DNDi
Drugs for Neglected Diseases *initiative*

CLINICAL TRIAL PROTOCOL SYNOPSIS

Long term follow-up study after end of treatment of clinical trial participants enrolled in: 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.'

Name of product(s)	N/A.
Drug Class	N/A
Phase	N/A
Indication	To assess the long-term recurrence rate in clinical trial participants treated in DNDi-FOSR-04-MYC
Protocol Number	DNDi-FOSR-05-MYC
Sponsor	DNDi, Chemin Camille Vidart, 15, 1202 GENEVA Switzerland Phone: +41 22 906 9230
National Coordinating Investigator/Principal Investigator	
SAC approval	Yes
Clinical Trial Protocol Synopsis Version / Date	v0.3_19 July 2022

Background Information and Trial Rationale	Eumycetoma is a fungal disease commonly caused by Madurella mycetomatis. The disease is chronic, granulomatous, and inflammatory. It usually involves subcutaneous tissues and leads to masses and sinuses from which fungal grains are discharged. It is most probably introduced as post trauma e.g., thorn prick. It is associated with major morbidity and can be disabling, disfiguring and highly stigmatizing. In advanced cases it may be fatal. Eumycetoma is the most prevalent in what is known as the mycetoma belt. The available drugs for the treatment of eumycetoma are expensive and require a long treatment period up to 12 months. By that time the mass is well encapsulated and is removed surgically. Despite prolonged medical treatment, causative organisms are commonly found to still be viable and can be cultured from the surgical specimen. Fosravuconazole belongs to the azole group and has been repurposed by DNDi from studies in Chagas' disease; it has a favorable safety profile and because of the long half-life, can be given once a week. Fosravuconazole is an orally available prodrug of ravuconazole which is rapidly converted to ravuconazole and provides substantial pharmacokinetic benefits over ravuconazole itself. The parent study: 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. The study had a total of 104 clinical trial participants enrolled with its First Patient First Visit on 9th May 2017 and Last Patient Last Visit on 10th June 2021. There were three arms in the study; all treatments were given for 12 months. • Arm 1: Fosravuconazole 300 mg weekly for 12 months. • Arm 2: Fosravuconazole 200 mg weekly for 12 months. • Arm 3: Itraconazole 400 mg daily for 12 months (as the standard treatment control arm). After End of Treatment visit at 12 months, one more follow-up visit was done at 15 months (End of Study visit). Results from the parent study demonstrated that: • No superiority of fosravuconazole arms over itraconazole (all with surgery); all 3 arms had similar cure rates • Per Protocol analysis shows efficacy of 69% to 83%. • The treatments were overall well tolerated and there were no severe or serious treatment-related safety issues during the trial, with good compliance. • When compliance is ensured and patients have access to adequate care, treatment outcome is satisfactory (approx. 70%) The purpose of the Long-Term Follow-up Study is to collect data on the recurrence of mycetoma lesions in patients who previously participated in the parent study.

	This data will provide additional information on recurrences more than 3 months after the end of treatment. The study is a retrospective descriptive study.
Trial Objectives	**Primary Objective** To assess the recurrence rate of the eumycetoma lesion, >3 months after the end of treatment (EOT) in all three study arms. **Secondary Objectives** 1) To determine the efficacy of fosravuconazole 200 mg or 300 mg monotherapy and that of itraconazole monotherapy, after long term follow-up (>3 months after EOT). 2) To describe the etiologic pathogen (subtype of fungus) after long term recurrence 3) To evaluate the recurrence of free survival for each treatment regimen after EOT. 4) To determine overall long-term efficacy of fosravuconazole 200 mg or 300 mg monotherapy and that of itraconazole monotherapy
Trial Endpoints	**Primary Endpoint** The recurrence of the eumycetoma lesion, >3 months follow-up after EOT **Secondary Endpoint(s)** 1) Evidence of no eumycetoma lesion, >3 months follow-up after EOT 2) The etiologic pathogen subtypes of fungus, >3 months follow-up after EOT 3) The recurrence free survival defined as time from EOT to recurrence. 4) Evidence of no eumycetoma lesion after long-term follow up
Trial Design	This is a retrospective descriptive study to detect recurrence of eumycetoma during long-term follow-up of at least 3 months after the end of treatment.

Main Entry Criteria Inclusion Exclusion	All clinical trial participants that were recruited in the parent clinical trial will be included except subjects who had recurrence of eumycetoma lesion before month 15. The parent clinical trial had enrolled 104 clinical trial participants with 26 having recurrence before month 15. Therefore, the long-term follow-up assessment will target 78 subjects. Inclusion criteria 1) Subjects must meet all the following inclusion criteria to be eligible for enrollment into the study: 2) Clinical trial participants who were previously enrolled and received investigational product (fosravuconazole) or standard of care treatment (itraconazole) in the DNDi-FOSR-04-MYC DNDi clinical trial. 3) Able and willing to give written informed consent for participation in this study, prior to the performance of any study procedures. Exclusion criteria 1) Any condition that, in the opinion of the Principal Investigator or designee, would preclude provision of informed consent or interfere with achieving the study objectives.
Study Duration	The recruitment of clinical trial participants will take place over a period of 5-6 months.
Study treatments	N/A

Statistics Sample size Randomisation Summary of analysis	**Sample size determination** All clinical trial participants that were recruited in the parent clinical trial will be included except subjects who had recurrence of eumycetoma lesion before month 15. The parent clinical trial had enrolled 104 clinical trial participants with 26 having recurrence before month 15. Therefore, the long-term follow-up assessment will target 78 subjects. **Efficacy Analysis** The primary analysis of recurrence rate for each study arm will be presented as the number and percentage of subjects with recurrence after long-term follow up along with the corresponding two-sided exact Clopper-Pearson 95% confidence interval (CI). The comparison of efficacy fosravuconazole 200 mg or 300 mg monotherapy versus that of itraconazole monotherapy after long term follow up will be done using logistic regression to allow adjustment for any possible baseline confounders. Recurrence free survival time will be defined as the time from the date of EOT (date of month 12 visit) to the date of first recurrence during the long term follow up. The recurrence free survival time will be censored at the last date of the long-term assessment for subjects who do not have recurrence. A Kaplan Meier survival method will be used to assess the recurrence free survival times with a log rank test performed to test significant differences in recurrence free survival times between the treatment groups. The incidence rate (IR) of each study group will be presented with corresponding 95% confidence intervals (CI). The IR will be calculated as the ratio of the number of subjects with recurrence during the long term follow up to the person-time at risk. The incidence rate ratio (IRR), which is also referred to as a relative risk (RR), will be calculated by dividing the incidence rate of recurrence in fosravuconazole 200 mg or 300 mg group and incidence rate of recurrence in the itraconazole group. In case there are confounders to consider, Cox regression will be used to estimate hazard ratio (HR) which can be interpreted as IRR with itraconazole as reference group.

Table 1- Schedule of events

Long-term Follow up Schedule of events	
Follow up study timeline in reference to EOT	>3 months visit
Vital Signs	X
Eumycetoma Exam	X
Mycetoma Signs & symptoms	X
Photography of eumycetoma lesion (2D)	X
Biopsy-Mycology and Histopathology	X
Medical imaging-Ultrasound	X
Culture	X
Adverse Events *(If assessed to be related to previous study treatment)*	X
Study Completion	X

Planning Information

Study Timelines

Final protocol available	July 2022
Study treatment supply available	N/A
FSFV	September 2022
Duration of recruitment period	4-5 months
Duration of follow-up period (if applicable)	N/A
LSLV	January 2023
Interim analysis	N/A
Final study report	March 2023

STUDY SCOPE

Target countries	Monocenter study- Sudan
Enrollment target	78 Clinical Trial Participants
Number of sites	One (10
Number of subjects per site	N/A
DSMB involvement	N/A

Partners involvement	Principal Investigator- Prof Ahmed H Fahal, Mycetoma Research Centre, Soba University Hospital Wendy W.J. van de Sande, Senior Researcher, Department of Medical Microbiology and Infectious Diseases, Erasmus MC, Rotterdam, The Netherlands; typing of isolates
Other special needs	N/A

Study Treatments Supply

N/A