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 #:	sNDA 019599 / SDN 321
Drug Name:	Naftin (naftifine hydrochloride) cream, 2%
Indication(s):	Treatment of tinea corporis among pediatric subjects
Applicant:	Merz Pharmaceuticals LLC
Date(s):	Stamp date: 1/13/2016 PDUFA: 1/13/2017
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III
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Keywords:
Tinea Corporis; Superiority

Table of Contents

1. EXECUTIVE SUMMARY

Naftin cream 2% was approved on 1/13/2012 for the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organism *Trichophyton rubrum* in adults ≥ 18 years of age. To fulfill a PREA postmarketing requirement, the applicant conducted a Phase 4 Double-Blind, Randomized, Placebo-Controlled, Multicenter, Parallel Group Evaluation of the Efficacy and Safety of NAFT-500 and NAFT-600 in Pediatric Subjects with Tinea Corporis (MUS90200/4024/1 from hereon denoted as Trial 4024), and submitted the results for Trial 4024 in this sNDA application.

The results showed that the Naftin cream 2% was superior to vehicle at Day 21 for the primary endpoint of complete cure which was defined as having negative mycology results (dermatophyte culture and KOH) and absence of erythema, induration, and pruritus (p=0.01 at a one-sided significance level of 0.025) as well as for the secondary endpoints of (i) effective treatment defined as negative KOH, negative culture sampled from the target lesions defined at baseline with erythema, induration, and pruritus sign/symptom scores of 0 or 1 on all lesions identified at baseline (p=0.001) as well as for (ii) mycological cure defined as negative KOH result and negative dermatophyte culture sampled from the site cultured at baseline or last site cultured most representative of overall severity from lesions present at baseline (p=0.001). Table 1 presents the reviewer's analysis for the primary and secondary efficacy endpoints at Day 21.

Table 1. Reviewer's Primary and secondary efficacy endpoint analysis results

Trial 4024				
Endpoint		Naftin N=91	Vehicle N=93	p-value
Primary	Complete Cure [(1)] at Day 21	42 (46%)	26 (28%)	0.01
Secondary	Effective Treatment [(2)] at Day 21	53 (58%)	32 (34%)	0.001
	Mycological Cure [(3)] at Day 21	57 (63%)	36 (39%)	0.001

Source: P-values were from the Chi-square test with a one-sided significance level of 0.025; the protocol-specified primary imputation method for handling missing data was to impute missing as treatment failure (MVTF).

(1) Complete Cure was defined as negative mycology results (dermatophyte culture and KOH) and absence of erythema, induration, and pruritus (scores of 0 on each),
(2) Effective Treatment was defined as negative KOH, negative culture, and erythema, induration, and pruritus grades of 0 or 1,
(3) Mycological Cure was defined as negative KOH and negative culture.

2. INTRODUCTION

2.1 Overview

2.2 Regulatory History

The applicant has the following two approved Naftin, 2% products as shown below:

- Naftin cream, 2% (approved on 1/13/2012) for the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organism *Trichophyton rubrum* in adults ≥ 18 years of age.
- Naftin gel, 2% (approved on 6/27/2013) for the treatment of interdigital tinea pedis caused by the organisms *Trichophyton rubrum, Trichophyton mentagrophytes*, and *Epidermophyton floccosum*.

In addition to the above, the applicant has the following approved naftifine products:

- 1% gel formulation (approval date: 6/18/1990) for the topical treatment of tinea pedis, tinea cruris, and tinea corporis caused by the organism *Trichophyton metagrophytes, Trichophyton tonsurans*, and *Epidermophyton floccosum*
- 1% cream formulation (approval date: 2/29/1988) for the topical treatment of tinea pedis, tinea cruris and tinea corporis caused by the organisms *Trichophyton rubrum, Trichophyton mentagrophytes*, and *Epidermophyton floccosum.*

Per the approval letter (1/13/2012) for the Naftin cream 2%, the sponsor was required to conduct the following studies as PREA postmarketing requirements:

"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."

"1857-2 PK/Efficacy/Safety study in pediatric subjects ages 2 years to 17 years 11 months with tinea corporis."

There was a Pre-NDA meeting on 5/16/2012 for IND 105603 and the sponsor inquired:

- (b) (4)
-

In response, the Agency commented that the proposal to include NAFT-600 arm appears reasonable; however, the trial design should be modified to include a Naftin gel vehicle arm, and a Naftin cream vehicle arm. Further, the Agency commented that we "cannot provide comment regarding (b) (4)

On 9/28/2012, the sponsor submitted the following Phase 4 protocols to pursue a pediatric claim for tinea corporis, and to fulfill the above "Phase 4 commitment".

- **MUS90200/4024/1:** "A Phase 4 Double-Blind, Randomized, Placebo-Controlled, Multicenter, Parallel Group Evaluation of the Efficacy and Safety of NAFT-500 and NAFT-600 in Pediatric Subjects with Tinea Corporis"
- **MUS90200/4025/1:** "A Phase-4 Open-Label, Multi-Center, Multiple-Application Pharmacokinetic Study of NAFT-500 and NAFT-600 in Pediatric Subjects with Tinea Corporis"

A statistical review that summarized the protocol MUS90200/4024/1 was signed off in DARRTS (dated: 11/30/2012), and at that time, general comments including the analysis population, method for handling of missing data, sample size were conveyed in an advice letter dated 5/15/2013.

In this sNDA application, the applicant submitted results from their Phase 4, double-blind, randomized, vehicle-controlled, multicenter, parallel group evaluation of the efficacy and safety of Naftin cream, 2% in pediatric subjects with Tinea Corporis (Trial 4024). In addition, the sponsor submitted results from their open-label Phase 4 trial as well (MUS90200/4025/1 from hereon denoted as Trial 4025).

Table 2 presents the study overview for Trial 4024.

Table 2. Clinical Study Overview for the Phase 4 Trial

Study	Study Population	Treatment Arms	N	Dates
4024 (N=181 FAS subjects)	• Males or Females ≥2 to <18 years of age • Presence of tinea corporis characterized by clinical evidence of a tinea infection of at least moderate erythema, moderate induration, and mild pruritus • KOH positive and culture positive baseline skin scrapings obtained from the site with the most severely affected lesion or a representative site of the overall severity	Naftin cream, 2%	88	8/20/2014 - 10/27/2015
		Vehicle cream	93	

Source: Reviewer table.

2.3 Data Sources

This reviewer evaluated the applicant's clinical study reports and clinical summaries, as well as the proposed labeling. This submission was submitted in eCTD format and was entirely electronic. Both SDTM and analysis datasets were submitted. The datasets in this review are archived at: \\cdsesub1\evsprod\nda019599\0077\m5\datasets\.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The applicant submitted electronic analysis datasets for review, and no requests for additional datasets were made to the applicant.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The study objective was to evaluate the safety and efficacy of Nafin cream, 2% applied once daily for 2 weeks, each compared to its vehicle in the treatment of pediatric subjects aged 2 to 17 years and 11 months with positive KOH, positive dermatophyte culture, and clinical signs and symptoms of tinea corporis.

A total of 318 subjects from 13 centers (U.S., Puerto Rico, Dominican Republic, Belize, Honduras, Panama, and El Salvador) were randomized in a 1:1 ratio to the following arms:

- Naftin cream 2%
- vehicle

The protocol specified using the block randomization to ensure balanced treatment assignment within each site. The enrollment criteria are summarized in Table 1.

Subjects applied the assigned study product once daily to the affected areas plus a 0.5-inch margin of healthy skin for two weeks, and return to the study center for a follow-up visit at Days 14 and 21. There were three planned visits for each subject: Day 1, Day 14 and Day 21.

The primary efficacy endpoint was the complete cure at Day 21 where complete cure was defined as negative mycology results (dermatophyte culture, KOH) and absence of erythema, induration and pruritus on all lesions identified at baseline.

For secondary endpoints, the sponsor proposed:

- Treatment effectiveness at Day 21 defined as negative KOH, negative culture sampled from the target lesions defined at baseline with erythema, induration, and pruritus sign/symptom scores of 0 or 1 on all lesions identified at baseline.
- Mycological cure at Day 21 defined as negative KOH result and negative dermatophyte culture sampled from the site cultured at baseline or last site cultured most representative of overall severity from lesions present at baseline.

The following were the analysis sets defined by the sponsor.

- Safety Evaluation Set (SES): all subjects exposed to the study medication at least once

- Full Analysis Set (FAS): subset of SES with positive culture at baseline for whom the primary efficacy endpoint is available (which the sponsor notes in the protocol is the case for all subjects, because dropouts and cases with missing information will be considered as not complete cures).
- Per Protocol Set (PPS): subset in the FAS without major protocol violations, and major protocol violations are defined as subjects with insufficient baseline signs and symptoms, unmet inclusion/exclusion criteria, treatment with forbidden concomitant medications, enrollment prior to study determined wash-out of concomitant medications, Visit 3 occurring outside of the visit window, missing or unknown Visit 3 KOH and dermatophyte result, missing or unknown erythema, scaling and pruritus scores at Visit 3.

The primary analysis population was the FAS.

The sponsor conducted a one-sided hypothesis tests as follows:

$$H_0(\text{null}): p_1 \leq p_0 \text{ vs. } H_a \text{ (alternate)}: p_1 > p_0$$

where p_0 and p_1 denote the proportion of complete cure in the cream vehicle, Naftin cream, 2%, respectively.

For the primary analysis method, the protocol originally specified using the Cochran-Mantel Haenszel (CMH) test stratified by site with a one-sided level of significance of 0.025; however, given that 4 of the 7 centers only had a single subject for analyses, the sponsor used the Chi-square test.

For the secondary efficacy analyses, the protocol specified using the Hochberg's procedure with overall level of α=0.025 (i.e., reject if both p-values are $\leq\alpha$ or if one p-value is $\leq\alpha/2$). For the analysis of the secondary efficacy endpoints, the Chi-square test was used.

For handling of missing data, the sponsor used missing value treated as failure (MVTF) as the primary imputation method, and used the last observation carried forward (LOCF) as a sensitivity analysis.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

Table 3 presents the disposition of subjects for Trial 4024. Trial 4024 randomized a total of 231 subjects (116 Naftin 2%; 115 vehicle), and after excluding 47 subjects that had negative mycology at baseline and 3 subjects that did not have any post-baseline assessments, the applicant considered a total of 181 subjects for their full analysis set (FAS) for efficacy analyses. A total of 4 randomized subjects discontinued the trial, and they were considered to be treatment failures per the protocol-specified primary imputation method.

Table 3. Subject Disposition

	Trial 4024	
	Naftin, 2%	Vehicle
Randomized; Safety	116	115
Applicant's Full Analysis Set (FAS[(1)])	88	93
Reasons excluded from FAS		
Negative mycology at baseline	25	22
No post-baseline efficacy data	3 [(2)]	0
Discontinued	4 (3%)	0 (0%)
Adverse Events	0	0
Withdrawal by subject	2	0
Lack of Efficacy	0	0
Loss to Followup	1	0
Protocol violation	0	0
Physician Decision	1	0
Other	0	0

Source: Applicant's Study Report, (1) FAS defined as subjects with positive culture at baseline for whom the primary efficacy endpoint is available; (2) subjects MUS90200_4024_1-S0402; MUS90200_4024_1-S0763; MUS90200_4024_S0764

Following the intent-to-treat (ITT) principle, this reviewer included those 3 subjects that did not have any post-baseline efficacy data (3 subjects). Therefore, the reviewer's FAS included 91 and 93 subjects for Naftin cream, 2% and vehicle, respectively.

Table 4 presents the baseline demographics for Trial 4024. The baseline demographics were generally balanced across the treatment arms. Approximately 61% of the subjects were male, 44% were white and 55% were black, and the mean age of the subjects was 8.8 years of age.

Table 4. Baseline demographic characteristics (FAS)

	Trial 4024	
	Naftin, 2%	Vehicle
FAS	91	93
Sex		
Female	35 (38%)	37 (40%)
Male	56 (62%)	56 (60%)
Race		
White	39 (43%)	42 (45%)
Black	51 (56%)	51 (55%)
Other	1 (1%)	0 (0%)
Age		
Mean ± SD	8.8 ± 4.2	8.8 ± 4.4
range	2, 17	2, 17
Median	9	8

Source: Reviewer's table

3.2.3 Results and Conclusions

Naftin cream 2% was superior to vehicle at Day 21 for the primary endpoint of complete cure which was defined as having negative mycology results (dermatophyte culture and KOH) and absence of erythema, induration, and pruritus (p=0.01). Naftin cream 2% was superior to vehicle at Day 21 for the secondary endpoints of the following: (i) effective treatment defined as negative KOH, negative culture sampled from the target lesions defined at baseline with erythema, induration, and pruritus sign/symptom scores of 0 or 1 on all lesions identified at baseline as well as (ii) mycological cure defined as negative KOH result and negative dermatophyte culture sampled from the site cultured at baseline or last site cultured most representative of overall severity from lesions present at baseline. Table 1 presents the reviewer's analysis for the primary and secondary efficacy endpoints at Day 21.

3.4 Evaluation of Safety

Table 5 presents the number of subjects with treatment emergent adverse events (TEAEs) by system organ class and preferred term occurring with an incidence rate of ≥1%.

Table 5. Treatment Emergent Adverse Events (TEAEs) by organ class and preferred term

	Naftin N=116	Vehicle N=115
Subjects with at least one TEAE	4 (3%)	10 (9%)
Infections and infestations	3 (3%)	5 (4%)
Nasopharyngitis	*2*	*2*
Upper respiratory tract infection	*1*	*2*
Pharyngitis bacterial	*0*	*1*
Nervous system disorders	0 (0%)	2 (2%)
Headache	*0*	*2*

Source: applicant's Table 17 (page 61; study report)

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Efficacy by Gender, Race, and Age

Table 6 presents the primary efficacy endpoint of complete cure by sex, race and age group (<9 vs. ≥9 years of age). Analyses by sex and race subgroups were generally consistent across the treatment arms, and for the efficacy by age subgroups, the treatment effect in the younger age group (≥2 and <9 years of age) was larger than those of the older age group (≥9 and <18 years of age).

Table 6. Primary efficacy endpoint by demographic characteristics

	Trial 4024	
	Naftin, 2%	Vehicle
FAS	91	93
Sex		
Female	16/35 (46%)	11/37 (30%)
Male	26/56 (46%)	15/56 (27%)
Race		
White	20/39 (51%)	13/42 (31%)
Black	22/51 (43%)	13/51 (25%)
Other	0/1 (0%)	0 (0%)
Age		
< mean (9 years of age)	19/44 (43%)	9/47 (19%)
≥ mean age (9 years of age)	23/47 (49%)	17/46 (37%)

Source: reviewer's table

4.2 Efficacy by Center

Table 7 presents the complete cure rates by study sites. It should be noted that 4 of the 7 sites had a single FAS subject for analysis. The treatment effects for the primary endpoint of complete cure at Day 21 by study center are presented in Table 7 below.

Table 7. Primary efficacy endpoint by site

Trial 4024			
Efficacy by Site		Naftin N=91	Vehicle N=93
By site	Primary Endpoint	42 (46%)	26 (28%)
	001126	0	1
	001279	0	1
	001293	1	0
	001307	1	0
	180001	16/29 (55%)	8/28 (29%)
	180002	8/28 (29%)	6/28 (21%)
	504001	17/32 (53%)	12/35 (34%)

Source: Reviewer table

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There were no major statistical issues affecting the overall efficacy conclusions. The amount of missing data was relative small, and the treatment effects were generally consistent across baseline demographic subgroups.

5.2 Conclusions and Recommendations

In the sNDA application, the applicant submitted results from one Phase 4 trial that was conducted to fulfill a PREA post-marketing requirement per the approval letter for Naftin cream 2% (approval letter dated: 1/13/2012) for the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organism *Trichophyton rubrum* in adults ≥ 18 years of age. In the Phase 4 trial, Naftin cream 2% was superior to vehicle at Day 21 for the primary endpoint of complete cure which was defined as having negative mycology results (dermatophyte culture and KOH) and absence of erythema, induration, and pruritus ($p=0.01$ at a one-sided significance level of 0.025) as well as for the secondary endpoints of (i) effective treatment defined as negative KOH, negative culture sampled from the target lesions defined at baseline with erythema, induration, and pruritus sign/symptom scores of 0 or 1 on all lesions identified at baseline ($p=0.001$) as well as for (ii) mycological cure defined as negative KOH result and negative dermatophyte culture sampled from the site cultured at baseline or last site cultured most representative of overall severity from lesions present at baseline ($p=0.001$). The reviewer's analysis for the primary and secondary efficacy endpoints at Day 21 is presented in Table 1.

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/s/

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08/12/2016

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08/12/2016