

Short Research Article

Efinaconazole 10% topical solution: treatment of mild to moderate toenail onychomycosis in Japanese subjects

Running Head: Efinaconazole in Japanese Patients with Onychomycosis

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 $\leq 10\%$ 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 (7.8%) associated with efinaconazole. Eleven patients (6.0%) treated with efinaconazole discontinued the study due to AEs.

26 **Conclusions:** Once daily efinaconazole topical solution, 10% may provide a useful
27 topical option in the treatment of mild to moderate onychomycosis among ethnic
28 Japanese patients.

29 30 **Introduction**

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

35
36 Epidemiology studies on onychomycosis and tinea pedis have been performed
37 across Europe and East Asia. The prevalence of onychomycosis has been estimated
38 as more than 10% in Japan, although direct, reliable epidemiological data are
39 lacking.⁴ A randomized survey of outpatients who visited a dermatologist for reasons
40 other than superficial fungal infection reported 18.6% of the study population
41 diagnosed with onychomycosis or tinea pedis in 2000, increasing to 24.1% by 2006;
42 almost two thirds (63.2%) used topical medication only.⁵ An earlier epidemiological
43 survey of dermatomycoses reported an increase of onychomycosis in the Summer,
44 with a greater prevalence among the aged population and in males.⁶ An
45 epidemiological investigation of workers in a dairy product company in Kanagawa,
46 central Japan, estimated an overall prevalence of tinea pedis and onychomycosis of
47 18%.⁷

48

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

57

58 **Materials and Methods**

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

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

68 Exclusion criteria included: history of immunosuppression and/or clinical signs
69 indicative of possible immunosuppression, known HIV infection, uncontrolled
70 diabetes mellitus, presence of toenail infection other than dermatophytes, severe

71 moccasin tinea pedis at screening/baseline, any disease/condition that might have
72 caused toenail abnormalities or interfered with the evaluation, and previous target
73 toenail surgery

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

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

82

83 *Efficacy evaluation*

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

89 *Safety evaluation*

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

92 **Statistical analysis**

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

96

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

102

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

107

108 **Results**

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

113 At baseline, the mean area of target toenail involvement of those Japanese patients

114 subsequently treated with efinaconazole topical solution, 10% was 35.6% compared
115 to 38.1% respectively with vehicle, and 36.7% in the total study population. The
116 mean number of affected non-target toenails was 2.4 for both treatment groups
117 (**Table 2**), compared with 2.8 in the total study population.

118 The majority (81.1%) of patients had at least one non-target toenail affected in
119 addition. Diabetes was reported in 7.0% of patients, and co-existing tinea pedis in
120 72.8% of patients (**Table 2**).

121 *Primary efficacy endpoint (Observed Case [OC])*

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

127 *Supportive and secondary efficacy endpoints (OC)*

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

131 Also, more patients achieved a complete or almost complete cure on efinaconazole
132 (38.2%, N=65) compared to vehicle (19.3%, N=11) at week 52 (P=.007); and 60.6%
133 (N=103) were considered treatment successes at week 52 ($\leq 10\%$ affected target
134 toenail) compared to 33.3% (N=19) on vehicle (P<.001), see **Figure 2**. By comparison,

135 49.3% and 18.7% of patients from the total study population achieved treatment
136 success with efinaconazole and vehicle respectively. See **Figure 3** for a
137 representative example of a Japanese subject treated with efinaconazole.

138 *Safety*

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

147 **Discussion**

148 The incidence of onychomycosis appears to be relatively high in Japanese patients,
149 and they form an important cohort in certain geographic regions of the US. In Japan,
150 the traditional practice of walking barefoot in the house, which facilitates the spread
151 of the infection to family members, is likely the primary reason for the especially
152 high prevalence and intensity of toenail fungal disease.

153

154 In our post hoc analysis of a phase 3 study on efinaconazole topical solution, 10%,
155 efficacy appears to be much greater than in those onychomycosis patients from US
156 or Canada study centers. There was a higher proportion of female patients in the
157 Japanese cohort which may have impacted these data, although disease severity

158 (based on affected target toenail) was similar to that reported in the overall study.⁸

159 Efficacy results in female patients treated with efinaconazole have previously been
160 reported to be higher than in male patients.¹⁰

161

162 The number of Japanese patients with co-existing tinea pedis was unusually high
163 compared to the overall pooled data from the two pivotal studies (72.8% versus
164 19.0%). Many of these patients had their co-existing tinea pedis treated
165 concomitantly, and this may also have impacted on the better efficacy results seen.

166

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

173

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

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

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218 **Table 1: Subject Demographics (Japanese sites Intent-To-Treat [ITT] population)**

	Japanese Subpopulation		Total Study Population	
	Efinaconazole (N=184)	Vehicle (N=59)	Efinaconazole (N=656)	Vehicle (N=214)
Age, y (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
Sex				
Male	121 (65.8%)	36 (61.0%)	489 (74.5%)	158 (73.8%)
Female	63 (34.2%)	23 (39.0%)	167 (25.5%)	56 (26.2%)

220

221 **Table 2: Subject Baseline Characteristics (Japanese sites ITT population)**

	Japanese Subpopulation		Total Study Population	
	Efinaconazole (N=184)	Vehicle (N=59)	Efinaconazole (N=656)	Vehicle (N=214)
Percent 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	20.0-50.0	20.0-50.0	20.0-50.0	20.0-50.0
Number of affected non-target toenails				
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 or more)	80 (87.9%) ²	24 (82.8%) ²	1088 (88.0%) ¹	364 (87.7%) ¹

¹Pooled data from the two phase 3 studies²percent calculated from total available data (N=91 and 29, respectively)

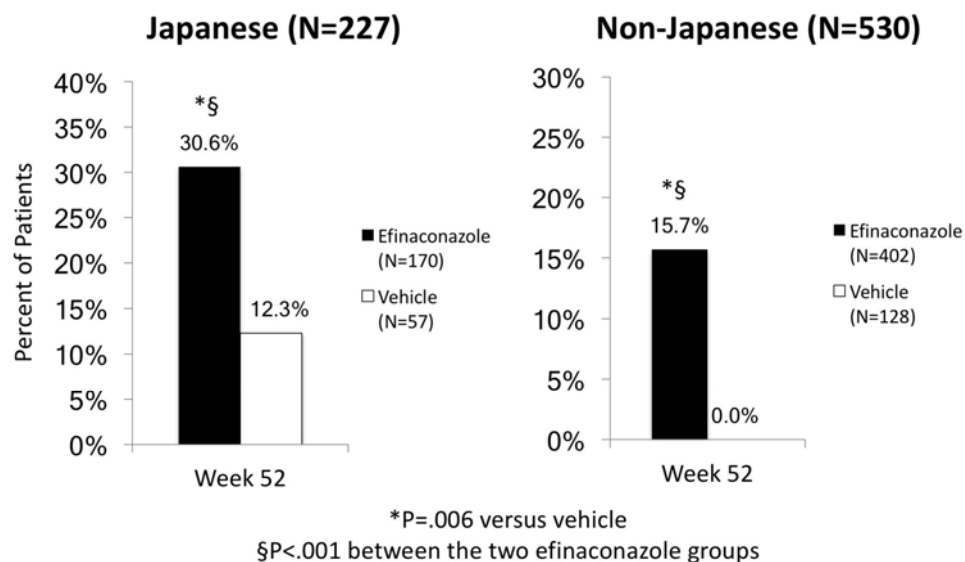
222

223 **Table 3: Summary of Treatment-Emergent Adverse Events (AEs)**224 **(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 (0.0%)
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%	100.0%
Related	7.8%	0.0%

225

Figure 1



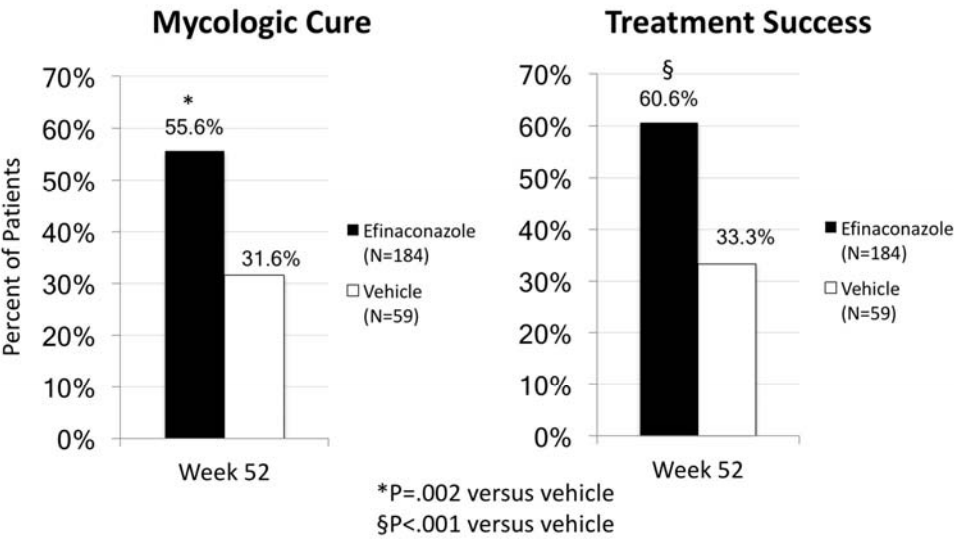
226

227 **Figure 1: Primary Efficacy Endpoint Complete Cure Week 52 (Observed Data):**

228 **JAPANESE (N=227) and NON-JAPANESE SUBPOPULATIONS (N=530). N-values at**

229 **Week 52**

Figure 2



230

231 **Figure 2: Secondary Efficacy Endpoint Mycologic Cure and Treatment Success Week**

232 **52 (Observed Case): JAPANESE SUBPOPULATIONS (N=243 at baseline)**

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238

239 **Figure 3. Representative example of a Japanese subject treated with**
240 **efinaconazole. Subject had 50% affected target toenail at baseline which was**
241 **completely cured by Week 52**
242

Figure 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

