5.4. A randomized, double-blind phase 3 proof-of-concept superiority trial of furonacrolone 200 mg or 300 mg weekly dose versus itraconazole 400 mg daily, all times in combination with surgery, in patients with eumycetoma in Sudan—Top line results

Ahmed Hassan Fahal1, Sahar Mutabar Bahatki1, El Samir Waksi Waked Mohamed1, Eman Siddig Ahmad1, Osema El Hadi Bakar4, Bako Adel Reyyan4, Lamta Ahmed Siddig1, Edward E. Zijlstra1, Peer Enoksson1, Peer Edler1, Martin Thaddaeus4, Martin Martin4, Ahmed Hadi Fahal1

Methods: This was a single-center (Mycomy Research Center, Khartoum, Sudan), comparative, double-blind, parallel-group, active-controlled, clinical superiority trial in patients with eumycetoma requiring surgery. Participants were randomized in a 1:1:1 ratio. At arm 1 participants took a loading dose of 500 mg on day 1, Day 2, and Day 5, followed by a weekly dose of 200 mg for a duration of 12 months. In arm 2 participants took foxaconazole 200 mg daily for 12 months. In arm 3 patients took itraconazole 400 mg daily for 12 months. All patients underwent surgery 6 months after treatment in which the remaining lesion was removed. Mycetoma lesions were between 2.0 to 5.4 cm in diameter. The age cut-off was 15 years. The diagnosis of m. syneyctoma was confirmed by PCR. Safety monitoring included, among others, severe, and serious treatment-related events.

Results: A total of 122 participants were screened and 104 participants were enrolled (18 foxaconazole 200 mg Foxa 500 mg 4 Fox 200 mg, and 36 in itraconazole 400 mg). Complete cure after 12 months (IOT) of treatment was demonstrated in terms of an absence of eumycetoma mass, sinus, and discharge, normal ultrasonography of the lesion site or normal MRI, and a negative fungal cultures 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 Per Protocol population. In addition, the influence of age, changes in clinical symptoms and signs, and duration of the lesion on outcome was examined. Cure was determined as follows:

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

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

Rogier Bruggeman1, Borna Nyaiki2, Eiman Siddig Ahmad1, Emanmed Edwar Siddig1, Thaddaeus Egmond1, Peer Edler1, Sahar Mutabar Bahatki1, Edward E. Zijlstra2, Ahmed Hadi Fahal1

1Realis University Medical Center, Nijmegen, Netherlands
2Drug for Neglected Diseases Initiative (DNDi), Nairn, Kenya
3Mycomy Research Center, Khartoum, Sudan
4Drug for Neglected Diseases Initiative (DNDi), Geneva, Switzerland

Methods: To evaluate the pharmacokinetics (PK) of foxaconazole (measured as itraconazole) and itraconazole in patients with eumycetoma caused by M. syneyctoma using a non-compartmental PK analysis. Methods: Participants received either 200 mg or 300 mg foxaconazole once weekly or 400 mg itraconazole daily for a total duration of 12 months. Plasma concentrations of itraconazole and iraconazole were measured on day 1, week 1, and on weeks 2, 3, 4, and months 3, 6, and 12 (at end of treatment) for analysis of PK parameters. The exact time of drawings 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 (ULC-UV). Itraconazole and itraconazole plasma concentrations thus were measured using a standard two-staged approach with non-compartmental analyses. Derived exposure parameters of itraconazole and iraconazole, including, but not limited to, Cmax, AUC, and %F were calculated. The model used was a simple baseline pharmacokinetics model and PK was explored. AUCs were determined when at least three subsequent samples within one dosing interval were available. Results: A total of 146 samples of foxaconazole in 34 participants and 226 samples of itraconazole in 36 participants were analyzed. The average total exposure (area under the curve) of foxaconazole (range) was 3.1 mg/l (0.01-12.35 mg/l) and 1.19 mg/l (0.01-5.35 mg/l). Derived Pharmacokinetic results will be communicated and discussed in the oral presentation.

5.5c. Using serum beta-glucan measurements and sequencing of the Madurella mycetomatis azole target genes to predict therapeutic outcome during azole treatment in human mycetoma

Berndt Nyaikong1, Emanmed Siddig1,2,3,4 Nyaiki Mhofu2, Borna Nyaiki2, Ed Zijlstra1, Annemarie Verton3, Sahar Bahatki1, Ahmed Fahal1, Wendy Van de Sande1

1EraMUC-ERA Medical University Hospital—Department of Medical Microbiology & Infectious Diseases, Rotterdam, Netherlands
2Mycomy Research Center, University of Khartoum, Khartoum, Sudan
3University of Khartoum, Faculty of medical laboratory sciences, Khartoum, Sudan
4Drug for Neglected Diseases Initiative (DNDi), Geneva, Switzerland

Methods: To evaluate the efficacy of serum beta-glucan measurements and sequencing of the Madurella mycetomatis azole target genes to predict therapeutic outcome during azole treatment in human mycetoma. The current recommended therapy is a combination of antifungal treatment such as itraconazole 200 mg daily for 6 months. Itraconazole is the current recommended drug and four-second generation itraconazole, the pro-drug of itraconazole, is currently clinically investigated. At the moment, there are no epidemiological cut-off values (ECV) for M. syneyctoma for either of these drugs or rapid diagnostic tests which can predict the therapeutic outcome of these treatments. Therefore, in this study, we determined whether there was a correlation between minimal inhibitory concentration (MIC) and the DNA sequence of the azole target gene CYP114. 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. syneyctoma, MIC determinations for itraconazole and voriconazole were determined in an anaerobic drool. Cytomycetoma isolates from the current recommended treatment for itraconazole, the pro-drug of itraconazole, is currently clinically investigated. At the moment, there are no epidemiological cut-off values (ECV) for M. syneyctoma for either of these drugs or rapid diagnostic tests which can predict the therapeutic outcome of these treatments. Therefore, in this study, we determined whether there was a correlation between minimal inhibitory concentration (MIC) and the DNA sequence of the azole target gene CYP114. 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. syneyctoma, MIC determinations for itraconazole and voriconazole were determined in an anaerobic drool. Cytomycetoma isolates from the current recommended treatment for itraconazole, the pro-drug of itraconazole, is currently clinically investigated. At the moment, there are no epidemiological cut-off values (ECV) for M. syneyctoma for either of these drugs or rapid diagnostic tests which can predict the therapeutic outcome of these treatments. Therefore, in this study, we determined whether there was a correlation between minimal inhibitory concentration (MIC) and the DNA sequence of the azole target gene CYP114. 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. syneyctoma, MIC determinations for itraconazole and voriconazole were determined in an anaerobic drool. Cytomycetoma isolates from the current recommended treatment for itraconazole, the pro-drug of itraconazole, is currently clinically investigated. At the moment, there are no epidemiological cut-off values (ECV) for M. syneyctoma for either of these drugs or rapid diagnostic tests which can predict the therapeutic outcome of these treatments. Therefore, in this study, we determined whether there was a correlation between minimal inhibitory concentration (MIC) and the DNA sequence of the azole target gene CYP114. 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. syneyctoma, MIC determinations for itraconazole and voriconazole were determined in an anaerobic drool. Cytomycetoma isolates from the current recommended treatment for itraconazole, the pro-drug of itraconazole, is currently clinically investigated. At the moment, there are no epidemiological cut-off values (ECV) for M. syneyctoma for either of these drugs or rapid diagnostic tests which can predict the therapeutic outcome of these treatments. Therefore, in this study, we determined whether there was a correlation between minimal inhibitory concentration (MIC) and the DNA sequence of the azole target gene CYP114. 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.