

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 8, 2004

FROM: Kathleen Fritsch, Ph.D., Biostatistics Reviewer
Division of Biometrics III, HFD-725

SUBJECT: STUDY DESIGN AND EFFICACY RESULTS FOR
TINEA PEDIS CLINICAL TRIALS

CLINICAL TRIAL DESIGN

This summary describes the common features of clinical trials for tinea pedis and presents efficacy results from some tinea pedis trials. Clinical trials for tinea pedis products typically enroll patients with positive KOH and clinical signs and symptoms. Only subjects found to have a positive baseline culture (which can take up to 4 weeks to determine) are evaluated for efficacy. Most treatments have been evaluated for either one or four weeks of use. In clinical trials, the primary time point for efficacy evaluation (point of cure) is at least two weeks, and may be as many as eight weeks, after completing therapy (six to nine weeks after starting therapy). Most trials evaluate the endpoints *complete cure* (negative KOH and culture and no signs or symptoms), *effective treatment* (negative KOH and culture and at most mild erythema or scaling), *negative mycology* (negative KOH and culture) and individual signs and symptoms. In most trials the primary efficacy endpoint is complete cure, although some trials have used effective treatment as the primary endpoint. The exact definition of the endpoints (especially effective treatment) differs from trial to trial. Protocols often have different entry criteria, such as minimum disease severity or whether subjects can have onychomycosis or plantar involvement at baseline. Many products have only been assessed in and approved for interdigital tinea pedis.

EFFICACY DATA FROM CLINICAL TRIALS

A review of NDAs submitted for both prescription and over-the-counter topical tinea pedis products over the past 15 years identified complete cure rate data from eight drug products or treatment regimens. Five active ingredients are represented and all data are from vehicle controlled studies. While it is difficult to compare efficacy results across products as patient populations, study procedures, and endpoints vary across trials, the following tables present complete cure rates for eight drug product formulations or treatment regimens coded by letter. Tables 1 and 2 present complete cure rates at the end of treatment and point of cure (primary efficacy timepoint) for 1-week products and 4-week products, respectively.

Table 1 – Complete Cure Rates for 1-Week Products for Tinea Pedis

Product Code	Point of Cure (Week)	Complete Cure Rate End of Treatment (Week 1)		Complete Cure Rate Point of Cure	
		Active	Vehicle	Active	Vehicle
A	6	1/253 (<1%)	1/265 (<1%)	37/253 (15%)	2/265 (1%)
B	6	4/82 (5%)	1/79 (1%)	24/78 (31%)	1/69 (1%)
C	8	1/58 (2%)	1/28 (4%)	12/58 (21%)	0/28 (0%)
D	9	0/131 (0%)	0/152 (0%)	26/131 (20%)	3/152 (2%)

Table 2 – Complete Cure Rates for 4-Week Products for Tinea Pedis

Product Code	Point of Cure (Week)	Complete Cure Rate End of Treatment (Week 4)		Complete Cure Rate Point of Cure	
		Active	Vehicle	Active	Vehicle
E	8	14/93 (15%)	7/92 (8%)	20/94 (21%)	6/92 (7%)
F	6	32/202 (16%)	16/195 (8%)	41/202 (20%)	8/195 (4%)
G	6	43/129 (33%)	8/138 (6%)	51/124 (41%)	6/128 (5%)
H	6	7/47 (15%)	2/44 (5%)	14/47 (30%)	6/44 (14%)

For 1-week treatments, less than 5% of subjects are completely cured at the end of treatment. The complete cure rate rises to 15-31% at point of cure (Week 6 – 9) for the four products. For the 4-week treatments, 15-33% of subjects are completely cured at the end of treatment (Week 4). The complete cure rate rises to 20-41% at point of cure (Week 6-8). The complete cure rates in the clinical trials at point of cure range from 15-41% for the eight products considered, with several products under each dosing regimen achieving a complete cure rate of about 20%.

Data on the clearance rates for the signs and symptoms of erythema, scaling, and pruritus are available for two drug products—one 1-week and one 4-week product. The percentage of subjects cleared of the sign or symptom at end of treatment and point of cure are presented in Table 3.

Table 3 – Signs and Symptoms Clearance Rates for Tinea Pedis

		Drug Product D		Drug Product F	
		EOT = Week 1 POC = Week 9		EOT = Week 4 POC = Week 6	
		<i>Active</i>	<i>Vehicle</i>	<i>Active</i>	<i>Vehicle</i>
Erythema	EOT	31/131 (24%)	36/152 (24%)	90/202 (45%)	48/195 (25%)
	POC	77/131 (59%)	47/152 (31%)	101/202 (50%)	48/195 (25%)
Scaling	EOT	2/131 (2%)	3/152 (2%)	42/202 (21%)	28/195 (14%)
	POC	36/131 (27%)	11/152 (7%)	63/202 (31%)	27/195 (14%)
Pruritus	EOT	60/131 (46%)	67/152 (44%)	143/202 (71%)	101/195 (52%)
	POC	105/131 (80%)	57/152 (38%)	145/202 (72%)	93/195 (48%)

EOT = End of Treatment, POC = Point of Cure.

For Drug Product D, few subjects were cleared of signs and symptoms (especially scaling) at the end of treatment (Week 1), and the effect is similar to vehicle. However, signs and symptoms do continue to improve and differentiate from vehicle after treatment has ended, with an additional 25-35% of subjects clearing each sign or symptom by Week 9. For Drug Product F, clearance rates for erythema and scaling improved slightly from Week 4 to Week 6. At their respective points of cure, the sign and symptom clearance rates for the two products are 50-59% for erythema, 27-31% for scaling, and 72-80% for pruritus.

In summary, few patients using 1-week treatments for tinea pedis experience full relief of signs and symptoms or complete cure at the end of treatment, though improvement may continue after treatment stops. If comparisons are made several weeks after completing treatment, at Weeks 6-9, most of the identified drug products exhibited similar complete cure rates (approximately 20-30%) from either 1-week or 4-week dosing regimens even though clinical trial conditions varied.