S4.4 A randomized, double blind phase 3 proof-of-concept superiority trial of itraconazole 200 mg or 300 mg weekly dose versus itraconazole 400 mg daily, all time 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, itraconazole (ICT) for monotherapy of either 200 or 300 mg weekly or 400 mg daily was as effective as (defined as complete cure at the end of Treatment (TRE), 12-week (W12) trial) or at the standard-of-care 12-month regimen of itraconazole (ICT-monotherapy) in patients with small to medium cutaneous eumycetoma lesions caused by M. syriacum.

Methods: This was a single-center (Mycetoma Research Center, Khartoum, Sudan), comparative, randomised, double-blind, parallel-group, active-controlled, clinical superiority trial in patients with eumycetoma requiring surgery. Participants were randomised in a 1:1:1:1 ratio. At entry 1 participants took a loading dose of 300 mg ICT or 200 mg for 1 week and 120 mg for 12 weeks. ICT was taken as 200 mg for W0-2, 150 mg for W3-12, then 50 mg for 12 weeks. In arms 2 participants took ICT 400 mg daily for 12 months. All patients underwent surgery after 6 months of treatment in which the containing lesion was removed. M. syriacum lesions were between 2 to ≤5 cm in diameter. The age cut-off was 15 years. The diagnosis of M. syriacum was confirmed by PCR. Safety monitoring was included, as well as others, and was a treatment-related endpoint. Results: Total of 122 participants were recruited and 104 participants were enrolled (41, 40, 33, 41) in the 300 mg ICT 400 mg ICT and 36 and 16 in ICT 400 mg (400 mg ICT as control arm). Complete cure at 12 months (EOT) of treatment was demonstrated in terms of an absence of eumycetoma masses, horses, 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 ITT population. Secondary efficacy analyses were performed in the PP population. In addition, the influence of age, changes in clinical symptoms and signs, and duration of the lesion on the outcome were examined. Safety was also compared.

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

S4.5 A randomized, double blind phase 3 proof-of-concept superiority trial of itraconazole 200 mg or 300 mg weekly dose versus itraconazole 400 mg daily, all time arms in combination with surgery, in patients with eumycetoma in Sudan—pharmacokinetic results

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Objectives: To evaluate the pharmacokinetics (PK) of itraconazole (ICT) in eumycetoma patients with small cutaneous forms caused by M. syriacum using a non-compartmental PK Analysis.

Methods: Participants received either 200 mg or 300 mg ICT once weekly or 400 mg ICT daily for a total duration of 12 months. Plasma concentrations of itraconazole and itraconazole metabolites were measured on day 1 (W0) and on weeks 2, 3, 4 and 5 (W2, W3, W4, and W5) after drug intake for analysis of population PK. The PK/r and PK/FC parameters were determined using a non-linear mixed-effects modeling approach.

Results: Results of the whole population are shown below. PK parameters were increased using ICT compared to ICT as a result of lower clearance and higher exposure. The exposure to ICT was increased due to the higher plasma concentrations and longer half-life of ICT compared to ICT. The ratio of ICT PK parameters to ICT was calculated. The PK parameters were compared to previous ICT PK parameters in the literature.

Conclusion: The PK parameters of ICT were increased compared to ICT in patients with cutaneous eumycetomas, with longer half-life and lower clearance leading to increased exposure. This is important to consider when interpreting clinical data from previous ICT PK studies in patients with cutaneous eumycetomas. These findings will be further investigated in a pharmacokinetic-pharmacodynamic study.

S4.5c Using serum beta-glucan measurements and sequencing of the Maduromycete eumycetoma zylo gene to predict therapeutic outcome during antifungal treatment in human eumycetomas

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Objectives: Eumycetomas are a neglected tropical disease characterized by large subcutaneous swellings and the formation of granulomas and most commonly caused by M. syriacum. The currently recommended therapy is a combination of antifungal (e.g., itraconazole) or surgery as a last resort. Itraconazole is currently recommended drug and four famous sequences of itraconazole, is currently clinically investigated. At the moment, there are no epidemiological cut-off values (ECV) for M. syriacum for either of these drugs or rapid diagnostic tests which can predict the therapeutic outcome of these treatments. Therefore, the objective of this study is to determine the ECV for these drugs and determine whether there was a correlation between minimal inhibitory concentration (MIC) and the DNA sequence of the zylo gene for C. fumigatus. We also assessed beta-glucan concentrations in the serum of eumycetoma patients during treatment to establish whether any of these values were predictive for therapeutic outcomes.

Methods: In order to determine the ECV for M. syriacum, MIC distributions for itraconazole and voriconazole were determined in an aerobically driven M. syriacum isolate using the Etest method. C. fumigatus sequences were sequenced and compared with those of other Candida and C. albicans. These sequences were used to build a database for the CARD database and the local cluster analysis. These results were used to predict the outcome of these treatments.

Conclusion: These results indicate that the use of beta-glucan measurements and sequencing of the zylo gene may be a useful tool for predicting therapeutic outcomes in eumycetomas.

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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Objectives: This study compared the diagnostic performance of commonly used eumycetoma diagnostic tests using sequencing of the internally transcribed spacer region (ITS) as the gold standard.

Methods: ITS sequences were obtained from 100 eumycetoma patients using the ITS-1 and ITS-2 primers. The ITS sequences were compared with the ITS sequences of eumycetoma and other fungal species using the BLAST search tool provided by NCBI. The sensitivity and specificity of the commonly used eumycetoma diagnostic tests were compared to the gold standard.

Results: The ITS sequences were compared with the ITS sequences of eumycetoma and other fungal species using the BLAST search tool provided by NCBI. The sensitivity and specificity of the commonly used eumycetoma diagnostic tests were compared to the gold standard.

Conclusion: The ITS sequences were compared with the ITS sequences of eumycetoma and other fungal species using the BLAST search tool provided by NCBI. The sensitivity and specificity of the commonly used eumycetoma diagnostic tests were compared to the gold standard.