

## S4.5a

**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 in combination with surgery, in patients with eumycetoma in Sudan—top line results**

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**Objectives:** To determine whether, in addition to surgery, fosravuconazole (Fos) monotherapy of either 200 mg or 300 mg weekly was more effective [defined as complete cure at the End of Treatment (EOT; 52-week) visit] than the standard-of-care 12-month regimen of itraconazole (Itra) monotherapy, in patients with small to moderate eumycetoma lesions caused by *Madurella mycetomatis*.

**Methods:** This was a single-center (Mycetoma Research Center, Khartoum, Sudan), comparative, randomized, double-blind, parallel-group, active-controlled, clinical superiority trial in participants with eumycetoma requiring surgery. Participants were randomized in a 1:1:1 ratio. In Arm 1 participants took a loading dose of Fos 300 mg on Day 1, Day 2, and Day 3, followed by a weekly dose of 300 mg for a total duration of 12 months. In Arm 2 participants took Fos 200 mg on Day 1, Day 2, and Day 3, followed by a weekly dose of 200 mg for a total duration of 12 months. In Arm 3 participants took Itra 400 mg daily for 12 months. All patients underwent surgery after 6 months of treatment in which the remaining lesion was removed. Mycetoma lesions were between 2 to ≤16 cm in diameter. The age cut-off was ≥15 years. The diagnosis of *M. mycetomatis* was confirmed by PCR. Safety monitoring included, among other, severe, and serious treatment-related events.

**Results:** A total of 122 participants were screened and 104 participants were enrolled (34 in Fos 300 mg, 34 in Fos 200 mg weekly, and 36 in Itra 400 mg). Complete cure after 12 months (EOT) of treatment was demonstrated in terms of an absence of eumycetoma mass, sinuses, and discharge; normal ultrasound of the lesion site or normal MRI; and a negative fungal culture from a surgical biopsy if a mycetoma mass was present. The complete cure rate was assessed in the mITT population. Secondary efficacy analyses were performed in the Per Protocol population. In addition, the influence of age, changes in clinical symptoms and signs, size, and duration of the lesion on outcome was examined. Safety was satisfactory and compliance was good.

**Conclusion:** This is the first randomized controlled trial in eumycetoma, comparing two azoles, fosravuconazole (two dosage regimens) and itraconazole, in combination with surgery. Detailed efficacy and safety results will be communicated and discussed in the oral presentation.

## S4.5b

**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 in combination with surgery, in patients with eumycetoma in Sudan—pharmacokinetic results**

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S4.5 Mycetoma Clinical Trial on fosravuconazole treatment in eumycetoma—Top Line Results, September 22, 2022, 10:30 AM - 12:00 PM

**Objective:** To evaluate the pharmacokinetics (PK) of fosravuconazole (measured as ravuconazole) and itraconazole in patients with mild to moderate eumycetoma caused by *Madurella mycetomatis* using a non-compartmental PK analysis.

**Methods:** Participants received either 200 mg or 300 mg ravuconazole once weekly or 400 mg itraconazole daily for a total duration of 12 months. Plasma concentrations of ravuconazole and itraconazole were measured on day 1 of week 1, and on weeks 2, 3, 4, and months 2, 3, 6, and 12 (at end of treatment) for analysis of population PK. The exact time of dosing on the days of sample collection, and the exact time of sample collection within the collection time window, were recorded. Plasma concentrations were quantified using Ultra-performance Liquid Chromatography with fluorescence detection (UPLC-UV). Ravuconazole and itraconazole plasma concentration-time data was performed using a standard two stage approach with non-compartmental analysis. Derived exposure parameters of ravuconazole and itraconazole, including, but not limited to, C<sub>max</sub> and AUC at steady state (AUCs), were calculated. The effect of covariates, such as baseline characteristics/demographics, on PK were explored. AUCs were determined when at least three subsequent samples within one dosing interval were available.

**Results:** A total of 766 samples of ravuconazole in 68 participants and 226 samples of itraconazole in 36 participants were analyzed. The average concentration of ravuconazole (range) was 3.1 mg/l (0.01-12.33 mg/l), and for itraconazole was 1.59 mg/l (0.01-5.53 mg/l).

Detailed Pharmacokinetic results will be communicated and discussed in the oral presentation.

## S4.5c

**Using serum beta-glucan measurements and sequencing of the *Madurella mycetomatis* azole target gene to predict therapeutic outcome during azole treatment in human mycetoma**

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S4.5 Mycetoma Clinical Trial on fosravuconazole treatment in eumycetoma—Top Line Results, September 22, 2022, 10:30 AM - 12:00 PM

**Objectives:** Eumycetoma is a neglected tropical disease characterized by large subcutaneous swellings and the formation of grains and most commonly caused by *Madurella mycetomatis*. The currently recommended therapy is a combination of antifungal therapy with an azole and surgery. Itraconazole is the current recommended drug and fosravuconazole, the pro-drug of ravuconazole, is currently clinically investigated. At the moment, there are no epidemiological cut-off values (ECV) for *M. mycetomatis* for either of these drugs or rapid diagnostic tests which can predict the therapeutic outcome of these treatments. Therefore, in this study, we determined the ECV for these drugs and determined whether there was a correlation between minimal inhibitory concentration (MIC) and the DNA sequence of the azole target gene CYP51A. We also assessed beta-glucan concentrations in the serum of mycetoma patients during treatment to establish whether any of these values were predictive for therapeutic outcomes.

**Methods:** In order to determine the ECV for *M. mycetomatis*, MIC distributions for itraconazole and ravuconazole were determined in genetically diverse clinical *M. mycetomatis* isolates using the ECOFFinder software. CYP51A sequences were sequenced and comparisons were made between the different CYP51A variants and the MIC distributions. Beta-glucan concentrations were measured in serum with the WAKO beta-glucan assay. Time points analyzed were 0, 22, 85, 176, 267, 358, and 455 days after the start of treatment.

**Results:** For *M. mycetomatis* the MICs ranged from 0.008 to 1 mg/l for itraconazole and from 0.002 to 0.125 mg/l for ravuconazole. The *M. mycetomatis* ECV for itraconazole was 1 mg/l and for ravuconazole 0.064 mg/l. In the wild-type population, two CYP51A variants were found for *M. mycetomatis*, which differed in one amino acid at position 499. The MIC distributions for itraconazole and ravuconazole were similar between the two variants. No mutations linked to decreased susceptibility were found. Before the start of treatment, beta-glucan concentrations ranged from below the detection limit to 217.9 pg/ml. Of these patients, 61.2% had a beta-glucan concentration above 7 pg/ml, the recommended cut-off value for positivity by the manufacturer, 72.8% had a beta-glucan concentration above 5.5 pg/ml, the recommended cut-off value for

*M. mycetomatis*. During the first months of azole treatment, the beta-glucan concentrations remained relatively stable. After surgery, a sharp decrease in beta-glucan concentration in serum was noted. At the end of the observation period, only 13 patients had a beta-glucan concentration above 7 pg/ml and 14 above 5.5 pg/ml. Of these patients, for only 3, there was clinical evidence of a recurrence. For the remaining 4 patients with clinical evidence of a recurrence, the beta-glucan concentration was below the cut-off value for positivity.

**Conclusion:** In conclusion, so far there was no link established with the initial in vitro susceptibility and failure or success of the treatment therapy. Beta-glucan levels, in general, remained high during azole treatment, and a sharp drop in beta-glucan concentration in serum was only noted after surgery. A positive beta-glucan concentration at the end of the treatment was not indicative of a recurrence.

## S4.5d

**Comparing the diagnostic performance of the commonly used eumycetoma diagnostic tests using sequencing of the internally transcribed spacer region as the gold standard**

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S4.5 Mycetoma Clinical Trial on fosravuconazole treatment in eumycetoma—Top Line Results, September 22, 2022, 10:30 AM - 12:00 PM

**Objectives:** Mycetoma is a neglected tropical implantation disease caused by 70 different infectious agents. Identifying the causative organism to the species level is essential for appropriate patient management. Ultrasound, histopathology, culture, and two species-specific PCRs are most commonly used methods for species identification in endemic regions. The aim of this study was to compare the diagnostic performance of these commonly used assays using sequencing of barcoding genes as the gold standard.

**Methods:** This descriptive cross-sectional study was conducted at the Mycetoma Research Center, University of Khartoum, Sudan. It included 222 patients suspected of fungal mycetoma caused by *Madurella mycetomatis*.

**Results:** In total 154 (69.3%) were correctly identified by ultrasound, histology, culture, and both species-specific PCRs. In 60 patients, at least one of the diagnostic tests failed to identify *M. mycetomatis*. A total of five patients had no evidence of eumycetoma, and for three, only the ultrasound was indicative of mycetoma. The two species-specific PCRs were the most sensitive and specific methods, followed by culture and histology. Ultrasound was the least specific as it only allowed differentiation between actinomycetoma and eumycetoma. The time to result was 9.38 minutes for ultrasound, 3.76 h for PCR, 8.5 days for histopathology, and 21 days for grain culturing.

**Conclusion:** Currently, PCR directly on DNA isolated from grains is the most rapid and reliable diagnostic tool to identify *M. mycetomatis* eumycetoma.

## P4

**COVID19-associated fungal infections**

Martin Hoenigl  
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Plenary session 4, September 22, 2022, 2:00 PM - 2:45 PM

Coronavirus disease 2019 (COVID-2019) associated invasive fungal infections (IFIs) have emerged as an important complication in a substantial number of critically ill COVID-19 patients, and three groups of fungal pathogens have increasingly been recognized as causes of superinfections: *Aspergillus*, *Mucorales*, and *Candida*. First reports of cases and case series of COVID-19-associated pulmonary aspergillosis (CAPA) have emerged during the first months of the pandemic. Prevalence rates varied widely due to the fact that CAPA was, and still remains, challenging to diagnose in patients with COVID-19-associated acute respiratory failure (ARF). The clinical picture and radiological findings of CAPA are unspecific and the primarily airway invasive growth in non-neutropenic patients and the late occurrence of angioinvasion in the course of the disease may complicate diagnosis. Current guidelines recommend treatment of CAPA during its early airway invasive phase, which may result in some overtreatment (i.e., treatment in patients that may not develop angioinvasive infection), given the independent contribution of CAPA to devastating mortality rates of around 50% that have been shown in multiple studies. This talk will also review the incidence of COVID-19-associated IFIs caused by *Mucorales*, and *Candida*, including *C. auris*, and will discuss—clinical risk factors, predisposing changes in the host environment, and immunological mechanisms involved in the pathogenesis of these coinfections, as well as current and future diagnostics and treatments.

## S5.1b

**Antifungal r resistance**

Danila Seidel  
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S5.1 Antifungal resistance, September 22, 2022, 3:00 PM - 4:30 PM

Resistance to clinical antimycotics in *Aspergillus fumigatus* has become an increasing threat in healthcare worldwide over the past two decades. Factors that contribute to this continuing trend are manifold, among others resistance emerge in environmental fungi through selection pressure due to fungicides widely used in agriculture and farming, resistant clones are diffused around the world through global travel and shipping routes, as well as prophylactic and long-term administration of antifungal agents in patients with chronic fungal disease creating selection pressure.

Physicians face particular challenges in their patients with invasive aspergillosis, with emerging resistance adding another layer of therapeutic complexity. We are beginning to gain an understanding of the clinical implications of the different patterns of resistance. First international studies have shown that resistance of *A. fumigatus* to clinical antifungal agents significantly hampers the successful treatment of patients.

This presentation aims to highlight the difficulties associated with antifungal resistance in *A. fumigatus* with a focus on hematological oncological patients.

## S5.1d

**Mechanisms of azole antifungal resistance in clinical isolates of *Candida tropicalis***

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S5.1 Antifungal resistance, September 22, 2022, 3:00 PM - 4:30 PM

**Objectives:** In tropical countries, the azole resistance in *Candida tropicalis* is on the rise. There are limited studies available regarding the azole resistance mechanisms in *C. tropicalis*. This study was designed to understand the molecular mechanisms of azole resistance in *C. tropicalis* by using genetic and bioinformatics approaches.

**Methods:** A total of 32 azole-resistant (R) and 10 azole-susceptible (S) clinical isolates of *C. tropicalis* were included in this study. All the isolates were subjected to complete gene sequencing of azole target genes including ERG11 to analyze the mutations which could lead the azole resistance. Four fragments were amplified, sequenced, and aligned to get full-length ERG11 gene. Inducible expression analysis of 17 other genes potentially associated with azole resistance was also evaluated. Homology modeling and molecular docking analysis were performed to study the effect of amino acid alterations in mediating azole resistance.

**Results:** Of the 32 resistant isolates, 12 (37.5%) showed A395T and C461T mutations in the ERG11 gene. The mean overexpression of CDR1, CDR3, TAC1, ERG1, ERG2, ERG3, ERG11, UPC2, and MKC1 in resistant isolates without mutation