

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204286Orig1s000**

**STATISTICAL REVIEW(S)**



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 #:** NDA 204286  
**Drug Name:** NAFT-600 (Naftin 2%) gel  
**Indication(s):** Tinea Pedis  
**Applicant:** Merz  
**Date(s):** Stamp date: 8/31/2012  
PDFUA: 6/30/2013  
**Review Priority:** Standard

**Biometrics Division:** Division of Biometrics III  
**Statistical Reviewer:** Carin Kim, Ph.D.  
**Concurring Reviewers:** Mohamed Alosh, Ph.D.

**Medical Division:** Division of Dermatologic and Dental Products  
**Clinical Team:** Milena Lolic, MD  
David Kettl, MD  
**Project Manager:** Strother Dixon

**Keywords:**  
Tinea Pedis, interdigital, moccasin

## Table of Contents

<b>1</b>	<b>EXECUTIVE SUMMARY .....</b>	<b>3</b>
<b>2</b>	<b>INTRODUCTION .....</b>	<b>5</b>
2.1	OVERVIEW.....	5
2.2	DATA SOURCES .....	6
<b>3</b>	<b>STATISTICAL EVALUATION .....</b>	<b>7</b>
3.1	DATA AND ANALYSIS QUALITY .....	7
3.2	EVALUATION OF EFFICACY .....	7
3.2.1	<i>Study Design and Endpoints</i> .....	7
3.2.2	<i>Statistical Methodologies</i> .....	8
3.2.3	<i>Patient Disposition, Demographic and Baseline Characteristics</i> .....	9
3.2.4	<i>Results and Conclusions</i> .....	12
3.3	EVALUATION OF SAFETY .....	14
<b>4</b>	<b>FINDINGS IN SPECIAL/SUBGROUP POPULATIONS .....</b>	<b>15</b>
4.1	GENDER, RACE, AGE, AND GEOGRAPHIC REGION .....	15
4.2	OTHER SPECIAL/SUBGROUP POPULATIONS .....	15
<b>5</b>	<b>SUMMARY AND CONCLUSIONS .....</b>	<b>16</b>
5.1	STATISTICAL ISSUES .....	16
5.2	COLLECTIVE EVIDENCE .....	16
5.3	CONCLUSIONS AND RECOMMENDATIONS .....	17
5.4	LABELING RECOMMENDATIONS .....	17

## 1. EXECUTIVE SUMMARY

The applicant submitted results from two Phase 3 trials (Studies MRZ 3015 and MRZ 3016) to support the efficacy claim of Naftin (NAFT-600) gel, 2% for the indication of “interdigital <sup>(b) (4)</sup> tinea pedis”. For the treatment of interdigital-type tinea pedis, NAFT-600 gel was statistically superior to vehicle in two studies ( $p < 0.001$ ). <sup>(b) (4)</sup>



The protocol-specified primary efficacy endpoint was the proportion of subjects with complete cure of **interdigital** tinea pedis at Week 6 where complete cure is defined as negative mycology results (dermatophyte culture and KOH) and absence of erythema, scaling and pruritus (grade 0 for each) evaluated using a 4-point severity grade (0=absent, 1=mild, 2=moderate, 3=marked).

The protocol-specified key secondary endpoints were the following:

- Mycological cure of **interdigital** tinea pedis: negative KOH results and negative dermatophyte culture at Week 6
- Effective treatment of **interdigital** tinea pedis: negative KOH, negative culture, and erythema, scaling and pruritus scores of 0 or 1 at Week 6.

The protocol stated that if the primary efficacy endpoint analysis provides a statistically significant result, then the key secondary efficacy endpoints will be tested using the same CMH test stratified by sites to show superiority of NAFT-600 over vehicle. To control the Type I error rate in testing for the secondary endpoints, the Hochberg step-up procedure was used; that is, if both p-values from the secondary endpoint analyses (one-sided) are  $\leq 0.025$ , both comparisons will be considered statistically significant. Alternatively, if this condition is not met, and if only one p-value is  $\leq 0.025$ , then it must be  $\leq 0.0125$  in order to be considered statistically significant.

Summaries of primary and key secondary efficacy results for interdigital tinea pedis are presented in the following table.

**Table 1. Applicant’s Analysis for Interdigital Type Tinea Pedis (Primary and Key Secondary efficacy endpoints)**

		<b>NAFT-600</b>	<b>Vehicle</b>	<b>p-value<sup>(4)</sup></b>
<b>Study MRZ 3015</b>		382	179	
Interdigital	Complete Cure <sup>(1)</sup>	64 (16.8%)	3 (1.7%)	<0.001
	Effective Treatment <sup>(2)</sup>	207 (54.2%)	11 (6.1%)	<0.001
	Mycological Cure <sup>(3)</sup>	250 (65.4%)	25 (14.0%)	<0.001
<b>Study MRZ 3016</b>		400	213	
Interdigital	Complete Cure <sup>(1)</sup>	104 (26.0%)	7 (3.3%)	<0.001
	Effective Treatment <sup>(2)</sup>	203 (50.8%)	15 (7.0%)	<0.001
	Mycological Cure <sup>(3)</sup>	235 (58.8%)	22 (10.3%)	<0.001

Source: Applicant’s Analysis.

(1) Complete Cure is defined as having negative mycology results (dermatophyte culture and KOH) and absence of erythema, scaling and pruritus at Week 6.

(2) Effective Treatment is having negative KOH, negative culture, and scaling, erythema, and pruritus grade of 0 or 1

(3) Mycological cure is having negative KOH and negative culture.

(4) P-values are calculated from a one-sided CMH test stratified by pooled sites (FAS, MVTF).

The protocol listed the following as “other secondary efficacy endpoints”:

- Complete cure of (b) (4) at Week 6
- Effective treatment of (b) (4) at Week 6
- Mycological cure of (b) (4) at Week 6.

For these endpoints, the applicant presented results using only the observed and available cases; however, included those subjects that do not meet the inclusion criteria at baseline (i.e., positive KOH and dermatophyte culture along with at least moderate erythema, at least moderate scaling, and at least mild pruritus). The analysis results after excluding those subjects that did not meet the inclusion criteria at baseline are provided in Table 2.



## 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)

The Naftin 2% cream was approved (sNDA 019599) for the indication of **interdigital tinea pedis**, tinea cruris and tinea corporis, and for that application, the applicant submitted statistically significant results from two trials with Naftin 2% cream: one in tinea cruris, and one in tinea pedis. For the tinea pedis trial, while the Agency previously commented that the applicant separately analyze efficacy and safety for each type of tinea pedis [REDACTED] (b) (4), the study's inclusion criteria did not specify the specific types of tinea pedis, and included subjects with all types of tinea pedis (i.e., interdigital, moccasin, and others).

### 2.1 Overview

On 6/2/2009 (SDN 1), the sponsor submitted a Phase 3 protocol for the indication of tinea pedis for Agency's comments. In an advice letter (dated: 11/13/2009), the Agency recommended that the sponsor conduct Phase 2 dose ranging studies, and provided general comments regarding the analysis set definition, primary imputation method, IGA scale for Phase 3 trials.

On 4/14/2010, there was a Guidance Meeting held between the Agency and the sponsor, and at that time, the sponsor's overall development program including their proposed Phase 3 trials was discussed. The Agency recommended that the sponsor conduct an appropriate dose-ranging study which investigates concentration, frequency of use and treatment duration to select the appropriate dose and to get estimate of treatment effect to be used for powering future Phase 3 trials. Further, the Agency asked the sponsor to clarify whether they plan to study a population with (and seek indication for) interdigital tinea pedis [REDACTED] (b) (4). The Agency further commented that the interdigital tinea pedis [REDACTED] (b) (4). Further, the Agency commented that the study should be powered for each type of tinea pedis and multiplicity should be addressed.

On 1/27/2011 (SDN 15), two identical Phase 3 protocols were submitted for review, and according to the protocols, the primary and key secondary efficacy endpoints were related to the interdigital type tinea pedis. The protocol listed the [REDACTED] (b) (4) endpoints as "other secondary endpoints", and stated that these would not be inferential in nature. For statistical comments, the Agency stated that details of the sensitivity and supportive analyses should be prespecified in the protocol rather than deferred to the statistical analysis plan. The Agency stated that the proposed primary imputation method was not clear.

On 5/18/2011 (SDN 19), the sponsor submitted two identical Phase 3 SAPs for Agency comments, and in an advice letter (10/14/2011), the Agency commented on the sponsor's primary imputation method that proposed to use the last observation carried forward (LOCF).

The Agency recommended that the sponsor consider a more scientifically and sound method for handling missing data, and recommended that the sponsor include alternate methods as sensitivity analyses to ensure that the efficacy results are not driven by the choice of the primary imputation method.

Per the Agency’s comments, the sponsor submitted amended SAPs and proposed to impute the missing values as treatment failures (MVTF) as the primary imputation method, and proposed to use LOCF and Worst Case Scenarios (WCS) as sensitivity analyses (SDN 25, stamp: 2/14/2012).

On 6/1/2012, there was a Pre-NDA meeting between the Agency and the sponsor (SDN 27, stamp date: 4/5/2012), and the sponsor included amended SAPs for Agency’s comments. As the study was already completed, the Agency would not concur with a specific approach for handling missing data at that time. Further, the Agency commented that whether the proposed method of imputing missing value treated as failure (MVTF) is reasonable for handling missing data depends on the proportion of dropouts in each treatment arm. In addition, the Agency provided general comments on the data format for the NDA submission as well as on the SAP for the ISE section.

An overview of the completed Phase 3 trials is summarized below.

**Table 3. Clinical Study Overview**

Study	Study Sites	Study Population	Treatment Arms	Number of Subjects	Dates
Study MRZ 3015	US (23 centers)	Male and female subjects $\geq 12$ years of age with clinical evidence (at least moderate erythema, moderate scaling, and mild pruritus) of interdigital or combined interdigital and moccasin types of tinea pedis confirmed by KOH and culture	NAFT-600	382	2/15/2011-1/3/2012
			Vehicle	179	
Study MRZ 3016	US (24 centers)		NAFT-600	400	2/10/2011-12/7/2011
			Vehicle	213	

Source: reviewer’s table

## 2.2 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. The datasets in this review are archived at the following locations:

<\\cdsesub1\EVSPROD\NDA204286\0000\m5\datasets\mrz-3015\analysis>  
<\\cdsesub1\EVSPROD\NDA204286\0000\m5\datasets\mrz-3016\analysis>

### 3. STATISTICAL EVALUATION

#### 3.1 Data and Analysis Quality

The applicant submitted electronic analysis datasets for review. The primary efficacy analyses could be conducted using the submitted analysis datasets.

#### 3.2 Evaluation of Efficacy

##### 3.2.1 Study Design and Endpoints

The protocol stated that the primary objective was “to evaluate the efficacy and safety of NAFT-600, applied once daily for 2 weeks, when compared to placebo for 2 weeks in the treatment with KOH and culture positive symptomatic tinea pedis”.

Study MRZ 3015 enrolled a total of 561 subjects (382 NAFT-600; 179 vehicle) from 23 U.S. centers, and Study MRZ 3016 enrolled a total of 613 subjects (400 NAFT-600; 213 vehicle) from 24 U.S. centers. For enrollment, male and female subjects  $\geq 12$  years of age with clinical evidence (at least moderate erythema, moderate scaling, and mild pruritus) of interdigital or combined interdigital and moccasin types of tinea pedis confirmed by KOH and culture were enrolled. According to the study report (page 36), if a subject had both types (interdigital and moccasin), then both areas were assessed separately using the following 4-point scale:

0	Absent (normal appearing skin)
1	Mild (barely abnormal)
2	Moderate (distinctly present abnormality)
3	Marked (intense involvement or marked abnormality)

Source: applicant’s study report (page 36)

The same evaluator was used for assessing the clinical signs and symptoms of disease severity within a subject throughout the trial, whenever possible.

Subjects were to apply the study product once a day for two weeks. The applicant’s study report stated that “all affected areas were treated, but only the areas noted as being the most clinically affected at the time of the visit was used for assessing the signs and symptoms”. Subjects were assessed on the following visits: Day 1, Weeks 2, 4 and 6.

According to protocol, the KOH-positive and culture-positive baseline skin scrapings were “obtained from the site most severely affected or a representative site of the overall severity”. The case report form (CRF) stated also that “if a subject has a diagnosis of both moccasin and interdigital type tinea pedis then a scraping of both areas with the most extensive scaling or representative site of overall severity should be obtained”. Based on the applicant’s mb.xpt data, all interdigital areas were assessed for KOH and culture at baseline; however, not all moccasin areas were subjected to KOH and culture at baseline.

According to the protocol, block randomization was used, and randomization was stratified by site. Subjects were randomized in a 2:1 ratio to NAFT-600: vehicle.

The protocol-specified primary efficacy endpoint is the following:

- The proportion of subjects with complete cure of interdigital tinea pedis at Week 6 where complete cure is defined as negative mycology results (dermatophyte culture and KOH) and absence of erythema, scaling and pruritus (grade 0 for each) evaluated using a 4-point severity grade (0=absent, 1=mild, 2=moderate, 3=marked).

The key secondary endpoints are the proportion of subjects with the following:

- Mycological cure of interdigital tinea pedis: negative KOH results and negative dermatophyte culture at Week 6
- Effective treatment of interdigital tinea pedis: negative KOH, negative culture, and erythema, scaling and pruritus scores of 0 or 1 at Week 6.

The protocol also listed the following as “other secondary endpoints” which are the proportion of subjects with the following:

- Complete cure of [REDACTED] (b) (4) at Week 6
- Effective treatment of [REDACTED] (b) (4) at Week 6
- Mycological cure of [REDACTED] (b) (4) at Week 6

### 3.2.2 Statistical Methodologies

According to the protocol, the primary analysis population is the full analysis set (FAS), which is a modified intent to treat population defined as “the subset of all subjects in the safety evaluation set (SES – all subjects who received study medication at least once) with a positive culture at baseline for whom the primary efficacy endpoint is available (which is the case for all subjects because dropouts and cases with missing information will be considered as not complete cures by definition)”. The per protocol (PP) population excluded subjects with the following major protocol violations:

- Subjects with insufficient baseline signs and symptoms
- Subjects with unmet inclusion/exclusion criteria
- Treatment with forbidden previous and/or concomitant medications
- Enrollment prior to study determined wash-out of concomitant medications
- Subject visit 4 (week 6) visit occurring outside of the expected visit window
- Missing or unknown visit 4 (week 6) KOH and dermatophyte culture results
- Missing or unknown erythema, scaling and pruritus scores at visit 4 (week 6)

The primary and secondary endpoints were analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by sites. The primary endpoint was tested using one-sided significance level of 0.025. Multiplicity for the two key secondary endpoints was controlled using the Hochberg’s method. For the Hochberg’s method, if the primary efficacy endpoint analysis provides a statistically significant result, then the two secondary efficacy endpoints are tested using the same method (one-sided level of significance of 0.025 using a CMH test) to show superiority of NAFT-600 over vehicle. If both p-values from the secondary endpoint analyses (one-sided) are

$\leq 0.025$ , both comparisons are considered statistically significant; if only one endpoint provides a p-value  $\leq 0.025$ , then it must be  $\leq 0.0125$  in order to be considered statistically significant.

For the analysis of the “other secondary endpoints”, the protocol stated that “these analyses will not be inferential in nature (page 43)”. The applicant did not include methods to adjust for the Type I error rate for these “other” secondary endpoints, and furthermore, not all subjects with (b)(4) assessed at baseline for positive KOH and positive culture at baseline.

For handling of missing data, the sponsor proposed to use missing values treated as failures (MVTf) method as the primary imputation method, and use LOCF and Worst Case Scenarios (WCS) method as sensitivity analyses. For the WCS, the sponsor imputed success for the missing data in the vehicle arm, and imputed failure for the missing data in the NAFT-600 arm.

### 3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Study MRZ 3015 enrolled 561 FAS subjects (382 to NAFT-600, 179 to vehicle), and Study MRZ 3016 enrolled 613 FAS subjects (400 to NAFT-600, 213 to vehicle). Approximately 11% and 8% of the subjects discontinued Study MRZ 3015 and Study MRZ 3016, respectively, before Week 6. The most common reason for discontinuation was lost to follow-up. Table 4 displays the patient disposition along with reasons for discontinuation.

**Table 4. Number (proportion) of subjects who discontinued the study: classified by reason for discontinuation**

	Study MRZ 3015		Study MRZ 3016	
	NAFT-600	Vehicle	NAFT-600	Vehicle
<b>Randomized Subjects (SES)<sup>(1)</sup></b>	<b>571</b>	<b>284</b>	<b>573</b>	<b>287</b>
<b>FAS<sup>(2)</sup> Subjects</b>	<b>382</b>	<b>179</b>	<b>400</b>	<b>213</b>
<b>Completed</b>	340 (89.0%)	157 (87.7%)	365 (91.3%)	200 (93.9%)
<b>Discontinued</b>				
<i>Adverse Event</i>	2	0	1	0
<i>Protocol violation</i>	9	5	5	2
<i>Lost to follow-up</i>	22	10	14	7
<i>Subject decision/withdrawal of consent</i>	9	5	11	4
<i>Other</i>	0	2	4	0

Source: reviewer’s analysis

- (1) Safety-Evaluation Set (SES): The SES population was the subset of all subjects who received study drug at least once.
- (2) Full-Analysis Set (FAS): The FAS population was the subset of the SES population with a positive culture at baseline. This was a modified intent-to-treat principle because the culture results were not available before the start of treatment.

The baseline demographics were generally balanced across treatment groups in Studies MRZ 3015 and 3016, though the gender groups were slightly imbalanced. About 78% of the subjects

were male. While the applicant is seeking for an indication of tinea pedis in subjects <sup>(b) (4)</sup> years of age and older, only 4 subjects were <18 years of age in Study MRZ 3015, and only 10 subjects were < 18 years of age in Study MRZ 3016. Approximately 54% and 66% of the subjects were white in Studies MRZ 3015 and 3016, respectively. The baseline demographics are presented in Table 5 below.

**Table 5. Demographics**

	Study MRZ 3015		Study MRZ 3016	
	NAFT-600	Vehicle	NAFT-600	Vehicle
<b>FAS <sup>(1)</sup> Subjects</b>	382	179	400	213
<b>Age</b>				
<18	3 (0.79%)	1 (0.56%)	7 (1.75%)	3 (1.41%)
18-64	352 (92.15%)	158 (88.27%)	357 (89.25%)	189 (88.73%)
≥65	27 (7.07%)	20 (11.17%)	36 (9.00%)	21 (9.86%)
<b>Sex</b>				
Female	103 (26.96%)	29 (16.20%)	79 (19.75%)	54 (25.35%)
Male	279 (73.04%)	150 (83.80%)	321 (80.25%)	159 (74.65%)
<b>Race</b>				
White	202 (52.88%)	105 (58.66%)	266 (66.50%)	144 (67.61%)
Black	157 (41.10%)	64 (35.75%)	114 (28.50%)	62 (29.11%)
Asian	5 (1.31%)	2 (1.12%)	6 (1.50%)	2 (0.94%)
Other	18 (4.71%)	8 (4.47%)	14 (3.50%)	5 (2.34%)

Source: reviewer's table

- (1) Full-Analysis Set (FAS): The FAS population was the subset of the SES population with a positive culture at baseline. This was a modified intent-to-treat principle because the culture results were not available before the start of treatment.

For the baseline disease severity of the interdigital type tinea pedis, approximately 90% and 87% of the subjects had moderate erythema in Studies MRZ 3015 and 3016, respectively, and approximately 70% and 66% of subjects had moderate scaling in Studies MRZ 3015 and 3016, respectively. For pruritus, subjects were generally evenly balanced across the severity (mild, moderate, marked) in both studies. In terms of interdigital type tinea pedis, all but three subjects (2 in NAFT-600, and 1 in vehicle) met the inclusion criteria as shown in Table 6 below.

**Table 6. Baseline disease severity (Interdigital)**

	Study MRZ 3015		Study MRZ 3016	
	NAFT-600	Vehicle	NAFT-600	Vehicle
<b>FAS<sup>(1)</sup> Subjects</b>	382	179	400	213
<b>Baseline culture (KOH and dermatophyte)</b>				
Positive	382 (100%)	179 (100%)	400 (100%)	213 (100%)
<b>Erythema</b>				
Absent	-	-	-	-
Mild	2 (0.52%)	1 (0.56%)	-	-
Moderate	348 (91.34%)	159 (88.83%)	345 (86.25%)	188 (88.26%)
Marked	31 (8.14%)	19 (10.61%)	55 (13.75%)	25 (11.74%)
Missing	1 (0.26%)	-	-	-
<b>Scaling</b>				
Absent	-	-	-	-
Mild	2 (0.52%)	-	-	-
Moderate	275 (71.99%)	122 (68.16%)	255 (63.75%)	148 (69.48%)
Marked	105 (27.49%)	57 (31.84%)	145 (36.25%)	65 (30.52%)
<b>Pruritus</b>				
Absent	-	-	-	-
Mild	92 (24.08%)	57 (31.84%)	113 (28.25%)	53 (24.88%)
Moderate	187 (48.95%)	79 (44.13%)	187 (46.75%)	107 (50.23%)
Marked	103 (26.96%)	43 (24.02%)	100 (25.00%)	53 (24.88%)

Source: reviewer's table

- (1) Full-Analysis Set (FAS): The FAS population was the subset of the SES population with a positive culture at baseline with at least one post-baseline assessment. This was a modified intent-to-treat principle because the culture results were not available before the start of treatment.

The baseline disease severity for the (b) (4) is summarized in Table 7. It should be noted several subjects did not meet the inclusion criteria of having positive KOH and positive dermatophyte culture at baseline along with having at least moderate erythema, at least moderate scaling, and at least mild pruritus. After excluding such subjects that do not meet the inclusion criteria, there were 175 subjects (115 in NAFT-600, 60 in vehicle), and 205 subjects (138 in NAFT-600, 67 in vehicle) in Studies MRZ 3015 and 3016, respectively. See Table A.1 in the Appendix for the site of KOH and culture collection on page 18 of this review.

**Table 7. Baseline disease severity of subjects with (b) (4) who meet the inclusion criteria (positive baseline culture along with minimum signs and symptoms)**

	Study MRZ 3015		Study MRZ 3016	
	NAFT-600	Vehicle	NAFT-600	Vehicle
	115	60	138	67
<b>Erythema</b>				
Moderate	104 (90.4%)	55 (91.7%)	129 (93.5%)	59 (88.1%)
Marked	11 (9.6%)	5 (8.3%)	9 (6.5%)	8 (11.9%)
<b>Scaling</b>				
Moderate	72 (62.6%)	35 (58.3%)	79 (57.3%)	35 (52.2%)
Marked	43 (37.4%)	25 (41.7%)	59 (42.8%)	32 (47.8%)
<b>Pruritus</b>				
Mild	34 (29.6%)	25 (41.7%)	50 (36.2%)	19 (28.4%)
Moderate	51 (44.4%)	22 (36.7%)	54 (39.1%)	38 (56.7%)
Marked	30 (26.1%)	13 (21.7%)	34 (24.6%)	10 (14.9%)

Source: reviewer's table

- (1) Full-Analysis Set (FAS): The FAS population was the subset of the SES population with a positive culture at baseline. This was a modified intent-to-treat principle because the culture results were not available before the start of treatment.

### 3.2.4 Results and Conclusions

According to the applicant's analysis of the primary and secondary efficacy results, both Phase 3 trials (MRZ 3015 and MRZ 3016) met the statistical significance level of 0.025. See Table 8 below for the analysis of the efficacy results.

**Table 8. Applicant's Analysis for Interdigital Type Tinea Pedis (Primary and Key Secondary efficacy endpoints)**

		NAFT-600	Vehicle	p-value <sup>(4)</sup>
<b>Study MRZ 3015</b>		382	179	
Interdigital	Complete Cure <sup>(1)</sup>	64 (16.8%)	3 (1.7%)	<0.001
	Effective Treatment <sup>(2)</sup>	207 (54.2%)	11 (6.1%)	<0.001
	Mycological Cure <sup>(3)</sup>	250 (65.4%)	25 (14.0%)	<0.001
<b>Study MRZ 3016</b>		400	213	
Interdigital	Complete Cure <sup>(1)</sup>	104 (26.0%)	7 (3.3%)	<0.001
	Effective Treatment <sup>(2)</sup>	203 (50.8%)	15 (7.0%)	<0.001
	Mycological Cure <sup>(3)</sup>	235 (58.8%)	22 (10.3%)	<0.001

Source: Applicant's Analysis.

(1) Complete Cure is defined as having negative mycology results (dermatophyte culture and KOH) and absence of erythema, scaling and pruritus at Week 6.

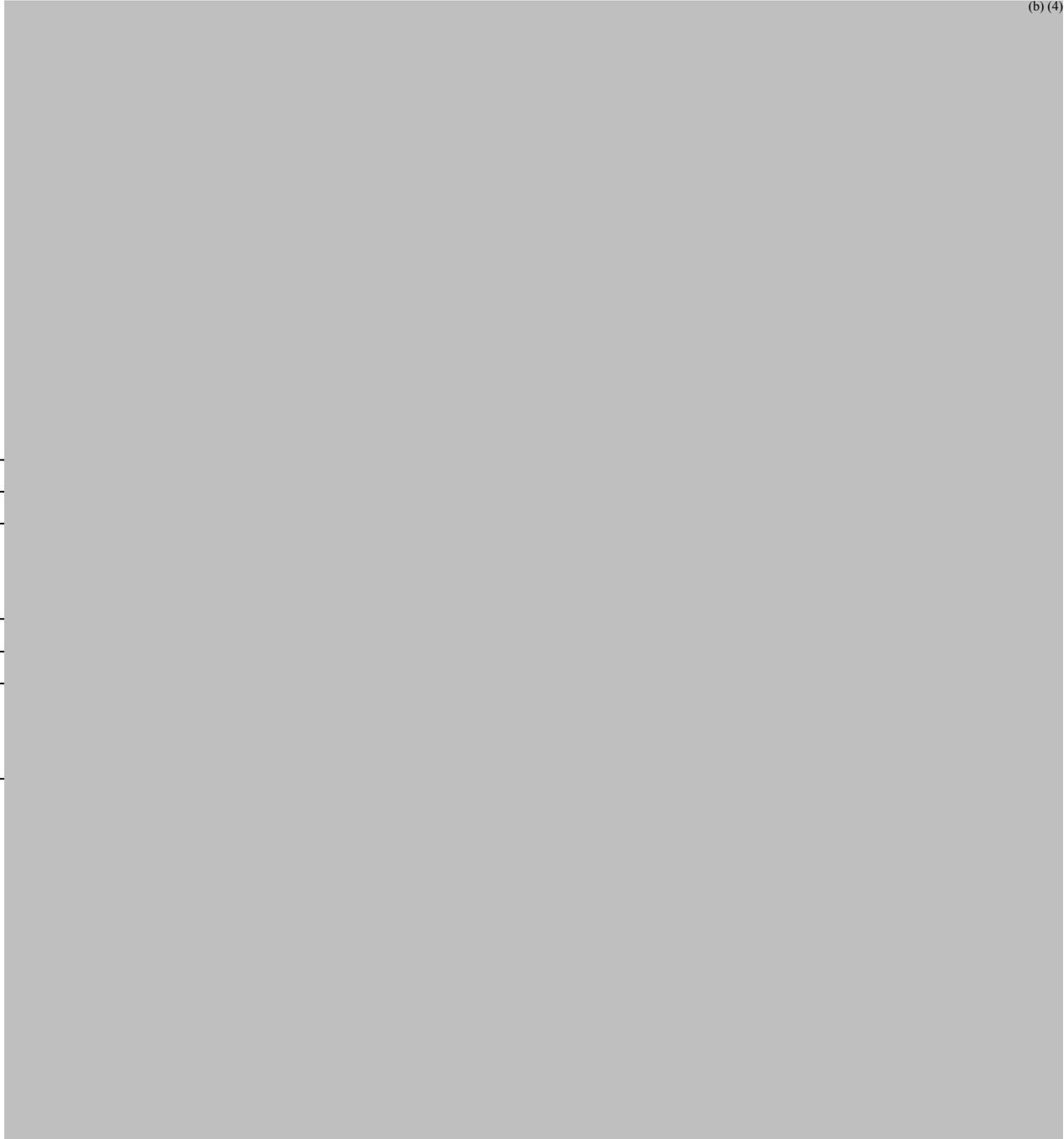
(2) Effective Treatment is having negative KOH, negative culture, and scaling, erythema, and pruritus grade of 0 or 1

(3) Mycological cure is having negative KOH and negative culture.

(4) P-values are calculated from a one-sided CMH test stratified by pooled sites (FAS, MVTF)

The applicant proposed to use LOCF and WCS as sensitivity analyses. For the sensitivity analysis using LOCF, it resulted in very similar results compared to that of the primary analysis.

Using the WCS imputation, the result for the primary efficacy endpoint analysis was not statistically significant anymore in Study MRZ 3015 ( $p=0.373$  for Study MRZ 3015;  $p<0.001$  for Study MRZ 3016). However, as this is the most extreme case where you impute all missing in NAFT-600 as failures, and impute all missing data in the vehicle as successes, this reviewer considered multiple imputation method, and created five multiple imputed datasets for Study MRZ 3015. All five datasets showed that the NAFT-600 was superior to Vehicle ( $p<0.001$ ).



### 3.3 Evaluation of Safety

The applicant reported the following treatment-emergent adverse events (TEAE) in their study report. Only the application site adverse events (AE) for the general disorders and administration site conditions are summarized below.

**Table 11. Number (%) of subjects with treatment-emergent adverse events**

Application site AE	Study MRZ 3015		Study MRZ 3016	
	NAFT-600 N=571 <sup>(1)</sup>	Vehicle N=284 <sup>(1)</sup>	NAFT-600 N=572 <sup>(1)</sup>	Vehicle N=287 <sup>(1)</sup>
Pain	3 (0.5%)	1 (0.4%)	2 (0.3%)	1 (0.3%)
Oedema Peripheral	1 (0.2%)	-	1 (0.2%)	-
Dermatitis	1 (0.2%)	-	-	-
Dryness	1 (0.2%)	1 (0.4%)	-	-
Erosion	1 (0.2%)	-	-	-
Fissure	1 (0.2%)	-	-	-
Paraesthesia	1 (0.2%)	-	1 (0.2%)	-
Swelling	1 (0.2%)	-	-	-
Pruritus	-	-	1 (0.2%)	-
Vessel puncture site pain	1 (0.2%)	-	-	-
Exfoliation	-	-	1 (0.2%)	1 (0.3%)
Rash	-	-	1 (0.2%)	-

Source: Applicant's tables 54 and 58, study report

(1) Safety evaluation set (SES).

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race, Age, and Geographic Region

Generally, treatment effect for the gender, race, age subgroups were higher in Study MRZ 3016 compared to those in Study MRZ 3015. This is also observed in comparing the overall treatment effect of the two trials. In Study MRZ 3015, the treatment effects were similar (approximately 14%) for both male and female subjects, whereas in Study MRZ 3016, the treatment effect for female subject (28%) was slightly higher than that of male subjects (21%).

**Table 12. Efficacy by Gender, Race and Age**

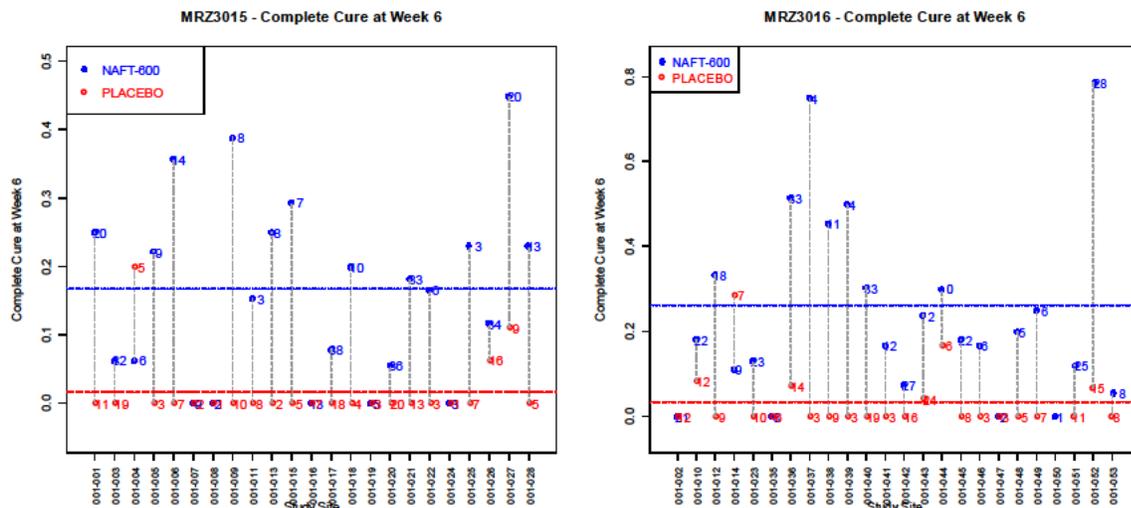
	Study MRZ 3015		Study MRZ 3016	
	NAFT-600	Vehicle	NAFT-600	Vehicle
<b>FAS<sup>(1)</sup> Subjects</b>	382	179	400	213
<b>Age</b>				
<b>&lt;18</b>	0/3 (0%)	0/1 (0%)	3/7 (42.86%)	0/3 (0%)
<b>18-64</b>	56/352 (15.91%)	3/158 (1.90%)	86/357 (24.09%)	6/189 (3.17%)
<b>≥65</b>	8/27 (29.63%)	0/20 (0%)	15/36 (41.67%)	1/21 (4.76%)
<b>Sex</b>				
<b>Female</b>	18/103 (17.48%)	1/29 (3.45%)	25/79 (31.65%)	2/54 (3.70%)
<b>Male</b>	46/279 (16.49%)	2/150 (1.33%)	79/321 (24.61%)	5/159 (3.14%)
<b>Race</b>				
<b>White</b>	48/202 (23.76%)	3/105 (2.86%)	82/266 (30.83%)	4/144 (2.78%)
<b>Black</b>	11/157 (7.01%)	0/64 (0%)	17/114 (14.91%)	2/62 (3.23%)
<b>Asian</b>	1/5 (20.0%)	0/2 (0%)	1/6 (16.67%)	0/2 (0%)
<b>Other</b>	4/18 (22.22%)	0/8 (0%)	4/14 (28.57%)	1/5 (20.0%)

(1) Full-Analysis Set (FAS): The FAS population was the subset of the SES population with a positive culture at baseline. This was a modified intent-to-treat principle because the culture results were not available before the start of treatment.

### 4.2 Other Special/Subgroup Populations

The efficacy results appear to be relatively consistent across the pooled study sites and the efficacy results by center plots are presented in Figure 3. The Breslow-Day test results also supported this conclusion with p-values of 0.206 and 0.133 for Studies MRZ 3015 and MRZ 3016, respectively.

**Figure 3. Efficacy results by center plots**



Source: reviewer's plots

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues

There were no major statistical issues affecting the overall conclusion for the primary and key secondary endpoints which are related to the interdigital-type tinea pedis. (b) (4)

### 5.2 Collective Evidence

The protocol-specified primary efficacy endpoint was the proportion of subjects with complete cure of interdigital tinea pedis at Week 6 where complete cure is defined as negative mycology results (dermatophyte culture and KOH) and absence of erythema, scaling and pruritus (grade 0 for each) evaluated using a 4-point severity grade (0=absent, 1=mild, 2=moderate, 3=marked).

The protocol-specified key secondary endpoints were the following:

- Mycological cure of interdigital tinea pedis: negative KOH results and negative dermatophyte culture at Week 6
- Effective treatment of interdigital tinea pedis: negative KOH, negative culture, and erythema, scaling and pruritus scores of 0 or 1 at Week 6.

Summaries of primary and key secondary efficacy results for each type of tinea pedis (b)(4) are presented in the following table.

**Table 13. Applicant’s Analysis for Interdigital Type Tinea Pedis (Primary and Key Secondary efficacy endpoints)**

		<b>NAFT-600</b>	<b>Vehicle</b>	<b>p-value<sup>(4)</sup></b>
<b>Study MRZ 3015</b>		382	179	
Interdigital	Complete Cure <sup>(1)</sup>	64 (16.8%)	3 (1.7%)	<0.001
	Effective Treatment <sup>(2)</sup>	207 (54.2%)	11 (6.1%)	<0.001
	Mycological Cure <sup>(3)</sup>	250 (65.4%)	25 (14.0%)	<0.001
<b>Study MRZ 3016</b>		400	213	
Interdigital	Complete Cure <sup>(1)</sup>	104 (26.0%)	7 (3.3%)	<0.001
	Effective Treatment <sup>(2)</sup>	203 (50.8%)	15 (7.0%)	<0.001
	Mycological Cure <sup>(3)</sup>	235 (58.8%)	22 (10.3%)	<0.001

Source: Applicant’s Analysis.

(1) Complete Cure is defined as having negative mycology results (dermatophyte culture and KOH) and absence of erythema, scaling and pruritus at Week 6.

(2) Effective Treatment is having negative KOH, negative culture, and scaling, erythema, and pruritus grade of 0 or 1

(3) Mycological cure is having negative KOH and negative culture.

(4) P-values are calculated from a one-sided CMH test stratified by pooled sites (FAS, MVTF)

### 5.3 Conclusions and Recommendations

Efficacy findings from the two Phase 3 trials (Studies MRZ 3015 and MRZ 3016) established that NAFT-600 was superior to vehicle in the treatment of interdigital tinea pedis at Week 6.

### 5.4 Labeling Recommendations

For the treatment of interdigital-type tinea pedis, NAFT-600 gel was statistically superior to vehicle in two studies (p<0.001).



(b)(4)

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

CARIN J KIM  
05/06/2013

MOHAMED A ALOSH  
05/06/2013

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number: 204286**

**Applicant: Merz**

**Stamp Date: 8/31/2012**

**Drug Name: Naftin 2% gel**

On **initial** overview of the NDA/BLA application for RTF:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comments</b>
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

**IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE?   Yes**

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

<b>Content Parameter (possible review concerns for 74-day letter)</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.		X		For the primary imputation method for handling missing data, the sponsor used "missing data imputed as failures". Whether or not this method is appropriate would depend on the proportion of dropouts in each treatment arm.

File name: 5\_Statistics Filing Checklist for a New NDA\_NDA 204286

# STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

## Reviewer Comments:

In this submission, the sponsor included several analysis datasets for two Phase 3 trials (MRZ 3015 and MRZ 3016). The submitted analysis datasets for MRZ 3015 appear to be acceptable; however, it should be noted that some of the individual analysis datasets of MRZ 3016 (Section 5.3.5.1.25.3) appear to refer to Study MRZ 3015. While the pooled datasets for the Integrated Summary of Efficacy and Integrated Summary of Safety sections (Section 5.3.5.3.25.3) include the missing individual datasets, not all variables from the individual datasets were included in the pooled datasets. Consequently, while this reviewer could perform efficacy analysis using the pooled datasets, this reviewer is unable to determine whether the level of detail (i.e., variables) in the pooled safety datasets would be sufficient for review from a clinical perspective. This reviewer recommends that the sponsor submit the missing individual datasets for MRZ 3016.

## Comments that were conveyed to the applicant on 10/18/2012:

Some of the analysis datasets of MRZ 3016 (Section 5.3.5.1.25.3) appear to refer to Study MRZ 3015 according to the "STUDYID" variable. As such, the following individual datasets are missing for MRZ 3016:

- adae.xpt (adverse event analysis)
- adcm.xpt (concomitant medications analysis)
- adlb.xpt (clinical lab analysis)
- adef.xpt (efficacy data analysis)
- adpe.xpt (physical examination analysis)
- advs.xpt (vital signs analysis)

The sponsor should submit the missing individual datasets for MRZ 3016.

Carin Kim

10/19/2012

---

Statistical Reviewer

Date

---

Supervisor/Team Leader

Date

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

CARIN J KIM  
10/19/2012

KATHLEEN S FRITSCH  
10/19/2012  
Signing for Mohamed Alosch