

Safety and Efficacy of Sertaconazole Nitrate Cream 2% in the Treatment of Tinea Pedis Interdigitalis: A Subgroup Analysis

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Sertaconazole nitrate is a broad-spectrum antifungal agent indicated in the United States for the treatment of tinea pedis interdigitalis. The objective of this subgroup analysis was to evaluate the safety and efficacy of sertaconazole nitrate cream 2%, specifically in participants with tinea pedis interdigitalis (ie, fungal skin disease of the toe web) of dermatophyte origin. A total of 92 participants were included in this analysis. The primary end points were eradication of the pathogen (confirmed by fungal culture results) and reduction in total clinical score (TCS) of at least 2 points. Secondary end points included reducing signs and symptoms and reporting adverse events (AEs). After 4 weeks of treatment, 88.8% (79/89) of evaluable participants achieved success on the primary end points. Most participants also demonstrated substantial improvement in signs and symptoms after 4 weeks of treatment: 63.7% (58/91) were free of erythema, 33.0% (30/91) were free of

desquamation, and 91.2% (83/91) were free of itch. The rate of reported AEs was low (8.7% [8/92]), and none were considered serious. These findings indicate that sertaconazole nitrate cream 2% is highly safe and effective in the treatment of tinea pedis interdigitalis.

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Cutaneous fungal infections are among the most common skin diseases, occurring in 10% to 20% of the US population.¹ In particular, tinea pedis interdigitalis is the most common type of cutaneous fungal infection, most frequently affecting men aged 20 to 40 years.^{1,2} Treatment primarily consists of topical antifungal agents. Sertaconazole nitrate is a topical imidazole derivative approved by the US Food and Drug Administration for the treatment of tinea pedis interdigitalis.³ It is a broad-spectrum agent with antifungal, anti-inflammatory, and antipruritic properties, as well as antibacterial activity against gram-positive bacteria.⁴⁻⁷ In clinical studies sertaconazole nitrate cream 2% has demonstrated efficacy in the treatment of tinea pedis and other superficial mycoses.⁸⁻¹⁰ Studies have reported substantially higher cure rates with sertaconazole than with vehicle or miconazole.^{8,10}

A prospective, randomized, controlled, multicenter study evaluated 2 different formulations of sertaconazole nitrate (cream 2% vs solution 2%) for the treatment of tinea corporis, tinea pedis interdigitalis, or corresponding candidosis (N=313). Approximately 90% of all participants treated with either formulation achieved eradication of the pathogen and reduction in total clinical score (TCS) over the 28-day study.¹¹ The primary objective of the current subgroup analysis was to

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evaluate the safety and efficacy of sertaconazole nitrate cream 2%, specifically in participants with tinea pedis interdigitalis (ie, fungal disease of the toe web) of dermatophyte origin. Secondary objectives included documenting fungal culture results, reduction in TCS of signs and symptoms, and adverse events (AEs) in the subpopulation.

Methods

This subgroup analysis accounts for participants with tinea pedis interdigitalis of dermatophyte origin (the subgroup analysis set) and excludes participants with infections only of the foot or due to other pathogens (eg, *Candida* species). The study from which this subgroup was drawn was a prospective, open-label, randomized, controlled, parallel-group, multicenter noninferiority therapy study comparing 2 formulations of sertaconazole nitrate 2% (cream vs solution) for the treatment of tinea corporis, tinea pedis interdigitalis, or corresponding candidosis.¹¹ The study was conducted in accordance with European Community Good Clinical Practice standards, and the final study protocol was approved by relevant ethics committees before study initiation. All participants provided informed consent. Twenty-four dermatologic centers in Germany participated.¹¹

The full methods of the parent study have been previously described.¹¹ In summary, eligible participants aged 18 to 70 years with presumed tinea corporis or tinea pedis interdigitalis resulting from dermatophyte infection or candidosis on a corresponding part of the body were randomized to treatment with either sertaconazole nitrate cream 2% or sertaconazole nitrate solution 2%. Information regarding concomitant illnesses was not recorded; therefore, the immunocompetence of study participants was not known. The study drug was applied twice daily for 28 days. The enrollment goal for the parent study was approximately 160 participants in each group.¹¹

Participants were evaluated at baseline (visit 1), after 2 weeks of treatment (visit 2), and after the 2 final weeks of treatment (visit 3).¹¹ At each visit specimens were obtained for fungal cultures and a clinical assessment was performed for signs and symptoms. Two Sabouraud glucose agar plates per sample with and without cycloheximide were tested under aerobic conditions at 30°C (1°C) for 28 days with daily readings. Specific dermatophyte species was not determined. If a fungal infection due to dermatophytes or *Candida* species could not be verified by fungal culture at baseline, the participant was excluded from the study.¹¹

Disease severity was determined based on the TCS of 5 signs and symptoms: erythema, desquamation, vesicles, pustules, and itch.¹¹ The signs and

symptoms were graded on a 4-point intensity scale (0=absent; 1=mild; 2=moderate; 3=severe). The TCS was calculated by adding the scores for each sign and symptom. To be included in the study, participants were required to have a TCS greater than or equal to 6 as well as fungal infection confirmed by microscopic examination at baseline.¹¹

Only participants with tinea pedis interdigitalis of dermatophyte origin, with or without additional mycosis of the foot, treated with sertaconazole nitrate cream 2% in the parent study were included in the subgroup analysis set for the current study. Participants with *Candida* or *Candida* and dermatophyte coinfection were excluded from the subgroup analysis. In the study population at large, mycosis was caused by dermatophytes alone in 91% of participants.¹¹ Statistical analysis was descriptive for each end point: eradication of the pathogen (confirmed by fungal culture results), reduction in TCS, and AEs.

Results

A total of 92 participants composed the subgroup analysis set for this study (62 men, 30 women). The location of mycosis was predominantly the interdigital space of the foot alone in 90 participants, and 2 participants had both mycosis of the interdigital space and foot mycosis, including glabrous skin at a different site. Complete data were available for 89 participants for the combined primary end point of eradication of the pathogen by visit 3 and reduction in TCS (overall success); TCS was not obtained for one participant at visit 3 (n=91), and fungal culture results were available for 89 of 92 participants at the final study visit.

For the primary end point, 89.9% (80/89) of participants had eradication of the pathogen and 97.8% (89/91) had reduction in TCS of at least 2 points by visit 3 (Table). Overall, 79 of 89 participants (88.8%) achieved both primary end points for successful treatment.

Improvements in the secondary end point—reduction in erythema, desquamation, and itch—are illustrated in the Figure. Each symptom improved from visit 1 to visit 3. At visit 3, 63.7% (58/91) of participants were free of erythema, 33.0% (30/91) were free of desquamation, and 91.2% (83/91) were free of itch. Most participants had either absent or mild symptoms by visit 3.

For the 2 participants with both tinea pedis interdigitalis and foot mycosis at a different site, improvements in primary and secondary end points at each site were not recorded separately. Therefore, improvements in tinea pedis interdigitalis versus foot mycosis cannot be differentiated for these 2 participants.

Adverse events were reported by 8 of 92 participants (8.7%) during the study; none were considered serious.

Success on the Primary End Points in the Subgroup Analysis Set (N=92)

End Point ^a	Participants, n (%) ^b	95% CI
Eradication of the pathogen by visit 3 (n=89)	80 (89.9)	81.7-95.3
Reduction in TCS ^c (≥ 2 points)(n=91)	89 (97.8)	92.3-99.7
Overall success (n=89) ^d	79 (88.8)	80.3-94.5

Abbreviations: CI, confidence interval; TCS, total clinical score.

^aBased on number of participants with evaluable data.

^bBased on participants with success for the primary end point. Percentage with respect to the total number of evaluable participants with available data.

^cTCS evaluated on a 4-point scale (0=absent; 1=mild; 2=moderate; 3=severe).

^dBased on number of participants with success for both primary end points.

Comment

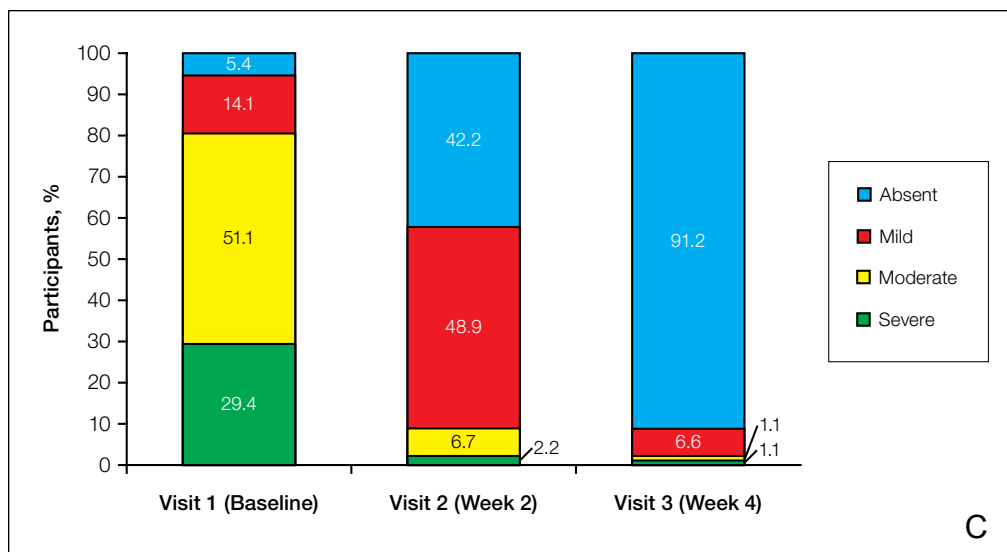
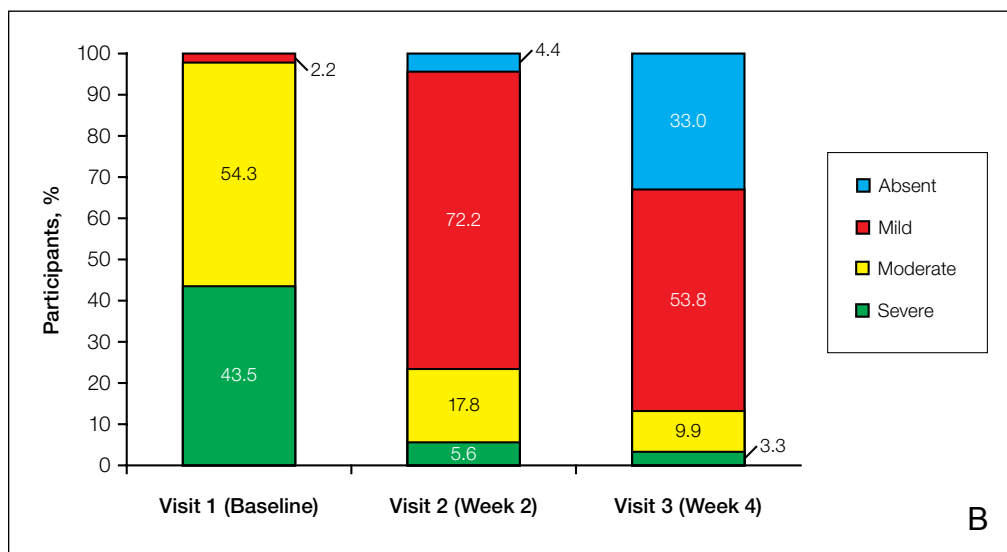
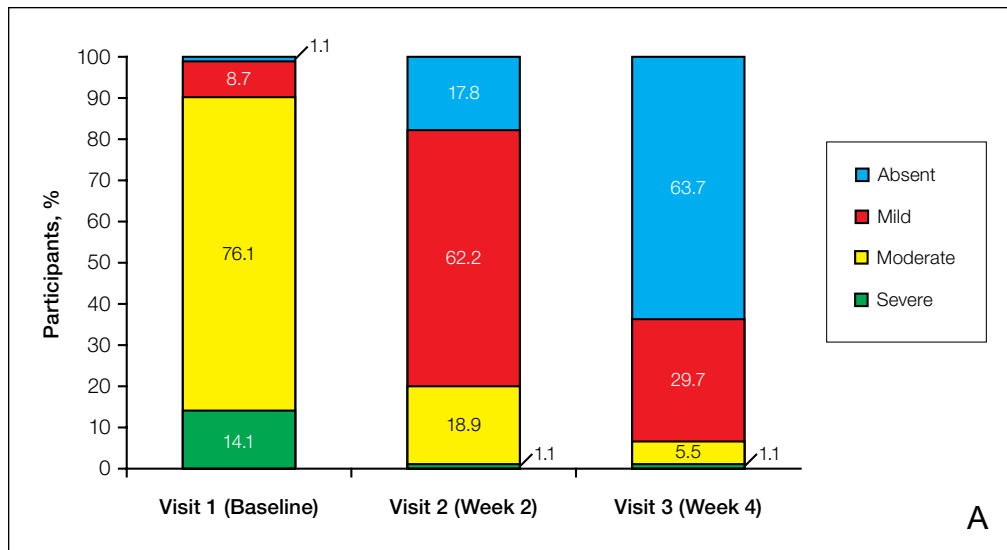
The results of this subgroup analysis clearly demonstrate that sertaconazole nitrate cream 2% is highly effective in eradicating the pathogens that cause tinea pedis interdigitalis and reducing associated signs and symptoms, including erythema, desquamation, and itch. These results are consistent with prior studies of sertaconazole nitrate cream in the treatment of superficial mycoses and confirm its efficacy in the treatment of tinea pedis interdigitalis.⁸⁻¹⁰

The findings of the subgroup analysis suggest that high cure rates are possible with sertaconazole nitrate. In a pair of randomized controlled studies reported by Savin and Jorizzo,¹⁰ sertaconazole nitrate cream 2% was compared with vehicle in 383 participants with tinea pedis interdigitalis. The investigators reported a rate of successful treatment outcomes (defined as the combined end point of mycologic cure and either marked improvement in signs and symptoms or unaffected appearance of skin) of 46.7% with sertaconazole nitrate cream 2% compared with 14.9% with vehicle.¹⁰ The findings of this subgroup analysis suggest that higher rates of treatment success (approaching 90%) are possible with sertaconazole nitrate cream 2%, with greater improvement also reported for erythema and itch. After 4 weeks of treatment, 63.7% of participants were free of erythema compared to 46.7% in the studies reported by Savin and Jorizzo,¹⁰ and itch resolved in 91.2% and 74.4%, respectively. Comparison of these results must be interpreted with some caution. For example, the end point of mycologic cure employed by Savin and Jorizzo¹⁰ required negative fungal culture and potassium hydroxide preparation results; by contrast, the current subgroup analysis employed only fungal culture results. Savin and Jorizzo¹⁰ also employed a randomized vehicle-controlled format and included

a larger participant population. Reasons for the disparity in treatment success rates are not clear but may relate to differences in participant population or means of assessment. Nevertheless, the findings of the subgroup analysis confirm the efficacy of sertaconazole nitrate cream 2% for the treatment of tinea pedis interdigitalis and suggest that high cure rates can be achieved.

Reduction in erythema and itch may be related both to eradication of the pathogen and the anti-inflammatory characteristics of sertaconazole nitrate. One preclinical study demonstrated that sertaconazole nitrate has substantially greater anti-inflammatory effects than other antifungal agents, including butoconazole nitrate, ciclopirox olamine, fluconazole, miconazole nitrate, terconazole, tioconazole, and ketoconazole.⁷ Sertaconazole nitrate was associated with notable inhibition of cytokine release and proliferation of stimulated lymphocytes in vitro, as well as reductions in edema, hypersensitivity, and itch response in animal models. Subsequent work by the same group identified activation of a p38 mitogen-activated protein kinase, cyclooxygenase 2, and prostaglandin E₂ pathway as the mechanism by which sertaconazole nitrate exerts its anti-inflammatory actions.¹²

Prior studies have reported few AEs with sertaconazole nitrate, with the highest reported rate of 20%.⁸⁻¹⁰ In keeping with prior studies, our analysis found that sertaconazole nitrate was safe and was associated with a low rate (8.7%) of AEs. Limitations of this study include its subgroup analysis design and the lack of a vehicle or active comparator group with a different active pharmaceutical ingredient. Although this study represents a reanalysis of data from a previously published study,¹¹ the current analysis provides evidence on the efficacy



Severity of signs and symptoms, including erythema (A), desquamation (B), and itch (C), at visit 1 (n=92), visit 2 (n=90), and visit 3 (n=91). Participants were treated with sertaconazole nitrate cream 2% for tinea pedis interdigitalis. Adapted with permission from Borelli et al.¹¹

of sertaconazole nitrate cream 2%, specifically in participants with tinea pedis interdigitalis of dermatophyte origin. With regard to the uncontrolled design of this study, prior vehicle-controlled studies have reported similarly good efficacy rates in the treatment of tinea pedis interdigitalis.¹⁰ The design of the current study also did not allow for assessment of relapse because the last study visit was conducted at the end of 28 days of treatment. Prior randomized placebo-controlled studies conducted by Savin and Jorizzo¹⁰ reported a 29.5% relapse rate 2 weeks following discontinuation of sertaconazole nitrate cream 2% compared with 66.7% with vehicle ($P < .0001$).

It also should be noted that sertaconazole nitrate cream 2% is indicated in the United States for tinea pedis interdigitalis caused by *Trichophyton rubrum*, *Trichophyton mentagrophytes*, or *Epidermophyton floccosum* in immunocompetent patients. Data regarding concomitant illnesses were not gathered in this study; therefore, no statement can be made with regard to the immunocompetence of the study population. Furthermore, the specific species of dermatophyte was not identified in this study. In the United States, *T rubrum* and *T mentagrophytes* are 2 of the most common dermatophytes isolated from skin lesions that account for approximately half or more of all dermatophyte isolates.¹³ In one study, *T rubrum* was present in 78.9% (30/38) of isolates from participants with tinea pedis in 16 states.¹⁴ Epidemiologic data regarding dermatophyte species in Germany, where the current study was conducted, suggest that these 2 species account for more than 90% of all dermatophytes isolated from skin lesions.¹³ Therefore, it is likely that the dermatophyte species responsible for tinea pedis interdigitalis in this analysis set were largely *T rubrum* and *T mentagrophytes*.

Future prospective studies could further evaluate the efficacy and risk for relapse associated with sertaconazole nitrate cream 2% in an immunocompetent population with tinea pedis interdigitalis caused by dermatophytes.

Conclusion

Sertaconazole nitrate cream 2% has become associated with high cure rates and improvement in the signs and symptoms of tinea pedis interdigitalis. In addition to broad-spectrum antifungal activity, this imidazole derivative has demonstrated anti-inflammatory, antipruritic, and antibacterial characteristics. The subgroup analysis reported here further demonstrates that high rates of eradication of the pathogen and clinical improvement can be achieved with sertaconazole nitrate cream 2%.

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