CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205175Orig1s000

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/Serial Number:	205175 / 000
Drug Name:	ECOZA (econazole nitrate) foam 1%
Indication(s):	Interdigital tinea pedis
Applicant:	AmDerma
Dates:	Submitted: 12/26/2012 PDUFA: 10/24/2013
Review Priority:	Standard review
Biometrics Division:	Division of Biometrics III
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Keywords: 505(b)(2), tinea pedis

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1 Executive Summary

Econazole foam 1% was superior to its vehicle in the treatment of interdigital tinea pedis in two studies. The studies enrolled subjects age 12 and older with a clinical diagnosis of interdigital tinea pedis involving at least two web spaces (at least moderate scaling and mild erythema) and positive KOH. Subjects had to have a positive fungal culture to be included in the modified intent-to-treat (MITT) population (the primary analysis population). Subjects applied treatment once daily for four weeks. Study 302 was a two-arm study (econazole foam vs. vehicle foam). Study 303 was a four-arm study (econazole foam, vehicle foam, econazole cream, and vehicle cream). Study 303 included an econazole cream arm as one component of the clinical bridge to the Agency's findings of safety for econazole cream for this 505(b)(2) application. The vehicle cream arm was included to maintain blinding. Both protocols were reviewed under Special Protocol Assessments and agreements were reached on the study design and endpoints.

The primary efficacy endpoint in both studies was complete cure (scores of 0 [none] on all signs and symptoms, negative KOH, and negative culture) at Day 43, two weeks after the end of treatment. The secondary endpoints were mycological cure (negative KOH and negative culture) and effective treatment (no or mild erythema and/or scaling [scores of 0 or 1] with all other signs and symptoms absent [scores of 0], negative KOH, and negative culture) at Day 43. The primary and secondary efficacy endpoints for econazole foam versus vehicle foam were all statistically significant at Day 43. The efficacy outcomes are summarized in Table 1.

Table 1 – Efficacy Results in Studies 302 and 303 (MITT)

Study 302	Econazole Foam N=82	Vehicle Foam N=83			P-value
Complete Cure	19 (23%)	2 (2%)			<0.001
Effective Treatment	40 (49%)	9 (11%)			<0.001
Mycological Cure	56 (68%)	13 (16%)			<0.001
Study 303	Econazole Foam N=91	Vehicle Foam N=83	Econazole Cream N=52	Vehicle Cream N=30	P-value[1]
Complete Cure	23 (25%)	4 (5%)	17 (33%)	1 (3%)	<0.001
Effective Treatment	44 (48%)	9 (11%)	27 (52%)	1 (3%)	<0.001
Mycological Cure	61 (67%)	15 (18%)	33 (63%)	1 (3%)	<0.001

[1] P-value of econazole foam versus vehicle foam. All p-values are from the CMH test stratified on analysis center.

Treatment effects were generally consistent across subgroups and centers. The conclusions were consistent across various assumptions regarding missing data, although many of the applicant's sensitivity analyses led to larger estimated treatment effects than the primary method of LOCF. However, this reviewer's post-hoc analyses that treated the missing data in a conservative way indicated that the treatment effect was robust to the handling of missing data.

2 Introduction

2.1 Overview

2.1.1 Clinical Studies

Econazole foam 1% is an antifungal intended for the treatment of interdigital tinea pedis. This product was submitted as a 505(b)(2) application with listed drug Spectazole cream. Because Spectazole cream has been discontinued from marketing, Fougera's econazole cream was used in the clinical studies. Econazole foam was evaluated in one Phase 2 and two Phase 3 studies. The Phase 2 study (Study 207) evaluated econazole foam 1%, econazole cream 1%, and vehicle foam in subjects with either interdigital or moccasin tinea pedis. The Phase 3 studies enrolled only subjects with interdigital tinea pedis. One of the Phase 3 studies (Study 302) was a two-arm study (econazole foam versus vehicle foam). The other Phase 3 study (Study 303) was a four-arm study (econazole foam, vehicle foam, econazole cream, and vehicle cream). The econazole cream arm was included in Study 303 as a component of the clinical bridge to the Agency's findings of safety for econazole. No formal efficacy comparisons between econazole foam and econazole cream were planned.

Study 302 enrolled 267 subjects with clinical signs of tinea pedis and positive KOH to econazole foam or vehicle foam. Of the enrolled subjects, 165 were found to have had positive baseline cultures and included in the MITT population. Study 302 was conducted in the U.S. and the Dominican Republic. Study 303 enrolled 358 subjects with clinical signs of tinea pedis and positive KOH to econazole foam, vehicle foam, econazole cream, or vehicle cream. Of the enrolled subjects, 256 were found to have had positive baseline cultures and included in the MITT population. Study 303 was conducted in the U.S. In both studies, treatment was applied once daily for four weeks. This review will focus on the two Phase 3 studies. For additional details on the design, see Table 2.

Table 2 – Clinical Studies Overview

Study Numbers	302 and 303				
Study Design	Randomized, double-blind, vehicle-controlled. Study 303 also included econazole cream and vehicle cream arms.				
Inclusion criteria	Age ≥ 12 years, clinical diagnosis of interdigital tinea pedis involving at least 2 web spaces with at least moderate scaling and mild erythema, and positive KOH. Subjects were not to have a concurrent tinea infection or have onychomycosis involving ≥ 20% of either great toenail or involvement of more than 5 toenails. Subjects needed positive culture to be in the MITT population.				
Treatment regimen	Once daily for 4 weeks. Treatment was applied to all clinically affected interdigital regions, plus a 1 inch margin of normal appearing skin.				
Primary endpoint	Complete cure at Day 43 [no evidence of clinical disease (i.e. scores of 0 for erythema, scaling, fissuring, maceration, vesiculation, and pruritus), negative KOH, and negative culture]				
Treatment arms and Sample Size		Randomized		MITT	
		302	303	302	303
	Econazole foam	132	119	82	91
	Vehicle foam	135	119	83	83
	Econazole cream	--	80	--	52
	Vehicle cream	--	40	--	30
Study location		Randomized			
		302	303		
	U.S.	186 (70%)	358 (100%)		
	Dominican Republic	81 (30%)	--		

2.1.2 Regulatory History

The IND for econazole foam was opened in 2008 with the protocol for the Phase 2 study (Study 207). Four meetings were held between the sponsor and the Agency during the IND development: Pre-IND (2007), End-of-Phase 2 (2009), Post-SPA (2010), and Pre-NDA (2012). Both Phase 3 studies (Studies 302 and 303) were evaluated under Special Protocol Assessments. Both protocols received Agreement letters and general agreement was reached on the study design, endpoints, and analysis, with one exception. The sponsor originally proposed designing Study 303 as a three-arm study without a vehicle cream arm. Based on the Agency's recommendation, the sponsor modified the design to include a vehicle cream arm in Study 303 so that the design aligned with the Agency's recommendations.

2.2 Data Sources

This reviewer evaluated the applicant's clinical study reports, datasets, clinical summaries, and proposed labeling. This submission was submitted in eCTD format and was entirely electronic. Both SDTM and analysis datasets were submitted for the Phase 3 studies. The analysis datasets used in this review are archived at \\cdsesub1\evsprod\NDA205175\0000\m5\datasets.

3 Statistical Evaluation

3.1 Data and Analysis Quality

The databases for the studies required minimal data management prior to performing analyses and no requests for additional datasets were made to the applicant.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Statistical Analysis

Study 302 is a randomized, double-blind efficacy and safety study of econazole foam 1% versus vehicle foam in the treatment of interdigital tinea pedis. Study 303 is a randomized, double-blind efficacy and safety study of econazole foam 1%, econazole cream 1%, vehicle foam, and placebo foam in the treatment of interdigital tinea pedis. The studies enrolled subjects age 12 and older with a clinical diagnosis of interdigital tinea pedis involving at least two web spaces (at least moderate scaling and mild erythema) and positive KOH. Subjects needed to have positive baseline fungal cultures to be included in the modified intent-to-treat (MITT) population. Treatment was applied once daily for four weeks. Subjects were evaluated on Days 1, 8, 15, 29, and 43. Efficacy assessments included individual signs and symptoms (erythema, scaling, fissuring, maceration, vesiculation, and pruritus), KOH, and culture. Each sign or symptom was evaluated at every visit on the following 4-point scale:

Table 3 – Signs and Symptoms Severity Scale

Score	Severity Grade	Description
0	None	No signs or symptoms present
1	Mild	Barely abnormal
2	Moderate	Distinctly present abnormality
3	Severe	Intense involvement or marked abnormality

KOH and culture outcomes were assessed at baseline (Day 1), end of treatment (Day 29), and post-treatment follow-up (Day 43). In addition, both the investigator and the subject assessed response to treatment on Days 29 and 43 using a 5-point scale (excellent, very good, good, fair, poor).

The primary efficacy endpoint was complete cure (scores of 0 [none] on all signs and symptoms, negative KOH, and negative culture) at Day 43. The secondary endpoints were mycological cure (negative KOH and negative culture) and effective treatment (no or mild erythema and/or scaling [scores of 0 or 1] with all other signs and symptoms absent [scores of 0], negative KOH, and negative culture) at Day 43. Multiplicity was controlled for the two secondary endpoints by analyzing them in sequential order: (1) mycological cure, followed by (2) effective treatment. The protocols also included several 'other' efficacy endpoints. These were

- Complete cure at Day 29
- Mycological cure at Day 29
- Effective treatment at Day 29

- Clinical improvement (good, very good, or excellent) on the investigator assessment of response to treatment on Days 29 and 43
- Clinical improvement (good, very good, or excellent) on the subject assessment of response to treatment on Days 29 and 43
- No or mild signs and symptoms (erythema, scaling, fissuring, maceration, vesiculation, and pruritus) and Days 29 and 43
- Change from baseline in the cumulative and individual signs and symptoms (erythema, scaling, fissuring, maceration, vesiculation, and pruritus) at each post-baseline visit

The primary and secondary endpoints were analyzed with the Cochran-Mantel-Haenszel (CMH) test stratified on analysis center. In Study 303, formal analyses comparing econazole foam and vehicle foam only were planned. The econazole cream arm was included as a component of the clinical bridge to the Agency's findings of safety for econazole, and the vehicle cream arm was included to promote blinding. Centers that did not enroll at least 8 econazole foam and at least 8 vehicle foam subjects were pooled into analysis centers (smallest center was pooled with the largest center that did not meet the sample size requirements, etc. until all analysis centers met the sample size requirements). Consistency of treatment response across analysis centers was assessed with the Breslow-Day test. If the Breslow-Day test was significant at an alpha level of 0.10, sensitivity analyses were to be conducted to assess the impact of extreme centers.

The protocol defined three analysis populations:

- MITT – all randomized subjects who were dispensed product and had positive baseline KOH and culture
- Per protocol – subset of MITT subjects who completed the Day 29 and Day 43 visits (unless discontinued for treatment-related adverse events or lack of treatment effect), met all inclusion/exclusion criteria, did not take interfering concomitant medications, and applied 80-120% of expected doses
- Safety – all randomized subjects who had at least one application of investigational product and at least one post-baseline evaluation

The primary analysis population for efficacy endpoints was the MITT. The primary method of handling missing data was last observation carried forward (LOCF). The protocols specified three sensitivity analyses for missing data. The first sensitivity analysis will impute all subjects with missing values as failures. The second sensitivity analysis will impute all subjects with missing values as successes. The third sensitivity analysis will use the subjects with available data to compute a 95% upper confidence bound for the proportion of subjects on the vehicle arm who are successes, and the 95% lower confidence bound for the proportion of subjects on the econazole foam arm who are successes. These bounds will be used to impute a proportion of subjects with missing data on each arm as successes (fractions of vehicle subjects will be rounded up and fractions of econazole foam subjects will be rounded down). For this analysis, the chi-square test will be used as the imputations are not done with regard to center.

3.2.2 Subject Disposition

Study 302 randomized 132 subjects to econazole foam and 135 subjects to vehicle foam. Of these subjects, 82 econazole foam and 83 vehicle foam subjects had positive baseline cultures and were included in the MITT population. The most common reason for study discontinuation was negative baseline culture. The next most common reason was lost to follow-up. See Table 4.

Table 4 – Disposition of Randomized Subjects (Study 302)

	Econazole Foam	Vehicle Foam
Subjects Randomized	132	135
Subjects in MITT	82 (62%)	83 (61%)
Subjects Completed	78 (59%)	80 (59%)
Subjects Discontinued	54 (41%)	55 (41%)
Reasons for discontinuation		
Negative baseline culture	47 (36%)	51 (38%)
Adverse event	0 (0%)	1 (1%)
Subject request	1 (1%)	0 (0%)
Non-compliance	1 (1%)	0 (0%)
Lost to follow-up	4 (3%)	3 (2%)
Other	1 (1%)	0 (0%)

Source: Reviewer analysis

Study 303 randomized 119 subjects to econazole foam, 119 subjects to vehicle foam, 80 subjects to econazole cream, and 40 subjects to vehicle cream. Of these subjects, 91 econazole foam and 83 vehicle foam subjects had positive baseline cultures and were included in the MITT population. The most common reason for study discontinuation was negative baseline culture. The next most common reason was lost to follow-up. See Table 5.

Table 5 – Disposition of Randomized Subjects (Study 303)

	Econazole Foam	Vehicle Foam	Econazole Cream	Vehicle Cream
Subjects Randomized	119	119	80	40
Subjects in MITT	91 (77%)	83 (70%)	52 (65%)	30 (75%)
Subjects Completed	82 (69%)	76 (64%)	49 (61%)	28 (70%)
Subjects Discontinued	37 (31%)	43 (36%)	31 (39%)	12 (30%)
Reasons for discontinuation				
Negative baseline culture	25 (21%)	31 (26%)	26 (33%)	9 (23%)
Adverse event	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Subject request	2 (2%)	2 (2%)	2 (3%)	1 (3%)
Investigator decision	0 (0%)	0 (0%)	0 (0%)	1 (3%)
Non-compliance	2 (2%)	2 (2%)	0 (0%)	0 (0%)
Lost to follow-up	6 (5%)	4 (3%)	2 (3%)	0 (0%)
Other	1 (1%)	4 (3%)	1 (1%)	1 (3%)

Source: Reviewer analysis

The disposition tables in this review differ slightly from the disposition tables in the applicant's study reports. The applicant's Table 10.1.2-1 (pg. 48 of the study report for Study 302 and pg. 60-61 of the study report for Study 303) is based on the safety population, rather than the all-randomized population (in other words, it excludes subjects who did not return for any follow-up visits, even though some subjects who are not included in the safety population are included in the MITT population). In addition, the applicant's tables distinguish between subjects who discontinued before the 'Day 29' visit ('discontinued during the treatment period'), and those who discontinued after the 'Day 29' visit, but before the 'Day 43' visit ('discontinued during the post-treatment period'). Subjects with visits around the Week 4 mark that were classified as 'early termination' visits are classified as discontinuing during the treatment period, even though they may have completed the full four weeks of treatment. As the distinctions between discontinuing during the treatment period and during the post-treatment period do not necessarily have any relation to the length of treatment, the distinction is not made in the reviewer's tables.

3.2.3 Baseline Characteristics

Baseline demographics were generally balanced across the treatment groups in the two studies. The demographics were similar among the all-randomized and the MITT population. The mean age of the subjects was approximately 41 years, with approximately 2% of subjects less than 18 years of age, and 4% of subjects 65 years of age or older. The majority of subjects were male (62-75%). In Study 302, 40% of subjects were white and 45% were black or African-American. Close to half of the subjects reported their ethnicity as Hispanic or Latino. In Study 303, approximately 60% of the subjects were white and 24% were black or African-American. Approximately 40% of the subjects reported their ethnicity as Hispanic or Latino. See Table 6 and Table 7.

Table 6 – Demographics (Study 302)

	Randomized		MITT	
	Econazole Foam N=132	Vehicle Foam N=135	Econazole Foam N=82	Vehicle Foam N=83
Age (years)				
Mean	41.7	42.4	40.1	41.3
Range	12-71	14-71	16-71	17-69
<18 years	4 (3%)	3 (2%)	2 (2%)	1 (1%)
18 to 64 years	123 (93%)	126 (93%)	77 (94%)	78 (94%)
65 + years	5 (4%)	6 (4%)	3 (4%)	4 (5%)
Gender				
Male	87 (66%)	79 (59%)	54 (66%)	49 (59%)
Female	45 (34%)	56 (41%)	28 (34%)	34 (41%)
Race				
White	53 (40%)	53 (39%)	32 (39%)	34 (41%)
Black or Afric.-Amer.	60 (45%)	60 (44%)	37 (45%)	37 (45%)
Other	19 (14%)	22 (16%)	13 (16%)	12 (14%)
Ethnicity				
Hispanic or Latino	65 (49%)	65 (48%)	44 (54%)	36 (44%)
Not Hispanic or Latino	67 (51%)	70 (52%)	38 (46%)	47 (57%)
Geographic Region				
United States	93 (70%)	93 (69%)	57 (70%)	64 (77%)
Dominican Republic	39 (30%)	42 (31%)	25 (30%)	19 (23%)

Source: pg 52 of study report for Study 302 and reviewer analysis.

Table 7 – Demographics (Study 303)

	Randomized			
	Econazole Foam N=119	Vehicle Foam N=119	Econazole Cream N=80	Vehicle Cream N=40
Age (years)				
Mean	40.9	42.0	41.2	39.7
Range	18-80	12-71	12-89	19-71
<18 years	0 (0%)	2 (2%)	2 (3%)	0 (0%)
18 to 64 years	114 (96%)	113 (94%)	73 (71%)	38 (95%)
65 + years	5 (4%)	4 (3%)	5 (6%)	2 (5%)
Gender				
Male	94 (79%)	89 (75%)	57 (71%)	27 (68%)
Female	25 (21%)	30 (25%)	23 (29%)	13 (32%)
Race				
White	73 (61%)	68 (57%)	50 (63%)	24 (60%)
Black or Afric.-Amer.	25 (21%)	34 (29%)	19 (24%)	8 (20%)
Am Ind./AK native	16 (13%)	14 (12%)	8 (10%)	4 (10%)
Other	5 (4%)	3 (3%)	3 (4%)	4 (10%)

<*Table continues on next page*>

Table 7 (Continued) - Demographics (Study 303)

	Randomized			
	Econazole Foam N=119	Vehicle Foam N=119	Econazole Cream N=80	Vehicle Cream N=40
Ethnicity				
Hispanic or Latino	51 (43%)	47 (39%)	32 (40%)	12 (30%)
Not Hispanic or Latino	68 (57%)	72 (61%)	48 (60%)	28 (70%)
Geographic Region				
United States	119 (100%)	119 (100%)	80 (100%)	40 (100%)
	MITT			
	Econazole Foam N=91	Vehicle Foam N=83	Econazole Cream N=52	Vehicle Cream N=30
Age (years)				
Mean	39.7	42.4	41.6	38.6
Range	19-87	12-71	18-89	19-71
<18 years	0 (0%)	2 (2%)	0 (0%)	0 (0%)
18 to 64 years	88 (97%)	77 (93%)	49 (94%)	29 (97%)
65 + years	3 (3%)	4 (5%)	3 (6%)	1 (3%)
Gender				
Male	71 (78%)	65 (78%)	38 (73%)	22 (73%)
Female	29 (22%)	18 (22%)	14 (27%)	8 (27%)
Race				
White	55 (60%)	53 (64%)	32 (62%)	18 (60%)
Black or Afric.-Amer.	21 (23%)	21 (25%)	15 (29%)	6 (20%)
Am Ind./AK native	12 (13%)	8 (10%)	3 (6%)	4 (13%)
Other	3 (3%)	1 (1%)	2 (4%)	2 (6%)
Ethnicity				
Hispanic or Latino	39 (43%)	33 (40%)	18 (35%)	11 (37%)
Not Hispanic or Latino	52 (57%)	50 (60%)	34 (65%)	19 (63%)
Geographic Region				
United States	91 (100%)	83 (100%)	52 (100%)	30 (100%)

Source: pg 64-65 of study report for Study 303 and reviewer analysis

The most common pathogen was *T. rubrum*, which was found in 85-90% of the positive baseline cultures. The remaining identified organisms were *E. floccosum, T. mentagrophytes,* and *T. tonsurans*. The baseline severity of erythema and scaling was generally balanced across treatment arms. See Table 8 and Table 9.

Table 8 – Baseline Disease Characteristics - MITT (Study 302)

		Econazole Foam N=82	Vehicle Foam N=83
Fungal culture result			
T. rubrum		69 (84%)	71 (86%)
E. floccosum		8 (10%)	7 (8%)
T. mentagrophytes		5 (6%)	3 (4%)
T. tonsurans		0 (0%)	1 (1%)
T. rubrum/T. mentag.		0 (0%)	1 (1%)
KOH Positive		82 (100%)	83 (100%)
Erythema	*Mild*	30 (37%)	28 (34%)
	Moderate	50 (61%)	48 (58%)
	Severe	2 (2%)	7 (8%)
Scaling	*Moderate*	68 (83%)	65 (78%)
	Severe	17 (17%)	19 (22%)
Cumulative Sign/Symptom Score[1]			
Mean (Std. Dev.)		9.0 (2.53)	9.0 (2.39)
Median		9	9
Range		4 - 16	4 - 16

[1] Sum of erythema, scaling, fissuring, maceration, vesiculation, and pruritus each graded from 0 to 3.
Source: pg 57 of study report for Study 302 and reviewer analysis.

Table 9 – Baseline Disease Characteristics - MITT (Study 303)

		Econazole Foam N=91	Vehicle Foam N=83	Econazole Cream N=52	Vehicle Cream N=30
Fungal culture result					
T. rubrum		83 (91%)	75 (90%)	46 (88%)	30 (100%)
E. floccosum		5 (5%)	2 (2%)	2 (4%)	0 (0%)
T. mentagrophytes		2 (2%)	6 (7%)	4 (8%)	0 (0%)
T. rubrum/E. floccosum		1 (1%)	0 (0%)	0 (0%)	0 (0%)
KOH Positive		91 (100%)	83 (100%)	52 (100%)	30 (100%)
Erythema	*None*	0 (0%)	0 (0%)	1 (2%)	0 (0%)
	Mild	32 (35%)	29 (35%)	17 (33%)	8 (27%)
	Moderate	57 (63%)	49 (59%)	31 (60%)	22 (73%)
	Severe	2 (2%)	5 (6%)	3 (6%)	0 (0%)
Scaling	*Moderate*	73 (80%)	64 (77%)	43 (83%)	23 (77%)
	Severe	18 (20%)	19 (23%)	9 (17%)	7 (23%)
Cum. Sign/Symptom Score[1]					
Mean (Std. Dev.)		8.6 (3.14)	8.5 (3.03)	8.3 (2.48)	8.4 (2.99)
Median		8	8	9	8
Range		3-16	3-15	3-13	3-16

[1] Sum of erythema, scaling, fissuring, maceration, vesiculation, and pruritus each graded from 0 to 3.
Source: pg 74-75 of study report for Study 303 and reviewer analysis.

3.2.4 Primary Efficacy Endpoint

Econazole foam was superior to vehicle foam on the primary efficacy endpoint of complete cure at Day 43 in both studies ($p<0.001$). Complete cure is defined as scores of 0 [none] on all signs and symptoms, negative KOH, and negative culture. The complete cure rate was analyzed with a CMH test stratified on analysis center. For the MITT analysis, the primary method of handling missing data was LOCF. The results of the MITT and per protocol analyses were similar. See Table 10 and Table 11.

Table 10 – Complete Cure Rates at Day 43 (Study 302)

	Econazole Foam	Vehicle Foam	P-value
MITT	19/82 (23%)	2/83 (2%)	<0.001
Per Protocol	18/75 (24%)	2/75 (3%)	<0.001

Source: pg 60 of study report for Study 302.

Table 11 – Complete Cure Rates at Day 43 (Study 303)

	Econazole Foam	Vehicle Foam	Econazole Cream	Vehicle Cream	P-value
MITT	23/91 (25%)	4/83 (5%)	17/52 (33%)	1/30 (3%)	<0.001
Per Protocol	16/63 (25%)	4/67 (6%)	16/45 (36%)	1/22 (5%)	<0.001

Source: pg 80-81 of study report for Study 303.

The primary method of handling missing data in the MITT population was LOCF, which is used in the analyses above. In Study 302, there were 3 econazole foam subjects and 3 vehicle foam subjects with missing Day 43 results. All 6 subjects were assessed as failures at their last available visit and were therefore imputed as not having complete cure. Thus the LOCF and imputing all missing as failures leads to identical results. Simiarly in Study 303, there were 11 econazole foam subjects and 7 vehicle foam subjects with missing Day 43 results. All 18 subjects were assessed as failures at their last available visit and thus using either LOCF or treating missings as failures leads to identical results.

For the analysis where all missing values are treated as successes, because the proportions of subjects with missing values is the same on both arms of Study 302, the estimated treatment effect is the same when all missing subjects are imputed as successes. However, in Study 303, because a greater proportion of subjects on the econazole foam arm were missing than on the vehicle foam arm, imputing all missing subjects as successes leads to a larger estimated treatment effect than is observed with the LOCF and missing as failures impuations. The applicant's third sensitivity analysis was designed to allocate missing subjects on the two arms based on the rates observed in subjects with complete data. For this analysis the 95% upper confidence bound for the proportion of subjects on the vehicle arm who are successes, and the 95% lower confidence bound for the proportion of subjects on the econazole foam arm who are successes are computed using the subjects with complete data. These bounds will be used to impute a proportion of subjects on each arm as successes (fractions of vehicle subjects will be rounded up and fractions of econazole foam subjects will be rounded down). Under this method, 0

econazole foam and 1 vehicle foam subject will be imputed as having complete cure in Study 302, and 2 econazole foam and 1 vehicle foam subject will be computed as having complete cure in Study 303. The results of the three sensitivity analyses are presented in Table 12 and Table 13, and the intermediate calculations for determining the number of subjects imputed as successes for the '95% Confidence Bound' method are presented in Table 14.

Table 12 – Complete Cure Results under Missing Data Sensitivity Analyses (Study 302)

	Econazole Foam N=82	Vehicle Foam N=83	P-value
Missing as Failure	19 (23%)	2 (2%)	<0.001
Missing as Success	22 (27%)	5 (6%)	<0.001
95% Bound Imputation	19 (23%)	3 (4%)	<0.001
Active-Failure/Vehicle-Success	19 (23%)	5 (6%)	0.001

Source: pg 73 of study report for Study 302 and reviewer analysis.

Table 13 – Complete Cure Results under Missing Data Sensitivity Analyses (Study 303)

	Econazole Foam N=91	Vehicle Foam N=83	P-value
Missing as Failure	23 (25%)	4 (5%)	<0.001
Missing as Success	34 (37%)	11 (13%)	<0.001
95% Bound Imputation	25 (27%)	5 (6%)	<0.001
Active-Failure/Vehicle-Success	23 (25%)	11 (13%)	0.038

Source: pg 100 of study report for Study 303 and reviewer analysis.

Table 14 – Calculations for the '95% Bound' Imputation

	Number Missing	Observed Successes	90% Confidence Interval	Imputed Successes
Study 302				
Econazole	3	19/79 (24%)	(0.161, 0.320)	floor(0.161*3) = 0
Vehicle	3	2/80 (3%)	(-0.004, 0.053)	ceiling(0.053*3) = 1
Study 303				
Econazole	11	23/80 (29%)	(0.204, 0.371)	floor(0.204*11) = 2
Vehicle	7	4/76 (5%)	(0.011, 0.095)	ceiling(0.095*7) = 1

Note: floor() rounds any fractional part down and ceiling() rounds any fractional part up.
Note: The 90% confidence interval is comprised of the lower 95% confidence bound and the upper 95% confidence bound.
Source: Reviewer analysis.

Note that all of the sensitivity analyses proposed by the applicant led to estimated treatment effects that were the same as or larger than the treatment effect estimates

produced by LOCF impuation (with the exception of the '95% Bound' imputation in Study 302 which decreased by 2%). In particular, treating all missing values as successes is very sensitive to any imbalances in the amount of missing data (if the active arm has a higher rate of missing data than the vehicle arm, then imputing all missing as success will increase the treatment effect). This was the case in Study 303. Rather, a sensitivity analysis is more useful if it will reduce the treatment effect (or increase variability) in the presence of increased levels of missing data, rather than increase the treatment effect. A conservative imputation would be to impute all subjects on the active arm as failures, and all subjects on the vehicle arm as successes. Such an analysis is also included in Table 12 and Table 13 above. In both studies, the treatment effect for complete cure remains statistically significant even when such an imputation is used. Thus we can conclude that the conclusions are not driven by the method of handling missing data.

3.2.5 Secondary Efficacy Endpoints

The protocols specified two secondary endpoints: mycological cure (negative KOH and negative culture) and effective treatment (no or mild erythema and/or scaling [scores of 0 or 1] with all other signs and symptoms absent [scores of 0], negative KOH, and negative culture). Both secondary endpoints were assessed for econazole foam versus vehicle foam and evaluated at Day 43. To control for multiplicity, the secondary endpoints were analyzed in sequential order (mycological cure followed by effective treatment). The mycological cure and effective treatment rates are statistically significant and the results are consistent with the complete cure results.

Table 15 – Secondary Endpoints at Day 43 – MITT (Study 302)

	Econazole Foam N=82	Vehicle Foam N=83	P-value
Mycological Cure	56 (68%)	13 (16%)	<0.001
Effective Treatment	40 (49%)	9 (11%)	<0.001

Source: pg 62 of study report for Study 302.

Table 16 – Secondary Endpoints at Day 43 – MITT (Study 303)

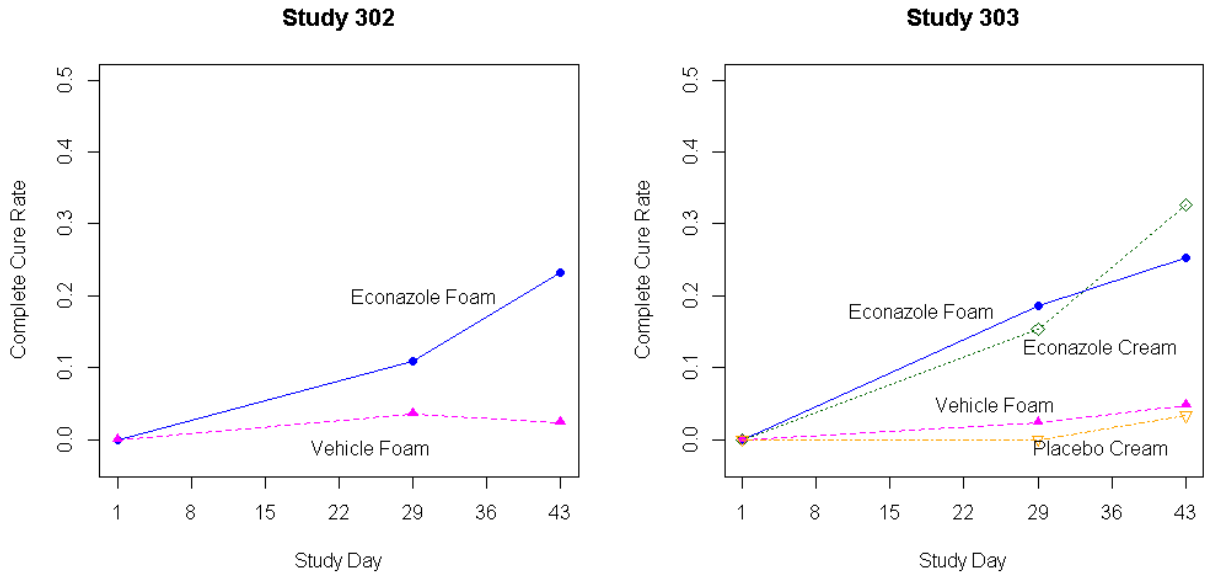
	Econazole Foam N=91	Vehicle Foam N=83	Econazole Cream N=52	Vehicle Cream N=30	P-value
Mycological Cure	61 (67%)	15 (18%)	33 (63%)	1 (3%)	<0.001
Effective Treatment	44 (48%)	9 (11%)	27 (52%)	1 (3%)	<0.001

Source: pg 83 of study report for Study 303.

3.2.6 Efficacy over Time

KOH and culture were assessed at baseline and Days 29 and 43. Thus complete cure can only be assessed at these visits. The difference in the complete cure rate between econazole foam and vehicle foam increased between Day 29 and Day 43. The results were similar for the two studies. See Figure 1.

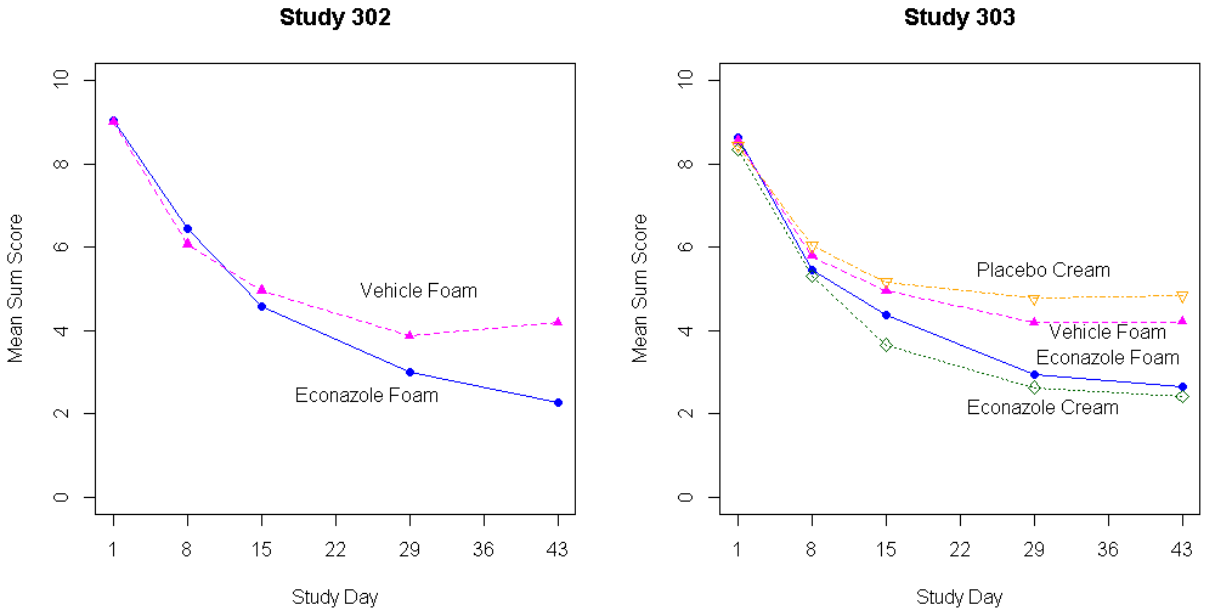
Figure 1 – Complete Cure Rate over Time



Source: Reviewer analysis.

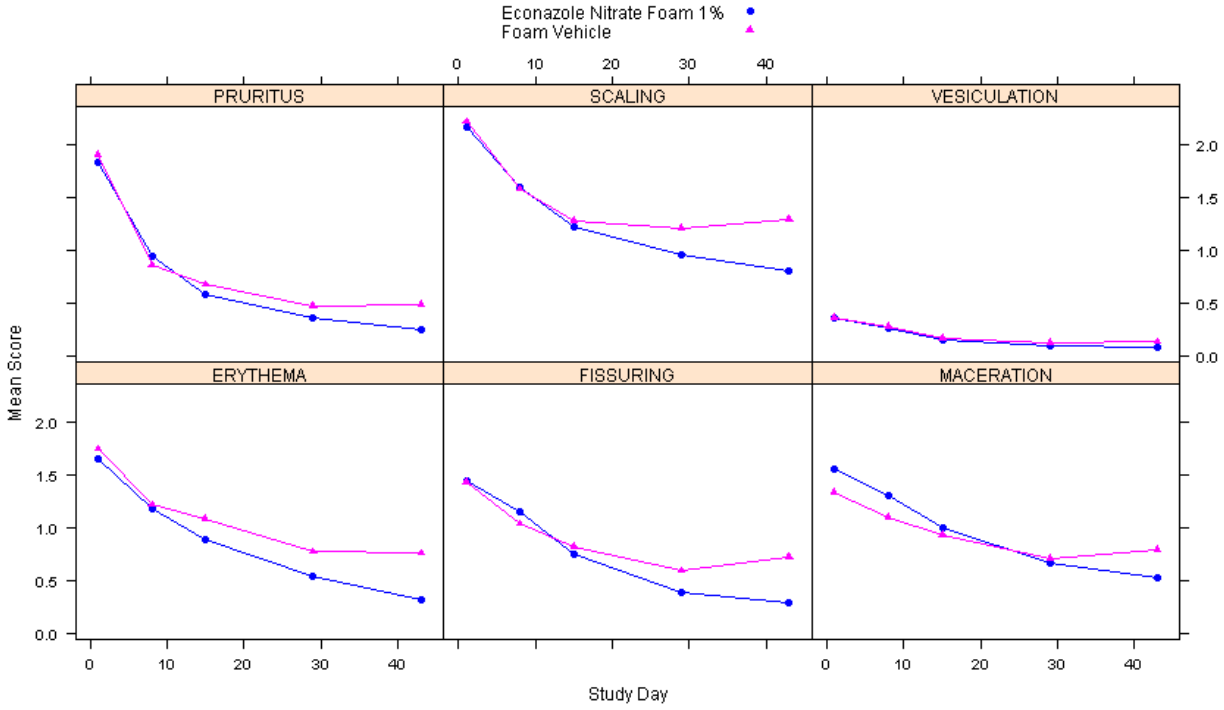
Although KOH and culture were only evaluated at baseline and Days 29 and 43, signs and symptoms (erythema, scaling, fissuring, maceration, vesiculation, and pruritus) were assessed on a scale from 0 to 3 at each visit. The signs and symptoms decreased on average during the study on all treatment arms, but the decrease was greater on the econazole arms than the vehicle arms. Figure 2 presents the means of the sum score for all 6 signs and symptoms at each visit. Figure 3 and Figure 4 present the mean scores for each of the individual signs and symptoms. All individual signs and symptoms showed trends of greater decrease in mean score for econazole foam versus vehicle foam during the studies.

Figure 2 – Mean Sum Score of Signs and Symptoms over Time



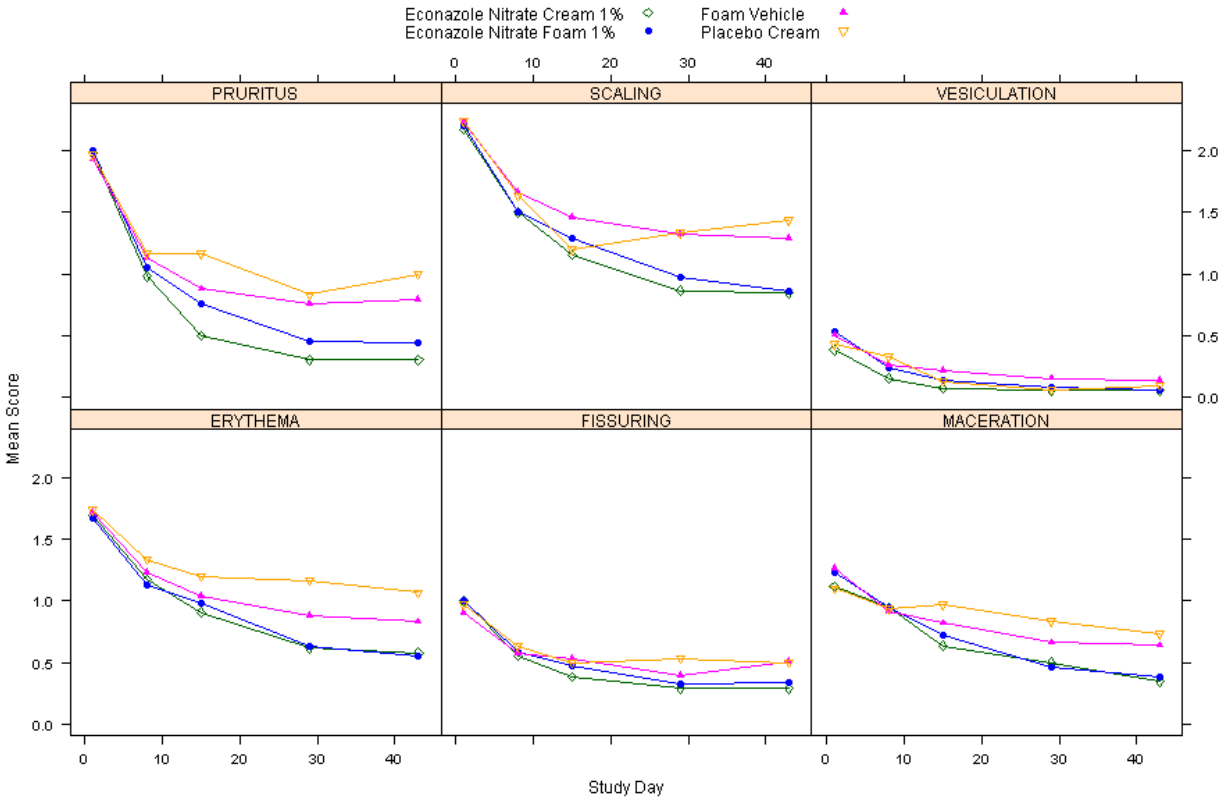
Source: Reviewer analysis.

Figure 3 – Mean Scores of Individual Signs and Symptoms over Time (Study 302)



Source: Reviewer analysis.

Figure 4 – Mean Score of Individual Signs and Symptoms over Time (Study 303)

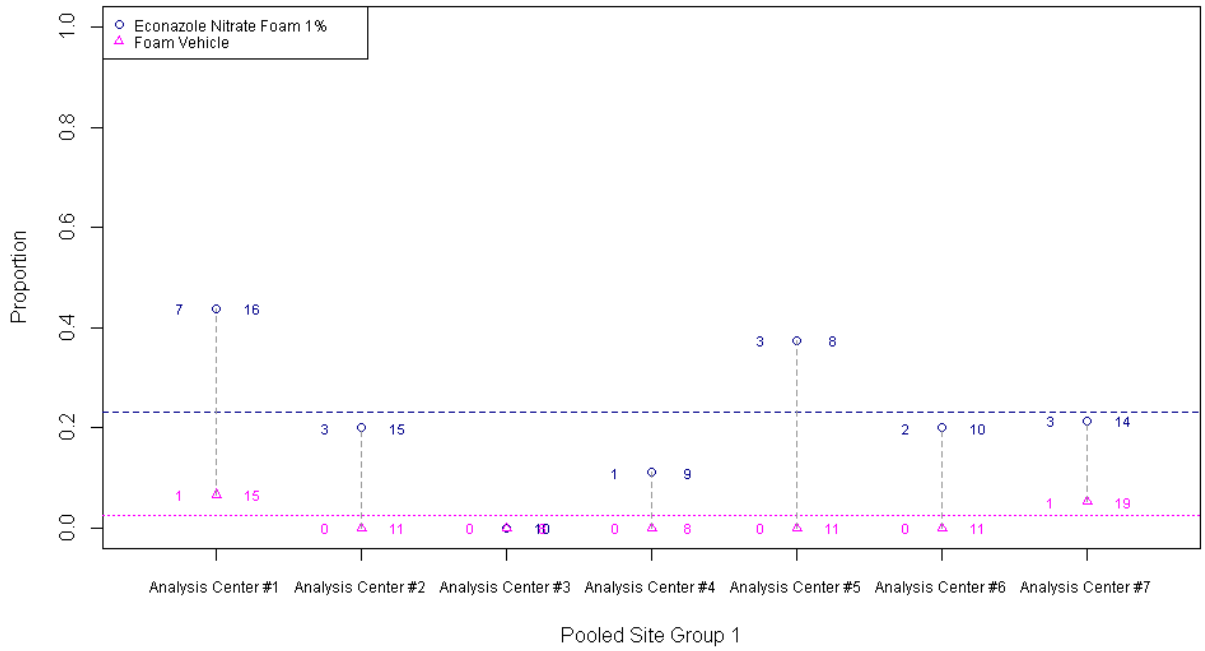


Source: Reviewer analysis.

3.2.7 Efficacy by Center

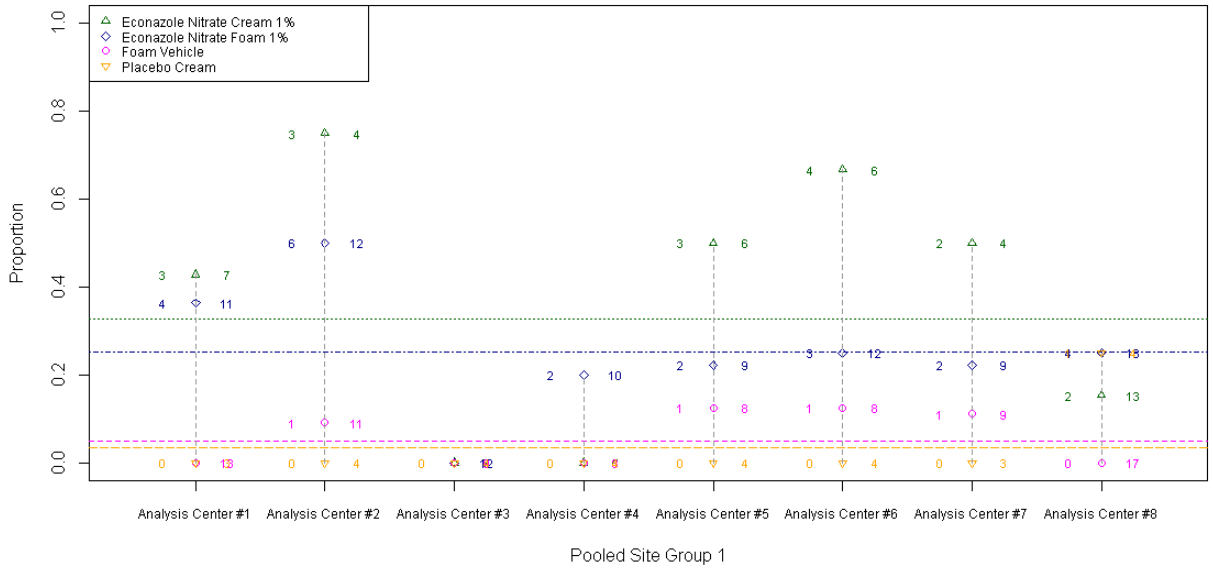
Study 302 was conducted at 14 centers, 12 in the U.S. and 2 in the Dominican Republic. Three of the centers (one in the U.S. and both of the Dominican Republic centers) enrolled at least 8 subjects on the econazole foam and vehicle foam arms, and were not pooled with other centers. The remaining 11 centers were combined into 4 analysis centers (2 to 4 centers per analysis center). Analysis centers 2 and 3 were the Dominican Republic centers; the remaining analysis centers were U.S. centers. Study 303 was conducted at 18 centers, all in the U.S. Two centers enrolled at least 8 subjects on the econazole foam and vehicle foam arms. The remaining 16 centers were combined into 6 analysis centers (2 to 4 centers per analysis center). Treatment effects were generally consistent across analysis centers, and no center is overly influential. The p-values from the Breslow-Day test for homogeneity (econazole foam and vehicle foam arms) were 0.868 for Study 302 and 0.580 for Study 303; neither test identified significant heterogeneity. See Figure 5 and Figure 6.

Figure 5 – Complete Cure Rate by Analysis Center (Study 302)



Source: Reviewer Analysis

Figure 6 – Complete Cure Rate by Analysis Center (Study 303)



Source: Reviewer analysis.

3.3 Evaluation of Safety

3.3.1 Extent of Exposure

The planned number of treatment applications was 28, and the mean and median number of applications of all treatment arms in the two studies was close to 28. The minimum number of applications among subjects known to have applied treatment at least once was 5 applications, and the maximum was 45. The amount of study product used was more variable, with some subjects using several times more product than was used by the median subject. The mean amount of econazole foam used was about 65 g, while the median was about 50 g and the maximum amount was 216 g. The amounts of vehicle foam used were similar. These calculations were computed in subjects with available data.

Table 17 – Extent of Exposure – Safety Population (Study 302)

	Econazole Foam N = 130	Vehicle Foam N = 134
Number of Applications	*N=127*	*N=132*
Mean (SD)	27.4 (3.13)	27.6 (3.01)
Median	28	28
Range	5 to 43	6 to 40
Amount used (g)	*N=122*	*N=128*
Mean (SD)	65.6 (43.62)	73.2 (49.54)
Median	51.5	59.3
Range	5 to 198	7 to 231

Note: Summary statistics are computed in subjects with available data.
Source: pg 86 of study report for Study 302.

Table 18 – Extent of Exposure – Safety Population (Study 303)

	Econazole Foam N = 116	Vehicle Foam N = 115	Econazole Cream N=79	Vehicle Cream N=40
Number of Applications	*N=114*	*N=113*	*N=78*	*N=39*
Mean (SD)	28.1 (4.14)	27.8 (3.99)	28.2 (2.98)	28.2 (3.57)
Median	28	28	28	28
Range	7 to 45	6 to 44	14 to 42	16 to 43
Amount used (g)	*N=105*	*N=108*	*N=75*	*N=37*
Mean (SD)	63.6 (43.79)	65.0 (47.75)	91.2 (78.20)	83.3 (88.26)
Median	49.4	52.3	63.3	49.3
Range	7 to 216	5 to 221	5 to 309	7 to 417

Note: Summary statistics are computed in subjects with available data.
Source: pg 119 of study report for Study 303.

3.3.2 Adverse Events

Similar proportions of econazole foam and vehicle foam subjects experienced adverse events during the study (13% vs. 12% respectively in Study 302 and 10% vs. 10% in Study 303). Few adverse events occurred in more than one subject per arm, and those that did (headache and nasopharyngitis) generally occurred in similar rates on all treatment arms. Two events were classified as probably or definitely related to treatment: application site dermatitis and application site pain. Both of these events occurred in vehicle foam subjects. See Table 19 and Table 20.

Table 19 – Adverse Events (Study 302)

	Econazole Foam N = 130	Vehicle Foam N = 134
Any Adverse Event	17 (13.1%)	16 (11.9%)
Gastrointestinal disorders (Oral pain)	1 (0.8%)	0 (0.0%)
General disorders and administration site conditions (Application site dermatitis)	0 (0.0%)	1 (0.7%)
Infections and infestations	6 (4.6%)	6 (4.5%)
Cystitis	1 (0.8%)	0 (0.0%)
Helicobacter gastritis	1 (0.8%)	0 (0.0%)
Influenza	1 (0.8%)	0 (0.0%)
Nasopharyngitis	2 (1.5%)	4 (3.0%)
Sinusitis bacterial	0 (0.0%)	1 (0.7%)
Upper respiratory tract infection	1 (0.8%)	1 (0.7%)
Injury, poisoning and procedural complications (Ligament injury)	1 (0.8%)	0 (0.0%)
Musculoskeletal and connective tissue disorders (Back pain)	1 (0.8%)	0 (0.0%)
Nervous system disorders (Headache)	6 (4.6%)	6 (4.5%)
Respiratory, thoracic and mediastinal disorders	2 (1.5%)	2 (1.5%)
Nasal congestion	1 (0.8%)	0 (0.0%)
Nasal dryness	0 (0.0%)	1 (0.7%)
Oropharyngeal pain	1 (0.8%)	0 (0.0%)
Pulmonary congestion	0 (0.0%)	1 (0.7%)
Rhinorrhea	0 (0.0%)	1 (0.7%)
Vascular disorders (Hypertension)	0 (0.0%)	1 (0.7%)

Source: pg 91 of study report for Study 302

Table 20 – Adverse Events (Study 303)

	Econazole Foam N=116	Foam Vehicle N=115	Econazole Cream N=79	Vehicle Cream N=40
Any Adverse Event	11 (9.5%)	11 (9.6%)	8 (10.1%)	5 (12.5%)
Ear and labyrinth disorders (Ear pain)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders	0 (0.0%)	2 (1.7%)	0 (0.0%)	0 (0.0%)
Nausea	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Vomiting	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Gen. disorders and admin. site cond.	0 (0.0%)	3 (2.6%)	0 (0.0%)	0 (0.0%)
Applic. site pain	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Fatigue	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Pain	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Immune sys. dis. (Hypersensitivity)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Infections and infestations	2 (1.7%)	3 (2.6%)	2 (2.5%)	3 (7.5%)
Bronchitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
Influenza	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
Local infection	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Nasopharyngitis	1 (0.9%)	0 (0.0%)	1 (1.3%)	1 (2.5%)
Oral herpes	0 (0.0%)	0 (0.0%)	1 (1.3%)	0 (0.0%)
Sinusitis	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
URTI	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Injury, poisoning and proced. compl.	3 (2.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Excoriation	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Laceration	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Procedural pain	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Investigations	0 (0.0%)	1 (0.9%)	2 (2.5%)	2 (5.0%)
Metab. and nutr. dis. (Type 2 diabetes)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Musculo and connective tissue dis.	1 (0.9%)	2 (1.7%)	1 (1.3%)	0 (0.0%)
Back pain	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Musculoskeletal pain	0 (0.0%)	1 (0.9%)	1 (1.3%)	0 (0.0%)
Nervous System Disorders (Headache)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Renal and urinary disorders	0 (0.0%)	2 (1.7%)	1 (1.3%)	0 (0.0%)
Hematuria	0 (0.0%)	1 (0.9%)	1 (1.3%)	0 (0.0%)
Nephrolithiasis	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Resp., thor. and mediast. disorders (Rhinorrhea)	1 (0.9%)	1 (0.9%)	1 (1.3%)	0 (0.0%)
Skin and subcutaneous tissue disorders	1 (0.9%)	0 (0.0%)	1 (1.3%)	0 (0.0%)
Dermatitis contact	0 (0.0%)	0 (0.0%)	1 (1.3%)	0 (0.0%)
Eczema	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

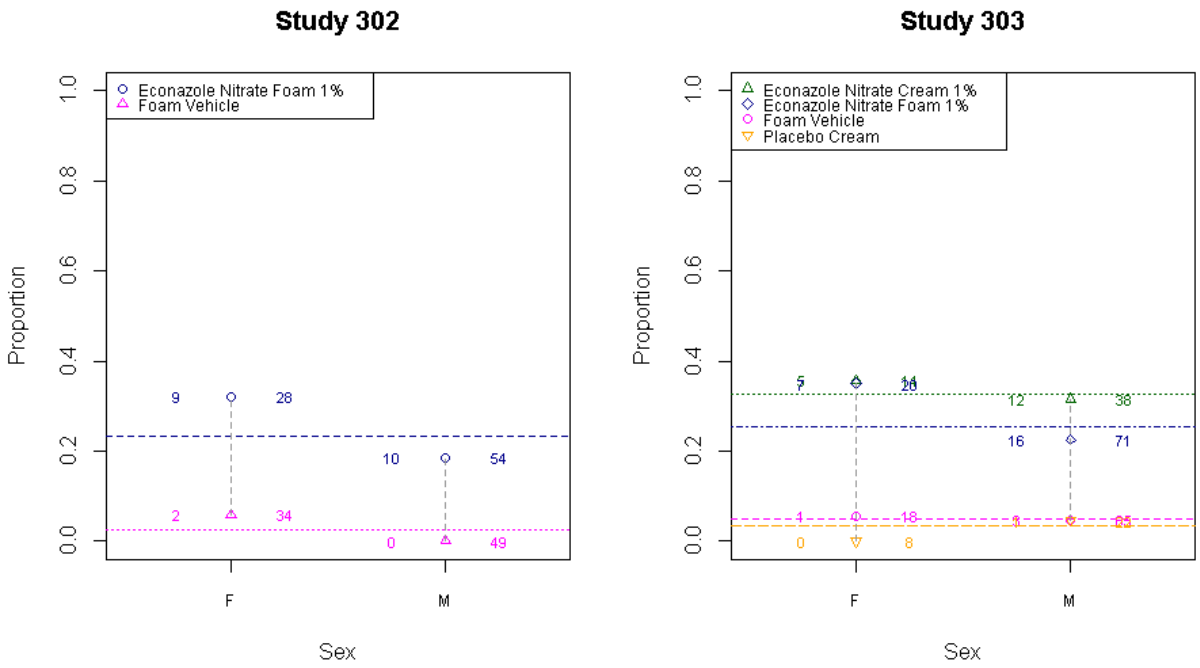
Source: pg 126 – 128 of study report for Study 303.

4 Findings in Special/Subgroup Populations

4.1 Gender, Race, Age, and Geographic Region

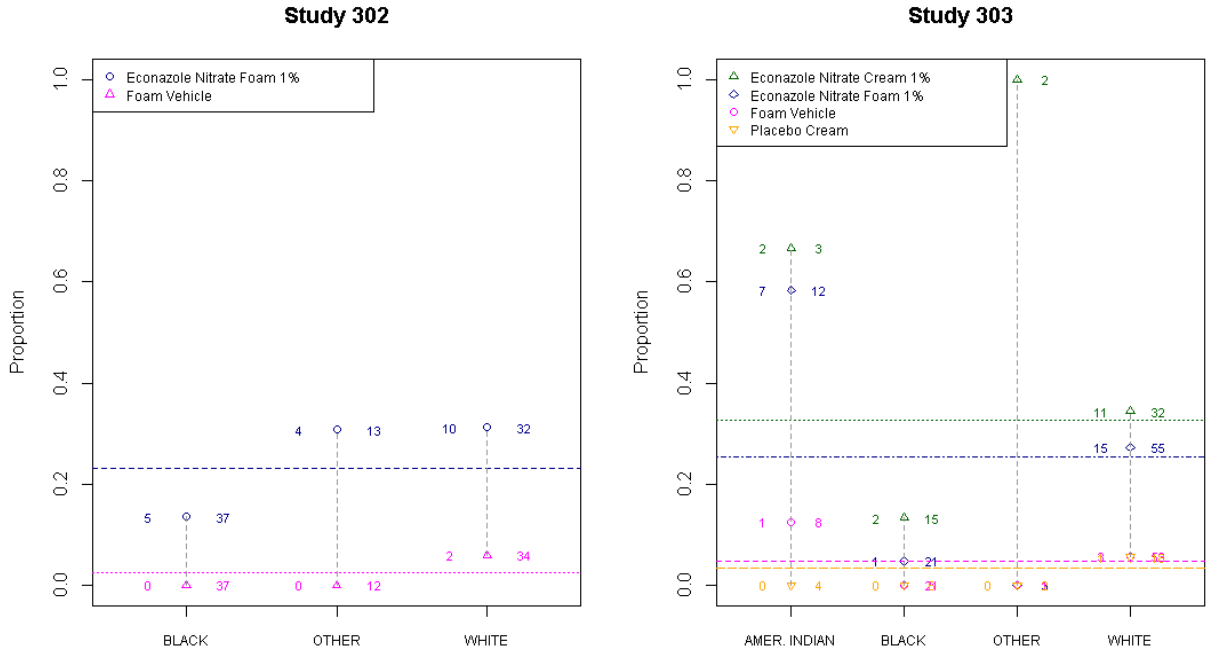
Treatment effects were generally consistent across gender, race, age and country subgroups, although some subgroups were small and there was some variability in magnitude. See Figure 7 through Figure 10.

Figure 7 – Complete Cure Rate by Gender



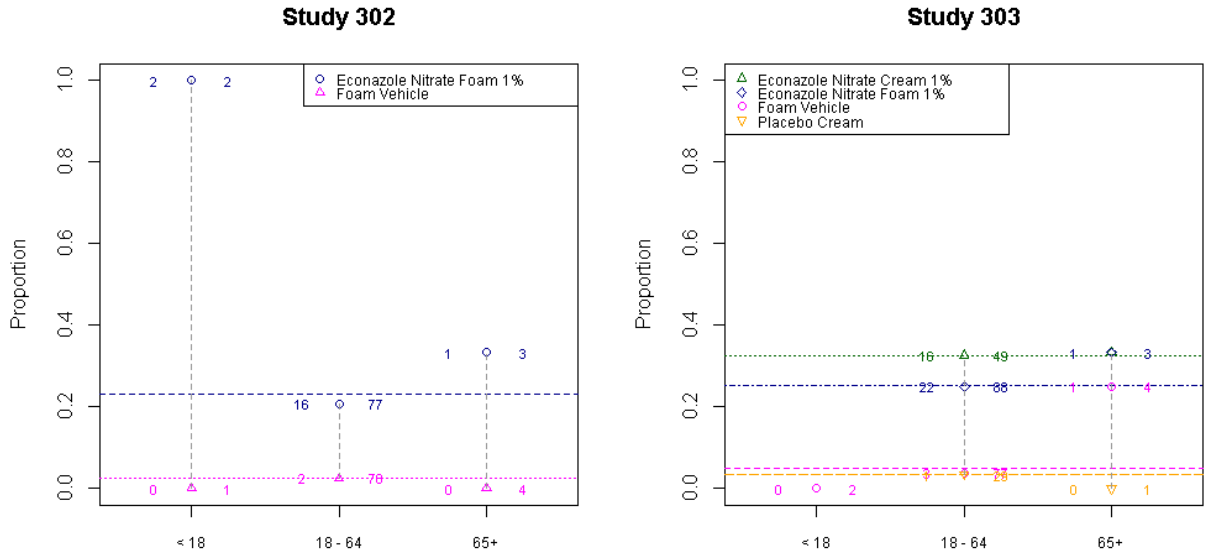
Source: Reviewer analysis.

Figure 8 – Complete Cure Rate by Race



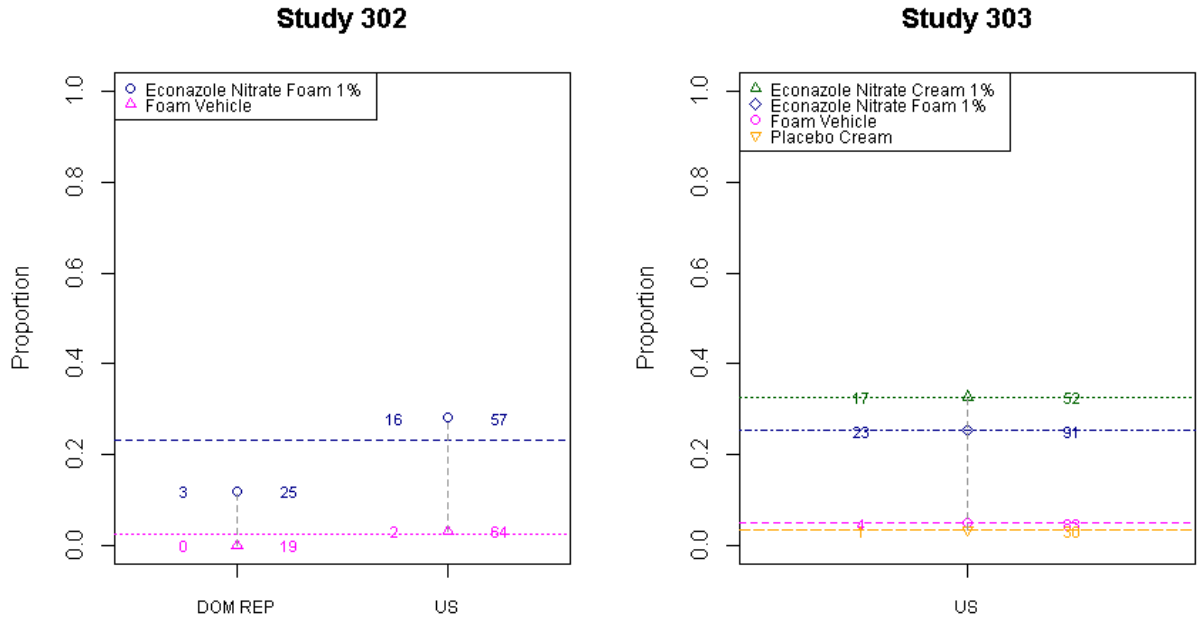
Source: Reviewer analysis.

Figure 9 – Complete Cure Rate by Age Group



Source: Reviewer analysis.

Figure 10 – Complete Cure Rate by Country

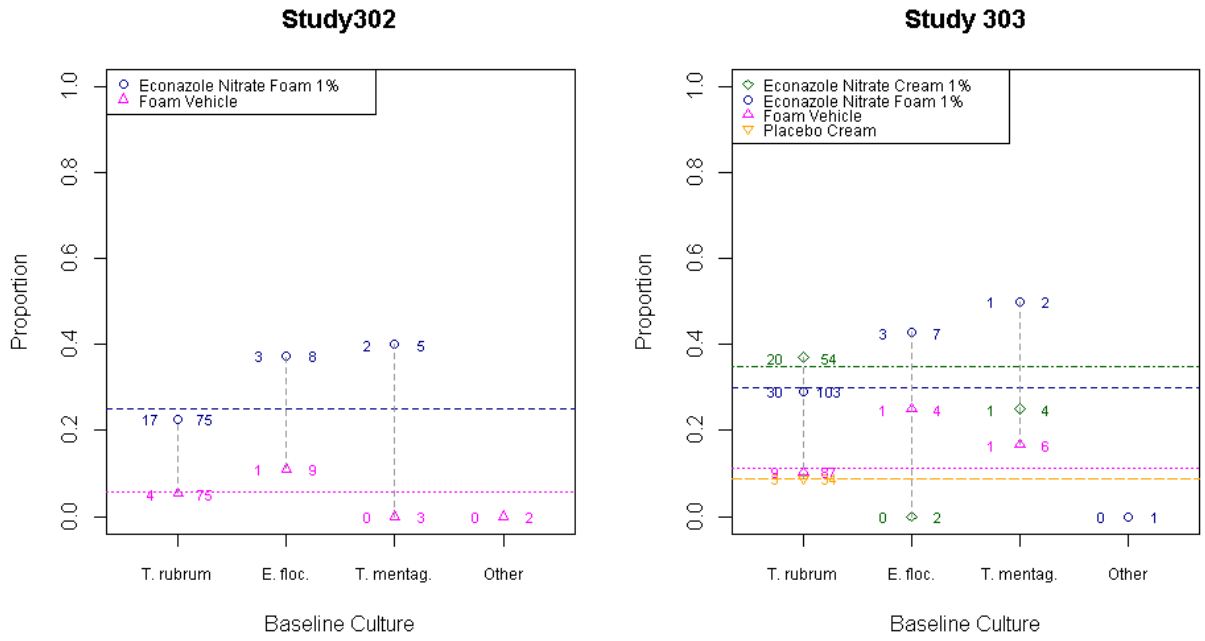


Source: Reviewer analysis.

4.2 Other Special/Subgroup Populations

The majority of subjects had baseline cultures with *T. rubrum*, though smaller numbers of subjects had baseline cultures with *E. floccosum, T. mentagrophytes, T. tonsurans*, or mixed pathogens. Treatment effects were generally consistent across the baseline pathogens, noting that all pathogens except *T. rubrum* had small sample sizes. See Figure 11.

Figure 11 – Complete Cure Rate by Baseline Pathogen



Source: Reviewer analysis.

5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

The applicant has evaluated the efficacy of econazole foam 1% in two studies for the treatment of interdigital tinea pedis. One study was a two-arm study (econazole foam vs. vehicle foam) and the other study was a four-arm study (econazole foam, vehicle foam, econazole cream, and vehicle cream). Study 303 included an econazole cream arm as one component of the clinical bridge to the Agency's findings of safety for econazole cream. The vehicle cream arm was included to maintain blinding. Both protocols were reviewed under Special Protocol Assessments and agreements were reached on the study design and endpoints.

Both studies demonstrated the superiority of econazole foam over vehicle foam for the primary efficacy endpoint of complete cure at Day 43 ($p<0.001$). The studies evaluated two secondary endpoints: mycological cure and effective treatment, which were evaluated in sequential order. The secondary endpoints were also statistically significant in both studies ($p<0.001$, sequential assessment). Treatment effects were generally consistent across subgroups and centers. The conclusions were consistent across various assumptions regarding missing data, although many of the applicant's sensitivity analyses led to larger estimated treatment effects than the primary method of LOCF. However, this reviewer's post-hoc analyses that treated the missing data in a conservative way indicated that the treatment effect was robust to the handling of missing data.

5.2 Conclusions and Recommendations

Econazole foam 1% was superior to its vehicle in the treatment of interdigital tinea pedis in two studies. The studies enrolled subjects age 12 and older with a clinical diagnosis of interdigital tinea pedis involving at least two web spaces (at least moderate scaling and mild erythema) and positive KOH. Subjects had to have a positive fungal culture to be included in the MITT population (the primary analysis population). Subjects applied treatment once daily for four weeks. The primary efficacy endpoint was complete cure (scores of 0 [none] on all signs and symptoms, negative KOH, and negative culture) at Day 43, two weeks after the end of treatment. The secondary endpoints were mycological cure (negative KOH and negative culture) and effective treatment (no or mild erythema and/or scaling [scores of 0 or 1] with all other signs and symptoms absent [scores of 0], negative KOH, and negative culture) at Day 43. The primary and secondary efficacy endpoints for econazole foam versus vehicle foam were all statistically significant at Day 43. The efficacy outcomes are summarized in Table 21.

Table 21 – Efficacy Results in Studies 302 and 303 (MITT)

Study 302	Econazole Foam N=82	Vehicle Foam N=83			P-value
Complete Cure	19 (23%)	2 (2%)			<0.001
Effective Treatment	40 (49%)	9 (11%)			<0.001
Mycological Cure	56 (68%)	13 (16%)			<0.001
Study 303	Econazole Foam N=91	Vehicle Foam N=83	Econazole Cream N=52	Vehicle Cream N=30	P-value[1]
Complete Cure	23 (25%)	4 (5%)	17 (33%)	1 (3%)	<0.001
Effective Treatment	44 (48%)	9 (11%)	27 (52%)	1 (3%)	<0.001
Mycological Cure	61 (67%)	15 (18%)	33 (63%)	1 (3%)	<0.001

[1] P-value of econazole foam versus vehicle foam. All p-values are from the CMH test stratified on analysis center.

Signatures/Distribution List

Primary Statistical Reviewer: Kathleen Fritsch, Ph.D.
Date: 8/27/2013

Statistical Team Leader: Mohamed Alosh, Ph.D.

cc:
DDDP/Walker
DDDP/Kettl
DDDP/Woitach
DDDP/White
DDDP/Gould
OBIO/Patrician
DBIII/Wilson
DBIII/Alosh
DBIII/Fritsch

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/s/

KATHLEEN S FRITSCH
08/27/2013

MOHAMED A ALOSH
08/27/2013
Concur with the review

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 205175 **Applicant:** AmDerma **Stamp Date:** 12/26/2012

Drug Name: Econazole nitrate foam 1% **NDA Type:** 505(b)(2) **Indication:** Tinea pedis

I. On **initial** overview of the NDA/BLA application identify and list any potential Refuse to File issues:

	Content Parameter for RTF	Yes	No	NA	Comments
1	Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc.	X			Some problems in organization in GSReview
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			Final protocols w/ description of amendments
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	X			
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE?

Yes

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

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
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			

74-DAY LETTER REQUESTS TO THE APPLICANT

None.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

SUBMISSION SUMMARY

This submission contains one Phase 2 study and two Phase 3 studies for econazole nitrate foam 1% in the treatment of tinea pedis. The Phase 2 study (D79-2902-07) evaluated econazole nitrate foam 1%, econazole nitrate cream 1%, and foam vehicle over a 4-week treatment period in subjects with interdigital or moccasin tinea pedis. The Phase 3 studies evaluated subjects with interdigital tinea pedis only. One Phase 3 study (079-2951-302) was a two-arm vehicle-controlled study that randomized 267 subjects with 165 included in the MITT population (82 econazole/83 vehicle). The other Phase 3 study (079-2951-303) was a four-arm study that randomized 358 subjects with 256 included in the MITT population (91 econazole foam/83 foam vehicle/52 econazole cream/30 cream vehicle). Both Phase 3 studies enrolled subjects age 12 and older with a clinical diagnosis of interdigital tinea pedis and positive KOH. Subjects had to have a positive culture to be included in the MITT population. Treatment was applied once daily to all affected areas and adjacent normal skin for 4 weeks. The primary efficacy endpoint was complete cure (scores of 0 for erythema, scaling, fissuring, maceration, vesiculation, and pruritus, plus negative KOH and negative culture) two weeks post-treatment (Day 43). In each study, the primary comparison was econazole foam vs. vehicle foam. In study 303, the econazole cream arm was included to support a clinical bridge between the dosage forms and the vehicle cream arm was included for blinding purposes.

Complete Cure at Two Weeks Post-Treatment (Day 43)

	Econazole Nitrate Foam	**Vehicle Foam**	**Econazole Nitrate Cream**	**Vehicle Cream**
Study 302	19/82 (23%)	2/83 (2%)	--	--
		$p < 0.001$		
Study 303	23/91 (25%)	4/83 (5%)	17/52 (33%)	1/30 (3%)
		$p < 0.001$		

ASSOCIATED IND: IND 77523
WERE PROTOCOLS REVIEWED UNDER A SPA? Yes.

Reviewing Statistician Date

Supervisor/Team Leader Date

cc:
NDA 205175 / 000
DDDP/Walker
DDDP/Kettl
DDDP/Woitach
DDDP/CAttinello
OBIO/Patrician
DBIII/Wilson
DBIII/Alosh
DBIII/Fritsch

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/s/

KATHLEEN S FRITSCH
02/08/2013

MOHAMED A ALOSH
02/08/2013