CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-422

BIOEQUIVALENCE REVIEW(S)

JUN 8 2004 DIV

REVIEW OF A BIOEQUIVALENCE STUDY WITH CLINICAL ENDPOINTS

ANDA	**76-422**
Drug Product:	Ciclopirox Lotion (Ciclopirox Olamine Topical Suspension USP, 0.77%)
Sponsor:	Altana Inc.
Reference Listed Drug:	Loprox® Lotion (Ciclopirox), 0.77%, Medicis, NDA 19824
Reviewer:	Carol. Y. Kim, Pharm.D.
Submission dates:	August 5, 2002 and February 2, 2004
Review date:	June 4, 2004

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I. Introduction

Loprox® Lotion is a broad-spectrum synthetic anti-fungal agent indicated for the topical treatment of tinea pedis, tinea cruris and tinea corporis caused by *Trichophyton rubrum, T. mentagrophytes, Epidermophyton floccosum and Microsporum candies;* in the treatment of cutaneous candidiasis (moniliasis) caused by *Candida albicans; and tinea (pityriasis) versicolor caused by Malasseszia furfur.* The patient is instructed to gently massage the lotion into the affected and immediate surrounding area twice daily. If a patient shows no clinical improvement after 4 weeks of treatment, the approved labeling recommends that the diagnosis be re-evaluated.

Tinea Pedis

Tinea Pedis is a dermatophytic infection of the feet, characterized by erythema, chronic diffuse desquamation, and /or bulla formation. *T. rubrum* is the most common cause of chronic tinea pedis and *T. mentagrophytes* causes more inflammatory lesions. Once established, the individual becomes a carrier and is more susceptible to recurrences[1]. The demonstration of hyphae on direct microscopy and isolation of dermatophyte on fungal culture confirm the diagnosis.

II. Background

The following protocols/Bio-INDs and control documents have been previously reviewed by the OGD for ciclopirox:

Submission Date	IND/Protocol Number	Drug Product (Sponsor)
August 14, 2002	CD# 02-472	Ciclopirox Gel, 0.77% (Altana)
June 6, 2000	IND 15-322	Ciclopirox Olamine Cream, 1% (Altana)
October 31, 2000	IND 15-328	Ciclopirox Olamine Lotion, 1% (Altana)

[1] Habif, Thomas. Clinical Dermatology: A Color Guide to Diagnosis and Therapy (3rd edition, 1996), p. 366.

III. Study Information

Protocol Number: ALT 00-0314-05

The OGD medical officer has accepted the sponsor's original protocol (IND 15-328/ #ALT 00-0314-05) and commented on January 8, 2001 that >50% of patients should have fungal cultures positive for *Trichophyton rubrum* since it is the most commonly infecting organism for *T. pedis*.

The sponsor has re-organized and submitted updated clinical study report on April 25, 2003. Per sponsor's request, only the updated version of clinical study report (April 18, 2003) organized by ———— was reviewed.

Title: A Multi-center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study to Determine the Therapeutic Equivalence of Two Ciclopirox Olamine 1% Formulations in the Treatment of Interdigital Tinea Pedis.

Reviewer's Comments: *Ciclopirox Olamine 1% is the same as Ciclopirox 0.77% (w/w). The USP defined topical suspensions as "liquid preparations containing solid particles dispensed in a liquid vehicle, intended for application to the skin" and reclassified some products previously labeled as "lotions" into this category. Therefore, to be consistent with the USP defined nomenclature classification, the sponsor identified their chemical name as ciclopirox olamine topical suspension, USP. Since the established name for their product is a topical lotion, it was used to identify the test product in this review.*

Objectives:

1. To evaluate the safety and therapeutic equivalence of a test product of ciclopirox olamine lotion, 1% (Altana Inc.) to Loprox® ciclopirox olamine lotion 1% (Medicis Pharmaceutical Corporation)
2. To evaluate its efficacy over its vehicle (placebo) in the treatment of interdigital tinea pedis.

Study Design:

A multi-center, double-blind, randomized, parallel group, placebo-controlled study comparing Altana's ciclopirox olamine lotion to Medicis pharmaceutical Corporation's Loprox® Lotion in patients with interdigital tinea pedis. Enrolled patients were randomized in a 2:2:1 ratio to receive one of 3 treatments twice daily for 28 days (4 weeks):

1. Test Product Group: Ciclopirox Olamine 1% (Altana, Inc.), Lot # E800
2. Reference Group: Loprox® Lotion (ciclopirox olamine) 1%, Lot # 01807
3. Placebo/Vehicle Group: Vehicle without active drug (Altana, Inc.), Lot # E983

Reviewer's Comments: *According to the medical officer's review of NDA 19-824 (9/14/88), Loprox® Lotion showed its effectiveness in the treatment for interdigital types of tinea pedis when caused by organisms such as Trichophyton rubrum, T. mentagrophytes, and Epidermophyton floccosum. In one placebo controlled study (Study 301A), the clinical results obtained from the*

plantar type of tinea were separately analyzed. Patients with plantar involvement showed little difference in response rate between the active and placebo lotion. This was an expected outcome because plantar type of tinea pedis is known to be more difficult to treat. The OGD medical officer has previously accepted this sponsor's protocol using interdigital tinea pedis patients for conducting a bioequivalence study with clinical endpoints.

Study Population:

Inclusion Criteria

Patients who satisfied ALL the following criteria were enrolled in the study:

1. Males and females at least 12 years of age with parental consent for patients 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, and 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 toe 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) at the same target site.
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 from the target test site.
5. A positive KOH result at study entry. Patients subsequently were to 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 were not positive for *Trichophyton rubrum*, *Trichophyton mentagrophytes*, or *Epidermophyton floccosum* or other causative dermatophytes.
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 patient 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 ability to complete the study as specified in the protocol.

Exclusion Criteria

Patients who satisfied ANY of the following criteria were excluded from the study:

1. Pregnancy or lactation.
2. Uncontrolled diabetes, peripheral vascular disease, neuropathy of the feet, or any significant medical conditions likely to compromise participation in the study or place the patient 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. Patient 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. Known 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 ciclopirox olamine or any components of the test medications.
12. Previous enrollment in this study.
13. Use of any topical antifungal therapy to the feet within 2 weeks before entry into the study.
14. Use of any systemic antifungal or systemic corticosteroid treatment within 2 months before entry into the study.
15. Use of any systemic antibiotic within 30 days before entry into the study.
16. Use of any topical steroid treatment at the infection site within 30 days before entry into the study.
17. Use of radiation therapy and/or anti-neoplastic agents during or within 12 weeks before entry into the study.
18. Treatment with Ciclopirox olamine or an investigational drug within 30 days before entry into the study.

Criteria for removal of patients from the study

Patients were removed from the study for any of the following reasons:

1. If the patient withdrew his or her consent for any reason;
2. If the investigator determined that it was in the patient's best interest to be discontinued in the event of intercurrent illness, adverse events, protocol violation, or other reasons;
3. Patients who in the investigator's opinion failed to respond to treatment or appeared to be worsening were discontinued.

Reviewer's Comment: *Patients that were discontinued by the investigator due to worsening of condition or lack of response should be included in the evaluable population as treatment failures.*

Study Procedures:

Baseline Visit (Visit 1): Day 1

- Evaluated for eligibility and obtained written informed consent. If the patient was less than 18 years of age, parental consent was obtained.
- Performed physical examination and collected medical/medication history.
- An initial foot examination and severity of infection were rated. Severity of clinical signs were evaluated by the investigator and clinical symptoms were evaluated by the patient as either "0=none (absent)", "1=mild (slight)", "2=moderate (definitely present)", or "3=severe (marked, intense)".
- Skin scrapings from the primary site were collected and used for KOH mounts and fungal cultures.
- If patient had bipedal infection, the investigator designated the most severely affected toe web as the targeted test site.
- A urine pregnancy test was obtained for a female with child-bearing potential.
- The study medications were dispensed and selected patients were instructed to apply them twice daily for 28 days.
- The first dose of study medication was applied under the supervision of a third-party dispenser who was not performing clinical evaluations. Patients were instructed to apply the study medication to all four interdigital toe webs of both feet twice a day for 28 consecutive days. Patients were also instructed not to bathe, shower, swim, or wash the treated areas for at least 4 hours after the application of study medication.

Interim Visit (Visit 2, Day 15 +4):

- Patients returned to the facility 2 weeks (15 + 4 days) after the baseline visit. On this day, the following procedures were performed:

  -Foot exam: clinical signs and symptoms assessment
  -Mycological examination: KOH and Fungal culture
  -Adverse Event (AE) monitoring
  -Concomitant medication monitoring
  -Medication Compliance check
  -Investigator's Global Assessment (IGE)

End-of-Treatment Visit (Visit 3; end of 4 weeks of treatment, Day 29 +6 days)

- Patients with baseline culture positive for dermatophyte(s), including *Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton Floccosum*, and others identified as causative deramatophytes by the laboratory were to return to the clinical facility 4 weeks (+6 days) after the screening visit. If baseline cultures failed to grow a dermatophyte, the patient was discontinued from the study at this visit. During this visit, the following procedures were performed:

-Foot exam: clinical signs and symptoms assessment
-Mycological examination: KOH and Fungal culture
-Adverse Event (AE) monitoring
-Concomitant medication monitoring
-Medication Compliance check
-Investigator's Global Assessment (IGE)

Follow-Up Visit (Visit 4; 2 weeks post treatment, Day 43 +6 days)

- Patients returned to the facility two weeks (+6 days) after the end-of-treatment visit. During this visit, the following procedures were performed:

-Foot exam: clinical signs and symptoms assessment
- Mycological examination: KOH and Fungal culture
-Adverse Event (AE) monitoring
-Concomitant medication monitoring
-Investigator's Global Assessment (IGE)
-Discharge from the study

Efficacy Evaluations

Foot Assessment

Clinical signs and symptoms [Screening/Visit 1 (Day 1), Visit 2 (Day 15), Visit 3 (Day 29), and Visit 4 (Day 43)]

Each clinical sign and symptom [1) Erythema (redness), 2) Scaling, 3) Maceration (moist, soft, broken-down skin), 4) fissuring/cracking at the target test site, 5) pruritus (itching by patient's rating) and 6) burning/stinging (by patient's rating)] was evaluated using the following 4-point scale:

0	None (absent)
1	Mild (slight)
2	Moderate (definitely present)
3	Severe (marked, intense)

Investigator's Global Evaluation (IGE): at all three post-baseline visits [Visit 2 (Day 15), Visit 3 (Day 29) and Visit 4 (Day 43)]

The investigator rated the condition of the target test site compared to baseline using the following 7-point IGE scale:

6=Complete cure (signs and symptoms present at entry have cleared. Erythema and scaling that are residual in nature and no signs of active disease may be present.)
5=Excellent (approximately 75% or more improvement in signs and symptoms present at entry, but less than complete improvement)

4=Good (approximately 50% or more improvement in signs and symptoms present at entry, but less than 75% improvement)
3=Fair (approximately 25% or more improvement in signs and symptoms present at entry, but less than 50% improvement)
2=Poor (some improvement in signs and symptoms present at entry, but less than 25 % improvement)
1=No Change (signs and symptoms unchanged from entry)
0=Worse (signs and symptoms deteriorated from entry)

Reviewer's Comment: *Investigator's Global Evaluation (IGE) similar to Physician Global Assessment should be a static description, not based on change from baseline. However, the category of "complete" used in this sponsor's evaluated primary endpoint is acceptable because it is considered the same as "clear" in a static score.*

Mycology

- Scraping was obtained from the target site on the following days: Baseline Visit (Day 1), Visit 2 (Day 15), Visit 3 (Day 29) and Visit 4 (Day 43)
- If the baseline KOH result was positive for hyphae on Day 1, the patient was enrolled into the study and a culture plate was inoculated with material from the same scraping. The culture was then sent to the mycology laboratory for speciation. To be included in the efficacy analysis, the baseline cultures should be positive *for Trichophyton rubrum, T. mentagrophytes, Epidermophyton floccosum or another causative dermatophyte.* Patient with baseline culture that failed to grow a dermatophyte was discontinued from the study at Day 29. Scrapings were taken at all post-baseline visits for KOH test and culture, even if the web had completely healed.

Concomitant medication use

1. Use of any systemic or topical antifungal medications, such as candicidin, amphotericin B, itraconazole, fluconazole, miconazole, clotrimazole, ketoconazole, oxiconazole, tioconazole, econazole, haloprinogen, terbinafine, tolnaftate, griseofulvin, or naftifine, was not permitted for the entire duration of the study. If treatment with any of these agents was required, the patient was dropped from the study.
2. Use of any other topical drug to the feet, including OTC antifungals, steroids, and foot powders, was prohibited during the study;
3. No systemic steroids or immunosuppressive agents were permitted;
4. Medications that may affect the course of tinea pedis were not permitted;
5. No medication, emollients, or treatment other than the study medications were to be applied to the treated areas.

Treatment Compliance

If a patient missed more than 6 consecutive applications or more than 12 total applications of study medication, the patient was discontinued from the study for non-compliance, and excluded from the per-protocol population.

Sample Size

The sample size of 445 patients were planned to obtain 288 evaluable patients, 115 in each active arm and 58 in the vehicle group. This sample size was to yield 80% power for a two-tailed alpha=0.05 comparison of the difference of two proportions. The sponsor estimated total cure of approximately 50% for their product versus not greater than 25% for the vehicle.

Data Evaluated by the Sponsor

Primary endpoint

1) The primary efficacy endpoint was a **total cure rate** in the Per Protocol Population (PP) defined as follows:

> **Total Cure**- Both Clinical cure (evidenced by IGE of "Complete") and Mycological Cure (both KOH and culture negative for dermatophytes) at Visit 4 (Day 43, 2 weeks post-treatment)

2) The test for sensitivity of the study to show a difference between products over the vehicle using the total cure at Day 43 (MITT) also should be demonstrated.

Secondary Endpoints

-Total cure rate at Visit 3 (Day 29)
-Clinical cure rate at Visit 3 (Day 29) and Visit 4 (Day 43)
-Mycological cure rate at Visit 3 (Day 29) and Visit 4 (Day 43)
-Signs and symptoms scores at Visit 3 (Day 29) and Visit 4 (Day 43)
-Investigator's Global Evaluation at Visit 3 (Day 29) and Visit 4 (Day 43)

Visit Window

The sponsor used the following visit window conventions for primary and secondary endpoints efficacy variables:

Visit	Target Day	Window
2	15	15 days to 19 days, inclusive
3	29	29 days to 35 days, inclusive
4	43	43 days to 49 days, inclusive

Reviewer's comments:

- *This study includes the accepted primary endpoint for the treatment of tinea pedis, total cure, defined as both clinical cure and mycological cure, at 2 weeks post-treatment.*
- *The OGD has previously accepted a clinical cure using Physician's Global Assessment rating of "complete", allowing for slight residual erythema, OR a total clinical signs and symptoms score of 2 or less with a severity of 1 or less for any individual signs and symptoms. However, the preferred definition of clinical cure is the more objective total signs and symptoms score of 2 or less with a severity of 1 or less for any individual signs and symptoms.*

- *Patients are considered as mycological cure if both KOH and culture results are negative for dermatophytes.*
- *Therefore, patients are considered as total cure if they are both clinical cure (evidenced by total signs and symptoms scores) and mycological cure (both KOH and culture negative for dermatophytes).*
- *The test and reference drug products must also be superior to placebo ($p<0.0$) in the MITT population) to demonstrate that the study is sufficiently sensitive to discern a difference between products*

Statistical Analyses

For the bioequivalence analysis, a 90% CI was constructed for the difference in the proportions of total cures between the test and reference products at Day 43. The interval was calculated using Wald's method with Yates' continuity correction. Bioequivalence was established if this 90% CI was contained within the interval of (-20%, +20%). The analysis in the PP population was considered primary and that in the MITT population as supportive.

The test for superiority of each active treatment over the vehicle (placebo) was based on the proportions of total cures at Day 43. These tests were conducted using two-sided Z-tests with Yates' continuity correction at the 0.05 level of significance. The analyses in the MITT population were considered primary and those in the PP population as supportive.

IGE scores and individual clinical signs and symptoms scores were analyzed using a CMH row mean score test, adjusting for site. The total scores for signs and symptoms were analyzed by two-way ANOVA or Friedman's test with factors of treatment and site.
For the total score of signs and symptoms, Friedman's test with factors of treatment and site was used instead of two-way ANOVA as initially proposed.

Reviewer's comment: *The FDA statistical consultation was requested to verify the sponsor's analysis.*

IV. RESULTS

The investigators, staff at the study sites, study monitors, and data management personnel were blinded to the patient assignment. Initial statistical analyses were performed by ——— and subsequent statistical re-analyses were performed by ——— on unblinded data. Only the updated clinical/statistical reports organized by ——— were reviewed.

On January 23, 2004, this reviewer asked the sponsor to provide a list of patients enrolled for each site and a copy of Case Report Form (CRF) for nine patients. The sponsor provided the requested items in the study amendment dated February 2, 2004.

CRO: ———

Study Sites: A list of 13 study sites is shown below.

Site Number	Number of patients enrolled (total=450)	Principal Investigator	Location
#01	34	, DPM	
#02	60	, MD	
#03	60	MD	
#04	60	MD	
#05	40	MD	
#06	17	MD, PhD	
#07	*	, MD	
#08	9	, MD	
#09	30	MD	
#10	27	MD	
#11	30	, MD	
#12	7	DO	
#13	30	, MD	
#14	46	, MD	
		MD	

*In the sponsor's study report, this site was listed as one of the clinical sites. However, in their electronic dataset, the sponsor did not provide any patient data from this site. A total number of patients at enrollment were reported as 450 patients, which is consistent with the sponsor's electronic data excluding site #7. See study amendment dated 2/2/04 for details.

Study Period: January 16, 2001 to November 19, 2001

Cohort

A total of 450 patients were enrolled into the study. One patient (#69) in the reference group did not apply the study medication. All other 449 patients were treated with the study medication: 180 with Altana's Ciclopirox Lotion, 179 with Loprox® Lotion, and 91 with Vehicle. The sponsor's analysis of patient enrollment (Table I) and patient discontinuation by reason (Table II) are shown below in details.

Table I: Patient Enrollment (per sponsor)

	Generic	Loprox®	Vehicle
Subjects Enrolled	180	179	91
Subjects Excluded from Intent-to-Treat Analysis	0 (0%)	1 (1%)	0 (0%)
Subjects Included in Intent-to-Treat Analysis[1]	180 (100%)	178 (99%)	91 (100%)
Subjects Excluded from Modified Intent-to-Treat Analysis	43 (24%)	39 (22%)	21 (23%)
Subjects Included in Modified Intent-to-Treat[2] Analysis	137 (76%)	140 (78%)	70 (77%)
Subjects Excluded from Per-Protocol Analysis	75 (42%)	65 (36%)	39 (43%)
Subjects Included in Per-Protocol Analysis[3]	105 (58%)	114 (64%)	52 (57%)

[1]All patients enrolled into the study and applied at least one dose
[2]All patients enrolled who met all entry criteria, including identification of a qualifying dermatophyte at baseline and had at least one post-baseline visit.
[3]All patients in the MITT who completed all protocol requirements or discontinued due to treatment failure. Patients should have data for all three major efficacy variables for Visit 3 and Visit 4 (i.e., KOH Preparation, fungal culture, and Investigator's Global Evaluation of Clinical Response to Treatment) unless discontinued due to adverse event at any time or treatment failure after receiving at least two weeks of study medication. Patient should be returned to the study site for Visit 3 (Day 29 + 6) and Visit 4 (Day 43 + 6) within the specified window unless discontinued due to adverse event at any time or treatment failure after receiving at least two weeks of study medication. Patients should not miss more than 6 consecutive applications of study medication and not miss more than 12 total applications.

Table II: Patient Discontinuations by Reason (per sponsor)

	Treatment		
	Generic	Loprox®	Vehicle
Number Randomized	180	179	91
Number Completed Study	133 (74%)	135 (75%)	67 (74%)
Number Discontinued	47 (26%)	44 (25%)	24 (26%)
LACK OF FUNGAL PATHOGEN AT BASELINE	36 (20%)	34 (19%)	17 (19%)
ADVERSE EVENT	0 (0%)	0 (0%)	0 (0%)
INSUFFICIENT THERAPEUTIC RESPONSE	0 (0%)	1 (1%)	1 (1%)
PROTOCOL VIOLATION	1 (1%)	1 (1%)	2 (2%)
LOST TO FOLLOW-UP	6 (3%)	4 (2%)	1 (1%)
ADMINISTRATIVE/OTHER	4 (2%)	4 (2%)	3 (3%)

Reviewer's Comments:

1. *The sponsor excluded six patients [T: 158 (5), 389 (5), 396 (5), 310 (9); Ref: 382 (5), 042 (10)] from the PP population because they received systemic antibiotics. The primary endpoint evaluation considers the outcome of the mycological cure in addition to the clinical response. The systemic effect of short-term antibiotic use in the course of tinea*

pedis is minimal. This reviewer concludes that the possible effect of antibiotics on the study outcome is not likely to be clinically significant. Therefore, including these patients into the evaluable population should not confound the study outcome. However, since this was specified in the protocol and has been consistently followed, it is acceptable to exclude these patients.

2. *The following nine patients were excluded by the sponsor due to 1) missing visit 3 data, 2) out of visit window at visit 3 or 3) missing result for three major efficacy variables for visit 3 or 4:*

Test	Ref	Vehicle
292 (01)	490 (12)	117 (01)
486 (12)		209 (13)
203 (13)		
204 (13), 350 (13), 122 (9)		

Since efficacy variables for visit 4 (primary endpoint) were available within accepted visit window and no other significant protocol violation was noted, they should be included in the evaluable population.

3. *Two patients in the reference group used prohibited medications but the sponsor included them in the PP population. Patient #005 (06) used Elocon® Cream for treatment of hand eczema, not related to tinea pedis, between Visit 1 and 2. Patient #304 (09) received clotrimazole for 3-day treatment of yeast infection between Visit 2 and 3. Since short-term use of these products for disease condition not related to tinea pedis is not likely to change the outcome of the study, this reviewer agrees with the sponsor's decision to include them in the evaluable population.*

4. *Two patients discontinued the study due to insufficient therapeutic response [R: 335 (14); V: 95 (14)]. Since they discontinued the study due to lack of effect, they should be considered as treatment failures at visit 4.*

5. *The sponsor excluded patient #474 (site 8, vehicle) due to missing three major efficacy variables for visit 3 or visit 4. Upon further examination of CRF, this reviewer noted that this patient discontinued the study after completing visit 3 due to not receiving benefit from the study treatment. This patient was compliant up to visit 3. Therefore, this patient should be considered as a treatment failure and included in the evaluable population at visit 4.*

6. *The sponsor also excluded patient #208 (site 13, reference) due to violation of inclusion criteria. This patient used condom without spermicide when the appropriate method of birth control was specified in the inclusion criteria as "condom with spermicide". Since this female patient's urine pregnancy test was negative at baseline and she completed visit 4 without any further known protocol violation, not accompanying spermicide for method of birth control is not likely to change the outcome of the study. Therefore, she should be included in the evaluable population.*

Demographics

One hundred forty three (143) females and 307 males were enrolled in the study. Baseline demographics, age, gender, and race were comparable and not statistically significant in all treatment groups. In the sponsor's reported ITT population, the majority of patients were Caucasian (58%); 62 patients were Black (14%), 3 patients were Asian (0.7%), 1 patient was Native American (0.2%), and 122 patients were of other races (27%). See Table III for the sponsor's analysis in details.

Table III ***Demographic Characteristics for Intent-to-Treat Patients***

Parameter		Generic (N=180)	Loprox® (N=178)	Vehicle (N=91)	p-value
Gender (n,%)	Male	123 (68%)	123 (69%)	60 (66%)	0.849[1]
	Female	57 (32%)	55 (31%)	31 (34%)	
Race (n,%)	CAUCASIAN	104 (58%)	104 (58%)	53 (58%)	0.095[1]
	BLACK	29 (16%)	24 (13%)	9 (10%)	
	ASIAN	0 (0%)	3 (2%)	0 (0%)	
	NATIVE AMERICAN	0 (0%)	0 (0%)	1 (1%)	
	OTHER	47 (26%)	47 (26%)	28 (31%)	
Age (years)	Mean ± SD	40.8 ± 16.0	39.8 ± 15.4	39.3 ± 16.8	0.761[2]
	Min - Max	12 - 85	12 – 83	12 - 78	
Weight (lbs)	Mean ± SD	182.0 ± 41.6	179.0 ± 37.6	180.6 ± 43.3	0.988[2]
	Min - Max	106.0 - 325.0	70.0 - 290.0	95.0 - 290.0	
Height (inches)	Mean ± SD	67.5 ± 3.7	67.6 ± 3.8	67.6 ± 4.1	0.921[2]
	Min - Max	58.0 - 77.0	56.0 - 75.0	60.0 - 76.0	

[1] P-values for treatment comparisons from Cochran-Mantel-Haenszel test for general association, adjusted for site.
[2] P-values for treatment comparisons from Friedman's test with factors of treatment and site.

Baseline signs and symptom scores

Baseline total signs and symptom scores for the MITT population analyzed by the sponsor are shown below in Table IV. Based on the sponsor's analysis, they were comparable in all three study groups and not shown to be statistically significant.

Table IV: Baseline Evaluation of Clinical Signs and Symptoms at the Target Test Site and Mycology Results for Modified Intent-to-Treat Patients

Characteristic		Generic (N=137)	Loprox® (N=140)	Vehicle (N=70)	p-value
ERYTHEMA	NONE	0 (0%)	0 (0%)	0 (0%)	0.334[1]
	MILD	0 (0%)	0 (0%)	0 (0%)	
	MODERATE	115 (84%)	125 (89%)	61 (87%)	
	SEVERE	22 (16%)	15 (11%)	9 (13%)	
SCALING	NONE	0 (0%)	1 (1%)	0 (0%)	0.874[1]
	MILD	2 (1%)	5 (4%)	1 (1%)	
	MODERATE	86 (63%)	85 (61%)	42 (60%)	
	SEVERE	49 (36%)	49 (35%)	27 (39%)	
MACERATION	NONE	52 (38%)	56 (40%)	37 (53%)	0.087[1]
	MILD	46 (34%)	50 (36%)	20 (29%)	
	MODERATE	31 (23%)	24 (17%)	12 (17%)	
	SEVERE	8 (6%)	10 (7%)	1 (1%)	
FISSURING/ CRACKING	NONE	62 (45%)	65 (46%)	39 (56%)	0.401[1]
	MILD	39 (28%)	44 (31%)	20 (29%)	
	MODERATE	31 (23%)	28 (20%)	9 (13%)	
	SEVERE	5 (4%)	3 (2%)	2 (3%)	
PRURITUS (SUBJECT'S RATING)	NONE	6 (4%)	13 (9%)	7 (10%)	0.331[1]
	MILD	24 (18%)	17 (12%)	13 (19%)	
	MODERATE	72 (53%)	80 (57%)	37 (53%)	
	SEVERE	35 (26%)	30 (21%)	13 (19%)	
BURNING/ STINGING (SUBJECT'S RATING)	NONE	51 (37%)	60 (43%)	30 (43%)	0.826[1]
	MILD	40 (29%)	31 (22%)	16 (23%)	
	MODERATE	34 (25%)	34 (24%)	17 (24%)	
	SEVERE	12 (9%)	15 (11%)	7 (10%)	
Total Signs and Symptoms	Mean ± SD	9.4 ± 2.7	9.0 ± 2.5	8.6 ± 2.8	0.276[2]
	Min - Max	5.0 - 16.0	5.0 - 15.0	4.0 - 15.0	
Organism(s) Isolated	T. rubrum	116 (85%)	110 (79%)	61 (87%)	
	E. floccosum	7 (5%)	13 (9%)	4 (6%)	
	T. mentagrophytes	15 (11%)	17 (12%)	5 (7%)	
	Other causative dermatophytes	0 (0%)	0 (0%)	0 (0%)	

[1] P-values for treatment comparisons from Cochran-Mantel-Haenszel test, adjusted for site.
[2] P-value for treatment comparison from Friedman's test with factors of treatment and site.

Reviewer's Comment: *The baseline individual and total signs and symptom scores for the MITT population were comparable in all three study groups. The sponsor's reported baseline characteristics for the PP population were also similar and comparable in all three study groups.*

Fungal Culture

The majority of patients had the baseline fungal culture positive for *Trichophyton rubrum* (82%) in the sponsor's PP population analysis. The other dermatophytes isolated were *Epidermophyton Floccosum* (6.2%) and *T. Mentagrophytes* (11.8%).

Efficacy/Bioequivalence

The sponsor's evaluated primary endpoint is a total cure, clinical cure using IGE of "complete" plus mycological cure (both KOH and culture negative), at Visit 4 (Day 43). The sponsor's statistical analyses for the PP and MITT populations are shown in Table V and VI.

TableV: Primary Efficacy Analysis: Total Cure Rate at Visit 4 (Day 43)

	Generic	Loprox®	Vehicle	90% CI for Bioequivalence of Generic to Loprox®	P-value for Generic vs. Vehicle	P-value for Loprox® vs. Vehicle
Per-Protocol Subjects (n,%)						
Visit 4	(N=105)	(N=114)	(N= 52)			
Cured	42 (40%)	38 (33%)	2 (4%)	(-4.95%, 18.29%)[1]	<0.001[2]	<0.001[2]
Not Cured	63 (60%)	76 (67%)	50 (96%)			
Modified Intent-to-Treat Subjects (n,%)						
Visit 4	(N=137)	(N=140)	(N= 70)			
Cured	53 (39%)	48 (34%)	2 (3%)	(-5.83%, 14.63%)[1]	<0.001[2]	<0.001[2]
Not Cured	84 (61%)	92 (66%)	68 (97%)			

[1]Total Cure = Complete cure by the Investigator's Global Evaluation of all treated areas plus mycological cure (negative KOH and culture for dermatophytes).
Confidence interval calculated using Wald's method with Yates' continuity correction.
[2]P-values for treatment comparisons from two-sided Z-test with Yates' continuity correction.

Table VI: Secondary Efficacy Analysis: Total Cure Rate at Visit 3 (Day 29)

	Generic	Loprox®	Vehicle	90% CI for Bioequivalence of Generic to Loprox®	P-value for Generic vs. Vehicle	P-value for Loprox® vs. Vehicle
Per-Protocol Subjects (n,%)						
Visit 3	(N=105)	(N=114)	(N= 52)			
Cured	16 (15%)	19 (17%)	2 (4%)	(-10.48%, 7.63%)[1]	0.065[2]	0.040[2]
Not Cured	89 (85%)	95 (83%)	50 (96%)			
Modified Intent-to-Treat Subjects (n,%)						
Visit 3	(N=137)	(N=140)	(N= 70)			
Cured	24 (18%)	25 (18%)	2 (3%)	(-8.60%, 7.93%)[1]	0.005[2]	0.004[2]
Not Cured	113 (82%)	115 (82%)	68 (97%)			

Total Cure = Complete cure by Investigator's Global Evaluation of all treated areas plus mycological cure (negative KOH and culture for dermatophytes).
[1] Confidence interval calculated using Wald's method with Yates' continuity correction.
[2] P-values for treatment comparisons from two-sided Z-test with Yates' continuity correction, or Fisher's exact test if appropriate.

Reviewer's Comments:

The OGD's accepted primary endpoint is a dichotomized total cure, combination of clinical cure and mycological cure. The clinical cure evidenced by clinical signs and symptoms score is preferred over the physician global assessment. A patient is considered a clinical cure if total signs and symptoms score is 2 or less and a severity score of individual signs and symptoms is no more than 1 (mild) for any of the 6 clinical parameters. A patient is considered as mycological cure if both KOH and culture results are negative. Therefore, summary statistical analysis by the FDA statistician was requested on the following primary and secondary endpoints:

Primary endpoint:

Total Cure Definition #1: total signs and symptoms score of 2 or less and a severity score of no more than 1 for any of the 6 clinical parameters plus mycological cure (negative KOH and culture) at visit 4 (Day 43)

Total Cure Definition #2: clinical cure evidenced by investigator global assessment(IGE) of "complete" plus mycological cure (negative KOH and culture) at visit 4 (Day 43). This is the same as the sponsor's defined primary endpoint.

Secondary endpoints:

1) *Total Cure defined by signs and symptoms total score of 2 or less and a severity score of no more than 1 for any of the 6 clinical parameters plus mycological cure at Visit 3 (Day 29).*
2) *Total Cure [IGE of "complete" cure and mycological cure] at Day 29 (end of treatment).*
3) *Clinical Cure evidenced by total signs and symptoms score at Visits 3 and 4.*
4) *Clinical Cure evidenced by IGE of complete at Visits 3 and 4.*
5) *Mycological Cure at Visits 3 and 4.*
6) *The 90% CI evaluation of bioequivalence as well as the test for the sensitivity of each active treatment vs. placebo were evaluated at each defined endpoint (end of treatment and follow-up).*

Based on the sponsor's defined total cure (IGE of "complete" clinical cure plus mycological cure), the proportional difference in total cure rates between the test and the reference products at the follow-up visit (Day 43) is within the (-20, +20). Because the sponsor unnecessarily included or excluded several patients from the ITT (MITT)/PP population analysis, the reanalysis and verification of the sponsor's data by the FDA statistician was requested.

Safety

No death or serious adverse event related to the study drugs occurred during the study. One patient (#002, site #6; Ref) was hospitalized for treatment of uterine adhesions and scarring, but it was thought not to be related to the study drug. No adverse event related to the study drug was reported by the sponsor. Of the 499 ITT patients, 66 patients experienced one or more treatment-emergent adverse events during the study. Although slightly higher number of patients experienced overall adverse events in the reference group compared to the test group, it was not statistically determined to be significant and all were considered not related to the study drug. Skin reactions not considered to be treatment related occurred in 9 patients (3 in the test, 4 in the reference, 2 in the vehicle). The sponsor's report for treatment-emergent adverse events is shown in Table VII.

Table VII.
Number of patients reporting treatment-emergent adverse events (per sponsor)

	Generic (N=180)	Loprox® (N=178)	Vehicle (N=91)	P-value for Generic vs. Loprox®
Adverse event(s) regardless of relationship to study medication	22 (12.2%)	34 (19.1%)	10 (11.0%)	0.047[1]
Adverse event(s) probably related or related to study Medication	0 (0%)	0 (0%)	0 (0%)	1.000[1]
Number Of patients With At Least One AE				
Mild: N (%)	8 (4.4%)	19 (10.7%)	6 (6.6%)	
Moderate: N (%)	11 (6.1%)	10 (5.6%)	3 (3.3%)	
Severe: N (%)	3 (1.7%)	5 (2.8%)	1 (1.1%)	

[1] P-values for treatment comparisons from Cochran-Mantel-Haenszel test for general association, adjusted for site.

Reviewer's comment: *No patient was discontinued due to an adverse event. The number of patients with skin-related adverse events was comparable among three study groups and all were considered not related to study drugs.*

V. Formulation

Component	*Ciclopirox (% w/w)	**Loprox® Lotion (mg/g)
Ciclopirox Olamine USP	1.00	10.0
Cocamide DEA		
Octyldodecanol NF		
Mineral Oil USP		
Stearyl Alcohol NF		
Cetyl Alcohol NF		
Polysorbate 60 NF		
Myristyl Alcohol NF		
Sorbitan Monostearate NF		
Lactic Acid USP		
Benzyl Alcohol NF		
Purified Water, USP		

*Based on the comparative formulation provided in vol. 1.1, p. 60
**Per medical officer's review of NDA 19-824 (9/14/88)

Reviewer's Comment: *The test and reference formulations are qualitatively the same.*

VI. Review of the Division of Scientific Investigation (DSI) report

Dr. ——— (site #2) and Dr. ——— (site #13) offices were previously inspected on ——— for ANDA ——— and Dr. ——— office (site #9) was inspected on ——— for ANDA ——— . For these three sites, a Form FDA-483 was issued for not complying with the final rule for reserving appropriate retention samples. Since the current study was initiated prior to the investigator being notified of these deficiencies, a DSI inspection was not requested for the current study.

Reviewer's Comments:
It is the sponsor's responsibility to assure that the clinical sites for all BE studies comply with the requirements for retention of study drugs as per 21 CFR 320.38 and 320.63. If the sponsor fails to comply with the Agency's regulation in any future study, the study may be found unacceptable and a new bioequivalence study may be requested.

VII. Review of the FDA Statistical Report (5/14/04)

The conclusion of the FDA statistical analysis supports the bioequivalence of the test and the reference products. The 90% CI of a total cure (both clinical cure and mycological cure) rate for the evaluable population at the primary endpoint (Visit 4, 2 weeks post-treatment) is within -.20 and +.20. The test and the reference products demonstrated superiority over the placebo/vehicle group at Visit 4 in the ITT population.

The FDA defined total cure (definition #1) was a clinical cure evidenced by total signs and symptom score of 2 or less and a severity score of no more than 1 for any of the 6 clinical

parameters plus mycological cure (negative KOH and culture) at Visit 4. The sponsor's defined total cure (definition #2) was a clinical cure evidenced by investigator global assessment (IGE) of "complete" plus mycological cure (negative KOH and culture) at Visit 4. As mentioned above, the FDA defined total cure is preferred over the sponsor's defined total cure.

Based on this reviewer's comments above, the FDA statistician provided the summary of the equivalence test for the evaluable population as shown below, and their conclusion is as follows:

Primary endpoints: FDA's (definition #1) and sponsor's (definition #2) total cure rates at visit 4.

Efficacy and equivalence analyses for primary endpoints

Population	Test* % successes (No. of successes)	Reference* % successes (No. of successes)	Placebo* % successes (No. of successes)	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%)
ITT**	N=137	N=141	N=70				
FDA's total cure	63.5 (87)	68.1 (96)	15.7 (11)	<0.001	<0.001		
Sponsor's total cure	38.7 (53)	34.0 (48)	2.9 (2)	<0.001	<0.001		
EP	N=111	N=116	N=55				
FDA's total cure	64.9 (72)	69.8 (81)	18.2 (10)			-16.1, 6.2	Yes
Sponsor's total cure	40.5 (45)	33.6 (39)	3.6 (2)			-4.5, 18.3	Yes

*: The rate of success equals the number of successes divided by the total number, then multiplied by 100.
#: The p-values were from Fisher's exact test (2-sided).
**ITT: all patients randomized to treatment, received treatment, and completed at least one post-baseline visit.

The secondary endpoints are also supportive of the primary endpoint results. The 90% CI of proportional difference in clinical cure, both defined by the FDA or the sponsor, and mycological cure falls within -0.20 and +0.20 at both Visit 3 and Visit 4.

VIII. Conclusion

The data presented in this ANDA 76-422 demonstrate that Altana Inc.'s Ciclopirox Lotion, 0.77%, is bioequivalent to the reference listed drug, Loprox® Lotion, 0.77%. The FDA statistical review confirms that the 90% CI of the proportional difference in total cure (both clinical cure and mycological cure) at the primary endpoint (Visit 4, 2 weeks post-treatment) is within -.20 and +.20. The test and the reference products also demonstrate superiority over Placebo group at Visit 4.

IX. Comments to be conveyed to Sponsor

The data submitted to ANDA 76-422, using the primary endpoint of total cure rate at Visit 4 (2 weeks post-treatment), are adequate to demonstrate bioequivalence of Altana Inc.'s Ciclopirox Lotion, 0.77%, with the reference listed drug, Medicis' Loprox® Lotion, 0.77%. Both active treatments demonstrated superiority over the placebo arm at Visit 4.

1. Please note that patients were considered a clinical cure if total signs and symptoms score is 2 or less and a severity score is no more than 1 (mild) for any of the 6 clinical parameters. Patients were considered a mycological cure if both KOH and fungal culture results were negative. Patients were considered a total cure if they were both clinical cure and mycological cure. This is the OGD's preferred accepted primary endpoint for this product.

2. The OGD also evaluated your version of total cure based on clinical cure evidenced by investigator global assessment of "complete" and mycological cure (negative KOH and fungal culture) at Visit 4. With this endpoint, the study supports bioequivalence of your product with the reference listed product. Both active treatment groups demonstrated superiority over the placebo arm for these endpoints at Visit 4.

3. Several clinical sites from your study were previously inspected for other generic products and the investigators were notified with several deficiencies. Since this study was initiated before comments were provided, an inspection was not requested at this time. However, it is your responsibility to assure that the clinical sites for all future BE studies comply with the requirements for retention of study drugs as per 21 CFR 320.38 and 320.63. If you fail to comply with the Agency's regulation in any subsequent study, the study may be found unacceptable and a new bioequivalence study may be requested.

Carol Y. Kim, Pharm.D.
Clinical Reviewer
Office of Generic Drugs

Date 6/4/04

Dena R. Hixon, M.D.
Associate Director for Medical Affairs
Office of Generic Drugs

Date 6/4/04

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs

Date 6/8/04

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:76-422 APPLICANT: Altana Inc.

DRUG PRODUCT: Ciclopirox Lotion (Ciclopirox Olamine Topical Suspension USP, 0.77%)

The Division of Bioequivalence has completed its review and has no further questions at this time.

The data submitted to ANDA 76-422, using the primary endpoint of total cure rate at Visit 4 (2 weeks post-treatment), are adequate to demonstrate bioequivalence of Altana Inc.'s Ciclopirox Lotion, 0.77%, with the reference listed drug, Medicis' Loprox® Lotion, 0.77%. Both active treatments demonstrated superiority over the placebo arm at Visit 4.

1. Please note that patients were considered clinical cure if total signs and symptoms score is 2 or less and a severity score is no more than 1 (mild) for any of the 6 clinical parameters. Patients were considered a mycological cure if both KOH and fungal culture results were negative. Patients were considered a total cure if they were both clinical cure and mycological cure. This is the OGD's preferred accepted primary endpoint for this product.

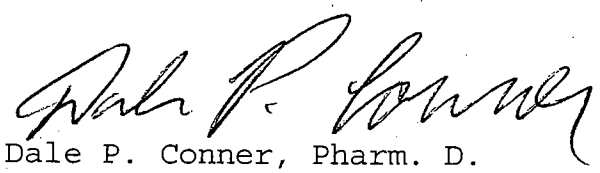
2. The OGD also evaluated your version of total cure based on clinical cure evidenced by investigator global assessment of "complete" and mycological cure (negative KOH and fungal culture) at Visit 4. With this endpoint, the study supports bioequivalence of your product with the reference listed product. Both active treatment groups demonstrated superiority over the placebo arm for these endpoints at Visit 4.

3. Several clinical sites from your study were previously inspected for other generic products and the investigators were notified with several deficiencies. Since this study was initiated before comments were provided, an inspection was not requested at this time. However, it is your responsibility to assure that the clinical sites for all future BE studies comply with the requirements for retention of study drugs as per 21 CFR 320.38 and 320.63.

If you fail to comply with the Agency's regulation in any subsequent study, the study may be found unacceptable and a new bioequivalence study may be requested.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 76422
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-600/ C.Kim
HGD-600/ D. Hixon

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Endorsements: (Final with Dates)
HFD-655/C. Kim CU 6/4/04
HFD-600/D. Hixon DRH 6/4/04
HFD-650/D. Conner NM 6/4/04

BIOEQUIVALENCY - ACCEPTABLE

submission dates:
August 5, 2002
February 2, 2004

1. Bioequivalence Study (STU); August 5, 2002 — Strength: 0.77% **Outcome: AC**

2. Study Amendment (STA); February 2, 2004 — Strength: 0.77% **Outcome: AC**

Outcome Decisions: **AC** - Acceptable
WC - Without charge
IC - Incomplete
UC - Unacceptable

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-422 SPONSOR : Altana, Inc.

DRUG AND DOSAGE FORM : Ciclopirox Lotion (ciclopirox olamine topical suspension USP, 0.77%)

STRENGTH(S) : 0.77%

TYPES OF STUDIES : Clinical Endpoint

CLINICAL STUDY SITE(S) : multiple sites

ANALYTICAL SITE(S) : N/A

STUDY SUMMARY: Study is acceptable

DISSOLUTION : N/A

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status: N/A	Inspection results: N/A
First Generic _____ New facility _____ For cause _____ other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Carol Y. Kim, Pharm. D.

INITIAL : CYK DATE : 6/4/04

ASSOCIATE DIRECTOR FOR MEDICAL AFFAIRS: Dena R. Hixon, M.D.

INITIAL : DRH DATE : 6/4/04

DIRECTOR, DIVISION OF BIOEQUIVALENCE : Dale P. Conner, Pharm. D.

INITIAL : DPC DATE : 6/4/04