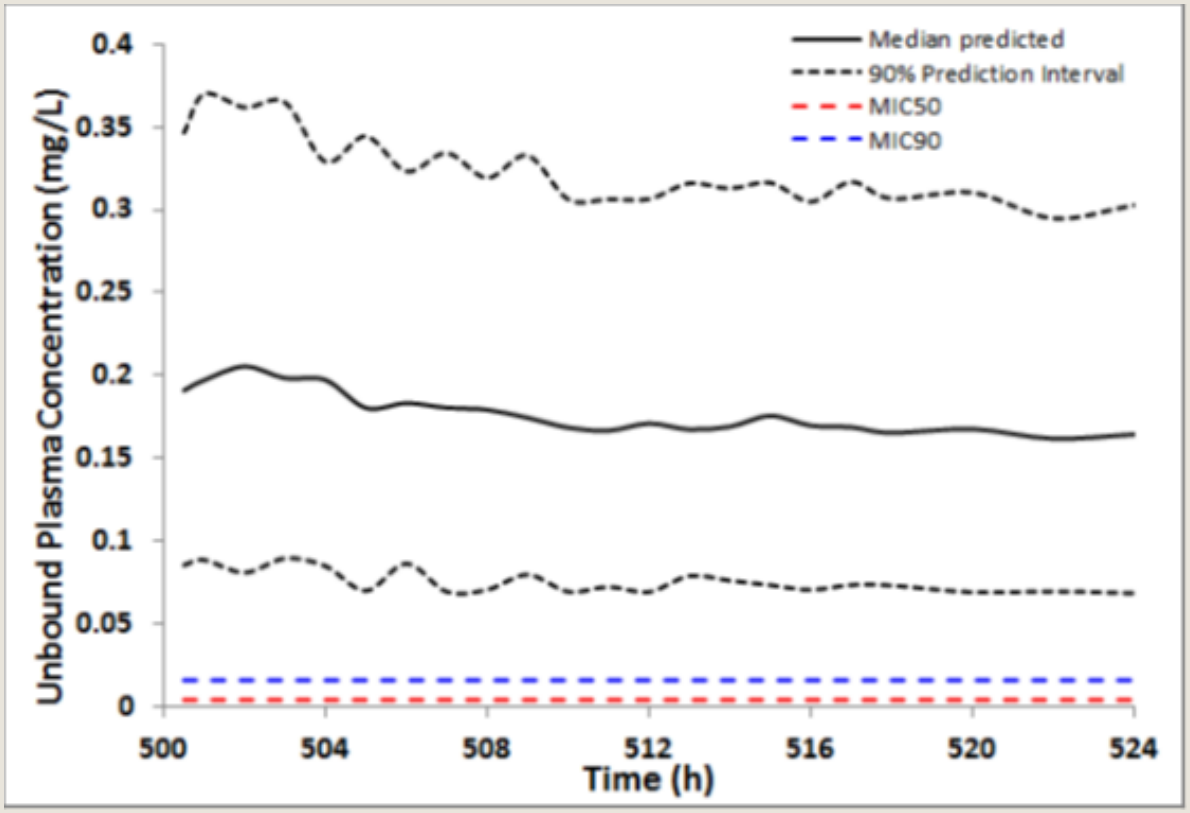
Fosravuconazole dose rationale

Modeling of plasma concentrations against Madurella mycetomatis



Dosing: fosravuconazole 200 mg on Day 1, 2, followed by weekly 200mg

OPEN ACCESS Freely available online

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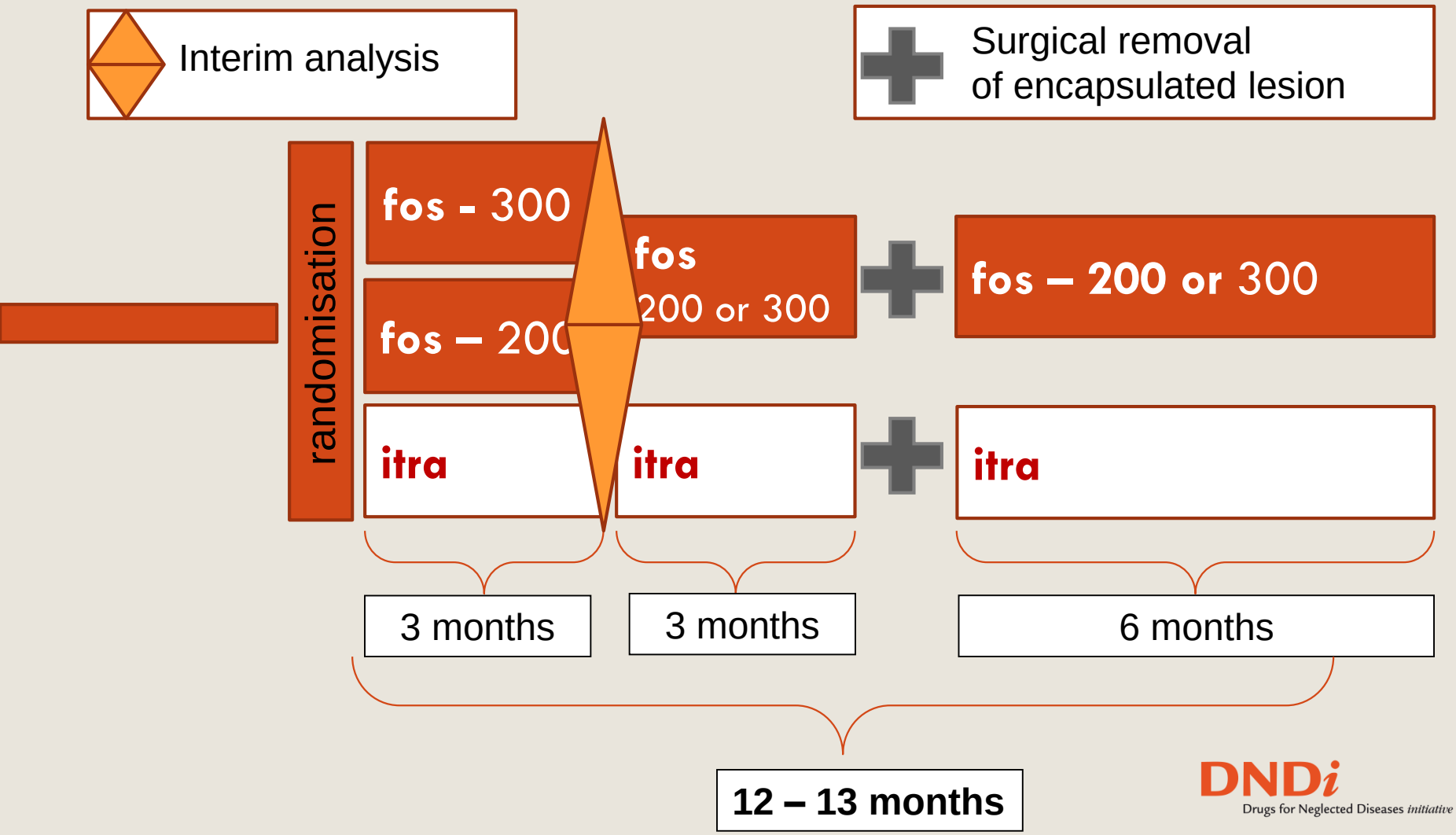
Madurella mycetomatis Is Highly Susceptible to Ravuconazole

Sarah Abdalla Ahmed[1,2,3*], Wendy Kloezen[4], Frederick Duncanson[5], Ed E. Zijlstra[6], G. Sybren de Hoog[2,3,7,8,9,10,11], Ahmed H. Fahal[12], Wendy W. J. van de Sande[4]

Study design:«drop the loser»



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Primary efficacy endpoint

- Complete cure at 12 months
- Assessment:
  - Absence of mycetoma mass, sinuses and discharge and
  - Normal lesion site or only fibrosis on sonogram and
  - Negative fungal culture from a surgical biopsy from the former mycetoma site
- Procedure:
  - Dimensional photographs will be taken at 0, 3, 6 and 12 months using strictly standardized conditions

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Statistical assumptions and approach

	Efficacy	Safety	Decision
fosravuconazole 300mg	>9/28 (>32.2%) and >10% to 200mg (excess rate)	Not worse than 200mg	
fosravuconazole 200mg	>9/28 (>32.2%)		dropped
itraconazole	≤ 9/28 (≤ 32.2%) or at least 10% less than 300mg		
fosravuconazole 300mg	> 9/28 (>32.2%) but not > 10% to 200mg		dropped
fosravuconazole 200mg	> 9/28		
itraconazole	≤ 9/28 (≤ 32.2%) or at least 10% less than 200 mg		
fosravuconazole 300mg	> 9/28 (32.2%)		
fosravuconazole 200mg	≤ 9/28 (≤ 32.2%)		dropped
itraconazole	≤ 9/28 (≤ 32.2%) or at least 10% less than 300mg		

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Inclusion criteria

- Subjects with suspected or confirmed eumycetoma caused by ***Madurella mycetomatis*:**
  - **mycetoma lesion >2 cm and <10 cm in diameter with no evidence of osteomyelitis or other bone involvement based on x-ray and/or bone scan and**
  - **the presence of grains that can be expressed from the mycetoma**
- **Single mycetoma lesion present on the foot or lower limb**
- No previous medical or surgical treatment for eumycetoma
- Age >18 years
- Availability for follow-up
- Negative serum pregnancy test
- If female of child bearing potential, using adequate contraception for the period of the trial plus 2 months after
- Written informed consent signed by subject or the subject's legal guard

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Advocacy efforts still needed

Mycetoma added to the «other neglected conditions» list of the WHO NTD (July 2013)
Draft resolution to add mycetoma to the NTD list during WHA in 2016

Meeting on the Creation of a Mycetoma Coalitio
Geneva
Thursday 23 May, 19.30 – 22.00

Mycetoma is a chronic, progressive, destructive inflammatory and a
commonly spreads to involve the skin, the deep structures and the bone
deformity and loss of function and it can be fatal. Untreated patients comr
infection, and

July 29, 2013 **MEDIA BRIEFING - MYCETOMA CONSORTIUM**

MEDIA BRIEFING - MYCETOMA

New hope for mycetom the flesh eating tropical disease

So neglected that re nputation is the main treatment

67th World Health Ass

Burden and mana ycetoma
Organized by the del dan, with support
e ses Initiative (DNDi)

oom XII - 18:00-19:45

will add 2015 WHA session

ASTMH 62nd Annual Meeting
November 13–17, 2013
Marriott Wardman Park
Washington, DC

Session Detail Add entire session to itinerary
Print

Session Number:	161
Session Title:	Mycetoma: A Forgotten Condition with High Morbidity
Session Type:	Symposium

T RESOLUTION WHA68 (2015)

urveillance and control of Mycetoma

The Sixty-eight World Health Assembly,

Having considered the report on surveillance and control of Mycetoma;

Conclusion

- Mycetoma is a devastating, debilitating and stigamising medical condition, not benefiting from high research attention
- Existing treatment option is extremely limited, with low efficacy, poor safety, lack of affordability
- Little epidemiological and scientific research are ongoing due to lack of attention
- Based on in vitro data, one promising drug, already tested in patients in otehr indications, will shortly be tested in Sudan
- Combined advocacy and R&D efforts are crucial to develop a pipeline of efficacious, safe and affordable candidates

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Acknowledgements

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- Professor Ed Zjilstra (Rotterdam Centre for Tropical Medicine)
- Wendy Van de Sande (Erasmus MC Rotterdam)
- Fred Duncanson, Makoto Asada, Mike Everson (Eisai)

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