CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76075

STATISTICAL REVIEW(S)

Statistical Review

ANDA 76-075
Drug Product: Econazole Nitrate Cream, 1%
Sponsor: Altana Pharmaceuticals, Inc.
Reference Listed Drug (RLD): Spectazole® cream, 1%,
Ortho-McNeil Pharmaceuticals
Submission Date: December 22, 2000

Reviewer: **Huaixiang Li, Ph.D., QMRS/OB/CDER**
Requestor: **Dena Hixon, MD, OGD/CDER, 9/5/02**
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Remark: The data sets (primary and primlocf) used in this analysis were supplied by the firm on CD-ROM and received on August 13, 2002 by OGD.

Objectives of the study

The primary objective of the study was to establish the bioequivalence of the test product, Altana Pharmaceuticals, Inc., Econazole Nitrate Cream, 1%, and the reference product, Ortho-McNeil, Spectazole® Cream, 1%, and to show superiority of the two active treatments to the placebo, a cream vehicle, in the treatment of tinea pedis.

Study Design

This was a 3 arm parallel double-blind study in subjects with signs and symptoms of tinea pedis. The three creams were the test product, Altana Pharmaceuticals, Inc., Econazole Nitrate Cream, 1%, the reference product, Ortho-McNeil, Spectazole® Cream, 1%, and the placebo, a cream vehicle.

A total of 447 subjects were enrolled and randomly assigned to three treatment groups in the study. At the enrollment visit, the subjects with clinical signs and symptoms of tinea pedis had a skin scraping taken from an area of active lesions for 10% KOH wet mount and fungal culture. The signs and symptoms, erythema, scaling, maceration, fissuring/cracking, pruritus/itching, and burning/stinging, were measured by using a score (0-4, none to severe). The eligible subjects, who had a positive fungal culture and met the eligibility criteria, were instructed to apply the cream to the clean, dry study foot twice a day for four weeks. The mycological evaluation (both KOH and culture test) and the physician's global assessment (complete, excellent, good, fair, poor, unchanged, to worse, coded a through g) were performed at visit 2 (2 weeks on treatment), visit 3 (4 weeks on treatment) and visit 4 (week 6, 2 weeks after the end of treatment).

Outcome Variables

This statistical analysis was focused on three endpoints to assess efficacy and equivalence in the study: the rate of mycological cure (both KOH and culture negative), the rate of

clinical cure (complete resolution on the physician's global assessment), and the rate of therapeutic cure defined as both a mycological cure and a clinical cure. In this review, for each of the three cure rates "cure" was interpreted as cure at *both* the week 4 visit (end of treatment) *and* the week 6 visit (2 weeks after end of treatment).

Statistical Analysis Methods

Efficacy Analysis

Tests of comparisons for therapeutic cure rate, mycological cure rate, and clinical cure rate were made between treatment arms at the (two-sided) 5% level significance. The efficacy analysis for each active treatment was tested separately by comparing it with the placebo. All treatment arms should be similar for sign/symptom scores at the enrollment visit. The active treatments should be more distinguishable from placebo as the study progressed.

The efficacy analyses for all variables were carried out by using Fisher's exact test for each active treatment versus placebo.

Equivalence Analysis

Based on the usual method used in OGD for binary outcomes, the 90% confidence interval for the difference in proportions between test and reference treatment should be contained within -.20 to .20 in order to establish equivalence.

The compound hypothesis to be tested is:

H_0: $p_T - p_R \leq -.20$

or $p_T - p_R \geq .20$

versus

H_A: $-.20 < p_T - p_R < .20$

where p_T = cure rate of test treatment p_R = cure rate of reference treatment

Let n_T = sample size of test treatment n_R = sample size of reference treatment

and $se = (\hat{p}_T(1 - \hat{p}_T)/n_T + \hat{p}_R(1 - \hat{p}_R)/n_R)^{1/2}$

The 90% confidence interval for the difference in proportions between test and reference was calculated as follows, using Yates' correction:

$L = (\hat{p}_T - \hat{p}_R) - 1.645\ se - (1/n_T + 1/n_R)/2$

$$U = (\hat{p}_T - \hat{p}_R) + 1.645\ se + (1/n_T + 1/n_R)/2$$

and reject H_0 if $L \geq -.20$ and $U \leq .20$

Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products.

We analyzed the data for efficacy and equivalence for mycological cure rate, clinical cure rate, and therapeutic cure rate for both Per Protocol (PP) and Modified Intent-to-treat (MITT) populations with and without LOCF (Last Observation Carried Forward). The PP and MITT populations were as defined by the sponsor.

Statistical Analysis Results

The following table shows the populations per treatment

numbers of patients	Altana	Ortho	Placebo	Total
ENROLLED	178	181	88	447
Excluded from MITT	45	53	26	124
Did not return for at least one follow-up visit	2	8	2	12
Lack of fungal pathogen at baseline	40	44	24	108
Violated exclusion/inclusion criteria	3	1	0	4
MITT	133	128	62	323
Excluded from PP	60	69	31	160
Did not return for at least one follow-up visit	2	8	2	12
Lack of fungal pathogen at baseline	40	44	24	108
Missing week 6 visit/week 6 efficacy variable	3	7	0	10
Outside week 6 visit window	12	8	4	24
Used prohibited medication	1	1	1	3
Violated exclusion/inclusion criteria	2	1	0	3
PP	118	112	57	287

Demographic and baseline

Overall, there were 237 males and 86 females in the MITT population. The treatment groups had similar percentage of male (69% for Altana, 76% for Ortho, and 77% for placebo). The mean age of the 323 subjects in the MITT population was 41.7 years and the age ranged from 12 to 92 years old. There were 41% White, 40% Black, and 19% Oriental. The sex, age, and race of subjects were comparably distributed among the three treatment groups for the MITT and PP populations.

An analysis of the frequencies and chi-square tests for homogeneity of sign/symptom scores for the MITT and PP populations at the enrollment visit was performed. There were no significant differences between treatment arms for all the signs/symptoms for both populations at the enrollment visit.

Efficacy and equivalence Analysis

We analyzed the data for efficacy and equivalence for mycological cure rate, clinical cure rate, and therapeutic cure rate for both Per Protocol (PP) and Modified Intent-to-treat (MITT) populations with and without LOCF (Last Observation Carried Forward).

The three cure rates incorporated the results at both the week 4 and week 6 visits. Clinical cure was defined by complete response based on the physician's global assessment.

Summary of the efficacy and equivalence analysis

Population	Test* % of cure (No. of cure)	Reference* % of cure (No. of cure)	Placebo* % of cure (No. cure)	P-value# for Test vs. placebo	P-value# for Reference vs. placebo	90% Confidence interval for Test vs. ref. (%)	90% CI is within (-20%, 20%)
Primary with LOCF							
PP$	118	112	57				
Mycological cure	79.7 (94)	82.1 (92)	14.0 (8)	<.001	<.001	-11.9, 6.9	Yes
Clinical cure	31.4 (37)	28.6 (32)	5.3 (3)	<.001	<.001	-8.0, 13.6	Yes
Therapeutic cure	28.8 (34)	26.8 (30)	3.5 (2)	<.001	<.001	-8.6, 12.6	Yes
MITT$	133	128	62				
Mycological cure	80.5 (107)	82.8 (106)	16.1 (10)	<.001	<.001	-11.0, 6.3	Yes
Clinical cure	30.8 (41)	25.8 (33)	6.5 (4)	<.001	0.002	-4.9, 15.0	Yes
Therapeutic cure	27.8 (37)	24.2 (31)	4.8 (3)	<.001	<.001	-6.1, 13.3	Yes
Primary without LOCF							
PP$	117	111	54				
Mycological cure	80.3 (94)	82.9 (92)	14.8 (8)	<.001	<.001	-11.9, 6.8	Yes
Clinical cure	31.6 (37)	28.8 (32)	5.6 (3)	<.001	<.001	-8.1, 13.7	Yes
Therapeutic cure	29.1 (34)	27.0 (30)	3.7 (2)	<.001	<.001	-8.6, 12.7	Yes
MITT$	129	121	59				
Mycological cure	80.6 (104)	82.6 (100)	15.3 (9)	<.001	<.001	-10.9, 6.8	Yes
Clinical cure	31.0 (40)	26.4 (32)	6.8 (4)	<.001	0.001	-5.6, 14.8	Yes
Therapeutic cure	27.9 (36)	24.8 (30)	5.1 (3)	<.001	<.001	-6.8, 13.1	Yes

*: The rate of cure equals the number of cured divided by the total number, then multiplied by 100.

#: The P-values were from the paired Fisher's exact test (2-sided).

$: The total number of subjects in each treatment group.

The test and reference treatments were significantly better than placebo for mycological cure rate, clinical cure rate, and therapeutic cure rate for both populations with and without LOCF.

The equivalence test was passed for mycological cure rate, clinical cure rate, and therapeutic cure rate for both populations with and without LOCF.

Safety

Please see the details in the Medical review's report.

Comments on the Sponsor's Equivalence Analyses

Medical Officer Note: The study report gave two definitions of Total Cure[1] and these were analyzed separately. Definition 1 is the definition given in the protocol and the standard definition for a primary outcome in tinea pedis studies. Total Cure is defined as those who had Complete resolution on the Physician's Global Assessment plus Mycological Cure (negative KOH and fungal culture). The second definition used expanded the clinical cure to Complete and Excellent response on the Physician's Global Assessment. There was no explanation given by the sponsor to justify this change and it was not listed in the changes in planned analyses. The sponsor did summarize the results stating that using the original definition their study fails to show bioequivalence between test and reference, but that it meets bioequivalence criteria using the second definition of Total Cure. This appears to represent a post hoc change in clinical endpoints based on a failure of the data to meet the original endpoint criteria for success.

The following is the summary for the sponsor's equivalence test. The equivalence test passed for the mycological cure rate, clinical cure rate (definition 2), and total cure rate (definition 2), but failed for the clinical cure rate (definition 1) and total cure rate (definition 1) for both populations with and without LOCF at the week 6 visit.

[1] The Total cure is equal to the traditional Therapeutic cure.

Data set/ Population / Variable	Cure number test	Total number test	Cure number reference	Total number reference	Cure percent test	Cure percent reference	Lower bound	Upper bound	Pass/ fail
Primary with LOCF									
PP									
Mycological	103	118	103	112	0.87	0.92	-0.12	0.03	P
Clinical (1)	68	118	51	112	0.58	0.46	0	0.24	F
Total (1)	64	118	49	112	0.54	0.44	-0.01	0.22	F
Clinical (2)	91	118	90	112	0.77	0.8	-0.13	0.06	P
Total (2)	85	118	86	112	0.72	0.77	-0.15	0.06	P
MITT									
Mycological	118	133	117	128	0.89	0.91	-0.1	0.04	P
Clinical (1)	78	133	55	128	0.59	0.43	0.05	0.27	F
Total (1)	74	133	53	128	0.56	0.41	0.03	0.25	F
Clinical (2)	104	133	101	128	0.78	0.79	-0.1	0.08	P
Total (2)	98	133	97	128	0.74	0.76	-0.12	0.08	P
Primary without LOCF									
PP									
Mycological	103	117	103	112	0.88	0.92	-0.11	0.03	P
Clinical (1)	68	117	51	112	0.58	0.46	0.01	0.24	F
Total (1)	64	117	49	112	0.55	0.44	-0.01	0.23	F
Clinical (2)	91	117	90	112	0.78	0.8	-0.12	0.07	P
Total (2)	85	117	86	112	0.73	0.77	-0.14	0.06	P
MITT									
Mycological	116	130	111	121*	0.89	0.92	-0.09	0.04	P
Clinical (1)	77	130	54	122	0.59	0.44	0.04	0.26	F
Total (1)	73	130	52	121*	0.56	0.43	0.02	0.25	F
Clinical (2)	103	130	98	122	0.79	0.8	-0.1	0.08	P
Total (2)	97	130	93	121*	0.75	0.77	-0.12	0.07	P

(1)=definition 1 for clinical cure. (2)=definition 2 for clinical cure.
*The subject 12-296 missed the value for mycological cure and total cure at the week 6 visit.

Conclusion

Efficacy: Our analysis showed that the test and reference products were both significantly better than placebo for therapeutic cure, mycological cure, and clinical cure for both PP and MITT populations with and without LOCF.

Equivalence: The equivalence test for Altana product versus Ortho product was passed for therapeutic cure, mycological cure, and clinical cure for both PP and MITT populations with and without LOCF.

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