CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76075

MEDICAL REVIEW

MEDICAL OFFICER REVIEW
April 8, 2002

ANDA 76-075
Drug Product: Econazole Nitrate Cream, 1%
Sponsor: Altana, Inc.

The sponsor has submitted an amendment dated 2/19/02 in response to the deficiency letter from the Office of Generic Drugs dated10/24/01. The comments concerned their bioequivalence study with clinical endpoints entitled: "A Multicenter, Double-Blind, Randomized, Vehicle-Controlled, Parallel Group Study, to Determine the Therapeutic Equivalence of Two Econazole Nitrate 1% Formulations in the Treatment of Interdigital Tinea Pedis".

The deficiencies are listed below with a summary of the sponsor's response.

Deficiency #1. *The study report gave two definitions of Total Cure, each analyzed separately. Definition 1 is given in the protocol and is 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 cure). The second definition expands the clinical cure to complete and excellent response on the Physician's Global Assessment. There was no explanation given to justify this change and it is not listed in the changes in the planned analyses. This definition is not accepted as a definition of cure for tinea pedis. You did summarize the results stating that when using the original definition, the study fails to show bioequivalence between test and reference, and when using the second definition, the study meets the bioequivalence criteria. This represents a post hoc change in clinical endpoints based on a failure of the data to meet the original endpoint criteria for success.*

In response to this deficiency, the sponsor requested a meeting with the FDA. The specific question posed by the sponsor is "Why is a generic manufacturer being held to a different standard than was used by the innovator to obtain approval of their product?"

The sponsor subsequently withdrew the meeting request and submitted the amendment currently under review. The statistician's report refers to the Summary Basis for Approval for NDA 18-751, the original approval for Spectazole® Cream 1%, and for NDA 18-751/S-006, approval of a labeling change from twice-daily dosing to once-daily dosing for tinea pedis. They point out that the primary efficacy endpoint evaluated by FDA was the percentage of subjects cured at the End-of-Treatment visit. The percentage of cured patients in

each treatment group who remained, or did not remain, cured at the Follow-up visit was evaluated without any formal statistical analyses.

> *Medical Officer Note: The primary endpoints for bioequivalence studies with clinical endpoints have been carefully selected in consultation with the appropriate new drug division. These are not always the same endpoints as those that are used to evaluate efficacy of a new drug product. The sponsor is referred to the "1990 Draft Guidance for the Performance of a Bioequivalence Study for Topical Antifungal Products". This guidance was prepared by the Office of Generic Drugs with consultation from the CDER division responsible for topical antifungal drug products. In discussing the primary endpoints, the guidance states: "While these comparisons should be evaluated at the end of treatment and at the two week follow up visits, primary weight will be given to the two week follow up evaluation in determining if bioequivalence has been established." The primary endpoint chosen by the sponsor in their reanalysis (submitted in this amendment) is the end of treatment visit clinical and mycological cure. This endpoint is not acceptable for this study and the analysis should be done using the data from these evaluations at the follow-up visit two weeks after the end of treatment.*

Deficiency #2. *You outlined several changes in the planned analyses in the study report and the method for carrying forward missing values for the MITT was further clarified. You introduced the concept of invalid visits for this population, including visits outside the prescribed time window and visits after a prohibited medication was taken. In these instances, the last valid observation was carried forward. Since the MITT population was not defined by adherence to the protocol, this method is not appropriate. Only missing visit data should be substituted by carrying the last observation forward.*

The sponsor clarified that the Last Observation Carried Forward (LOCF) was only used for missing visits.

Deficiency #3. *Patient number 06-002 was listed as a withdrawal because of an insufficient therapeutic response and should therefore be included in all analysis populations as a treatment failure.*

The sponsor acknowledged that this patient was discontinued as a treatment failure. The protocol for this study stated that treatment failure dropouts were to be included in the PP analysis population only if they had received at least 14 days of treatment. This protocol was reviewed by the Office of Generic Drugs and found acceptable. Patients #06-002 received only 7 doses of treatment before stopping the medication on her own.

Conclusion

The sponsor's reanalysis uses the wrong primary endpoint. The original analysis of the sponsor using the correct clinical cure definition fails to demonstrate bioequivalence of their product to the reference listed drug.

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Office of Generic Drugs

MEDICAL OFFICER REVIEW

ANDA 76-075
Drug Product: Econazole Nitrate Cream, 1%
Sponsor: Altana, Inc.

Title: A Multicenter, Double-Blind, Randomized, Vehicle-Controlled, Parallel Group Study, to Determine the Therapeutic Equivalence of Two Econazole Nitrate 1% Formulations in the Treatment of Interdigital Tinea Pedis

Protocol Number: ALT 01/99

Contract Research Organization:

Data Entry and Management and Statistical Analysis:

Dermatophyte Cultures:

Study Period: First patient entered – March 15, 2000
Last patient completed – September 25, 2000

Background

The sponsor submitted a protocol under IND and this was reviewed and found acceptable. The study was designed based on the FDA Draft Guidance for the Performance of a Bioequivalence Study for Topical Antifungal Products (Feb 1990) as well as earlier studies of the bioequivalence of topical antifungals in the treatment of tinea pedis , also sponsored by Altana Inc. and managed by

Study Changes from Protocol

The protocol and the conduct of the completed study have been compared. The medical officer review of the protocol is included below and any changes from the protocol defined criteria, definitions, and study conduct are itemized as Medical Officer Notes.

Study Objectives

1. To establish the therapeutic equivalence of econazole nitrate 1% cream (Altana, Inc.) applied once daily to Spectazole® Cream 1% (Ortho McNeil Pharmaceuticals) applied once daily in the treatment of tinea pedis.

2. To determine whether Spectazole® Cream 1% and its generic equivalent are significantly different from the econazole vehicle base in antifungal properties.

   Medical Officer Note: The sponsor added "and/or safety" at the end of objective 2.

Study Design

This is a multicenter, vehicle-controlled, randomized, parallel-group study to compare the test drug, econazole nitrate 1% cream (Altana, Inc.), with a reference drug, econazole nitrate 1% cream (Spectazole ® cream, Ortho-McNeil Pharmaceuticals), and vehicle (the vehicle of the test drug) in the treatment of tinea pedis. Approximately 444 subjects will be enrolled into the study in order to obtain 288 evaluable subjects, 115 in each active treatment arm, and 58 in the vehicle group. The study will be conducted at 12 investigational centers.

Inclusion/Exclusion Criteria

Inclusion Criteria

Subjects who satisfy ALL the following criteria may be enrolled in the study:

1. Males and females at least 12 years of age with parental consent for subjects under 18 years of age. Females must be non-pregnant and non-lactating and either postmenopausal, surgically sterile, or using adequate birth control measures. Acceptable methods of birth control are abstinence, oral contraceptives, implants, diaphragm plus spermicide, tubal ligation, sponge, IUD, condom plus spermicide.
2. Outpatients with a definite clinical and mycological diagnosis of interdigital tinea pedis, i.e., dermatophytosis of one or more of the interdigital webs.
3. A minimum signs and symptoms score of 2 for erythema (on a scale of 0-3, where 2 indicates moderate severity) at the baseline target test site (the most severely affected toe web) AND a minimum signs and symptoms index score of 2 for either scaling or pruritus (on the same 0-3 point scale).
4. Diagnosis of tinea pedis confirmed by the presence of segmented fungal hyphae on direct microscopic examination of a KOH mount obtained from skin scrapings form the target test site.
5. A positive KOH result at study entry. Subjects subsequently will be withdrawn from the study at visit 3 (Day 29) if the fungal culture results of skin scrapings obtained at baseline from the target test site are not positive for Trichphyton rubrum, Trichophyton mentagrophytes, or Epidermophyton floccosum or other causative dermatophyte.

6. Good health and freedom from any clinically significant disease, other than tinea pedis, that might interfere with the study evaluations.
7. Providing of written informed consent. If the subject is a minor, the parent or legal guardian must also sign the informed consent.
8. Willingness and ability to comply with the requirements of the study, particularly with respect to treatment dosing requirements, visit schedule, and therapy prohibitions, and able to complete the study as specified in the protocol.

Exclusion Criteria

Subjects who satisfy ANY of the following criteria may not be enrolled in the study:

1. Pregnancy or lactation.
2. Uncontrolled diabetes, peripheral vascular disease, neuropathy of the feet, or any significant medical condition likely to compromise participation in the study or place the subject at risk.
3. History of atopic dermatitis, contact dermatitis, or psoriasis involving the feet.
4. Concurrent oral, vaginal, or mucocutaneous candidiasis.
5. Concurrent bacterial skin infections.
6. Confluent, diffuse moccasin-type tinea pedis of the entire plantar surface.
7. Significant systemic disease, such as immunological deficiencies.
8. Subject history of unresponsive dermatophyte infections, including unresponsiveness to oral antifungal drugs for tinea pedis.
9. Consumption of excessive amounts of alcohol, use of drugs, or a condition that would compromise compliance with this protocol.
10. Requirement for treatment during the study with an antifungal agent or antibiotic for a systemic or skin infection, other than tinea pedis.
11. Known hypersensitivity to econazole or any components of the test medications.
12. Previous enrollment in this study.
13. Concurrent medications:
    a. Medications not approved by the Sponsor and Investigator(s).
    b. Medications that may affect the course of tinea pedis may not be used during the study.
    c. Any topical antifungal therapy to the feet within two weeks before entry into the study.
    d. Any systemic antifungal or systemic corticosteroid treatment within two months before entry into the study.
    e. Any systemic antibiotic within 30 days before entry into the study.
    f. Any topical steroid therapy at the infection site within 30 days before entry into the study.
    g. Use of radiation therapy and/or anti-neoplastic agents during or within 12 weeks before entry into the study.
    h. No medication, emollients, or treatment other than those used in the study preparation are to be applied to the treatment areas.
    i. Treatment with Econazole or an investigational drug within 30 days before entry into the study.

Medical Officer Note: The following exclusion criterion was not listed in the final report list of exclusion criteria: Any systemic antifungal or systemic corticosteroid treatment within two months before entry into the study. The data set should be reviewed to see whether this exclusion criterion would affect the analysis populations.

Sample Size Determination

The sample size was calculated based on the following assumptions to yield a power of 80% for a two-tailed alpha = 0.05 comparison of the difference of two proportions:

1. Cure rate (combined clinical and mycological) 2 weeks after daily 4 week treatment for the reference product, based on reports of efficacy, is 38%.
2. Cure rate (combined clinical and mycological) 2 weeks after 4 weeks of treatment for the placebo is </=14%.

The sponsor estimates that 444 enrolled subjects would yield 288 evaluable subjects. The placebo arm would have to have 58 evaluable patients and the active treatment arms 115 evaluable subjects each.

Study Medications

The three study drugs are as follows:

1. Test Product – Econazole nitrate 1% cream (Altana, Inc.)
2. Reference – Econazole nitrate 1% cream (Spectazole ®, Ortho-McNeil Pharmaceuticals)
3. Vehicle – vehicle of test product matched to active drug (Altana)

Study Procedures

Visit 1 – Screening Visit

The following examinations will be conducted prior to documentation of a positive KOH result:

1. Written informed consent
2. A medical history and current medication usage
3. A brief physical exam
4. A rapid urine pregnancy test for all women of chilbearing potential
5. A foot exam to confirm the clinical diagnosis of interdigital tinea pedis
   A target test site with the most severe involvement will be identified and recorded in the subject's case report form. If both feet are involved the one

most severely affected will be chosen. The following signs and symptoms will be scored:

a. Erythema - redness
b. Scaling - scaling
c. Maceration – moist, soft, broken-down skin
d. Fissuring/cracking – fissuring/cracking
e. Pruritus – itching (subject's rating)
f. Burning/stinging – burning/stinging (subject's rating)

Severity will be evaluated using the following scale:

0 = none (absent)
1 = mild (slight)
2 = moderate (definitely present)
3 = severe (marked, intense)

6. Skin samples for KOH wet mount and fungal culture will be obtained from the target test site. For entry into the study, dermatophytes (fungal hyphae) must be clearly identified by the investigator on the KOH wet mount.

Subjects who meet all the selection criteria, including a positive KOH, will be assigned a number in numerical sequence according to the order of presentation. Treatment assignment will be made using a computer-generated randomization schedule. Study medications will be dispensed and the subject will be instructed on application and bathing restrictions.

Visit 2 – After 2 weeks of treatment (15 + 4 days)
Visit 3 – 4 weeks of treatment (29 + 6 days)
Visit 4 – 2 weeks after completion of treatment (43 + 6 days)

The following examinations will be conducted at each visit:

1. The baseline target site will be evaluated as defined in Visit 1.

2. The investigator will provide a global evaluation of the subject's response to treatment by comparing all treated areas with their baseline conditions. The following scale will be used:
   a. Complete – Signs and symptoms present at entry have cleared. Erythema and scaling that is residual in nature and not signs of active disease may be present.
   b. Excellent – Approximately 75% or more improvement in signs and symptoms present at entry, but less than complete improvement.
   c. Good – Approximately 50% or more improvement in signs and symptoms present at entry, but less than 75% improvement.
   d. Fair – Approximately 25% or more improvement in signs and symptoms present at entry, but less than 50%.
   e. Poor – Some improvement in signs and symptoms present at entry, but less than 25%.
   f. Change – Signs and symptoms unchanged from entry.

g. Worse – Signs and symptoms deteriorated from entry.

3. KOH and fungal culture will be done on skin scrapings from the target site.
4. Adverse events will be assessed.
5. Concomitant medications will be reviewed.
6. Compliance will be assessed by collecting used medication tubes and information on the number of missed applications. This will be recorded by an independent observer.

A review of baseline cultures for dermatophytes will be conducted at Visit 3. Those subjects whose cultures were negative at baseline will be dropped from the study after safety evaluations have been performed.

Subjects will be evaluated, when possible, by the same investigator at each study visit. If this is not possible a trained designee will perform the evaluations/tests when the investigator is unable to. Study medication will be dispensed by an independent third-party who is neither performing the clinical nor the laboratory evaluations. The investigator will be blind to the subject's treatment assignment.

Concomitant Medication

The following systemic or topical antifungal medications are not permitted during the course of the study: candicidin, amphotericin B, itraconazole, fluconazole, miconazole, clotrimazole, ketoconazole, oxiconazole, tioconazole, ciclopirox, haloprinogen, terbinafine, toinaftate, griseofulvin, or naftifine. Any other topical foot drug, including OTC antifungals, steroids, and foot powders is prohibited. Systemic steroids or immunosuppressive agents are also forbidden. Use of these products would lead to a subject being dropped from the study.

Subject Withdrawal

Subjects will be removed from the study for the following reasons:

- If the subject withdraws his or her consent for any reason.
- If the subject has a negative culture for specified dermatophytes (*Trichophyton rubrum, Trichophyton mentagrophytes,* or *Epidermophyton floccosum*) or other causative dermatophytes at Visit 3.
- If the subject is classified as a treatment failure (after 2 weeks or more treatment with no improvement).
- If there is a clinically meaningful laboratory abnormality that in the opinion of the investigator prevents continuation.
- If an adverse event occurs for which the subject desires to discontinue treatment or the investigator determines that it is in the subject's best interest to be discontinued.
- If there is a significant protocol violation
- Administrative reasons.

Subjects removed from the study for reasons other than treatment failure, adverse events, or a clinically meaningful laboratory abnormality will be replaced.

> *Medical Officer Note: A number of these criteria were changed but the changes would not result in substantive changes in the remaining cohort.*

Adverse Events

At each visit patients will be asked about any adverse events they have experienced. The event, it's severity and duration, the action taken, and the Investigator's opinion as to drug relatedness will be documented.

Data Analysis

Subject Evaluability Criteria

Evaluable subjects (efficacy) must satisfy the following criteria:

- KOH positive for fungal hyphae at baseline.
- Positive culture for *Trichophyton rubrum, Trichophyton mentagrophytes, or Epidermophyton floccosum* or other causative dermatophytes at baseline.
- Target test site with signs/symptoms score >/=2 for erythema AND >/=2 for either scaling or pruritus at baseline.
- KOH and culture performed after 2 weeks of treatment, 4 weeks of treatment, and 2 weeks post-treatment (Day 43).
- No systemic antifungal or other topical antifungal therapy on the feet during the study and have used no other exclusionary medications.

The primary efficacy parameter is total cure. This is defined as complete cure on the Investigator's global evaluation of all treated areas at Day 43 PLUS mycological cure (negative KOH and culture for dermatophytes) at Day 43.

> *Medical Officer Note: The study report gave two definitions of Total Cure 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 secondary efficacy parameters are the following:

1. The percentage of subjects with complete plus almost complete clinical cure.
2. The percentage of subjects with a mycological cure.
3. The severity of clinical signs and symptoms at the test target site according to a signs and symptoms index score:

- Erythema – redness
- Scaling – scaling
- Maceration – moist, soft, broken-down skin
- Fissuring/cracking – fissuring /cracking
- Pruritus – itching (subject's rating)
- Burning/stinging – burning/stinging (subject's rating)

These signs/symptoms will be rated on the following 0-3 scale:

0 = None (absent)
1 = Mild (slight)
2 = Moderate (definitely present)
3 = Marked (intense, severe)

Medical Officer Note: The sponsor outlined several changes in the planned analyses in the study report. The method for carrying forward missing values for the MITT was further clarified. The sponsor introduced the concept of invalid visits for this population. These included visits outside the prescribed time window (either early or late), and visits after a prohibited medication was taken. In these instances, the last valid observation was carried forward. Since the MITT population is not defined by adherence to the protocol, this method is not appropriate. Only missing visit data should be substituted by carrying the last observation forward.

Analysis Populations

Two populations will be evaluated for efficacy:

1. Per Protocol population– This will consist of all randomized subjects who met all inclusion/exclusion criteria, had a positive confirmatory baseline fungal culture, complied with the minimum treatment course, had data for all three major efficacy variables (i.e., KOH preparation, fungal culture, and Investigator's Global Evaluation of Clinical Response to Treatment), returned to the investigative site for Visit 4 within the specified window (i.e., Day 43 + 6) unless dropped due to either a treatment failure or an adverse event, and did not have any protocol violations.

2. Modified-Intent-to-Treat population – This will consist of all randomized subjects who met inclusion/exclusion criteria, received at least one dose of study medication, and returned for at least one post-baseline visit. The Last Observation Carried Forward (LOCF) approach will be used for missing/invalid visits only for subjects discontinuing due to treatment-related adverse events or treatment failures. When no post-baseline data is available, data from Visit 1 will not be carried forward.

The Safety Population will consist of all subjects who received at least one dose of study medication.

Efficacy Analyses

The sponsor will compare the test and reference products in their proportions of total cures at Week 6 (Day 43). A one-sided 95% confidence interval of the difference in total cure will be constructed, and equivalence will be concluded if the lower limit of the confidence interval is no less than 20% the proportion of total cure rate in the Spectazole ® group.

Medical Officer Note: A two-side confidence interval should be constructed and the confidence interval must be contained within the +0.2, -0.2 interval.

Medical Officer Note: The Sponsor made this change.

Separate comparisons of the vehicle with the two active compounds (test and reference) will be carried out for the differences in proportions of total cures at Week 6. The Cochran-Mantel-Haenszel test, stratified by center, will be used at the 0.05 alpha level using a two-tailed test. Site and investigator differences will be examined using this test and the Breslow-Day tests. Secondary analyses will include the proportion of total cures at all study visits, individual analyses of investigator's assessments of all treated areas, and KOH and fungal culture results at all study visits. These analyses will compare the test and reference and the two actives to the vehicle. Subgroup analyses of the total cure outcome will also be carried out using logistic regression models. Possible subgroups include age, sex, race, and baseline disease status categories.

Safety comparisons will be made by summarizing the occurrence of adverse events by event and body system and tabulating severity and relationship to study medication.

SUBMITTED STUDY REPORT

Study Objectives

1. To establish the therapeutic equivalence of econazole nitrate 1% cream (Altana, Inc.) applied once daily to Spectazole® Cream 1% (Ortho McNeil Pharmaceuticals) applied once daily in the treatment of tinea pedis.

2. To determine whether Spectazole® Cream 1% and its generic equivalent are significantly different form the econazole vehicle base in antifungal properties and/or safety.

Study Design

This was a multicenter, vehicle-controlled, randomized, parallel-group study that compared the following three treatment regimens:

1. Econazole nitrate 1% cream (Altana, Inc.), test drug, Lot # C660
2. Econazole nitrate 1% cream (Ortho-McNeil Pharmaceuticals), reference drug, Lot # 29G801
3. Vehicle control (Altana, Inc.), Lot # C673

applied once daily for 28 days.

Study Centers

The study was conducted at 13 centers listed below:

Site #	Principal Investigator	Location	# Enrolled/Evaluable
1	Dr. Clyde M. Caperton	Bryan, TX	50/30
2	Dr. Steven Davis	San Antonio TX	25/17
3	Dr. Stephen Huffman	Wenatchee WA	30/18
4	Dr. Terry Jones	Huntsville TX	16/ 7
5	Dr. Lewis H. Kaminester	North Palm Beach, FL	51/27
6	Dr. David L. Kaplan	Overland Park KS	45/26
7	Dr. H. Irving Katz	Fridley MN	36/29
8	Dr. Anne W. Lucky	Cincinnati OH	8/ 6
9	Dr. Lawrence C. Parish	Philadelphia PA	14/10
10	Dr. Phoebe Rich	Portland OR	32/18
11	Dr. David Rodriguez	Miami FL	60/43
12	Dr. Ronald Savin	Hartford CT	50/37
13	Dr. Daniel M. Stewart	Clinton Township MI	30/23

Blinding and Randomization

The three creams were identical in color and consistency. They were packaged in tubes covered with black opaque plastic. The tear-off portion of the label had the drug product identity under an opaque scratch-off cover and an adhesive backing. This was adhered to the patient's CRF. Patients were consecutively assigned to treatment groups by a computer-generated randomization list.

RESULTS

Study Population

A total of 447 patients were enrolled and randomized, 178 were in the test arm, 181 in the reference arm, and 88 in the vehicle arm. Table I lists the safety, MITT, and per protocol populations and the exclusions and reasons for exclusion from the MITT and per protocol populations, according to the Sponsor.

Table I
Subject Distribution in Analysis Populations

Population	Test	Reference	Vehicle	Total
Enrolled	178	181	88	447
Safety	178	181	88	447
MITT	136	129	62	327
Exclusions				
Negative fungal culture	38	47	23	108
Non compliance	2	0	2	4
Lost to follow-up	2	5	1	7
Admin/Other	0	0	0	0
Total	42	52	26	120
Per Protocol	120	114	57	291
Exclusions				
Negative fungal culture	38	47	23	108
Non-compliance w protocol	16	13	7	36
Lost to follow-up	4	6	1	11
Admin/Other	0	1*	0	1
Total	58	67	31	156

* This patient withdrew consent after receiving study drug.

Review of the exclusions from both analysis populations did not reveal major discrepancies compared to the sponsor's allocations. Patient 06-002, however, was not included in the per protocol population because they received less than 14 days of treatment and was noted to have an insufficient therapeutic response. This patient was listed as a withdrawal because of the insufficient therapeutic response and should therefore be included in all analysis populations as a treatment failure.

> *Medical Officer Note: Patient #06-002 was listed as a withdrawal because of an insufficient therapeutic response and should therefore be included in all analysis populations as a treatment failure.*

Baseline Demographics and Disease Manifestations

Baseline demographics and symptoms/signs were similar for each treatment group in both the MITT and per protocol populations.

Efficacy and Bioequivalence Analyses

The primary endpoint was Total Cure. This was a composite score including Clinical Cure and Mycological Cure. Although the sponsor used two definitions for Clinical Cure,

only their Definition 1 is the accepted definition for cure in this condition. The sponsor did not specify why they used the second definition and it is presumed to be because the usual definition did not meet the criteria for bioequivalence. The primary outcomes using Definition 1 are presented below in Table II.

Table II
Total Cure Rates

Total Cure Rate	Test	Reference	Vehicle	p-value	90% CI
MITT population	55.1%	42.2%	14.5%	T or R vs. V <0.001	
PP Population	54.6%	43.4%	14.5%	T/R = 0.051	-0.49, +22.02

Both active drug products were shown to be more efficacious than the vehicle. However, the test and reference drug did not meet bioequivalence criteria.

Safety

Fifty patients experienced 66 adverse events during the study. These are categorized by severity and relationship to study drug in Table III. The two events classified as severe were back pain and a toothache. Most adverse events were intercurrent illnesses, accounting for 58 events. Only 3 were thought to possibly have a relationship to the study drug. These three were described as follows: burning sensation, depression, and contact dermatitis.

Table III
Adverse Events by severity and relationship to study drug

	Test	**Reference**	**Vehicle**
Severity			
Any	20 (11%)	27 (15%)	8 (9%)
Mild	16	11	0
Moderate	21	8	2
Severe	6	2	0
Relationship to study drug			
# Patients/# events	20/27	27/31	8/8
Intercurrent illness	24	26	8
Remote	2	3	0
Possible	1	2	0
Probable	0	0	0

Conclusion

This study fails to demonstrate bioequivalence between econazole nitrate 1% cream (Altana, Inc.) and Spectazole® Cream 1% (Ortho McNeil Pharmaceuticals) in the treatment of tinea pedis.

Mary M. Fanning, MD, PhD
Associate Director for Medical Affairs
Office of Generic Drugs