U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	019599 ; 204286
Supplement #:	S-012 (for NDA 019599); S-001 (for NDA 204286)
Drug Name:	Naftin (naftifine hydrochloride) cream, 2% and Naftin (naftifine hydrochloride) gel, 2%
Indication(s):	Treatment of tinea pedis, tinea cruris, and tinea corporis in subjects age≥12 years (NDA 019599); Treatment of interdigital tinea pedis in subjects aged≥12 years (NDA 204286)
Applicant:	Merz Pharmaceuticals LLC
Stamp Date:	December 20, 2013
PDUFA Date:	October 20, 2014
Review Priority:	Standard
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Keywords: Open-label maximal use study

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1 EXECUTIVE SUMMARY

In order to fulfill the PREA postmarketing requirements, the applicant conducted an open-label, maximal use study in 22 pediatric subjects aged 12 to 17 years 11 months under maximal clinical use conditions with the primary objectives to quantify the pharmacokinetics of NAFT-500 and NAFT-600. As the completed trial was an open-label, maximal use trial that did not include a vehicle arm, efficacy results from such trial are subject to bias as no comparator arm was included. In addition, the sample size (22 pediatric subjects and 6 adult subjects) is too small to draw a reasonable conclusion about efficacy. (b) (4)

2 INTRODUCTION

The applicant has the following approved naftifine products:

- 1% gel formulation (approval date: 6/18/1990)
- 1% cream formulation (approval date: 2/29/1988)
- 2% cream formulation (approval date: 1/13/2012)
- 2% gel formulation (approval date: 6/27/2013).

The Agency's approval letters for the 2% cream and gel formulations specified that, for PREA postmarketing requirements, "according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act/FDCA" the Agency required the following postmarketing studies be reported to the Agency:

- PMR 1857-1 "PK/Safety/Tolerability study under maximal use conditions in subjects ages 12 years to 17 years 11 months with a minimum of at least 18 evaluable subjects with tinea pedis and tinea cruris towards the upper end of disease severity in the patient population." (NDA 019599)

- PMR 1867-2 "PK/Efficacy/Safety study in pediatric subjects ages 2 years to 17 years 11 months with tinea corporis." (NDA 019599)

- PMR 2050-1 "Pharmacokinetic/Safety/Tolerability trial under maximal use conditions in adolescent subjects ages 12 years to 17 years 11 months with a minimum of at least 18 evaluable subjects with tinea pedis interdigital type". (NDA 204286)

In the application, the applicant referenced PMR 1857-1 and PMR 2050-1 above, and included their final Clinical Study Report for the following trial:

- Study MUSC90200/1023/0 entitled "an open-label, multicenter, multiple-application, pharmacokinetic study of NAFT-500 in pediatric subjects with tinea cruris and tinea pedis and NAFT-600 in pediatric subjects with tinea pedis".

As part of the application, the applicant also proposed labeling changes and stated that they (b) (4).

This review summarizes the completed trial long with the proposed labeling change.

2.1 Overview

The completed trial was an open-label, multicenter trial with four investigators in the Dominican Republic, Honduras, and the United States with the following primary objectives:

> (1) "To quantify the pharmacokinetics of NAFT-500 in pediatric subjects aged 12 to 17 years, 11 months with tinea cruris and tinea pedis under maximal clinical use conditions for 2 weeks of once daily application in treatment group one. Maximal use condition was defined as having both feet and bikini area affected for NAFT-500,
> (2) To quantify the pharmacokinetics of NAFT-600 in pediatric subjects aged 12 to 17 years, 11 months with tinea pedis under maximal clinical use conditions for 2 weeks of once daily application in treatment group two. Maximal use condition was defined as having both feet affected for NAFT-600. Maximal use condition was defined as having both feet affected for NAFT-600".

The protocols specified that the secondary objectives were to evaluate subject efficacy, tolerability, and safety after 2 weeks of once daily application of both products (NAFT-500 and NAFT-600).

Table 1: Study submitted by the applicant

	Phase and Design	Treatment Period	# of Subjects per Arm	Study Population
MUSC 90200/ 1023/0	Postmarketing, open-label, maximal use study	2 weeks of treatment	NAFT-500 (22 pediatric subjects + 6 adult subjects) NAFT-600 (22 pediatric subjects + 6 adult subjects)	Male or female subjects aged 12-17 years 11 months of any race: NAFT-500: tinea pedis, tinea cruris confirmed by a positive KOH from both feet and bikini area NAFT-600: Tinea pedis confirmed by positive KOH from both feet.

Source: Reviewer's table.

Efficacy was evaluated at Days 7, 14, and 28. For NAFT-500, efficacy was assessed individually on the foot and the groin, and for NAFT-600, only the foot was assessed for tinea pedis.

The applicant stated that the following efficacy variables were "summarized":

1) Complete cure at Days 7, 14, 28, defined as negative mycology results from the central laboratory (dermatophyte culture and KOH), and absence of erythema, scaling, and pruritus (grade 0 for each).
2) Treatment effectiveness at Days 7, 14, 28, defined as negative KOH, negative culture and erythema, scaling, and pruritus scores of 0 or 1
3) Mycological cure at Days 7, 14, 28, defined as negative KOH result and negative dermatophyte culture
4) Clinical success at Days 7, 14, 28, defined as erythema, scaling, and pruritus scores of 0 or 1
5) Clinical cure at Days 7, 14, 28, defined as erythema, scaling, and pruritus scores of 0.
6) Subject Satisfaction Assessment scores at Days 7, 14, 28.
7) Investigator's Global Assessment (IGA) scores at Days 7, 14, 28.

According to the sponsor, they used the exact methods to calculate the 90% confidence intervals (CI) for the percentages of subjects with the outcome of interest above.

The applicant provided the following results for NAFT-500 treatment arm.

Table 2. Applicant's Results of Complete Cure, Treatment Effectiveness, Mycological Cure, Clinical Success, and Clinical Cure on Day 28 (NAFT-500).

	Foot		Groin	
Efficacy Parameter	**Pediatric (N=22) n (%) [90% CI]**	**Adult (N=6) n (%) [90% CI]**	**Pediatric (N=22) n (%) [90% CI]**	**Adult (N=6) n (%) [90% CI]**
Complete cure	13 (59.1) [39.5, 76.7]	0	14 (63.6) [43.9, 80.4]	1 (16.7) [0.9, 58.2]
Effective treatment	14 (63.6) [43.9, 80.4]	0	14 (63.6) [43.9, 80.4]	3 (50.0) [15.3, 84.7]
Mycological cure	15 (68.2) [48.5, 84.0]	1 (16.7) [0.9, 58.2]	16 (72.7) [53.2, 87.4]	4 (66.7) [27.1, 93.7]
Clinical success	20 (90.9) [74.1, 98.4]	4 (66.7) [27.1, 93.7]	20 (90.9) [74.1, 98.4]	4 (66.7) [27.1, 93.7]
Clinical cure	18 (81.8) [63.1, 93.5]	1 (16.7) [0.9, 58.2]	18 (81.8) [63.1, 93.5]	2 (33.3) [6.3, 72.9]

90% CI = confidence interval, FAS = full analysis set, n = number of observations, N = number of subjects in the treatment group and analysis set

Source: Applicant's results (page 9)

The applicant provided the following results for NAFT-600 treatment arm.

Table 3. Applicant's Results of Complete Cure, Treatment Effectiveness, Mycological Cure, Clinical Success, and Clinical Cure on Day 28 (NAFT-600).

Efficacy Parameter	Pediatric (N=22) n (%) [90% CI]	Adult (N=5) n (%) [90% CI]
Complete cure	6 (27.3) [12.6, 46.8]	0
Effective treatment	12 (54.5) [35.3, 72.9]	1 (20.0) [1.0, 65.7]
Mycological cure	14 (63.6) [43.9, 80.4]	1 (20.0) [1.0, 65.7]
Clinical success	18 (81.8) [63.1, 93.5]	4 (80.0) [34.3, 99.0]
Clinical cure	9 (40.9) [23.3, 60.5]	1 (20.0) [1.0, 65.7]

90% CI = confidence interval, FAS = full analysis set, n = number of observations, N = number of subjects in the treatment group and analysis set

Source: Applicant's results (page 12)

2.2 Applicant's Proposed Labeling Changes

(b) (4)

3 Labeling Recommendations

In order to fulfill the PREA postmarketing requirements, the applicant conducted an open-label, maximal use study in 22 pediatric subjects aged 12 to 17 years 11 months under maximal clinical use conditions with the primary objectives to quantify the pharmacokinetics of NAFT-500 and NAFT-600. As the completed trial was an open-label, maximal use trial that did not include a vehicle arm, efficacy results from such trial are subject to bias as no comparator arm was included. In addition, the sample size (22 pediatric subjects and 6 adult subjects) is too small to draw a reasonable conclusion about efficacy. (b) (4)

SIGNATURES/DISTRIBUTION LIST

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