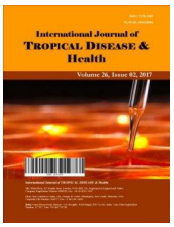

*International Journal of TROPICAL DISEASE & Health*

*29(1): 1-7, 2018; Article no.IJTDH.36283*
*ISSN: 2278–1005, NLM ID: 101632866*

# Efinaconazole 10% Topical Solution: Treatment of Mild to Moderate Toenail Onychomycosis in Japanese Subjects

**Theodore Rosen[1*] and Tina Lin[2]**

*[1]Department of Dermatology at Baylor College of Medicine, Houston, Texas, USA.*
*[2]Valeant Pharmaceuticals North America LLC., Bridgewater, New Jersey, USA.*

**Authors' contributions**

*This work was carried out in collaboration between all authors. Authors TR and TL designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Both authors managed the analyses of the study and managed the literature searches. All authors read and approved the final manuscript.*

***Article Information***

DOI: 10.9734/IJTDH/2018/36283
Editor(s):
(1) Jorge Paredes Vieyra, Universidad Autonoma De Baja California, Campus Tijuana, Mexico.
Reviewers:
(1) Shari Lipner, Weill Cornell Medicine, USA.
(2) K. R. Raghavendra, Mysore Medical College and Research Institute, India.
Complete Peer review History: http://www.sciencedomain.org/review-history/23157

***Short Research Article***

***Received 22nd August 2017***
***Accepted 8th January 2018***
***Published 13th February 2018***

## ABSTRACT

**Objective:** To evaluate efficacy, safety, and tolerability of efinaconazole topical solution, 10% in a cohort of Japanese patients with mild to moderate toenail onychomycosis.
**Methods:** A subgroup analysis of patients, aged 22-70 years, randomized to receive efinaconazole topical solution, 10% or vehicle from a multicenter, double-blind, vehicle-controlled 48-week study evaluating safety and efficacy. The primary end point was complete cure rate (0% clinical involvement of target toenail, and both negative potassium hydroxide examination and fungal culture) at Week 52.
**Results:** The primary end point, complete cure, was achieved in 30.6% of patients treated with efinaconazole compared to 12.3% with vehicle (Observed case, P=.006), and was significantly better than that seen in the non-Japanese patients (P<.001). Treatment success (percent affected target toenail ≤10% at week 52) for efinaconazole was 60.6% compared to 33.3% with vehicle (P<.001). The majority of adverse events (AEs) were mild (16.6%) or moderate (81.1%) and few

**Corresponding author: Email: vampireted@aol.com;*

(7.8%) associated with efinaconazole. Eleven patients (6.0%) treated with efinaconazole discontinued the study due to AEs.
**Conclusions:** Once daily efinaconazole topical solution, 10% may provide a useful topical option in the treatment of mild to moderate onychomycosis among ethnic Japanese patients.

*Keywords: Efinaconazole; onychomycosis; japanese subjects.*

## 1. INTRODUCTION

Onychomycosis is the most common nail disease in adults, representing up to 50% of all nail disorders, and is nearly always associated with *tinea pedis*.[1,2] Epidemiology data indicate a prevalence of 13.8% in the US,[3] with a number of factors contributing to an increasing incidence.

Epidemiology studies on onychomycosis and tinea pedis have been performed across Europe and East Asia. The prevalence of onychomycosis has been estimated as more than 10% in Japan, although direct, reliable epidemiological data are lacking.[4] A randomized survey of outpatients who visited a dermatologist for reasons other than superficial fungal infection reported 18.6% of the study population diagnosed with onychomycosis or tinea pedis in 2000, increasing to 24.1% by 2006; almost two thirds (63.2%) used topical medication only [5]. An earlier epidemiological survey of dermatomycoses reported an increase of onychomycosis in the Summer, with a greater prevalence among the aged population and in males [6]. An epidemiological investigation of workers in a dairy product company in Kanagawa, central Japan, estimated an overall prevalence of tinea pedis and onychomycosis of 18% [7].

It is estimated that about 1.5 million Japanese live in the US, especially in Hawaii and California. Clinical data on the treatment of onychomycosis in this population is lacking. Two identical 52-week prospective, multicenter, randomized, double-blind studies in 1655 patients (18-70 years) assessed the safety and efficacy of efinaconazole topical solution, 10% in the treatment of onychomycosis [8,9]. We provide a post hoc analysis of the Japanese patients in the first of these studies, and compare safety and efficacy data to the non-Japanese population studied in precisely the same manner.

## 2. MATERIALS AND METHODS

Multicenter, randomized, double-blind, vehicle-controlled studies were designed to evaluate the efficacy, safety, and tolerability of efinaconazole topical solution, 10% relative to its vehicle in 870 male and female patients (aged 18 to 70 years) with mild-to-moderate toenail onychomycosis [8].

Eligibility criteria included: clinical diagnosis of DLSO affecting at least one great toenail, target toenail uninfected length ≥ 3 mm (from the proximal nail fold), thickness ≤3 mm, evidence of toenail growth, positive potassium hydroxide (KOH) microscopy, and culture of dermatophyte or mixed dermatophyte/*Candida* ≤ 42 days prior to baseline.

Exclusion criteria included: history of immunosuppression and/or clinical signs indicative of possible immunosuppression, known HIV infection, uncontrolled diabetes mellitus, presence of toenail infection other than dermatophytes, severe moccasin tinea pedis at screening/baseline, any disease/condition that might have caused toenail abnormalities or interfered with the evaluation, and previous target toenail surgery.

Patients who presented with 20%-50% clinical involvement of the target toenail were randomized (3:1) to apply blinded study drug once daily to the toenails for 48 weeks.

The study was funded by Dow Pharmaceutical Sciences, Inc., a wholly owned subsidiary of Valeant Pharmaceuticals North America, LLC; and conducted in accordance with the ethical principles specified in the Declaration of Helsinki and in compliance with requirements of local regulatory committees. All subjects provided written informed consent.

### 2.1 Efficacy Evaluation

The primary efficacy end point was complete cure rate (0% clinical involvement of target toenail, and both negative potassium hydroxide examination and fungal culture) at week 52. Secondary end points included mycologic cure and treatment success (<10% clinical involvement of the target toenail). All secondary end points were assessed at week 52.

## 2.2 Safety Evaluation

Safety assessments included monitoring and recording of adverse events (AEs) throughout the study, until week 52.

## 2.3 Statistical Analysis

The intent-to-treat (ITT) population included all subjects randomized and dispensed study drug. The safety population included all subjects who received/had at least one dose of study drug, and one post-baseline assessment.

Efficacy endpoints were compared using Cochran-Mantel-Haenszel (CMH) tests (stratified by analysis center) at a 5% significance level. Unaffected new toenail growth was analyzed using a two-way variance analysis. Missing efficacy data were imputed using the last observation carried forward (LOCF) method; no imputations for missing safety data were performed.

All AEs were recorded and classified using the Medical Dictionary for Regulatory Activities (MedDRA version 12.1). A Fisher's exact test was used to compare the incidences of treatment-emergent adverse events (TEAEs) and treatment-related AEs occurring with frequencies ≥1%.

## 3. RESULTS

The study included 157 (64.6%) male and 86 (35.4%) female patients with mild-to-moderate onychomycosis from Japan (Table 1, intent-to-treat [ITT] subjects). By comparison, 490 (78.1%) male and 137 (21.9%) female patients were enrolled from the US and Canadian study centers (ITT subjects).

At baseline, the mean area of target toenail involvement of those Japanese patients subsequently treated with efinaconazole topical solution, 10% was 35.6% compared to 38.1% respectively with vehicle, and 36.7% in the total study population. The mean number of affected non-target toenails was 2.4 for both treatment groups (Table 2), compared with 2.8 in the total study population.

The majority (81.1%) of patients had at least one non-target toenail affected in addition. Diabetes was reported in 7.0% of patients, and co-existing tinea pedis in 72.8% of patients (Table 2).

## 3.1 Primary Efficacy Endpoint (Observed Case [OC])

At week 52, 52 (30.6%) of onychomycosis patients were complete cures with efinaconazole compared with 7 (12.3%) on vehicle (P=.006). Efficacy rates with efinaconazole were almost two-fold greater than those seen in the non-ethnic Japanese patients from US and Canada (15.7%, P<.001), where no patients achieved a complete cure with vehicle, see Fig. 1.

## 3.2 Supportive and Secondary Efficacy Endpoints (OC)

At week 52, 55.6% (N=95) Japanese onychomycosis patients achieved mycologic cure on efinaconazole compared with 31.6% (N=18) on vehicle (P=.002). Mycologic cure became significant versus vehicle as early as week 24, see Fig. 2.

Also, more patients achieved a complete or almost complete cure on efinaconazole (38.2%, N=65) compared to vehicle (19.3%, N=11) at

**Table 1. Subject demographics (Japanese sites Intent-To-Treat [ITT] population)**

| | Japanese subjects | | All study subjects | |
|---|---|---|---|---|
| | **Efinaconazole n=184** | **Vehicle n=59** | **Efinaconazole n=656** | **Vehicle n=214** |
| Age (years) (SD) | | | | |
| Mean | 56.0 (9.9) | 56.6 (9.0) | 52.4 (10.9) | 51.9 (11.9) |
| Median | 58.0 | 58.0 | 54.0 | 54.0 |
| Range | 22.0-70.0 | 27.0-70.0 | 20.0-71.0 | 18.0-70.0 |
| Gender | | | | |
| Male | 121 (65.8%) | 36 (61.0%) | 489 (74.5%) | 158 (73.8%) |
| Female | 63 (34.2%) | 23 (39%) | 167 (25.5%) | 56 (26.2%) |

**Table 2. Subject baseline characteristics (Japanese sites ITT population)**

| | Japanese subjects | | All study subjects | |
|---|---|---|---|---|
| | **Efinaconazole n=184** | **Vehicle n=59** | **Efinaconazole n=656** | **Vehicle n=214** |
| % Involvement of affected toenail | | | | |
| Mean (SD) | 35.6 (10.1) | 38.1 (10.5) | 36.7 (10.4) | 36.8 (10.6) |
| Median | 40.0 | 40.0 | 40.0 | 40.0 |
| Range | 20-50 | 20-50 | 20-50 | 20-50 |
| Number affected non-target nails | | | | |
| Mean (SD) | 2.4 (1.8) | 2.4 (1.7) | 2.8 (1.7) | 2.8 (1.7) |
| Median | 2.0 | 2.0 | 3.0 | 3.0 |
| Range | 0.0-5.0 | 0.0-5.0 | 0.0-5.0 | 0.0-5.0 |
| Diabetes Reported | 12 (6.5%) | 5 (8.5%) | 82 (6.6%)[1] | 30 (7.2%)[1] |
| Tinea Pedis Reported | 130 (70.7%) | 47 (79.7%) | 233 (18.9%)[1] | 82 (19.7%)[1] |
| Disease Duration ≥ 1 year | 80 (87.9%) | 24 (82.8%) | 1088 (88.0%)[1] | 364 (87.7%)[1] |

*NOTE: 1 = Pooled data from two phase 3 studies*

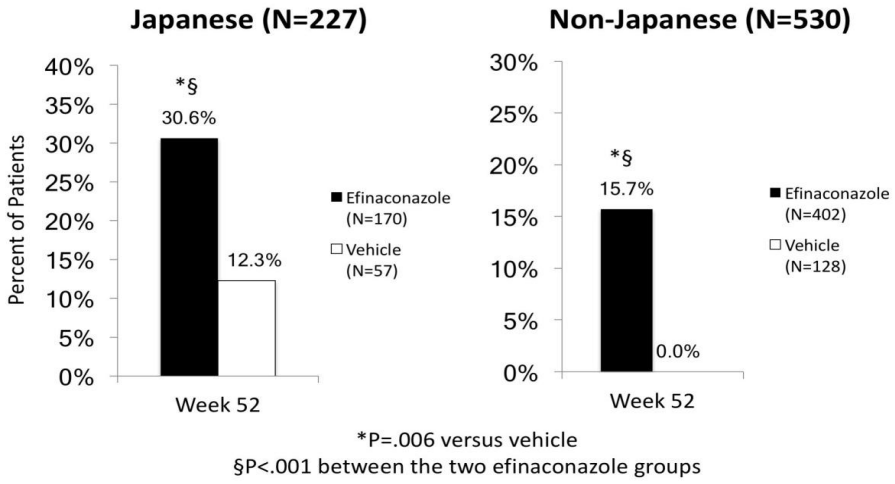


**Fig. 1. Primary efficacy endpoint complete cure week 52 (Observed Data): Japanese (N=227) and non-Japanese subpopulations (N=530). N-values at Week 52**

week 52 (P=.007); and 60.6% (N=103) were considered treatment successes at week 52 (≤10% affected target toenail) compared to 33.3% (N=19) on vehicle (P<.001), see Fig. 2. By comparison, 49.3% and 18.7% of patients from the total study population achieved treatment success with efinaconazole and vehicle respectively. See Fig. 3 for a representative example of a Japanese subject treated with efinaconazole.

### 3.3 Safety

Overall, efinaconazole AE rates in the Japanese population were similar to those reported with vehicle (67.4% vs 71.2%). Adverse events were generally mild (16.6% with efinaconazole and 12.5% with vehicle) or moderate (81.1% and 87.5% respectively) in severity, not related to study medication (92.2% and 100% respectively) and resolved without sequelae. Eleven (6.0%) of subjects discontinued as a result of AEs following efinaconazole treatment (compared with zero treated with vehicle), see Table 3. By comparison 10 (1.1%) and 1 (0.3%) patient from the US and Canadian cohorts discontinued due to AEs.

## 4. DISCUSSION AND CONCLUSION

The incidence of onychomycosis appears to be relatively high in Japanese patients, and they form an important cohort in certain geographic

**Table 3. Summary of treatment-emergent adverse events (AEs) (Safety Subjects Japanese Sites)**

| | Efinaconazole | Vehicle |
|---|---|---|
| Number of Subjects | 184 | 59 |
| Subjects with ≥1 AE | 124 (67.4%) | 42 (71.2%) |
| Subjects who discontinued study due to AE | 11 (6.0%) | 0 (0.00) |
| AE Severity | | |
| Mild | 16.6% | 12.5% |
| Moderate | 81.1% | 87.5% |
| Severe | 2.4% | 0.0% |
| Relationship of AE to study drug | | |
| Not related | 92.2% | 100% |
| Related | 7.8% | 0.0% |

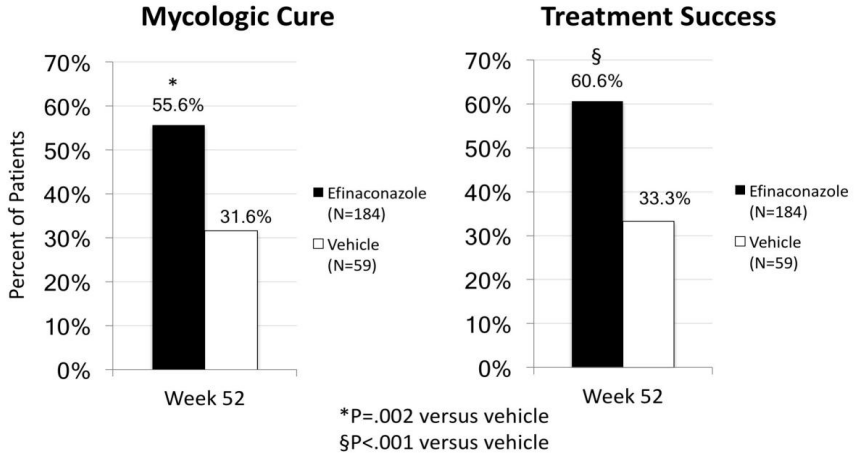


**Fig. 2. Secondary efficacy endpoint mycologic cure and treatment success week 52 (Observed Case): Japanese Subpopulations (N=243 at baseline)**

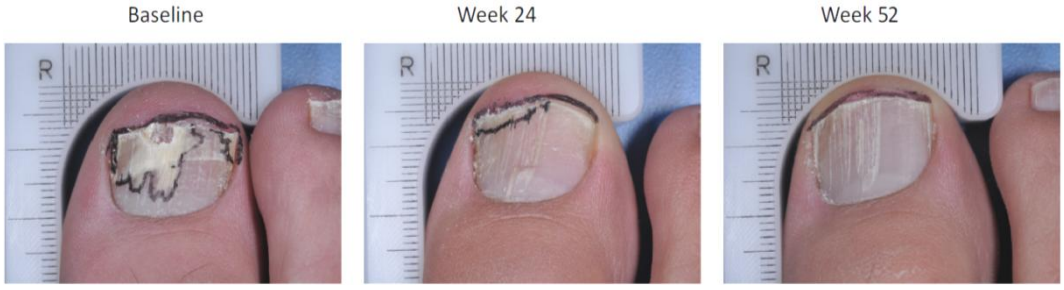


**Fig. 3. Representative example of a Japanese subject treated with efinaconazole. Subject had 50% affected target toenail at baseline which was completely cured by Week 52**

regions of the US. In Japan, the traditional practice of walking barefoot in the house, which facilitates the spread of the infection to family members, is likely the primary reason for the especially high prevalence and intensity of toenail fungal disease.

In our post hoc analysis of a phase 3 study on efinaconazole topical solution, 10%, efficacy appears to be much greater than in those onychomycosis patients from US or Canada study centers. There was a higher proportion of female patients in the Japanese cohort which may have impacted these data, although disease severity (based on affected target toenail) was similar to that reported in the overall study [8]. Efficacy results in female patients treated with efinaconazole have

previously been reported to be higher than in male patients [10].

The number of Japanese patients with co-existing tinea pedis was unusually high compared to the overall pooled data from the two pivotal studies (72.8% versus 19.0%). Many of these patients had their co-existing tinea pedis treated concomitantly, and this may also have impacted on the better efficacy results seen.

The number of AEs reported, and their severity appeared higher than in the overall patient population, however very few AEs were related to study medication, and the level of discontinuation (6.0%) was still relatively low. The most common AE was dermatitis at the site of drug application. Although there are differences in reporting of AEs in several countries [11], it is not known whether this factor may have influenced the findings.

There are a number of limitations with our study. Firstly, a study period of 52 weeks may be too brief to evaluate a clinical cure in onychomycosis. It is not known whether continued improvement would occur with either longer treatment courses or longer follow-up. Also, this was a post hoc analysis and the pivotal studies were not set up specifically to study Japanese patients with onychomycosis, where demographics and study disposition may not be representative of the general Japanese population, or any cultural or social differences seen in those Japanese living in the US or Canada.

Our analysis shows that once daily efinaconazole topical solution, 10% may provide an especially useful topical option in the treatment of mild-to-moderate onychomycosis in Japanese patients.

## CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the author(s).

## ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the author(s).

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

## REFERENCES

1. Scher RK, Coppa LM. Advances in the diagnosis and treatment of onychomycosis. Hosp Med. 1998;34:11-20.
2. Gupta AK, Jain HC, Lynde CW, et al. Prevalence and epidemiology of onychomycosis in patients visiting physicians' offices: a multicenter Canadian survey of 15,000 patients. J Am Acad Dermatol. 2000;43:244-8.
3. Ghannoum MA, Hajjeh RA, Scher R, et al. A large-scale North American study of fungal isolates from nails: the frequency of onychomycosis, fungal distribution, and antifungal susceptibility patterns. J Am Acad Dermatol. 2000;43(4):641-648.
4. Hiruma M. Onychomycosis: Recent progress in the epidemiology, diagnosis and treatment. Nippon Ishinkin Gakkai Zasshi. 2006;47(2):69-73.
5. Watanabe S, Haranda T, Hiruma M, et al. Epidemiological survey of foot diseases in Japan: Results of 30,000 foot checks by dermatologists. J Dermatol. 2010;37(5): 397-406.
6. Nishimoto K. An epidemiological survey of dermatomycoses in Japan, 2002. Nihon Ishinkin Gakkai Zasshi. 2006;47(2):103-111.
7. Manyama R, Hiruma M, Yamauchi K, et al. An epidemiological and clinical study of untreated patients with tinea pedis within a company in Japan. Mycoses. 2003;46(5-6):208-212.
8. Elewski BE, Rich P, Pollak R, et al. Efinaconazole 10% solution in the treatment of toenail onychomycosis: two phase 3 multicenter, randomized, double-blind studies. J Am Acad Dermatol. 2013;68:600-608.
9. Gupta AK, Elewski BE, Sugarman JL. The efficacy and safety of efinaconazole 10% solution for treatment of mild to moderate onychomycosis: A pooled analysis of two phase 3 randomized trials. J Drugs Dermatol. 2014;13(7):815-820.

10. Rosen T. Evaluation of gender as a clinically relevant outcome variable in the treatment of onychomycosis with efinaconazole topical solution 10%. Cutis. 2015;96:193-197.

11. Matsuda S, Aoki K, Kawamata T, et al. Bias in spontaneous reporting of adverse drug reactions in Japan. PLoS One. 2015;10(5):e0126413.



*Peer-review history:*
*The peer review history for this paper can be accessed here:*
*http://www.sciencedomain.org/review-history/23157*