SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Investigational Product	JNJ-16269994 (itraconazole)

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Prepared by: Janssen Research & Development, LLC;

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Title of Study: Itraconazole in the Management of Superficial Fungal Infections in India: A Pilot Study

Coordinating Investigator: Sanjeev Handa, MD, FAMS, FAAD, FRCP PPD India

Study Center(s): India (04 sites: Nagpur [13], Chandigarh [12], Chennai [10], and Mangalore [05])

Publication (Reference): None

Study Period: 16 August 2019 (Date first participant signed informed consent) to 20 March 2020 (Date of last observation for last participant recorded as part of the database)

Phase of Development: Phase 4

Objectives: The objectives of this pilot study were:

Primary objective:

- Estimate the proportion of participants prescribed itraconazole for *Tinea cruris* or *Tinea corporis* who had clinical response after 7 days of treatment.

Secondary objectives:

- Estimate the proportion of participants prescribed itraconazole for *T. cruris* or *T. corporis* who had mycological response after 14 days of follow-up.
- Association of the clinical response with plasma drug concentrations of itraconazole and hydroxy-itraconazole at Day 7.
- Association of the clinical response with the baseline sensitivity pattern of causative fungi at Day 7.
- Estimate the proportion of participants with clinical response after 14 days of follow-up. Estimate the extent to which clinical improvement at Day 7 predicts clinical improvement at Day 14.

Exploratory (tertiary) objective:

- Evaluate the proportion of participants that came for follow-up after 7 days of treatment.

Methodology:

This was a real-world, prospective, non-randomized, open-label, multicenter, interventional, longitudinal pilot study conducted in India. The study was conducted to evaluate the treatment outcomes and risk factors associated with clinical response in adult participants with *T. cruris* or *T. corporis* after being treated with itraconazole as a part of their clinical care.

The interventions in this study were the systematic evaluation of clinical response, isolation of cultures of causative organism from the lesions, and determination of plasma concentrations of itraconazole and hydroxy-itraconazole. The study consisted of 3 phases: a 3-day Screening Phase, a 7-day open-label Treatment Phase followed by a 7-day Observation Phase, and end of study visit at Day 14.

Number of Participants (planned and analyzed):

Number of participants planned: 50
Number of participants (All Enrolled Analysis Set, Safety population): 37
Number of participants (Intent-to-treat [ITT] Analysis Set): 28
Number of participants (Pharmacokinetics [PK] population): 28

The recruitment time planned for this pilot study was 4 months, however, the period was extended to 10 months due to the Coronavirus Disease-2019 (COVID-19) pandemic. The data available within the 10 months of recruitment were used for analysis.

Diagnosis and Main Criteria for Inclusion:

The target population consisted of adult men and women (18 to 60 years of age, both inclusive) clinically diagnosed with *T. cruris* or *T. corporis* with or without history of treatment, and were prescribed itraconazole 200 mg/day (study agent) orally for the treatment of *T. cruris* or *T. corporis.* All participants had signed an informed consent form and women participants (of childbearing potential) have had a negative β-human chorionic gonadotropin at Screening before start of the prescribed itraconazole.

Participants with following main criteria were not included in the study, if it was determined upon prestudy examination that they had:

- Presence of other dermatoses such as psoriasis, seborrheic, or atopic dermatitis, infections with organism with known or established resistance to itraconazole, or co-existing fungal infection of other body area.
- Received oral itraconazole, topical antifungal, or corticosteroid therapy (within 14 days before screening), other systemic antifungal or corticosteroid therapy (which was not discontinued for at least 30 days prior to start of prescribed itraconazole), and/or received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 3 months before the planned first dose of itraconazole or currently enrolled in an investigational study.
- A proven or suspected infection with *Fusarium* species (spp), mucorales, or other agents considered not susceptible to itraconazole by the treating physician.
- History of ventricular dysfunction such as congestive heart failure (CHF) or received treatment for CHF, liver or renal insufficiency; significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, psychiatric, or metabolic disturbances at any time prior to the start of study; known achlorhydria or on treatment of gastric acidity; or known allergies, hypersensitivity, or intolerance to itraconazole or its excipients or to any other azole or participants had consumed drugs that were cytochrome P-450 (CYP) 3A4 substrates.

- Pregnant, or breastfeeding women, or women of childbearing potential planned to become pregnant or men who planned to father a child; while enrolled in this study or within 2 weeks after the last dose of study agent.
- Any condition for which, in the opinion of the investigator, participation was not in the best interest of the participant or that could prevent, limit, or confound the protocol-specified assessments.

Test Product, Dose and Mode of Administration, Batch No.: Itraconazole capsules prescribed by treating physicians were dispensed by the pharmacies of participants' choice. Participants were instructed to take their prescribed dose of itraconazole orally each day after a full meal. The dosage was a 200 mg capsule or 2 capsules of 100 mg each. The capsules were to be taken once daily, on Day 1 after screening through Day 7. Total duration of treatment was decided by the treating physician as part of the participant's clinical care and standard of practice. Itraconazole was not provided by the sponsor and it was purchased by the participant directly from the pharmacy, thus batch numbers are not applicable.

Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable.

Duration of Treatment: The study duration, including the enrollment and follow-up (telephone) was a maximum of up to 7 days, if the participants completed Day 7 visit or a maximum of up to 14 days, if they completed Day 14 visit.

Criteria for Evaluation

Efficacy Evaluations

- The Clinical Evaluation Tool was used to assess the severity of signs and symptoms with a total score from 0 to 18 at each visit (baseline, at Day 7, and at Day 14).
  - The total scores at Day 7 and at Day 14 were compared with baseline scores and were used to define the percentage of clinical improvement. The percentage of clinical improvement was used to classify the clinical efficacy using the Investigator Global Evaluation Tool.
  - A score from 1 to 5 was assigned at Day 7 and at Day 14 based on the percentage of clinical improvement. Clinical response was defined as having scores 1 or 2 ("healed" or "markedly improved").
- Plasma concentrations of itraconazole and hydroxy-itraconazole were assessed against the clinical outcomes.
- Skin scrapings for culture and sensitivity analysis were collected to evaluate the baseline resistance to itraconazole and its association with clinical outcomes.
- Antifungal sensitivity testing was carried out with a microdilution method according to the Clinical and Laboratory Standards Institute (CLSI) M27 guidelines. The minimum inhibitory concentration (MIC) of itraconazole of fungal pathogens from each individual participant was determined before administration of study agent.

Safety Evaluations

Clinical evaluation of adverse events (AEs) and laboratory assessments were performed by the treating physician, based on the standard-of-care.

Statistical Methods

No formal hypothesis testing was conducted as this was a pilot study. The sample size was not calculated based on power. The point estimate and the corresponding 95% confidence intervals (CIs) for the efficacy endpoints were provided. The populations used for analysis included PK population, efficacy population (based on ITT analysis set), and safety population.

RESULTS

Of the 40 enrolled participants, 20 (50%) participants completed the study and an equal number of participants terminated study participation prematurely. A total of 37 participants were treated with study treatment. Out of 37 participants who received the study treatment, 17 (45.9%) participants discontinued study treatment. The most common reasons for study treatment discontinuation were "Other reasons" by 13 (35.1%) participants. "Other reasons" included the COVID-19 related reasons (6 participants did not continue the site visit due to complete lockdown).

The mean (SD) age of participants was 35.5 (12.73) years. Of the 40 participants, majority (25 [62.5%]) were male. The median Clinical Evaluation Tool Signs and Symptoms (CET SS) total score was 5.5 (range: 2 to 10). Potassium hydroxide (KOH) mount from skin scrap was positive for 37 (92.5%) participants.

Majority (9 of the 11) of the participants had taken antihistamines for systemic use as a prior medication and 2 of the 11 participants received medications for pre-existing comorbid conditions of Type-2 diabetes mellitus and hypothyroidism.

A total of 12 major protocol deviations were reported in the study. The deviations were due to the COVID-19 related reasons (5 participants) and inadvertent missed by the sites to perform skin scrapping culture and sensitivity test on Day 14 (7 participants).

PHARMACOKINETIC RESULTS: A total of 28 participants were included in the PK population and provided samples on Day 7. Following oral administration of 200 mg (once daily) itraconazole or reference itraconazole, concentrations of itraconazole and hydroxy-itraconazole were quantifiable in plasma prior to dosing on Day 7 in 23 of the 26 available samples with a lower limit of quantification (LLOQ) of 20 ng/mL for both the analytes. Of the 3 participants who had plasma concentrations below quantification limit (BQL) prior to dosing on Day 7, one participant also had no quantifiable plasma concentrations of itraconazole and hydroxy-itraconazole at 2 hours and 4.5 hours postdose. Mean plasma concentrations for itraconazole and hydroxy-itraconazole were comparable between nonresponders (participants with a clinical response score of 3 to 5) and responders (participants with a clinical response score of 1 or 2) on Day 7.

EFFICACY RESULTS: The results showed that estimated proportion of the participants with clinical response of "healed" or "markedly improved" based on Investigator Global Evaluation Tool after 7 days of treatment was 42.9% with 95% CI (24.53%, 61.19%).

Eight of the 13 participants (61.5%; 95% CI: 35.09%, 87.98%) had mycological response after 14 days follow-up. Two of the 13 participants had positive culture and the isolated microorganism was *Trichophyton mentagrophytes* species complex at baseline and Day 7 visit, thus mycological failure was concluded for 2 of the participants.

For itraconazole, the MIC values were reported between $\leq$0.03 mcg/mL to 0.5 mcg/mL for 32 participants. There was no association of the causative fungi MIC at baseline with the clinical response at Day 7.

Associations of the clinical response at Day 7 with plasma drug concentrations of itraconazole and hydroxy-itraconazole were assessed by the scatter plots. These plots indicated that there was no association between the highest and lowest observed plasma concentrations of itraconazole and hydroxy-itraconazole versus clinical response scores at Day 7.

The estimated ratio for proportion of the participants with clinical response after 14 days of follow-up was 2.1. Thus, the responders showed approximately a 2-fold improvement in the clinical response at Day 14 compared with Day 7.

SAFETY RESULTS: Of the 37 participants, 1 participant was withdrawn from study participation due to the treatment-emergent adverse event (TEAE) of *Tinea cruris* (Preferred Term), reported as "worsening of *T. cruris*" by the treating physician. No serious adverse events (SAEs) and deaths were reported during the study. There were no clinically significant changes in vital signs.

STUDY LIMITATIONS: The current study was an open-label, non-randomized pilot study and was terminated early by the sponsor due to the COVID-19 pandemic. Thus, interpretation of study results was difficult and definitive conclusions could not be reached.

CONCLUSIONS: A total of 40 participants were enrolled in the study. Of the total participants, only 50% of the participants completed the study. The results showed that estimated proportion of the participants with clinical response of "healed" or "markedly improved" based on Investigator Global Evaluation Tool after 7 days of treatment was 42.9%. The estimated proportion of the participants with mycological response at Day 14 was 61.5% (8 of the 13 participants). Of them, 2 participants had mycological failure, both with *T. mentagrophytes* species complex isolated at baseline and Day 7 visit.

There was no association of the causative fungi MIC at baseline with clinical response at Day 7. Minimum inhibitory concentration values for itraconazole were within the susceptibility range for all cultured dermatophytes. There was no correlation between plasma concentrations of itraconazole or hydroxy-itraconazole and clinical response at Day 7 visit. Overall, the treatment setting was challenging, with a lack of correlation between PK results and observed outcome, along with an absence of itraconazole resistance in the causative organisms.

In conclusion, the pilot study helped to understand the challenges associated with the treatment of dermatomycosis in India as well as the feasibility (design and execution) of conducting a real-world, full study for such condition, if warranted. However, due to premature termination of the study, the results were difficult to interpret and reaching unequivocal and definitive clinical conclusions was not possible.

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