CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-022

MEDICAL REVIEW(S)

Medical Officer's Review of NDA 21-022
Original

1.1 NDA Submission number/type NDA 21-022/3S

1.2 Applicant identification

Hoechst Marion Roussel, Inc.
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1.3 Submission/Review Dates

1.3.1 Date of submission (date of applicant's letter)	12-18-98
1.3.2 CDER stamp date	12-18-98
1.3.3 Date submission received by reviewer	01-04-99
1.3.4 Date review initiated	02-09-99
1.3.5 Date review completed	11-23-99

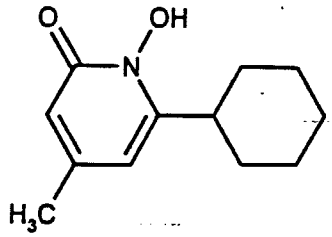
1.4 Drug Identification

1.4.1 Generic name Ciclopirox

1.4.2 Proposed trade name Tradename

1.4.3 Chemical name 6-cyclohexyl-1-hydroxy-4-methyl-2(1H)-pyridinone

1.4.4 Chemical structure



1.4.5 Molecular formula: $C_{12}H_{17}NO_2$

1.4.6 Molecular weight: 207.3

1.5 Pharmacologic Category: Antifungal

1.6 Dosage form: Lacquer (Solution)

1.7 Route of Administration: Topical

1.8 Proposed Indication & Usage section

Loprox® Nail Lacquer 8% is indicated for the topical treatment of mild to moderate onychomycosis without lunula involvement due to *Trichophyton rubrum* [redacted] It is indicated for the treatment of fingernails and toenails.

1.9 Proposed Dosage & Administration section

[redacted]

1.10 Related Drugs

Formulations of ciclopirox olamine or ciclopirox for topical treatment of fungal infections reviewed by the FDA under INDs or NDAs sponsored by Hoechst-Roussel Pharmaceuticals Inc. (HMRI) are as follows:

Table 1 Related NDAs

NDA Number	Drug Name	Indication	Date of Approval
19-824	Loprox® (ciclopirox olamine) Lotion 1%	Topical treatment of the following dermal dermatophyte infections: tinea pedis, tinea corporis, and tinea cruris; candidiasis (moniliasis) due to Candida albicans; and tinea (pityriasis) versicolor due to Malassezia furfur	12/30/88
18-748	Loprox® (ciclopirox olamine) Cream 1%	Topical treatment of the following dermal dermatophyte infections: tinea pedis, tinea corporis, and tinea cruris; candidiasis (moniliasis) due to Candida ablicans; and tinea (pityriasis) versicolor due to Malassezia furfur	12/30/92
20-519	Loprox® (ciclopirox olamine) Gel 0.77%	Topical treatment of the following dermal dermatophyte infections: inderdigital tinea pedis, tinea corporis, and tinea cruris. Topical treatment of seborrheic dermatitis of the scalp	07/21/97

Table 2 Related INDs

IND Number	Drug Name	Indication	Date of Submission
—	Loprox® (ciclopirox) Nail Lacquer 8%	Dermatophyte infection of the fingernails and toenails	06/27/88
—			

Table 3 Inactivated INDs

IND Number	Drug Name	Indication	Date of Submission	Date of Inactivation

Related Reviews: Biopharm Review dated: 10-08-99
Pharm/Tox Review DSF sign-off date: 09/24/99
Statistical Review dated: 09-22-99
Chemistry Review dated: 09-13-99
Microbiology Review dated: 10-13-99

Material Reviewed

1.11.1 **NDA Volumes Reviewed**

This review is based on the following volumes: 1.1 (Overall Summary), 1.3, 1.24, 1.25 – 1.62 (Clinical Data Section), 1.94 – 1.95 (Non-US Clinical Studies- Data Listings), 1.96 – 1.97 (Non-US Post Marketing Studies-Data Listings), and 1.98 - 1.100 (Case Report Forms Section).

1.11.2 **Other Documents Reviewed**

Document Identification	Source	Date
IND	Sponsor	06-30-99

1.11.3 **Amendments with Dates**

Document Identification	Date Received
NDA 21-022 NC	02-17-99
NDA 21-022 NC	02-17-99
NDA 21-022 NC	02-19-99
NDA 21-022 NC	03-09-99
NDA 21-022 NC	03-10-99
NDA 21-022 BM	04-21-99
NDA 21-022 SU	04-21-99
NDA 21-022 NC	04-26-99
NDA 21-022 NC	05-06-99
NDA 21-022 BP	05-19-99
NDA 21-022 BM	08-06-99

Amendments with Dates (continued)

Document Identification	Date Received
NDA 21-022 BM	08-23-99
NDA 21-022 NC	09-03-99
NDA 21-022 NC	09-15-99
NDA 21-022 NC	09-22-99
NDA 21-022 BM	09-28-99
NDA 21-022 BL	09-28-99
NDA 21-022 NC	09-29-99
NDA 21-022 BS	09-30-99

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1.12 **Regulatory Background**

The sponsor originally submitted IND —— on June 29, 1988; however, the IND was inactivated on April 29, 1991. According to the sponsor, the IND was inactivated because of lack of efficacy of Protocols 211 and 212. On October 25, 1993, a teleconference was held between the sponsor and the Agency to discuss the clinical program for the nail lacquer and re-activation of IND ——— On April 28, 1994 the IND was re-activated. An End-of-Phase II Meeting was held on September 11, 1995 between the sponsor and the Division. An End of Phase 2 teleconference was held on November 18, 1995 between the sponsor and the Division. During the March 11, 1996 meeting with the Division, the sponsor presented a proposed planimetric method that was to be used to denote those patients with at least ≥ 90% clearance of the nail plate. A pre-NDA Meeting was held between the sponsor and the Division on August 18, 1997.

Reviewer's comments:

Specific recommendations made by the Division to the sponsor during the End of Phase 2 (EP-2) Meeting held on September 11, 1995 are discussed in detail under Clinical Studies Section (Section 8). Information provided to the sponsor during the EP-2 Meeting included confirmation that the primary efficacy endpoint recommended by the Division is 100% clearance of the nail plate with negative mycology, the proposed planimetric approach to presenting the data was acceptable, and that demonstration of safety and efficacy for toenails will allow labeling claims for fingernails. Study dates provided by the sponsor for Studies 312 and 313 are 06/25/94 to 03/26/96 and 07-13-94 to 04-12-96, respectively.

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3 Chemistry/Manufacturing Controls

The dosage forms used in the US clinical studies were listed as HOE 296b-Nail Lacquer (Formula Code B) and HOE 296b-Nail Lacquer Placebo (Formula Code A) where a placebo arm existed. For the repeat insult patch study to assess irritation and sensitization potential (Study 1003), HOE 296 nail lacquer formulation (Formula Code A and B) was used.

Reviewer's comment:
Chemistry reviewer has verified (verbal communication with clinical team leader on November 22, 1999) that the formulation used in Studies 312 and 313 was the final "to be marketed" formulation.

4 Animal Pharmacology/Toxicology

The sponsor references results of pre-clinical toxicology data presented under the following NDAs:

- NDA 18-748 for Loprox® Cream 1%, containing ciclopirox as the olamine salt
- NDA 19-824 for Loprox® Lotion 1%, containing ciclopirox as the olamine salt
- NDA 20-519 for Loprox® Gel .077%, containing ciclopirox as the free acid

The following nonclinical toxicology studies were presented in this submission (See Pharm/Tox for review):

- Acute toxicity (ciclopirox olamine (HOE 296) and free acid in mice and rats (orally and intraperitoneally
- Multidose toxicity (subacute and chronic toxicity of HOE, ciclopirox olamine, was studied in mice, rats, guinea pigs, rabbits, and dogs by various routes of administration and for varying lengths of time
- Reproductive-teratology studies in mice, rats, rabbits , and monkeys
- Acute oral toxicity of HOE 296b 8% nail lacquer in rats
- Primary dermal irritation study of HOE 296b 8% nail lacquer in rabbits
- Primary eye irritation study in rabbits
- Mutagenicity studies In Vitro
- Evaluation of Gantrez ®ES 435
- Acute oral toxicity in rats

No repeated-dose toxicity studies were performed with the nail lacquer formulation.

Significant findings include oral dose-dependent myocardial degeneration observed in rats to which 30, 100, and 300 mg/kg/day ciclopirox olamine was administered and in dogs to which 30 mg/kg/day ciclopirox olamine was administered. In repeated oral toxicity studies, serum drug levels associated with toxic doses were between 20 and 35 µg/mL (nontoxic levels were between 6 and 10µg/mL). According to the sponsor, daily doses of 10 mg/kg (ciclopirox olamine/body weight) did not reveal clinical evidence of systemic toxicity of the substance or organ toxicity after necropsy and histological examination as in earlier oral toxicity studies in rats and dogs.

Reviewer's comment: *The sponsor did not present the earlier oral toxicity studies in rats and dogs in which daily doses of 10mg/kg (ciclopirox olamine/body weight) did not reveal clinical*

evidence of systemic toxicity of the substance or organ toxicity after necropsy and histological examination.

Based on the margin of safety established from animal studies and absorption studies in humans, it is safe to assume that topical applications of ciclopirox nail lacquer should not produce any significant toxicity in humans. According to the Pharm/Tox Review (DSF sign-off date: 09-24-99), the sponsor states the following: the topical application of 0.339g (27.12 mg ciclopirox) of the lacquer formulation will cover all the fingernails and toenails including 5 mm proximal and lateral fold area plus onycholysis to a proximal extent of 50%. In an in vitro study, according to the Pharm/Tox Review, a maximum of 0.07% (0.111mg/m^2 of nail) of the applied dose of radiolabeled ciclopirox in 8% nail lacquer formulation penetrated through the excised human toenails. Based on these results, the margin of safety based on NOEL in rats and dogs will be 540 and 1,802 times, respectively. Assuming100% absorption of ciclopirox, the margin of safety will be between 4 and 12 times.

Additionally, according to the review, based on systemic tolerability studies in subjects with distal subungual onychomycosis, the average maximal serum level of 31 ± 28 ng ciclopirox/mL was achieved after two months of therapy. This was 159 times lower than the lowest toxic dose (4,920 ng/mL), and 115 times lower than the highest nontoxic dose (3,570 ng mL) in animals.

Ciclopirox nail lacquer 8% was tested in the Ames test and did not demonstrate mutagenic potentiai. In an *in-vitro* cell transformation assay (mouse embryo cell BALB/C3T3) the lacquer formulation tested positive with and without metabolic activation. These findings were thought due to the Gantrez® ES 435 (alkyl monoester resin) used in the nail lacquer formulation. The resin also has tested positively in this assay, but did not demonstrate mutagenic potential in the mouse lymphoma and unscheduled DNA synthesis (UDS) tests.

Ciclopirox nail lacquer 8% was shown to be a primary eye irritant in a primary eye irritation study in rabbits. The nail lacquer formulation was considered a non-irritant on shaved intact and abraded skin of rabbit skin.

Reviewer comment: *According to the Pharm/Tox Reviewer (verbal communication) Gantrez® ES 435 (alkyl monoester resin) used in the nail lacquer formulation is safe for use in humans. According to the written Pharm/Tox review, it is possible that the c3T3 assay, which is considered predictive of carcinogenesis, was confounded because of the film-forming nature of the resin.*

5 Microbiology

The sponsor cross-references the NDA 20-519, Loprox Gel, for microbiology information (See Microbiology Review).

6 Human Pharmacokinetics/Pharmacodynamics

Pharmacokinetic, pharmacodynamic, and dermatotoxicity studies conducted in humans were submitted. These studies are described under Overview of Safety, Section 10. The sponsor presented results of three *in vitro* and two *in vivo* penetration studies. See the Biopharm Review for details of these studies.

7 Human Clinical Experience

Tinea ungium is defined as a dermatophyte infection of the nail plate. For this NDA review "onychomycosis due to dermatophytes" is the terminology used interchangeably with tinea ungium.

Onychomycosis due to dermatophytes is primarily caused by dermatophytes of the genus *Trichophyton.* The infection can lead to crumbling and destruction of the nails. Although onychomycosis may be asymptomatic, it is generally accepted that the onychomycotic nail constitutes a reservoir of fungus that can cause repeated infection of the plantar surfaces of the soles and interdigital spaces leading to symptomatic tinea pedis. It may also lead to the infection of other parts of the skin, e.g., tinea cruris and tinea corporis by transfer of fungus. Current approved therapies for onychomycosis are limited to oral therapies. Some oral therapies are associated with serious adverse reactions. This topical approach to therapy of onychomycosis with ciclopirox nail lacquer is novel.

Ciclopirox is a hydroxypyridone antifungal agent, differing in structure and mechanism of action from other marketed antifungal agents, most of which are azoles or allylamines. Ciclopirox olamine is available in the USA in 1% cream and lotion formulations for the treatment of tinea pedis, corporis and cruris, as well as for the treatment of cutaneous candidiasis and tinea versicolor. It is marketed in the United States (US) as Loprox® Cream 1% and Loprox® Lotion 1% formulations.

Ciclopirox inhibits the growth of pathogenic dermatophytes and yeasts. Ciclopirox acts by chelation of polyvalent cations (Fe^{3+} or Al^{3+}) resulting in inhibition of the metal-dependent enzymes that are responsible for degradation of peroxides within the fungal cell.

The free acid of ciclopirox has been shown to have properties similar to its olamine salt in preclinical and clinical studies. The free acid of ciclopirox has been shown to have nearly identical properties to its olamine salt in preclinical and clinical studies. An alkali soluble nail lacquer vehicle has been developed for ciclopirox to facilitate treatment of onychomycosis.

7.1 Foreign experience

Ciclopirox nail lacquer 8% is approved in 54 countries. According to the sponsor, approximately [redacted] bottles have been sold worldwide since 1992; however, the total number of patients cannot be directly assessed. Various ciclopirox and ciclopirox olamine formulations are available throughout the world.

Foreign Marketing History—

Marketing approval received but product not yet launched:

Country	Date Approval Received
[redacted]	[redacted]

Marketing application submitted in the following countries but marketing approval not yet received:

Country	Date of Submission
[redacted]	[redacted]

Marketing application submitted but not approved:

Country	Date of Nonapproval
[redacted]	

Approval was received after NDA submission in the following countries:

Country	Trade Name	Approval Date
Indonesia	Loprox	July 29, 1998
Iraq	Batrafen	May 23, 1998

Ciclopirox is marketed under tradenames of Batrafen, Loprox, Mycoster, Mycofen, Nagel Batrafen, and Ciclochem. A list of countries where approved with launch dates follows.

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Table 4 **Ciclopirox Nail Lacquer 8% Launch Dates**

Country	Launch Date (year)
Antilla (Bahamas, Bermuda, Barbados, Jamaica, Haiti, Aruba, and Curacao)	1994
Argentina	1992
Austria	1996
Bolivia	1995
Brazil	1996
Bulgaria	1996
Chile	1994
China	1996
Columbia	1997
Costa Rica	1994
Cyprus	1996
Czech Republic	1996
Denmark	1993
Dominican Republic	1994
Ecuador	1996
El Salvador	1994
France	1992
Germany	1992
Guatemala	1994
Honduras	1994
Hong Kong	1997
Israel	1995
Italy	1996
Korea	1994
Mexico	1997
New Zealand	1995
Nicaragua	1994
Panama	1994
Paraguay	1995
Peru	1994
Poland	1996
Romania	1996
Russia	1995
Singapore	1997
Slovak Republic	1996
Spain	1998
Thailand	1996
Trinidad/Tobago	1994
Turkey	1997
Ukraine	1997
Uruguay	1997

7.2 Post-Marketing Experience

According to the sponsor, there have been no rejections of applications, suspensions, or restrictions of distribution for safety reasons. The sponsor submitted results of post-marketing surveillance for the nail lacquer and a World Health Organization (WHO) database query for

post-marketing adverse experiences reports for any ciclopirox containing products. Additionally, the Agency's Adverse Events Reporting System (AERS) database was queried. The results of these queries are addressed in Section 10, Overview of Safety.

According to the sponsor, it is estimated that worldwide since 1988 about [redacted] patients (including those in clinical trials) have been prescribed ciclopirox cream, gel, lotion, [redacted] or nail lacquer. Of the [redacted] subjects have used the ciclopirox nail lacquer 8% during the past six years.
Under post-marketing surveillance, a synopsis was submitted for post approval Study No. E2/HOE296NL/5/D/C009/NM (92-0296-049-Pr). The study results and comments are also found in Section 10.

8 Clinical Studies

8.1 Introduction

The sponsor lists the NDA for ciclopirox nail lacquer, 8% as a 505(b)(1) application. This dosage form has been studied under IND [redacted]

Seven clinical studies conducted in the US were submitted by the sponsor in support of this NDA. These studies are listed in Table 7. Two identical clinical trials (Study 312 and 313) for treatment of distal subungual tinea unguium of the toenails were identified as Phase III studies. Study 320 was an open-labeled safety study for patients previously enrolled in Studies 312 and 313. Additionally, 22 non-US trials were conducted. Comments on these non-US studies are located in 8.6 under Clinical Studies.

Studies 211 and 212 were conducted by the sponsor in the treatment of distal subungual tinea unguium of the fingernails and identified by the sponsor as Phase II studies. According to the sponsor, studies 211 and 212 were submitted in support of safety.

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Special studies submitted include Pharmacokinetic Study 111 and one dermatoxicity study, Study 1003, to assess irritation and sensitization potental. Phototoxicity Potential Assay and Photocontact Allergenicity Assay studies were not submitted to the NDA. The absorption maximum listed for ciclopirox is 302 ±2 nm (Vol. 1.1, pg. 189). As there is absorption in the UVB/UVA/visible spectrum, phototoxic and photocontact allergic potential studies are necessary. These studies should have been conducted with the "final to-be-marketed" formulation.

A summary listing of the seven clinical studies including enrollment follows in Table 5.

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Table 5 Summary Listing of All US Studies Submitted

Partial Extraction of Sponsor's Table R1 Table of Clinical Studies Conducted in the US

Protocol # Design	Completion Status (Start Date)	Treatment Dose	Number Subjects Treated	Frequency	Age Range	M/F W/N W	Treatment Duration
Phase I Open-Label US Study							
111 open label uncontrolled	Complete (5/89)	CIC 8%	5	1/day	34-74	4/1 5/0	24 weeks
Phase I Intra-individual Controlled (Dermatotoxicity) US Study							
1003 randomized controlled observer blind	Complete (11/96)	CIC 8% 50 mg VEH 50 mg PET 50 mg	230 230 230	each subject received all treatments (3/week)	19-74	40/190 225/5	4 weeks
Phase 2/3 Vehicle-Controlled US Studies[1]							
211 randomized DB, VC Parallel group	Complete (11/88)	CIC 8% VEH	42 43	1/day 1/day	18-79	73/12 83/2	24 weeks
212 randomized DB, VC Parallel group	Complete (10/88)	CIC 8% VEH	54 56	1/day 1/day	18-91	100/10 94/16	24 weeks
312 randomized DB, VC Parallel group	Complete (7/94)	CIC 8% VEH	112 111	1/day 1/day	18-70	175/48 208/15	48 weeks —
313 randomized DB, VC Parallel group	Complete (7/94)	CIC 8% VEH	119 118	1/day 1/day	19-70	183/54 207/30	48 weeks
— Phase 3 Open-Label Extension US Study[2]							
320 open-label uncontrolled	Complete (6/95)	CIC 8%	281	1/day	21-70	223/58 259/22	48 weeks

Source: Statistical Table I.1

CRFs=Case report forms; M=male subjects, F=female subjects; W=white subjects; NW=non-white subjects; DB=double blind, VC=vehicle-controlled; CIC 8%=ciclopirox nail lacquer 8%, VEH=vehicle, PET=petrolatum.

[1] Total number of subjects in the Phase II/III vehicle-controlled studies: CIC 8%=327; VEH=328.

[2] 281 subjects were treated with CIC in the open-label extension study; 138 received VEH in preceding double-blind studies (312 and 313).

8.2 Indication #1 **Distal Subungual Tinea Ungium of the Toenails**
8.2.1 Trial #1 **Sponsor's Study 312 (HOE 296NL/8/USA/312/NM)**

Title: "A DOUBLE-BLIND STUDY OF THE SAFETY AND EFFICACY OF CICLOPIROX (HOE 296NL) NAIL LACQUER 8% VERSUS ITS LACQUER VEHICLE IN SUBJECTS WITH DISTAL SUBUNGUAL TINEA UNGUIUM OF THE TOENAILS"

8.2.1.1 Objective/Rationale

This study is designed to compare the safety and efficacy of 8% ciclopirox nail lacquer with that of the vehicle in the treatment of subjects with distal subungual tinea unguium of the toenails.

8.2.1.2 Design

This is a multi-center, randomized, stratified, double-blind, vehicle-controlled, parallel group study conducted in the United States at 9 centers. Eligible subjects were randomized to either study treatment, stratified by center and severity of target nail involvement (≤40% or ≥40%). During the 48-week treatment period, visits were scheduled every 4 weeks. Mycological assessments and photographs for planimetry were taken every 3 months. Subjects with clinically cured target toenails could enter a 12 to 24-week post-treatment phase.

8.2.1.3 Protocol Overview

8.2.1.3.1 Population/Procedures

Inclusion Criteria

Subjects fulfilling the following criteria were enrolled:

1) Subjects must be between 18 and 70 years of age, of any race and of either sex.
2) Subjects must be in good general health as confirmed by a medical history and physical examination.
3) Subjects must present with clinically diagnosed stable or exacerbating distal subungual tinea unguium of at least one great toenail (i.e., the target nail) at Day 1.
4) Subjects must have between 25-60% of the area of the target toenail involved (confirmed by computerized planimetry of the photographs taken at Screen).
5) A positive KOH examination must be obtained from specimens taken from the target nail at the Baseline (Day 1) visit.
6) A positive dermatophyte culture must be obtained from specimens taken from the target nail within 28 days prior to the Day 1 visit.
7) Subjects or their guardians must sign a statement of informed consent.
8) Subjects must be able to understand the requirements of the study, abide by the restrictions and return for all the required examinations.
9) Female subjects must be post-menopausal for: at least one year, or have had a hysterectomy, or have had a tubal ligation, or agree to use oral/systemic contraceptives or an intrauterine device (IUD) starting at least 28 days prior to study entry and throughout

the study, or agree to use a spermicide in combination with barrier methods of contraception throughout the study.

10) Female subjects of childbearing potential must have: had a normal menstrual flow within approximately one month prior to study entry, and a negative serum pregnancy test (serum β-submit HCG RIA) within 7 days prior to Day 1. Results must be available prior to the first application of test medication. Note: urine pregnancy tests must be performed at each visit.

Reviewer Comment:
Entry criteria specified 25–60% involvement at Baseline. According to the Meeting Minutes of a teleconference between the sponsor and the Division on 10-25-93, cultures at baseline should be positive with less than 25% involvement at Baseline. According to the sponsor (Vol. 1.34, pg. 56), it was agreed with the FDA to extend the area of nail involvement at baseline to 20% - 65% as per FDA Contact Reports 09-17-96 and 09-20-96. Baseline cultures were not addressed in the FDA Contact Report.

Exclusion Criteria

The following subjects must not be enrolled:

1) Subjects with nail infections due to organisms other than dermatophytes (e.g., Candida).
2) Subjects with white superficial or proximal subungual tinea unguium.
3) Subjects with other abnormalities of the target nail that could prevent obtaining a normal appearing nail if clearing of tinea unguium is achieved (i.e. chemical damage, tumors, genetic disorders affecting the nail, pigmentary disorders).
4) Subjects with "spikes" of disease in the target nail extending to the cuticle.
5) Subjects with severe plantar or moccasin tinea pedis (defined by blistering, pustules, or inability to ambulate).
6) Subjects with any disease/condition that might cause nail abnormalities or may interfere with the evaluation of the test materials (i.e., psoriasis, immune dysfunction, collagen-vascular diseases, lichen planus, peripheral vascular disease, traumatic onychodystrophy due to chronic stimuli).
7) Subjects with structural deformities of the target nail or the foot that would interfere with photography and subsequent planimetric analyses.
8) Subjects who have a history of immunosuppression and/or clinical signs indicative of possible immunosuppression (e.g., extensive, persistent or unusual distribution of dermatomycoses, explosive or extensive seborrheic dermatitis, recent or recurrent herpes zoster, or persistent herpes simplex.)
9) Subjects who have had a clinically important disease within 90 days of the study (e.g., myocardial infarct).
10) Subjects who are insulin dependent diabetics. Diabetic patients who follow dietary restrictions or who require oral hypoglycemic agents will be allowed to enroll if no overt signs of foot neuropathies are present.
11) Subjects who require medication for control of epilepsy.

12) Subjects with abnormal findings - physical or laboratory – which are considered by the investigator to be clinically important and indicative of conditions that might complicate interpretation of study results.
13) Subjects who are pregnant (confirmation by pregnancy testing), or who plan to become pregnant within the study time frame, or who are nursing.
14) Subjects suspected or known to be HIV positive (HIV testing is not required).
15) Patients who have a recent history or who currently are known to abuse alcohol or drugs.
16) Subjects with known hypersensitivity to any components of the test materials.
17) Subjects requiring or using any systemic or topical medication that may interfere with study results (e.g., systemic antifungals, topical antifungals, systemic corticosteroids, systemic retinoids, immunosuppressives).
18) Subjects who have used more than one 2-week course of oral corticosteroid therapy or one intramuscular corticosteroid injection during the previous year.
19) Subjects who use steroid inhalers on a regular basis.
20) Subjects using or requiring topical corticosteroids regularly (defined as repeated monthly usage).
21) Subjects having used any systemic antifungal therapy within 24 weeks prior to the Screen visit. (Note: local treatment of vaginal candidiasis is allowed).
22) Subjects having used topical antifungal therapy within 14 days prior to the Screen visit. (Note: no washout of Loprox Cream 1% is required).
23) Subjects using any nail polish products or other nail cosmetic products on any of the toenails or on the fingernails designated for treatment within 7 days prior to the start of treatment.
24) Subjects who have received any investigational drugs or devices or who have participated in any investigational drug/device study within 28 days prior to the start of treatment. Note: Investigational systemic antifungal agents must be washed out for 24 weeks prior to the Screen visit .
25) Subjects who require or who have had within 90 days of the start of treatment any drug known to have a well-defined potential for toxicity to a major organ (e.g., chloramphenicol).
26) Subjects with a history of poor cooperation, non-compliance with medical treatment, or unreliability.
27) In determining the length of the washout, the last day therapy was used should be counted as Day 0.

Reviewer's comment: *A rationale was not provided for exclusion of the following: insulin-dependent diabetics, patients requiring medication for epilepsy, and patients with a history of clinically important disease within 90 days of study (e.g., myocardial infarction). These exclusion criteria could ultimately be reflected in the product label.*

Screening, Randomization, Application of Study Medication, Concomitant Therapy, Visits, and Evaluations

Screening

Screening visits were conducted to confirm the diagnosis prior to the initiation of treatment. Specimen for mycological evaluations (KOH examination and culture) were obtained from the target nail and the target nail was photographed at a screen visit which was within 28 days prior

to Day-1. Photographs were taken at this visit and analyzed by computerized planimetry to determine the extent of involvement of the target nail. Subjects meeting the screening eligibility criteria (following the mycological evaluations, photography, physical examination and medical history, and laboratory assessments), were enrolled into the study. At this time, subjects were assigned a subject identification number.

Randomization

Subjects were centrally randomized into one of two treatment groups (ciclopirox nail lacquer 8% or ciclopirox nail lacquer vehicle, 1:1). Subjects were stratified at Day 1 by percent of involvement (determined by planimetric measurements from Screen visit photographs).

Clarification of terminology used in the NDA review between the Division and sponsor follows:

Table 6 Clarification of Terminology

Division's Terminology	Definition	Sponsor's Terminology
Complete Cure	Investigator's Global of clear, KOH negative, and Culture negative	Treatment Cure
Effectively Treated/Almost Clear	≤10% nail involvement, KOH negative, and culture negative	Treatment Success
Mycological cure	KOH negative and culture negative	Mycological cure

Protocol Amendments

Two protocol amendments were submitted to the Division. Protocol Amendment A (dated September 1, 1994) and Protocol Amendment A and B (dated May 6, 1996). Noteworthy protocol changes made by Amendment B (May 6, 1996) are listed below.

- Post-treatment phase was shortened from 6 months (24 weeks) to 3 months (12 weeks) for subjects whose target nails clear clinically and mycologically.
- Allowed use of acetone-based nail polish removers by the investigators at monthly visits.
- Efficacy Variable was amended to reflect the change of the primary efficacy variable from the investigator's assessment of the global improvement of the target nail to planimetric measurements of photographs of the target nail.
- Removed reflex testing of specimens after elevated LDH levels. This had not been done during the study. The only reflex testing that had been consistently performed was on specimens where a high panic laboratory value for creatine kinase was obtained (CK >400 U/L). In these cases, analysis for CK-MB was performed.
- Revised the statistical methods to reflect the change in the primary efficacy variable.

Reviewer's comments:

The Division did not recommend change of the primary efficacy variable from the investigator's assessment of the global improvement of the target nail to planimetric measurements of photographs of the target nail. A written clinical review from the Division of IND [redacted] Submission 070 (stamp dated 05-19-98) addressed the definition of primary efficacy variable. The sponsor was advised that the Division did not concur with the sponsor's definition of treatment success determined by the primary efficacy variables photographic planimetry of the target nail and mycological evaluations (KOH and culture). Treatment Success was defined by the sponsor as equal to or less than 10% involvement of the target nail with negative

mycological findings. As discussed with the Sponsor during the Pre-NDA Meeting on August 18, 1997, the primary efficacy endpoint recommended is negative mycology (KOH and culture) with clear nail; however, other endpoints would be considered.

The Sponsor indicated during the September 11, 1995 End-Of-Phase 2 meeting that [redacted] did not include the [redacted] score of 90% normal nail plates after treatment; therefore, the sponsor proposed the use of planimetry. Planimetry, as proposed at the October 1995 meeting and subsequently presented by the sponsor at the March 11, 1996 meeting with the Division, was acceptable as an approach to be used to demonstrate the subset of patients with at least 90% normal nail plate after treatment.

The major focus of discussions on 3/11/96 had been the adequacy of the planimetry method as opposed to changing primary efficacy variables. The examination of the submitted photographs and the focus of discussion during the meeting of 3/11/96 directly concerned the suitability of the technique of planimetric measurements of photographs of the target nail. During the pre-NDA meeting on 8/18/97 between the Sponsor and the Division, the Division reiterated that the planimetric approach to presenting data to the Agency is acceptable and the primary efficacy end-point recommended is complete cure (negative mycology with clinical absence of great toenail involvement-global of 0). Completely cured are patients who are 100% cleared with a negative KOH and negative culture. Secondary endpoints should include time to achieve complete cure, treatment success (patients with at least a 90% clear nail and with a negative KOH and negative culture), and mycological success (negative KOH and culture).

Concomitant Medications and Routine Hygiene

Normal (routine) hygiene and foot care practices were allowed. Fungal infections (such as tinea pedis or tinea cruris) should be treated with Loprox (ciclopirox olamine) Cream 1%.

Visits and Evaluations

Treatment was applied once daily for 48 weeks. Subjects were evaluated at return visits every 4 weeks with a 12-week post-treatment phase for those subjects whose target toenail was clinically and mycologically cured during the treatment period. Seven posttreatment visits were scheduled during which time no study medication was to be applied. Subjects whose target toenails were not clinically and mycologically cured and who completed 48 weeks of treatment could enroll in the open-label study, Protocol 320.

Reviewer's comment: *After completion of 48 weeks of treatment, Post-Treatment or Point-of-Cure assessments should have been made for all subjects prior to enrollment into Protocol 320. According to Meeting Minutes of a teleconference between the sponsor and the Agency on 10-25-93, post-treatment follow-up was discussed with the sponsor. Complete Cure was defined as mycological cure (negative KOH and culture) and 100% clearing of clinical signs, maintained for at least 3 to 6 months posttreatment. The Division was leaning towards 6 months at that time; however, the posttreatment assessment was shortened to 3 months at the End-of-Phase 2 meeting of 10-05-95.*

In general, post-treatment follow-up appears to have been an integral part of recommendations by the Agency in studies for anti-fungal agents in treatment of superficial dermatophytoses since

at least 1984. The sponsor incorporated post-treatment follow-up assessments, not limited to Complete Cures only, in studies conducted by the sponsor in 1988 – 1989 (Studies 211 and 212).

Application of Study Medication

Each subject was dispensed two to four 3 g bottles of test material. New bottles (up to 48) were dispensed as needed. All toenails were treated regardless of involvement. Only affected fingernails were treated. Applications were made once daily for 48 weeks and removed every 7 days. The lacquer was to be applied evenly over the entire nail plate and the proximal and lateral nail fold areas, approximately 5 mm onto folds. If possible, lacquer also was applied to the nail bed, hyponychium and the ventral surface of the nail plate when it is free of the nail bed. Subjects were to wait until at least 8 hours had elapsed after applying the materials before washing their feet. Patients were to file away loose nail materials and trim nails as required every seven days (i.e., on the day that the lacquer was removed).

Nail Preparation

At return visits during treatment, the nail lacquer was to be removed prior to clinical evaluations and mycological evaluations of the target nail. At all visits, the target great toenail was trimmed at least to the distal groove. At designated visits photographs were required. When photographed, the lateral and medial boundaries of the distal groove nail were marked with a pen that was supplied by the sponsor. The distal groove could be estimated, if necessary. The affected area of the target nail was to be delineated with a fine continuous line and then photographed.

After photography, the nail was trimmed further, if required and specimens for mycological evaluation were obtained at designated visits. Each investigator could use his/her preferred method to clip the nail. Excessive horny material was filed off prior to retreatment applications. Excessive debridement or drilling of the nail was not permitted. Investigators were instructed to aggressively clip nail at screening (Day-28) and at follow-up sessions according to the instruction sheet that accompanied the 01-02-96 Photographic Reference Guide (Protocols 312/313) for the IND (IND [redacted] Submission 053).

Reviewer's comments: Nail trimming was an integral part of protocol procedures and should be considered adjunctive therapy. The protocol did not specify whether the nail was trimmed prior to global evaluation.

At the request of the Division, the sponsor submitted photographs for the Complete Cure and Almost Clear subsets. Contrary to the protocol, the target toenails were trimmed past the distal groove prior to photographic documentation in many of the photographs examined. Additionally, it was apparent that nails were aggressively trimmed.

Assessments

Global improvement of the target nail was evaluated at each return visit. Estimates of the percent area involved were made for all non-target nails at Day I and at each return visit. The target nail was photographed at Day 1 and after 12, 24, 36, and 48 weeks of treatment and 12 weeks post-

treatment. Photographs taken at these visits were analyzed by computerized planimetry to determine the area of the unaffected nail plate. Assessment of the growth of target nail plate (and the contralateral unaffected nail, if applicable) were made from the photographs every 12 weeks by following the distal progression of a notch made in the nail plate. Estimates of the percent area involved were made for all non-target nails at Day I and at each return visit.

Complete Clearing of Disease

Clinical Clearance - If the target nail was clinically clear, the investigator was to conduct all of the scheduled monthly visit procedures. In addition, samples for mycological evaluation (KOH and culture) were to be obtained. Even if the KOH exam was negative, the patient was to be instructed to continue to apply the test material until the next scheduled visit since culture results were not available for 21 days. The next scheduled visit was to be scheduled at least 21 days after this visit. The post-treatment visit was scheduled if the subject continued with a global assessment of clear and negative mycology. Application of the test material was to be discontinued during the post-treatment phase.

Mycological Evaluations

Mycological evaluations (KOH and culture) were made of specimens from the target nail. These evaluations were scheduled at Screen (Day -28), Day 1, and after 12, 24, 36 and 48 weeks of treatment and at Week 12 post-treatment (if applicable). Subungual hyperkeratosis was evaluated at Day I and at each return visit for every treated nail.

Reviewer's comment: *Mycological assessments at Post-Treatment (Week-12 or 24) should have been applicable for all enrolled subjects.*

Planimetric measurements of the involved nail area (Target Nail)

Computerized planimetric measurements of the involved area of the target nail were to be made from standardized photographs. The affected area as a percentage of the whole nail area was used for further computations.

Reviewer's comments: *Inconsistencies were noted between global assessments of cleared and computerized photographic planimetric measurements of zero. According to the sponsor as noted above, planimetry cannot be used to distinguish minimal residual disease from cure. Hence, the establishment of cure remains a clinical decision. However, the planimetric values widely varied in the Cleared subset (e.g., ranged from [redacted] in study 312). These inconsistencies prompted a review of photographs for the Complete Cure and Almost Clear subsets.*

Continuation of Treatment by Enrollment into Protocol 320

At the conclusion of the 48 week treatment period, any subject who continued to exhibit clinical and/or mycological signs of disease on the target nail, who qualified and who desired could continue on 48 week open-label treatment using ciclopirox nail lacquer 8% (Protocol 320).

Reviewer's comment: *Post-Treatment follow-up was scheduled only for patients with Complete Cure, defined as no visible signs of infection (global improvement score = 0) plus a negative KOH exam and a negative culture. Post-treatment follow-up or Point-of-Cure assessments should have been made for all patients prior to enrollment into Protocol 320, an open-labeled study. A washout period is needed to eliminate inhibitory effects of the active drug and vehicle for demonstration of efficacy.*

Protocol Violations

The following protocol violations were defined by the sponsor as having potential to interfere substantially with the study outcome.

- Dosing schedule violations: missing or exceeding the test material application schedule regimen by more than three applications per seven-day period
- Use of prohibited previous or concomitant treatments
- Missing consecutive visits without confirmation of adequate dosing with test material during the treatment period
- Missing baseline mycology
- Baseline percentage nail involvement as assessed by planimetry outside the 20-65% range
- Use of wrong study medication
- Removal of target nail
- Violation of key entry criteria (negative culture)

Other protocol violations could invalidate certain observations from the efficacy analysis only on the visit in question (e.g., return visits outside the acceptable visit ranges).

Safety

According to the sponsor, safety was assessed as follows:

- Occurrence of local and systemic adverse events.
- Changes in physical examinations and in clinical laboratory values (hematology, serum chemistry (including CPK and CPK-MB levels), urinalysis).
- Serum pregnancy tests were performed for women of childbearing potential within 7 days of Day 1; urine pregnancy tests were performed at each return visit during the treatment period.
- Systemic cicloprox levels were evaluated at two centers (investigators 026 and 085). Blood samples for systemic cicloprox levels and its glucuronide metabolite were collected at Day and every 12 weeks (Weeks 12, 24, 36 and 48 during treatment and post-treatment weeks 2 and 4) for determination of the serum levels of ciclopirox.

Reviewer's comment: *Although the sponsor assessed local safety via the COSTART "skin and appendages" sections, it would be preferable to have a targeted assessment of nail bed and adjacent skin irritation included in the case report form. These events should be reported without regard to causality.*

8.2.1.3.2 Evaluability Criteria

8.2.1.3.3 Endpoints, Efficacy, and Safety Variables

The regressing clinical outcome subsets evaluated for this review will be the patients who achieved "complete cure", those who achieved "almost clear", and those with "negative mycology". These were evaluated at 48 weeks, 48 weeks (last observation carried forward) and at the final treatment visit plus 12 – 24 weeks (FTV + 12 – 24 weeks), also known as Proof of Cure (POC) time point or Post-Treatment Visit. As per protocol, the clinical trial was scheduled

for 48 weeks with a post-study follow-up period initially 24 weeks ± 7 days. The post-study follow-up period was changed per Amendment to 12 weeks ± 7 days.

Endpoint

The sponsor has submitted three definitions for Endpoint with the NDA submission.

- Endpoint was defined in the NDA submission (Vol. 1.34, Section 8.1.2, pg. 78, Table R11) as "Last post-Baseline visit for any subject.
- Endpoint was defined in the text under Section 8.1.2 (Vol. 1.34, Section 8.1.2, pg. 78) as "...Endpoint (= individual last value).
- Endpoint was defined (09-27-99 submission) as "Endpoint is the last available non-missing assessment during treatment period of 48 weeks.

Reviewer's Comments:

The Endpoint as defined by the sponsor appears to be more consistent with Last Observation Carried Forward (LOCF). Endpoint data presented by the sponsor did not include post-treatment follow-up data. Residual drug is present at both of the sponsor's assessments for end of study and endpoint. An endpoint definition could not be located in the original protocol or amendments.

It is the opinion of this Reviewer that efficacy endpoint assessments should also include post-treatment assessments where the inhibitory effect of active drug would not provide false-negative culture results. Previous applications that have been approved for the treatment of onychomycosis each demonstrated statistical superiority of active treatment group (clear nail and negative mycology) when compared to the placebo group. This success was demonstrated at a time point beyond the End of Treatment, in order to demonstrate that the drug product alone was not having an inhibitory effect upon the culture results.

Scoring Scales

Global improvement compared to Day 1 evaluations were assessed as follows:

0 = Cleared:	100% clearance of clinical signs of disease corroborated by absence of investigator markings on photograph
1 = Excellent Improvement	75% but less than 100% clearance of clinical signs of disease
2 = Moderate Improvement	50% to less than 75% clearance of clinical signs of disease
3 = Slight Improvement:	Less than 50% clearance of clinical signs of disease
4 = No Change:	No detectable improvement from Baseline evaluation
5 = Exacerbation:	Flare of area being studied and/or increase in area of involvement

The subungual hyperkeratosis of each nail was evaluated at Baseline and at each return visit during treatment and post-treatment (if applicable) using the following scale:

0 = none/absent 1 = present

Percentage Area Involved

The percentage of area involved of all treated fingernails and all non-target toenails was visually estimated at Day 1 and at each return visit using the following scale:

0 = No involvement 2 = 50 - <100% involvement
1 = 0 - <50% involvement 3 = 100% involvement

Reviewer's comment:

The only Global Improvement Score used to delineate an efficacy outcome category was "Cleared" defined by the sponsor as 100% clearance of clinical signs of disease corroborated by absence of investigator markings on photograph. The global assessment of "Cleared" (plus negative mycology) was used to define the sponsor's Treatment Cure (Complete Cure) Group only. The scoring scale above does not include 90% clearance of clinical signs of disease. Computerized planimetry was used to define this subset of patients with ≤ 10% involvement since the sponsor's scoring scale listed above did not include this level.

Demonstration of outcomes for the treatment of onychomycosis were discussed with the sponsor during the EP-2 Meeting between the sponsor and the Division on 09-11-95 and can be schematically represented by three regressing subsets:

1. *Completely clear nail with negative mycology (KOH preparation and culture)*
2. *Almost clear nail (90%) with negative mycology*
3. *Negative mycology alone*

Preferred topical dosage regimens

The subject was questioned at the Week 48 visit regarding a preferred dosing regimen of once daily, twice weekly, or once weekly applications for treatment of distal subungual tinea unguium.

At the final treatment phase visit, the subject rated the overall cosmetic acceptability using the following scale:

0 = Excellent	2 = Fair
1 = Good	3 = Poor

Reviewer's comment: *The objective of the sponsor's query of patient's preferred dosing regimen (once daily, twice weekly, or once weekly) is unclear. Dosing regimen should be based on science (dose ranging, efficacy, etc.) as demonstrated during conduct of the clinical trial.*

8.2.1.3.4 Statistical Methods

The sponsor's primary efficacy variable was time to occurrence of treatment success defined as 10% or less remaining involvement of the target nail in combination with a negative culture and negative KOH examination (Vol. 1.34, pg. 104). The sponsor's primary analysis compared time to occurrence of treatment success for the per protocol (PP, primary analysis) and intent-to-treat (ITT) populations (Vol. 1.34, pg.002). Efficacy analyses were performed for the per protocol (PP, primary analysis) and intent-to-treat (ITT) populations. The PP analyses included all efficacy data up to the time of any major protocol violation. Two-tailed tests were used, and results were considered significant if $p \leq 0.05$.

Reviewer's comments: *The sponsor's primary efficacy variable was time to occurrence of treatment success defined as 10% or less remaining involvement of the target nail in combination with a negative culture and negative KOH examination (Vol. 1.34, pg. 104).*

The sponsor's primary analysis compared the time to the occurrence of treatment success for the two treatment groups using the Cox Proportional Hazard (CPH) model. The Kaplan-Meier method was used to estimate the median time to success. The CPH model was used for the secondary efficacy variables. Efficacy variables were compared at 12, 24, 36, 48 weeks and at the individual Endpoints (the last post-Baseline visit for any given subject) using the Cochran-Mantel-Haenszel (CMH) test for general association stratified by investigator.

ITT Population was defined as all subjects having received at least one dose of randomized study medication. The PP Population was defined as all ITT subjects meeting all selection criteria at Baseline, except area of involvement, for which the range was extended to 20-65%.

Reviewer's comment: *The Division's statistical results are based on Fisher Exact Test although Cochran-Mantel-Haenszel tests (CMH) is usually recommended. See Statistical Review for rationale.*

For the purposes of this review, the sponsor's ITT consists of all patients who had a positive KOH at baseline and a positive dermatophyte culture at baseline or within 28 days prior to baseline and were dispensed study drug. Those randomized subjects with negative cultures at Baseline are usually discontinued from the study and categorized as ***Delayed Exclusions****, but in this case the culture positivity in the 28 days prior to baseline was acceptable.*

Baseline characteristics such as age, sex, race, etc. were summarized and presented as means, standard errors and percentages where appropriate. Frequency distributions were constructed. Means and categories were compared between treatment groups for homogeneity using either analysis of variance or Mantel Haenszel tests.

According to the sponsor, all subjects treated with test material were evaluated for safety. Treatment Emergent Adverse Events (TEAE) data and laboratory data were organized by subject listings, by body system, and by decreasing rate of incidence. Adverse events were listed and tabulated by body system. Tables were generated for adverse events possibly/probably related to study drug or irrespective of relationship to study drug and by decreasing rates. Laboratory data was listed and summarized by descriptive statistics (mean, median, and range). Abnormal laboratory values (those falling outside the normal range) were compared to the baseline distribution. Predefined change abnormal (PCAs) and last visit predefined change abnormal (LPCAs) was listed and summarized. Clinically noteworthy abnormal laboratory values were tabulated.

8.2.1.4 Results - Study 312 (Study Dates: July 25, 1994 - June 24, 1996)

Patient Disposition

Two hundred and twenty-three patients were randomized to treatment at nine centers. The investigators were:

No.	Name and Address
026	Raza Aly, PhD Dermatology Research #1 Irving Street AC34 University of California San Francisco, CA 94143
041	Manuel R. Morman, PhD, MD The Columns 47 Orient Way Rutherford, NJ 07070
046	Richard Scher, MD Columbia-Presbyterian Med Ctr Center-Atchley Pavilion Rm. 750, 161 Ft, Washington Ave New York, NY 10032
052	Ann W. Lucky, MD Derm Research Associates, Inc. 7591 Five Mile Road, Ste 312 Cincinnati, OH 45230
072	Jon Hanifin, MD Oregon Health Sciences University Department of Dermatology, L-468 3181 SW Sam Jackson Road Portland, OR 97201
075	Nicholas Lowe, MD Clinical Research Specialists 2001 Santa Monica Blvd. W409 Santa Monica, CA 90404
083	Terry M. Jones, MD VIP Research 2901 East 29th St., Ste. 117 Bryan, TX 77802
085	Sewon Kang, MD University of Michigan Med Ctr 1910 Taubman Center 1500 E. Medical Center Dr Ann Arbor, MI 48109
087	Matthew Stiller, MD Mass General Hospital Warren Bld. 505 Boston, MA 02114

There were 223 patients randomized to treatment out of 525 subjects screened. There were 302 screening failures; however, multiple entries were possible. Screening failures were listed as follows:

Table 7 Screening Failures

Screening Failures	Total (N= 302)
Negative or missing mycology	164
Area of involvement< 25% or >60%	49
Other	117

Enrolled patients were stratified by percent involvement at Baseline among the nine centers. Number of subjects by Investigator and Stratum Per Protocol Subjects follows:

Table 8 Percent Involvement at Baseline (Sponsor's Table 1.3, Vol. 1.34)

	20% to < = 40% Involvement			> 40% to < = 65% Involvement		
Inv./Center #	HOE 296NL	Vehicle	Total	HOE 296NL	Vehicle	Total
Aly (026)	10	10	20	5	4	9
Morman (041)	7	5	12	4	7	11
Scher (046)	10	7	17	5	7	12
Lucky (052)	6	6	12	7	7	14
Hanifin (072)	9	12	21	3	2	5
Lowe (075)	1	1	2	4	3	7
Jones (083)	3	2	5	4	8	12
Kang (085)	6	2	8	8	6	14
Stiller (087)	10	7	17	5	7	12
Total	62	52	114	45	51	96

Reviewer's comment: *There does not appear to be a difference between percent involvement at Baseline between the active group and vehicle groups*

8.2.1.4.1 Demographics, Evaluability Study 312

Table 9 Demographics (ITT Population) (Sponsor's Table 2.2, Vol. 1.34)

Characteristic	Ciclopirox (HOE 296NL)	Vehicle	Between Treatment p-Value*
No. of subjects	112	111	
Sex			0.347
Male	85 (76%)	90 (81%)	
Female	27 (23%)	21 (20%)	
Ages (Yrs)			0.308
Mean	50.4	48.6	
SD	12.26	13.23	
Median	50.0	50.0	
Range	20 – 70	18 –70	
Race			0.413
White	106 (95%)	102 (92%)	
Black	1	2	
Hispanic	4	7	
Other	1	0	

*P-Value is from Mantel-Haenszel test (two-tailed) was performed.

Both active and vehicle groups were similar.

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Table 10 Study 312 Infecting Organisms (ITT)

Genus +species	Ciclopirox (HOE 296 NL	Vehicle
Trichphyton rubrum	102 (96%)	100 (97%)
Trichphyton mentagrphytes	4 (4%)	3 (3%)
Other dermatophyte	-	-

Table 11 Study 312 Completion Status (Sponsor's Table 1.2, Vol. 1.34)

	Intent to Treat Subjects		Per Protocol Subjects	
	HOE 29NL	Vehicle	HOE 29NL	Vehicle
No. of subjects randomized	112	111	107	103
No. of subjects treated	112	111	107	103
No. of subjects included in analysis of:				
Global Evaluation	110	109	106	103
Mycological Evaluation	105	105	102	100
Area of involvement	107	107	103	101
Completed Study	89	84	88	80
Did not complete Study	23	27	19	23
Entered Post-treatment	5	1	5	1
Entered Protocol 320	70	65	69	63
Reason for not completing Study				
Does not meet protocol criteria	5	5	2	2
Moved/lost to follow-up	6	5	5	5
Safety: AE/ intercurrent medical problem	0	1	0	1
Safety: laboratory	0	1	0	1
Lack of efficacy	1	3	1	3
Subject request	3	4	3	4
Other	1	0	1	0

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8.2.1.4.2 Efficacy Endpoint Outcomes

8.2.1.4.2.1 Clinical

For the Intent-to-Treat population (ITT) there were 112 in the active group and 111 in the vehicle group.

Complete Cure

ITT Population with Complete Cure at End of Study (Week 48) with Post-treatment Follow-up data at 12 and 24 Weeks are listed below. At the 12-week post-study follow-up, there were two active-group patients (026/0116 and 052/0402) and one vehicle-group patient (052/0404) in this category. These patients maintained a clear target nail with negative mycology, and remained Complete Cures at 24 weeks post-treatment.

Table 12 Sponsor's Clinical Endpoint Results Study 312 (ITT population): Active (N = 112) Vehicle (N = 111)

Endpoints	End of Study		Post-week-12		Post-week-24	
	Group		Group		Group	
	Active	Vehicle	Active	Vehicle	Active	Vehicle
Completely Cured	5	1	3	1	2	1
Effectively Treated	1	0	No post study data available			
Mycological Cure	20	13	No post study data available			
Totals	26	14	3	1	2	1

Five patients out of the six listed by the sponsor as Treatment Success had post-treatment follow assessments. They are as follows:

Table 13 Patients with Post-Study Follow-up (Proof of Cure) Data

Patient I.D. # Active Group (Infecting organism)	End of Study Mycology Results	Post-treatment Follow-up					
		Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
026/0104 *(T. rubrum)*	Culture (-) KOH (-)						Culture (+) KOH (+)
026/0116 *(T. rubrum)*	Culture (-) KOH (-)			Culture (-) KOH (-)			Culture (-) KOH (-).
041/0218 *(T. rubrum)*	Culture (-) KOH (-)						Not evaluable*
052/0402 *(T. mentag.)*	Culture (-) KOH (-)			Culture (-) KOH (-)			Culture (-) KOH (-)
087/0926 *(T. mentag.)*	Culture (-) KOH (-)				Culture (-) KOH (+)		Culture (+) KOH (+)
Vehicle							
052/0404 *(T. rubrum)*	Culture (-) KOH (-)			Culture (-) KOH (-)			Culture (-) KOH (-).

* Submission received 8-6-99 listed this patient as not evaluable.

Table 14 Complete Cure (ITT Population)

The following table was partially extracted from the Draft Statistical Review (dated 09-22-99):

	Week 48	LOCF-48 wk.	12 Week (+ LOCF)	24 Week (+ LOCF)
Loprox				
Cure	4	4	2	2
N	91	112	110	111
%	4.4	3.6	1.8	1.8
Vehicle				
Cure	1	1	1	1
N	83	110	110	110
%	1.2	0.9	0.9	0.9
CMH p-value	0.231	0.184	0.559	0.573
Fisher p-value	0.370	0.369	1.000	1.000

Table 15 Sponsor's Assessment of Incidence of Treatment Cure

Sponsor's Table R 12, Vol. 1.34 Incidence of Treatment Cure
Combined strata
Treatment Cure: KOH negative, culture negative, and global evaluation score =clear

Time Point	PP Ciclopirox n/N[1]	PP Ciclopirox %[1]	PP Vehicle n/N[1]	PP Vehicle %[1]	PP CMH statistic stratified by center p-value	ITT Ciclopirox n/N[1]	ITT Ciclopirox %[1]	ITT Vehicle n/N[1]	ITT Vehicle %[1]	ITT CMH statistic Stratified by center p-value
Week 12	0/101	0	0/92	0	--	0/102	0	0/100	0	--
Week 24	0/96	0	0/90	0	--	0/97	0	0/94	0	--
Week 36	1/86	1	1/76	1	0.895	1/87	1	1/80	1	0.95
Week 48	5/86	6	1/74	1	0.073	5/87	6	1/77	1	0.061
Endpoint[2]	6/106	6	1/103	1	0.055	6/110	6	1/109	1	0.059

[1] Figures denote proportion and percentage of subjects achieving treatment success. Percentages are rounded to whole numbers.
[2] Last post-baseline visit for any subject.
Source: Statistical table 7.1.1; 7.2

Reviewer's comments:

Both the Division and the sponsor defined the same regressing subsets; however, the number of patients in these categories differed and the sponsor's subsets did not regress. Endpoint definitions and the statistical tests used in data analysis also differed. For example:

		ITT Patient Population (Completely Cured)	
	End of Study (Wk. 48)	Endpoint (Wk. 48 LOCF)	Endpoint (12 Weeks + LOCF)
Division	N=4	N=4	N=2
Sponsor	N=5	N=6 (Last post-baseline visit for any subject)	

Ordinarily, a discrepancy of one or two patients would not necessarily have a significant impact on p-values; however, when the numbers of successes are small, the difference of one or two patients might impact the p-value. Therefore, requests for additional data (photographs and individual listings) were made to clarify these discrepancies between the Division and sponsor.

The following assessments were made prior to evaluation of the photographs of the Cleared and Almost Clear subsets.

Table 16 Division Complete Cure/Sponsor Treatment Cure (Study 312)

Investigator	*Subject*	*Sponsor Week 48*	*Sponsor Endpoint*		*Division Week 48*	*Division Week 48 (LOCF)*	*% Clear (Week) Planimetric Measurement*
Active							
026	*0104*	*Yes*	*Yes*		*Yes*	*Yes*	*3.26 (48)*
	0116	*Yes*	*Yes*		*Yes*	*Yes*	*6.44 (48)*
041	*0218 (1)*	*Yes*	*Yes*		*No*	*No*	*27.55 (40)*
052	*0402*	*Yes*	*Yes*		*Yes*	*Yes*	*3.27 (48)*
072	*0511*	*No*	*Yes*		*No*	*No*	*7.23 (40)*
087	*0926*	*Yes*	*Yes*		*Yes*	*Yes*	*3.32 (48)*
Vehicle							
052	*0404*	*Yes*	*Yes*		*Yes*	*Yes*	*0.69 (48)*

(1) Patient 041/0218 was excluded from the Division's End of Study efficacy analysis because Complete Cure was achieved at Week 52 (day 365) instead of Week 48.

The sponsor's subsets did not regress, that is, all subjects with a global of cleared (100% clearance of clinical signs of disease) were not included with the Almost Clear (≤10% nail involvement) subset. The sponsor's subsets were computed using different decision rules.

Additionally, inconsistencies were noted in that there were global assessments of cleared and computerized photographic planimetric measurements of greater than zero. While evaluating the photographs to assess the positive planimetry in cleared patients, it became apparent that there were some patients with a global of clear who could be considered to have a nail that did not appear to be clear.

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The following table contains a summary of the reviewer's assesssment of the completely cured group after evaluation of the photographs.

Only the date of the global assessment is listed; however, all other measures listed for that patient in Table 19 were made at the same visit. Planimetric measurements submitted by the sponsor for these patients are listed in Table 19 and this Reviewer's assessments of the photographs are included.

Table 17 Treatment Cure/Complete Cure at Week 48

Treatment Group	Inv/ Subject #	ITT	PP	Results for Sponsor's Treatment Cure at Week 48				Reviewer's Photo Assessment
				Global (Date)	KOH	Culture	Planimetric Measurement	
Active (HOE296NL)	026/0104	Yes	Yes	Cleared (10-24-95)	Neg.	Neg.	3.26	Questionable
	026/0116	Yes	Yes	Cleared (09-20-95)	Neg.	Neg.	6.44	Questionable
	041/0218*	Yes	Yes	Cleared (01-15-96)	Neg.	Neg.	NA	Not Clear
	052/0402	Yes	Yes	Cleared (09-15-95)	Neg.	Neg.	3.27	Questionable
	087/0926	Yes	Yes	Cleared (08-04-95)	Neg.	Neg.	3.32	Clear
Vehicle	052/0404	Yes	Yes	Cleared (08-15-95)	Neg.	Neg.	0.7	Questionable

*Patient 041/0218 was excluded from the Division's Week 48 Efficacy analysis; however, was included in the sponsor's efficacy analysis.

Endpoint Comparison

There were differences between the Division and sponsor number of patients at Endpoints because the Division and the sponsor defined Endpoint differently. As previously discussed, endpoint was defined by the sponsor (09-27-99 submission) as "Endpoint is the last available non-missing assessment during treatment period of 48 weeks.

End of treatment and end of treatment plus a post-treatment follow-up period or "Proof of Cure" assessment were assessed during this review. LOCF was also assessed at these time points.

Sponsor's and Reviewer's Endpoint Assessments follows in Table 20.

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Table 18 Treatment Cure (Complete Cure) Endpoint Assessments Comparison
Sponsor's / Reviewer's Endpoint Assessments (Note: the Reviewer's Endpoint assessment is not LOCF)

Inv/ Subject #	Results for Sponsor's Treatment Cure at Week 48 (end of treatment)				Post-Treatment Data (Treatment Cure/Complete Cure)								Endpoint Assessment		
													Sponsor		Re-viewer
	Week 48				Post Week 12				Post Week 24						
	Culture	KOH	Global	Planimetric	Culture	KOH	Global	Planimetric	KOH	Culture	Global	Planimetric	ITT	PP	ITT
Active HOE296NL															
026/0104	Neg.	Neg.	Cleared	3.26			EI	0.9	Pos.	Pos.	MI	6.4	Yes	Yes	No
026/0116	Neg.	Neg.	Cleared	6.44	Neg.	Neg.	Cleared	10.0	Neg.	Neg.	Cleared	8.4	Yes	Yes	No
041/0218	Neg.	Neg.	Cleared	NA	Neg.	Neg.	Cleared					NE	Yes	Yes	No
052/0402	Neg.	Neg.	Cleared	3.27	Neg.	Neg.	Cleared	0.0	Neg.	Neg.	Cleared	0.9	Yes	Yes	No
072/0511	Excluded by sponsor from Wk. 48												Yes	Yes	No
087/0926	Neg.	Neg.	Cleared	3.32	Pos.	Pos.	Cleared	6.8	Pos.	Pos.	Cleared	4.4	Yes	Yes	Yes
Vehicle															
052/0404	Neg.	Neg.	Cleared	0.7	Neg.	Neg.	Cleared	0.0	Neg.	Neg.	Cleared	0.0	Yes	Yes	Yes

Blank spaces = no data available /NE = not evaluable
Global Assessments
Global Evaluation (C= cleared, EI = Excellent Improvement, MI = moderate Improvement, NC = no change)
Yes = Complete cure; No = Not complete cure

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Reviewer's comments:

It became apparent that complete clearing of clinical signs of disease is subjective and perhaps a difficult endpoint to assess in a disease like onychomycosis. Complete clearing may mean different things to different investigators. Additionally, it can be difficult in some instances to rely on photographs for re-assessment because of many variables (e.g., distance, lighting, focus, etc.); however, this Reviewer's photographic assessments were more consistent with the planimetic measurement results than the Investigator's assessment of "clear".

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Almost Clear/Effectively Treated/Treatment success: ≤10% nail involvement, KOH negative, and culture negative

The Division and sponsor's assessments follow in Tables 22 and 23, respectively.

Table 19 Treatment Success/Almost Clear/Effective Treatment (ITT Population)

The following was table partially extracted from the Draft Statistical Review (dated 09-22-99):

	Week 48	LOCF-48 wk.	12 Week (+ LOCF)	24 Week (+ LOCF)
Loprox				
Cure	6	7	2	2
N	80	108	106	107
%	7.5	6.5	1.9	1.9
Vehicle				
Cure	1	1	1	1
N	69	109	109	109
%	1.4	0.9	0.9	0.9
CMH p-value	0.090	0.028	0.559	0.573
Fisher p-value	0.125	0.035	0.618	0.620

Table 20 Sponsor's Assessment of Incidence of Treatment Success

Sponsor's Table R 11, Vol. 1.34 Incidence of Treatment Success
Combined strata
Treatment Success: ≤10% nail involvement, KOH negative, and culture negative

	PP					ITT				
	Ciclopirox		Vehicle		CMH statistic stratified by center	Ciclopirox		Vehicle		CMH statistic stratified by center
Time Point	n/N[1]	%[1]	n/N[1]	%[1]	p-value	n/N[1]	%[1]	n/N[1]	%[1]	p-value
Week 12	1/100	1	1/92	1	0.915	1/101	1	1/98	1	0.937
Week 24	2/92	2	1/87	1	0.557	2/93	2	1/91	1	0.524
Week 36	5/82	6	1/69	1	0.119	5/83	6	1/73	1	0.107
Week 48	6/81	7	1/74	1	0.071	6/82	7	1/77	1	0.064
Endpoint[2]	8/103	8	1/101	1	0.018	8/107	8	1/107	1	0.019

[1] Figures denote proportion and percentage of subjects achieving treatment success. Percentages are rounded to whole numbers.
[2]Last post-baseline visit for any subject. (Source: Statistical table 7.1.1; 7.2)

According to the sponsor, time-to-event analysis includes subjects with success at any time during the study. The Endpoint analysis includes only subjects with success at Endpoint (= individual last value). Primary efficacy analysis was Time to Occurrence of Treatment Success defined as 10% involvement of the target nail and negative culture and KOH examination. The sponsor's secondary efficacy analysis was Incidence of Treatment Success. As previously stated, the sponsor's Treatment Success is equivalent to the Division's Effectively Treated category.

Reviewer's comment: *Differences in the number of patients were previously discussed in this Section. Differences in the statistical tests used and the rationale for these differences (e.g., Fisher Exact Test was used by the Division, CMH was initially recommended by the Division and used by the Sponsor) are discussed in the Statistical Review.*

Study 312 Mean Percent Area from Planimetric Measurements (ITT Population)

Table 21 The following table was partially extracted from the Draft Statistical Review (dated 09-22-99):

	Week 48	LOCF-48 wk.	LOCF (60 Weeks)	
Loprox				
LS Mean	37.9	39.4	39.3	
Std Err	2.3	1.9	1.9	
N	72	107	107	
Vehicle				
LS Mean	43.6	43.9	44.7	
Std Err	2.5	1.9	1.9	
N	62	107	107	
p-value*	0.0954	0.0886	0.0454	

* - From ANOVA test of treatment differences (Type 3 SSQ)
** - Contracts defining LS Means redefined (effectively investigator 75 deleted)

According to the Statistical Review, at the 0.05 level, neither this test or the test for the corresponding LOCF group are statistical significant ($p \leq 0.0954$ and $p \leq 0.0886$, respectively).

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Mycological Cure

	Active	Vehicle	p-value
Negative culture and negative KOH			
Week 48	26/84 (31%)	8/73 (11%)	(0.002)
Endpoint	30/102 (29%)	13/100 (13%)	(0.001)
Negative culture			
Week 48	75/82 (92%)	26/69 (38%)	(<0.001)
Endpoint	91/107 (85%)	40/103 (39%)	(<0.001)
Negative KOH			
Week 48	28/85 (33%)	19/74 (26%)	(0.344)
Endpoint	31/103 (30%)	26/100 (26%)	(0.345)

Reviewer's comment:

There is an apparent drug effect at Week 48. For Mycological Cure, according to the sponsor, statistical significance of active over vehicle was achieved at Week 48 (p-value 0.002) and Endpoint (p-value 0.001). Sustained efficacy in post treatment or Proof of Cure cannot be validated.

The Division's statistical review found statistically significant ($p \leq 0.011$ and $p \leq 0.002$ at week 48 and LOCF 48 weeks, respectively) differences of active over vehicle in the ITT Population. However, it is unknown whether these results are sustained post-treatment.

As previously noted from Table 13, Patients with Post-Study Follow-up (Proof of Cure) Data, of the four patients in the active group with Complete Cure, there were 2 (50%) relapses. Both culture and KOH became positive in these instances.

Efficacy Conclusion:

Complete Cure/Treatment Cure

The initial Statistical Review was based on acceptance of the data as presented (i.e., Global Assessment of "Cleared" without examination of the corresponding photographs). For the **primary efficacy variable,** Complete Cure/Treatment Cure, statistical significance between ciclopirox nail lacquer and its vehicle was not demonstrated at the end of week 48 for the ITT or Week 48 (LOCF). A statistically significant difference between ciclopirox nail lacquer and its vehicle was not demonstrated at either post-treatment time points, 12 or 24 weeks. Global Assessment of "Cleared" was not as clear-cut after review of the photographs. There was substantial improvement over Baseline in the photographs examined; at least one photograph

(#041/0218) did not appear Clear to two Division Reviewers. Assessment of the photographs did not change the statistical outcome.

Almost Clear/Effective Treatment/ Treatment Success

For Almost Clear/Effective Treatment/ Treatment Success, at LOCF (48 weeks), the differences are barely significant. No statistically significant differences between ciclopirox nail lacquer and its vehicle were demonstrated at the end of Week 48 and post-treatment Week 12 (+LOCF) for the ITT population. There did not appear to be inconsistencies between the reviewer's assessment of the photographs and the planimetric assessment of the nail for Almost Clear/Effective Treatment/ Treatment Success or at least a 90% clear target nail.

Mycological Cure

The results are statistically significant at $p \leq 0.011$ and $p \leq 0.002$, at Week 48 and LOCF Week 48, respectively. At Post Weeks 12 and 24, there are no statistically significant differences.

For all categories, nail trimming was an integral part of the protocol, being conducted weekly by the patient and more aggressively on a monthly basis by the investigator. Any successes are likely to be due both to application of ciclopirox topical solution and nail trimming.

Reviewer's comments:

The sponsor was unable to demonstrate statistical superiority of ciclopirox topical solution, 8% over vehicle for this endpoint in Study 312. The sponsor was able to barely demonstrate statistical superiority of ciclopirox topical solution, 8% over vehicle for the sponsor's chosen primary efficacy endpoint Treatment Success/Almost Clear.

The sponsor's outcome groups are not always consistent with the regressing subsets The sponsor's efficacy endpoints, Treatment Success and Treatment Cure, were computed using different methods: (i.e., Global Improvement Score and computerized planimetry). A Global Improvement Score of 100% clear should correlate with planimetric scoring values.

There were differences in patient outcome assessments between the sponsor and the Division; however, the numbers of patients were somewhat similar. The Division included patients in the Almost Clear Subset that the sponsor excluded. It appears that the sponsor excluded patients with a global assessment of cleared from the Treatment Success category if planimetric measurements were not available at the visit although the inference would have been that there were 100% clear with no involvement. There were very few global assessments of cleared that coincided with planimetric measurements of zero. This illustrates the inconsistencies between the global assessment of clear and planimetric measurements.

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8.2.1.4.3 Safety

Local Safety

Specific local sign assessments (e.g., application site reaction or local erythema scoring) were not performed. The following table of Treatment Emergent Adverse Events (TEAEs) Possibly or Probably Causally Related to Test Material is presented to provide local safety data; however, these data were not identified as such by the sponsor.

Reviewer's comment: *Although the sponsor assessed local safety via the COSTART "Skin and Appendages" sections, it would be preferable to have a targeted assessment of nail bed and adjacent skin irritation included in the case report form. These events should be reported without regard to causality.*

Table 22 TEAEs Possibly or Probably Causally Related to Test Material
(Sponsor's Table R22, Vol. 1.34, pg. 94)

	Ciclopirox		Vehicle	
	N	%	N	%
Total No. of Subjects Treated	112	100	111	100
No. With TEAE	9	8	3	3
Application site reaction	3	3	2	2
Burning Sensation Skin	0	0	1	1
Skin Disorder	0	0	1	1
Nail Disorder	2	2	0	0
Rash	4	4	0	0

Reviewer's comment: *The most frequently occurring TEAE considered causally related to the test material in the ciclopirox group was rash (ciclopirox: 4% [4/112]; vehicle: none). Rash terminology included periungual erythema, proximal nail fold erythema, slight erythema around PNF, etc. These AEs are more consistent with application site reactions. Although the active drug appears to be somewhat of an mild irritant, there were no known drop-outs due to irritation.*

Ciclopirox Serum Levels

Centers 026 and 085 were designated to collect blood samples for determination of ciclopirox including its glucuronide metabolite. Sampling occurred at Weeks 12, 24, 36, and 48. Ciclopirox serum levels above the limit of quantification [redacted] at one or more visits were found in 9/51 subjects. Seven of these subjects had used concomitant ciclopirox-containing medication. The highest measured value was 24.5 ng/mL.

Table 23 Serum Ciclopirox Levels (Study 312)

Treatment Group	Inv/Sub	Highest ciclopirox serum level (ng/mL)	Week of Study Recorded	Concomitant Loprox (ciclopirox) Yes	No	
Active	026/0112	12.5	Wk-12		X	
	026/0126	11.5	Wk-48	X		
	026/0130	19.5*	Wk-12	X		
	085/0806	24.5	Wk-48	X		
	085/0809	13.0	Wk-48	X		
	085/0812	18.9	Wk-48	X		
	085/0828	15.6	Wk-12	X		
Vehicle	026/0115	11.4	Wk-48	X		
	026/010	12.6	Wk-48	X		

* Subject 026/0130 had multiple detectable ciclopirox serum levels.

Reviewer's comment: (See Biopharm comments)
Atrial fibrillation recorded as an AE for Subject 085/0812, a 68-y.o.male. Other AEs reported during detectable serum ciclopirox levels were mostly upper respiratory in nature. However, the highest recorded concentration was more than 800 times lower than the lowest concentration measured at a toxic dose in animals (20 µg/ml) and more than 200 times lower than the lowest measured at a non-toxic dose in animals (6 µg/ml).

Subjects with adverse events within 30 days of detectable ciclopirox levels are listed in Table 57, Section 10.2.1 of this review. Atrial fibrillation was the only cardiac related AE recorded and probably was not related. The onset was Day-322 with end Day-336 for subject 085/0812, a 68-y.o.male. This cardiac event and detectable ciclopirox level occurred during the same period. A normal cardiac examination was recorded for subject 085/0812 at entry. Prior cardiac history was not provided. The significance of this AE associated with a detectable level of ciclopirox is unknown.

The contribution of and or significance of concomitant use of Loprox are not clear; however, as observed in the vehicle group concomitant use of Loprox contributes to detectable levels. It would have been useful to present the data delineating the sources of the detectable ciclopirox levels.

Clinical Laboratory Analyses
In addition to general routine clinical laboratory assessments (hematology, urinalysis, and serum chemistry) the sponsor monitored creatine kinase (CPK) levels. Any serum sample that had an elevated CK level of >400 U/L (high panic level was to be automatically analyzed for the isoenzyme muscle-brain band (CK-MB). Abnormal laboratory values were to be explained if they were considered clinically important abnormalities and results.

Reviewer's comment: *The sponsor did not provide a rational for monitoring creatine kinase (CPK) levels with reflex CK-MB level determinations. The MB isoenzyme of CK is not present in significant concentrations in extracardiac tissue and is therefore a more specific indicator of cardiac muscle injury than CPK. Abnormal CK-MB levels were selected by this Reviewer for presentation because of the implications of possible cardiac toxicity.*

As mentioned in Section 4, Animal Pharmacology/Toxicology, oral dose-dependent myocardial degeneration was observed in rats and dog studies; therefore, the abnormal CK-MB levels are of concern because of the higher concentration of ciclopirox in the nail lacquer formulation and concomitant therapy with other approved ciclopirox containing products. However, according to the Pharm/Tox Review, it is safe to assume that topical applications of ciclopirox nail lacquer should not produce any significant toxicity in humans based on the margin of safety established from animal studies and absorption studies in humans.

Abnormal serum creatine phosphokinase- MB (CK-MB) levels were as follows:

Table 24 Abnormal Serum Creatine Phosphokinase-MB (ng/mL) Normal Range: 0-4.999 (Study 312)

Sponsor's Data Listing 14.2, Vol. 1.38 (Abnormal Lab. Values During Treatment – Subjects With No Baseline Data) Study 312.

INV/ SUBJ	Sex, Age (yr.)	Week 12	Week 24	Week 28	Week 36	Week 40	Week 48	F/U
HOE 296NL								
041/0225	F 53	-	9.000H	-	-	-	-	-
041/0228	M 29	-	4.500	-	-	-	6.600H	-
046/0324*	M 52	-	-	-	6.900H	-	-	-
052/0413	M 63	-	-	-	-	-	9.900 H	-
087/0903*	M 63	-	6.700H	4.200	-	-	-	-
087/0929*	M 52	-	7.800H	-	-	-	-	-
Vehicle								
042/0401	M 62	-	-	-	-	13.000H	-	-
052/0412**	M 43	-	-	-	9.800H	-	12.700H	10.200#H
								10.100#H
083/0711	M 55	-	-	-	-	-	11.600H	-
087/0922*	M 47	15.400xH						
		10.600xH						
		11.200 H						

*Subjects with ciclopirox listed as concomitant medication.
**Subject 052/0412 was dropped from Study 320 because of elevated CK-MB levels.

Two patients, 087/0922 and 052/0412, were discontinued from the study because of abnormal CK-MB levels. Both patients were enrolled in the vehicle group; however, 087/0922 had ciclopirox exposure with concomitant use of ciclopirox 1% cream. The investigators attributed the elevated levels in both subjects to exercise.

Reviewer's comments:
Ten patients were reported to have abnormal CK-MB levels. Seven of the 10 patients were either in the active group and or used ciclopirox as concomitant medication. According to the sponsor, the elevated CK-MB values found in the placebo and active groups are distributed in a statistically random manner between the individual time segments (weeks 12, 24,36, 40, and f/u. The elevated CK-MB values found in both groups exhibit no relationship to reported AEs, dose modification or concomitant ciclopirox cream medication. Additionally, neither placebo nor active group patients complained of cardiac symptoms.

All subjects treated with test material were evaluated for safety. The adverse events that follow are listed and tabulated by body system irrespective of relationship to study drug.

Reviewer's comments:
The patients are grouped for adverse events reporting according to study arm assignment (i.e., active vs. vehicle) as customarily presented in an NDA. This presentation is satisfactory for evaluating relationships to local safety; however, for comparisons of systemic effects of ciclopirox the following sub-groups would have been preferable: ciclopirox nail lacquer 8%, ciclopirox nail lacquer 8% + concomitant ciclopirox, vehicle, and vehicle + concomitant ciclopirox.

Study 312

Table 25 Treatment Emergent Adverse Events (TEAE) (Sponsor's Table 20.1.1, Vol. 1.34)
Rates By Body System Irrespective of Relationship to Study Drug

	HOE 296NL		Vehicle	
	No.	%	No.	%
Total No. of Subjects Treated	112	100.0	111	100.0
No. without TEAE	24	21.4	17	15.3
No. with TEAE	88	78.6	94	84.7
Body As A Whole	34	30.4	45	40.5
Accidental injury	11	9.8	24	21.6
Flu syndrome	13	11.6	12	10.8
Hernia	1	0.9	4	3.6
Infection	3	2.7	4	3.6
Pain in extremity	4	3.6	3	2.7
Back pain	4	3.6	3	2.7
Allergic reaction	2	1.8	2	1.8
Pain	2	1.8	2	1.8
Abdominal pain	1	0.9	1	0.9
Carcinoma	0	0.0	1	0.9
Cyst	0	0.0	1	0.9
Fever	0	0.0	1	0.9
Neck pain	2	1.8	1	0.9
Neck rigidity	2	1.8	1	0.9
Neoplasm	1	0.9	1	0.9
Surgery	3	2.7	1	0.9
Infection superimposed	1	0.9	0	0.0
Sepsis	1	0.9	0	0.0
Cardiovascular System	8	7.1	8	7.2
Hypertension	1	0.9	5	4.5
Cardiovascular disorder	0	0.0	2	1.8
AV block second degree	0	.0	1	0.9
Migraine	1	0.9	0	0.0
Angina pectoris	1	0.9	0	0.0
Atrial fibrillation	1	0.9	0	0.0
Chest pain	1	0.9	0	0.0
Congestive heart failure	1	0.9	0	0.0
Coronary artery disorder	1	0.9	0	0.0
Coronary artery occlusion	1	0.9	0	0.0
Hemorrhage	1	0.9	0	0.0
Digestive System	28	25.0	28	25.0
Gastroenteritis	2	1.8	5	5.4
Periodontal abscess	4	3.6	5	5.4
Diarrhea	3	2.7	4	3.6
Gastrointestinal disorder	4	3.6	3	2.7
Tooth disorder	1	0.9	3	2.7
Sore throat	3	2.7	2	1.8
Aphthous stomatitis	0	0.0	1	0.9
Constipation	0	0.0	1	0.9

Rates By Body System Irrespective of Relationship to Study Drug (continued)

	HOE 296NL		Vehicle	
	No.	%	No.	%
Duodenal ulcer	1	0.9	1	0.9
Dyspepsia	1	0.9	1	0.9
Esophagitis	1	0.9	1	0.9
Gastritis	0	0.0	1	0.9
Gastrointestinal fullness	0	0.0	1	0.9
Glossitis	0	0.0	1	0.9
Liver function test abnormal	0	0.0	1	0.9
Nausea	1	0.9	1	0.9
Rectal bleeding	1	0.9	1	0.9
Rectal disorder	1	0.9	1	0.9
Cholecystitis	1	0.9	0	0.0
Gastrointestinal pain	1	0.9	0	0.0
Gingivitis	2	1.8	0	0.0
Gum disorder	1	0.9	0	0.0
Intestinal obstruction	1	0.9	0	0.0
Melena	1	0.9	0	0.0
Stomach ulcer	2	1.8	0	0.0
Tooth caries	2	1.8	0	0.0
Vomiting	1	0.9	0	0.0
Hemic & Lymphatic System	**5**	**4.5**	**0**	**0.0**
Ecchymosis	1	0.9	0	0.0
Lymphadenopathy	2	1.8	0	0.0
Purpura	1	0.9	0	0.0
Thrombocytopenia	1	0.9	0	0.0
Metabolic & Nutritional Disorder	**3**	**2.7**	**2**	**1.8**
Gout	1	0.9	1	0.9
Hyperglycemia	0	0.0	1	0.9
Hypercholesterolemia	2	1.8	0	0.0
Musculo-Skeletal System	**17**	**15.2**	**13**	**11.7**
Athralgia	10	8.9	6	5.4
Arthritis	1	0.9	2	1.8
Bone fracture (not spontaneous)	1	0.9	2	1.8
Myalgia	1	0.9	2	1.8
Arthrosis	0	0.0	1	0.9
Joint disorder	1	0.9	1	0.9
Myopathy	0	0.0	1	0.9
Bone disorder	1	0.9	0	0.0
Bursitis	1	0.9	0	0.0
Muscle cramps	1	0.9	0	0.0
Tendinous contracture	1	0.9	0	0.0
Tenosynovitis	1	0.9	0	0.0
Nervous System	**17**	**15.2**	**15**	**13.5**
Headache	11	9.8	8	7.2
Depression	4	3.6	2	1.8
Neuralgia	0	0.0	2	1.8
Ataxia	0	0.0	1	0.9
Paresthesia	0	0.0	1	0.9
Vertigo	0	0.0	1	0.9
Insomnia	1	0.9	0	0.0

Rates By Body System Irrespective of Relationship to Study Drug (continued)

	HOE 296NL		Vehicle	
	No.	%	No.	%
Neuropathy	1	0.9	0	0.0
Tremor	1	0.9	0	0.0
Respiratory System	**53**	**47.3**	**45**	**40.5**
Upper respiratory infection	34	30.4	35	31.5
Rhinitis	10	8.9	6	5.4
Sinusitis	13	11.6	4	3.6
Asthma	1	0.9	1	0.9
Bronchitis	1	0.9	1	0.9
Cough increased	1	0.9	1	0.9
Pharyngitis	1	0.9	1	0.9
Pneumonia	0	0.0	1	0.9
Respiratory disorder	1	0.9	1	0.9
Epistaxis	1	0.9	0	0.0
Laryngitis	4	3.6	0	0.0
Voice alteration	1	0.9	0	0.0
Skin and Appendages	**52**	**46.4**	**46**	**41.4**
Fungal dermatitis	16	14.3	23	20.7
Rash	9	8.0	9	8.1
Contact dermatitis	3	2.7	5	4.5
Maculopapular rash	2	1.8	4	3.6
Nail disorder	10	8.9	3	2.7
Skin disorder	2	1.8	3	2.7
Application site reaction	3	2.7	2	1.8
Herpes simplex	2	1.8	2	1.8
Skin benign neoplasm	3	2.7	2	1.8
Skin hypertrophy	4	3.6	2	1.8
Acne	1	0.9	1	0.9
Alopecia	0	0.0	1	0.9
Burning sensation skin	1	0.9	1	0.9
Eczema	0	0.0	1	0.9
Herpes zoster	1	0.9	1	0.9
Seborrhea	0	0.0	1	0.9
Skin carcinoma	3	2.7	1	0.9
Skin discoloration	0	0.0	1	0.9
Urticaria	1	0.9	1	0.9
Breast carcinoma	1	0.9	0	0.0
Furunculosis	1	0.9	0	0.0
Pruritus	1	0.9	0	0.0
Special Senses	**4**	**3.6**	**7**	**6.3**
Conjunctivitis	0	0.0	3	2.7
Abnormal vision	0	0.0	1	0.9
Ear disorder	1	0.9	1	0.9
Eye disorder	0	0.0	1	0.9
Otitis media	1	0.9	0	0.0
Lacrimation disorder	1	0.9	0	0.0
Otitis externa	1	0.9	0	0.0
Urogenital System	**8**	**7.1**	**8**	**7.2**
Urinary tract infection	2	1.8	4	3.6
Prostatic carcinoma	0	0.0	2	1.8
Dysmenorrhea	0	0.0	1	0.9
Kidney calculus	2	1.8	1	0.9
Menstrual disorder	0	0.0	1	0.9

Rates By Body System Irrespective of Relationship to Study Drug (continued)

	HOE 296NL		Vehicle	
	No.	%	No.	%
Urinary incontinence	0	0.0	1	0.9
Vaginitis	0	0.0	1	0.9
Bladder carcinoma	1	0.9	0	0.0
Penis disorder	1	0.9	0	0.0
Prostatic disorder	4	3.6	0	0.0

Reviewer's comments:

Nail disorders were reported in 10 (8.9%) patients on active treatment and 3 (2.7%) in the vehicle group. Of the nail disorders, 6 were reported as ingrown toenail in the active group and one reported in the vehicle group. For nail disorders, there does appear to be a relationships to therapy; however, the effects are unknown.

Six of the nine reports of rash were confined to the foot in the active group; however, none of the CFR entries were located on the foot or hand in the vehicle group (Data Listing 13.1, Vol. 1.38). As previously addressed, rash terminology listed included periungual erythema, proximal nail fold erythema, slight erythema around PNF, etc. These AEs are more consistent with application site reactions and are propably related to therapy. Although the active drug appears to be somewhat of an mild irritant, there were no known drop-outs due to irritation.

Tinea pedis was the term most often cited under fungal dermatitis from CRF entries. The implication or significance of this finding is not clear.

As previously stated, the following subgroup comparisons of systemic adverse events would have been preferable: Ciclopirox nail lacquer 8%, Ciclopirox nail lacquer 8% + concomitant ciclopirox, Vehicle, and Vehicle + concomitant ciclopirox. However, although AE reports referable to the cardiovascular system appear to be evenly distributed (8.7 [7.1%] and 8.7 [7.2%]), as presented in the Table above, there is a difference in cardiovascular symptoms reported. For example, the majority of AEs reported for the vehicle group were as follows: hypertension 5 (4.5%), 2 (1.8%) related to cardiac function (e.g., second degree block Wenckebach block, and intermittent systolic murmur mid-systolic click), and one migraine. In the active group there was one report of hypertension, one report of hemorrhage, one migraine, and 7 related to cardic function (e.g., angina pectoris, atrial fibrillation, chest pain, congestive heart failure, cornary artery disorder, and coronary occlusion). The significance of this difference is unknown.

There were no deaths reported for the study or dropouts reported due to ciclopirox use.

8.2.1.5 Reviewer's Comments/Conclusions of Study Results

Efficacy:

1) *For the endpoint Complete Cure/Treatment Cure, the efficacy of ciclopirox nail lacquer 8% over vehicle was not demonstrated at Week 48, Week 48 (LOCF), or at either post-treatment follow visit.*

2) *For the endpoint Almost Clear/Treatment Success/Effectively Treated, at LOCF (48 weeks), the differences between active and vehicle are barely significant. For Almost Clear/Treatment Success/Effectively Treated, no statistical significant difference between ciclopirox nail lacquer and its vehicle was demonstrated at the end of Week 48 and post-treatment Week 12 (+LOCF) for the ITT population. Whether a test of statistical significance is meaningful for measures in the post treatment period because of the small sample sizes might be debatable; however, these numbers were small due to lack of efficacy in the Complete Cure group and lack of planned post treatment follow-up in any other subset.*

3) *For the endpoint Mycological Cure, the results are statistically significant at $p \leq 0.011$ and $p \leq 0.002$, at Week 48 and LOCF Week 48, respectively. However, valid conclusions can not be drawn regarding eradication of the infecting organism at Week 48 alone because of the presence of (and potential inhibitory effects of) the active drug and vehicle. For Mycological Cure at Post Weeks 12 and 24, there are no statistically significant differences; however, the numbers are small and it is debatable whether a test of statistical significance is meaningful.*

Safety:

1) *Abnormal CK-MB levels were detected in 10 patients. Seven of the 10 patients were either assigned the active group or used concomitant ciclopirox. However, according to the sponsor, the elevated CK-MB values found in the placebo and active groups are distributed in a statistically random manner between the individual time segments (weeks 12, 24,36, 40, and f/u. The elevated CK-MB values found in both groups exhibit no relationship to reported AEs, dose modification or concomitant ciclopirox cream medication. Additionally, neither placebo nor active group patients complained of cardiac symptoms.*

   Additionally, based on animal findings, there appears to be a sufficient margin of safety demonstrated between human exposures to ciclopirox nail lacquer 8% formulation and animal exposures at the cardiotoxic doses.

2) *The majority of reported AEs under skin and appendages for the active group were probably related to treatment. Rash (included periungual erythema, proximal nail fold erythema, slight erythema around PNF, etc), nail disorder (ingrown toenails, onycholysis, detachment, etc). Although the active drug appears to be somewhat of a mild irritant, there were no known drop-outs due to irritation.*

3) *As presented, no clinically significant differences in laboratory evaluations between the active and vehicle groups were noted.*

4) *No deaths were reported in either treatment arm.*

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8.2 Indication #1 **Distal Subungual Tinea Ungium of the Toenails**

8.2.2 Trial #2 **Sponsor's Study 313 (HOE 296NL/8/USA/313/NM)**

"A DOUBLE-BLIND STUDY OF THE SAFETY AND EFFICACY OF CICLOPIROX (HOE 296NL) NAIL LACQUER 8% VERSUS ITS LACQUER VEHICLE IN SUBJECTS WITH DISTAL SUBUNGUAL TINEA UNGUIUM OF THE TOENAILS"

Study Dates: July 13, 1994 - April 12, 1996

8.2.2.1 Objective/Rationale

This study is designed to compare the safety and efficacy of 8% ciclopirox nail lacquer with that of the vehicle in the treatment of subjects with distal subungual tinea unguium.

8.2.2.2 Design

This is a multicenter, randomized, stratified, double-blind, vehicle-controlled, parallel group study. The design and conduct of this study was identical to Study 312.

8.2.2.3 Protocol

8.2.2.3.1 **Population/Procedures**

The protocol was identical to Study 312 as previously described.

8.2.2.4 Study 313 - Results

Five hundred and sixty-four subjects were screened. Of the 564 subjects screened, 327 subjects were listed as screening failures. The sponsor lists 237 subjects as the randomized population. The investigators and centers were:

No.	Investigator	No.	Investigator
028	H. Irving Katz, MD Clinical Study Minnesota Center 7201 University Ave. NE Fridley, MN 55432-3313	036	Philip Fleckman, MD Dermatology Box 356524 University of Washington Seattle, WA 98195-6524
044	Michael Taylor Jarratt, MD Pharmaco LSR Health Research Ctr. 2901 N. IH 35 Austin, TX 78722	047	Jerome L. Shupack, MD NYU Medical Center 560 First Ave New York, NY 10016
063	David M. Pariser, MD Virginia Clinical Research, Inc. 601 Medical Tower Norfolk, VA 23507	064	Daniel Stewart, DO Midwest Cutaneous Research 43900 Garfield, Ste. 106 Clinton Township, MI 48038
066	Norman Levine, MD University of Arizonia Health Science Center Section of Dermatology 1500 North Campbell Tucson, AZ 85724	086	David J. Friedman, MD 50 Maude Street Providence, RI 02908
088	Ronald P. Rapini, MD Dept. of Dermatology Texas Tech University Health Sciences Center 3601 Fourth Street Lubbock, TX 79430	089	Charles McDonald, MD 50 Maude Street Providence, RI 02908 (Note: Dr. McDonald replaced Dr. Freidman)

Number of subjects by Investigator and Stratum Per Protocol Subjects follows:

Table 26 Number of Subjects by Investigator (Sponsor's Table 1.3)

	20% to < = 40% Involvement			> 40% to < = 65% Involvement		
Inv./Center#	HOE 296NL	Vehicle	Total	HOE 296NL	Vehicle	Total
Katz (028)	9	10	19	6	5	11
Fleckman (036)	13	9	22	2	4	6
Jarratt (044)	7	11	18	7	4	11
Shupack (047)	10	7	17	5	6	11
Pariser (063)	5	5	10	5	4	9
Stewart (064)	2	6	8	10	9	19
Levine (066)	12	9	21	3	4	7
Freidmen (86)	6	3	9	3	8	11
Rapini (088)	8	7	15	1	1	2
Total	72	67	139	42	45	87

Reviewer's comment: *There does not appear to be a difference between percent involvement at Baseline between the active group and vehicle groups. The stated entry criteria required 25 – 60% involvement at Baseline; it is unknown when the protocol was amended to encompass 20% involvement.*

Screening failures were listed as follows:

Table 27 Screening Failures

Screening Failures	Total (N= 327)
Negative or missing mycology	148
Area of involvement< 25% or >60%	43
Other	146

8.2.2.4.1 Demographics, Evaluability (Study 313)

Table 28 Demographics (ITT Population) Sponsor's Table 2.2 (Partial Extraction)

Characteristic	Ciclopirox (HOE 296NL)	Vehicle	Between Treatment p-Value*
No. of subjects	119	118	
Sex			0.514
Male	94 (79%)	89 (75%)	
Female	25 (21%)	29 (25%)	
Ages (Yrs)			0.735
Mean	49.6	50.1	
SD	11.88	12.19	
Median	49.0	50.2	
Range	19 – 70	23 –70	
Race			0.715
White	103 (87%)	104 (88%)	
Hispanic	6	6	
Black	4	6	
Oriental	4	0	
Other	2	2	

*P-Value is from Mantel-Haenszel test (two-tailed) was performed.

The active and vehicle groups were similar.

Table 29 Infecting Organisms (ITT)

Genus +species	Ciclopirox (HOE 296 NL	Vehicle
Trichphyton rubrum	114 (96%)	112 (95%)
Trichphyton mentagrphytes	5 (4%)	5 (4%)
E. floccosum	0 (0%)	1 (1%)

Table 30 Study 313 Completion Status (Sponsor's Table 1.2)

	Intent to Treat Subjects		Per Protocol Subjects	
	HOE 29NL	Vehicle	HOE 29NL	Vehicle
No. of subjects randomized	119	118	114	112
No. of subjects treated	119	118	114	112
No. of subjects included in analysis of:				
Global Evaluation	118	117	114	112
Mycological Evaluation	113	114	109	109
Area of involvement	115	113	111	107
Completed Study	96	94	94	90
Did not complete Study	23	24	20	22
Entered Post-treatment	7	0	7	0
Entered Protocol 320	75	73	73	70
Reason for not completing Study				
Does not meet protocol criteria	7	7	4	7
Unreliable	5	6	5	5
Moved/lost to follow-up	3	2	3	2
Safety. AE/intercurrent med. Problem	0	1	0	1
Lack of efficacy	1	3	1	3
Subject request discontinuation	7	5	7	4

Reviewer's comment: *Seven patients from the active group entered post-treatment. One subject in the vehicle group had post-treatment data recorded; however, was not listed above.*

8.2.2.4.2 Efficacy Endpoint Outcomes

8.2.2.4.2.1 Clinical

The following patients had post-treatment assessments.

Study 313

Table 31 Patients with Post-treatment Data (ITT Population)

Patient I.D. # Active Group (Infecting Organism)	End of Study	Post-Treatment Follow-up					
		Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
028/1116 *(T. rubrum)*	X			KOH (-) Culture (+)			KOH (+) Culture (-)
036/1202 *(T. rubrum)*	X			KOH (+) Culture (-)			
036/1211* *(T. rubrum)*	X			KOH (-) Culture (-)			
036/1220 *(T. rubrum)*	X			KOH (-) Culture (-)			
036/1224* *(T. rubrum)*	X			KOH (-) Culture (-)			
and 047/1422* *(T. rubrum)*	X			KOH (-) Culture (-)			KOH (-) Culture (-)
063/1509 *(T. rubrum)*	X			KOH (-) Culture (+)			
088/1802** *(T. mentag.)*	X			KOH (-) Culture (-)			
Vehicle							
036/1219 *(T. rubrum)*	X			KOH (+) Culture (+)			

*Baseline cultures negative

**Post-treatment Week 12 global assessment was excellent improvement (not clear)

Patient 044/1308 and 044/1314 were classified as Complete Cure at the end of the study; however, there is no post-study follow-up data for these patients.

Reviewer's comment: *Patient 044/1308 had negative mycology and global assessment of cleared at Week 38 and follow-up one month later. According to the protocol, during this period between Week 36 (4/17/95) and follow-up (5/11/95) the nail lacquer was to be applied. Therefore, the negative mycology result was obtained with residual drug present. It not clear why this patient did not enter post-treatment assessment.*

Patient 044/1314 had negative mycology and global assessment of cleared at Week 48. There is no post-treatment follow-up for this patient.

It is unclear why patient 036/1219 had a post-study follow-up. This patient did not have a global of clear at 48 weeks. Only patients with a global of clear were followed and cultured during the post-study period.

As noted in Study 312, photographs were reviewed because of the inconsistencies noted in the Complete Cure subset and "none zero" planimetric values. Also, inconsistencies noted in patient response categories at end of study and endpoint as in Study 312.

A summary of clinical outcomes follows:

Table 32 Clinical Outcomes ITT Population Active (N = 119)Vehicle (N = 118)

Endpoints	End of Study		Post-treatment Week-12		Post-treatment Week-24	
	Group		Group		Group	
	Active	Vehicle	Active	Vehicle	Active	Vehicle
Completely Cured	9	0	4	0	2	0
Effectively Treated	5	1	1	0		
Mycological Cure	19	8	No post study data available			
Totals	33	9	5	0	2	0

Completely Cured

As previously stated, Completely Cured may be a difficult endpoint to assess. Also, the primary efficacy endpoint of 100% clearance of clinical signs of disease is subjective and what appears clear to one investigator might not appear clear to another. Some photographs with "non zero" planimetric values appeared clinically clear and others did not.

Table 33 Treatment Cure/Complete Cure at Week 48 (Study 313)

Treatment Group	Inv/ Subject #	ITT	PP	Results for Sponsor's Treatment Cure at Week 48				Reviewer's Photo Assessment
				Global (Date)	KOH	Culture	Planimetric Measurement	
Active (HOE296NL)								
	028/1116	Yes	Yes	Cleared (07-10-95)	Neg.	Neg.	1.2	Not Clear
	036/1202	Yes	Yes	Cleared (02-02-96)	Neg.	Neg.	11.8	Not Clear
	036/1211	Yes	Yes	Cleared (08-14-95)	Neg.	Neg.	0.7	Questionable
	036/1224*	Yes	Yes	Cleared (02-17-96)	Neg.	Neg.	5.0	Questionable
	044/1308*	Yes	Yes	Cleared (04-17-95)	Neg.	Neg.	0.3	Questionable
	044/1314	Yes	Yes	Cleared (06-29-95)	Neg.	Neg.	No reading	No Photo
	047/1422	Yes	Yes	Cleared (10-05-95)	Neg.	Neg.	6.5	? Clear
	063/1509	Yes	Yes	Cleared (01-12-96)	Neg.	Neg.	Not evaluable	Photo not evaluable
	088/1802	Yes	Yes	Cleared (09-20-95)	Neg.	Neg.	1.3	Questionable

* Patients 036/1224 and 044/1308 did not have valid data at Week 48

The statistical analysis results follow in Tables 38 - 41 based on data prior to evaluation of the photographs. It was determined by the Division's Statistician that elimination of at least 5 patients categorized as Complete Cure would be required to change the p-value. Elimination of at least 5 patients categorized as Complete Cured was unlikely because of the subjective nature of the endpoint assessment; therefore, re-analysis was not performed. The following was partially extracted from the Statistical Review (dated 10-06-99):

Study 313

Table 34 Complete Cure (ITT Population)

Week	48	LOCF-48 wk.	12 Week (+ LOCF)	24 Week (+ LOCF)
Ciclopirox nail lacquer				
Cure	8	10	3	2
N	95	118	115	111
%	8.4	8.5	3.5	2.7
Vehicle				
Cure	0	0	0	0
N	85	117	117	117
%	0.0	0.0	0.0	0.0
CMH p-value	0.004	0.001	0.066	0.134
Fisher p-value	0.007	0.002	0.122	0.240

Treatment differences are statistically significant ($p \leq 0.007$ and $p \leq 0.002$, respectively) at 48 weeks and the corresponding LOCF point. Statistical significance was not demonstrated between ciclopirox nail lacquer and its vehicle for Complete Cure at either time point in the post-treatment period.

Almost Clear/Effectively Treated

Table 35 Almost Clear/Effectively Treated/Treatment Success (ITT Population)

Week	48	LOCF-48 Wk..	12 Week (+ LOCF)	24 Week (+ LOCF)
Ciclopirox nail lacquer				
Cure	11	14	3	2
N	86	116	113	111
%	12.5	12.1	3.5	2.7
Vehicle				
Cure	0	1	0	0
N	92	115	115	115
%	0.0	0.9	0.0	0.0
CMH p-value	0.003	0.001	0.058	0.125
Fisher p-value	0.002	0.001	0.122	0.240

For the Almost Clear/Effectively Treated/Treatment Success (ITT Population) at the end of week 48 and 48 Week (LOCF), the differences are statistically highly significant ($p \leq 0.002$ or $p \leq 0.001$, respectively).

Mycologic Cure

Table 36 Study 313 Mycological Cure (ITT Population)

Week	48	LOCF-48 wk.	12 Week (+ LOCF)	24 Week (+ LOCF)
Ciclopirox nail lacquer				
Cure	34	42	5	2
N	85	119	114	110
%	40	36.2	3.4	2.6
Vehicle				
Cure	10	11	0	0
N	86	114	114	114
%	11.6	9.6	0.0	0.0
CMH p-value	0.001	0.001	0.020	0.132
Fisher p-value	<0.001	<0.001	0.060	0.242

At both Week 48 and 48 +LOCF, the differences between the negative mycology (KOH and culture) are statistically significant between active over vehicle ($p \leq 0.001$ respectively). At Post Week 12 and 24, there is no statistically significant difference (roughly $p \leq 0.060$ and $p \leq 0.242$).

Of the eight patients in the active group with Complete Cure, 3 (38%) relapsed at Posttreatment Week 12. Culture and KOH became positive in two of these instances.

Study 313 Mean Percent Area from Planimetric Measurements (MITT Population)
According to the Statistical Review at Week 48 and its corresponding LOCF point, differences are statistically significant ($p \leq 0.0268$ and $p \leq 0.0396$, respectively), though the evidence is not robust.

Reviewer's comments:

Efficacy results for Study 313 are favorable for Complete Cure, for Almost Clear/Effectively Treated and for Mycological Cure. After evaluation of the photographs, a test for statistical significance was not performed.

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8.2.2.4.3 Safety

Local Safety

As in Study 312, specific local signs were not assessed (e.g., application site reaction or local erythema scoring) were not performed.

Study 313

Table 37 TEAEs Possibly or Probably Related to Test Material (Sponsor's Table R21)

	Ciclopirox		Vehicle	
	N	%	N	%
Total # of subjects Treated	119	100	118	100
No. with TEAE	14	11.8	7	5.9
Rash	11	9.2	2	1.7
Nail disorder	3	2.5	3	2.5
Pain in Extremity	0	0.0	1	0.8
Hemorrhage	0	0.0	1	0.8
Headache	0	0.0	1	0.8
Application site reaction	0	0.0	1	0.8

Data Listing 13.1 (Vol. 1.47, pg. 300) rash was recorded as periungal erythema (10), erythema along sides of the great to (1), subungual erythma proximal left (1), toe eight inflammed (1), skin irritation surrounding toe (1), heat rash (1), dermatitis right chest (1), rash right inner thigh (1), and flare of stasis dermatitis.

Rash was the most common TEAE related to test material among the 9% (11/119) of the ciclopirox subjects and 2% (2/118) of the vehicle subjects.

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Systemic Safety Outcomes (Study 313)

Abnormal serum creatine phosphokinase- MB (CK-MB) levels were as follows:

Table 38 Abnormal Laboratory Values Serum Creatine Phosphokinase MB (ng/mL) NR: 0-4.999 Sponsor's Data Listing 14.2 (Abnormal Lab. Values During Treatment – Subjects With No Baseline Data)

INV/ SUBJ	Sex, Age (yr.)	Week 24	Week 36	Week 48
HOE 296NL				
063/1528*	F 61	5.700 H	-	-
086/1913*	M 49	5.000 H	5.300 H	-
Vehicle				
064/1604*	M 33	-	-	5.800 H
066/1726*	M 69	5.600 H	-	-

*concomitant cicloprox 1% cream use

Reviewer's comment: *Athough there appears to be an equal distribution of patients with abnormal CK-MB levels between active and vehicle, actually all of the subjects listed above had exposure to ciclopirox-containing products (Vol.1.45, Data Listing 3) and confirmed by the sponsor's submission received 09-28-99.*

As previously stated in Study 312, based on animal studies, it is safe to assume that topical applications of ciclopirox nail lacquer should not produce any significant toxicity in humans.

According to the sponsor, the elevated CK-MB values found in the placebo and active groups are distributed in a statistically random manner between the individual time segments (weeks 12, 24,36, 40, and f/u. The elevated CK-MB values found in both groups exhibit no relationship to reported AEs, dose modification or concomitant ciclopirox cream medication. Additionally, neither placebo nor active group patients complained of cardiac symptoms.

Systemic Ciclopirox Levels:

Investigator's 036, 044, and 047 measured ciclopirox serum levels. The lower limit of quantification of ciclopirox in the serum was [redacted] Ninety (90) subjects were assessed. Twenty-three (17 ciclopirox subjects, 6 vehicle subjects) had post-Baseline ciclopirox serum levels at or above the limit of quantification.

Table 39 Detectable Ciclopirox Levels

Treatment Group	Inv/Sub	Highest ciclopirox serum level (ng/mL)	Week of Study Recorded	Concomitant Loprox (ciclopirox) Yes	No
Active	036/1202	16.1	40	X	
	036/1209	11.4	48	X	
	036/1213	16.9	48	X	
	036/1218	10.8	24	X	
	036/1220	14.8	Post-Wk.-4		X
	036/1221	12.9	48	X	
	036/1226	12.4	12	X	
	036/1227	22.4	36	X	
	044/1309	17.4	12	X	
	044/1314	16.8	12		X
	044/1316	10.7	48	X	
	044/1321	10.6	12		X
	044/1330	10.3	36	X	
	047/1405	24.6	36		X
	047/1412	16.3	12	X	
	047/1417	10.3	12		X
	047/1426	11.0	Baseline		X
Vehicle	036/1225	11.8	24	X	
	044/1319	11.1	48	X	
	047/1404	23.4	48	X	
	047/1413	10.2	Baseline		X
	047/1419	11.6	24		X
	047/1421	12.6	screen	X	

Numerous AEs were recorded among patients with detectable ciclopirox serum levels. None of the reported AEs were cardiac in nature. The most frequent similar complaint was upper respiratory. There did not appear to be any correlation or constellation of similar AEs.

Reviewer's comment: (See Biopharm comments) *Systemic absorption from the concomitant ciclopirox cream is apparent from the data listed above; however, no conclusion regarding the effect of the concomitant use of ciclopirox 1% cream can be drawn. The reason for detection of ciclopirox levels present at screen or baseline is not clear.*

As in Study 312, all subjects treated with test material were evaluated for safety. The adverse events are listed and tabulated by body system irrespective of relationship to study drug in Table 36 that follows. Again, the patients are grouped for adverse events reporting according to study arm assignment (i.e., active vs. vehicle) as customarily presented in an NDA. This presentation is satisfactory for evaluating relationships to local safety; however, for comparisons of systemic effects of ciclopirox the sub-groups previously mentioned would have been preferable.

Table 40 Treatment Emergent Adverse Events (TEAE) Sponsor's Table 20.1. Rates By Body System Irrespective of Relationship To Study Drug (Study 313)

	HOE 296NL		Vehicle	
	No.	%	No.	%
Total No. of Subjects Treated	119	100.0	111	100.0
No. without TEAE	12	13.4	16	13.6
No. with TEAE	103	86.6	102	86.4
Body As A Whole	**39**	**32.8**	**41**	**34.7**
Accidental injury	17	14.3	10	8.5
Back pain	6	5.0	8	6.8
Flu syndrome	7	5.9	7	5.9
Surgery	1	0.8	6	5.1
Pain in extremity	2	1.7	5	4.2
Asthenia	1	0.8	3	2.5
Infection	5	4.2	3	2.5
Pain	2	1.7	3	2.5
Abdominal pain	0	0.0	2	1.7
Cyst	1	0.8	2	1.7
Hernia	0	0.0	2	1.7
Allergic reaction	1	0.8	1	0.8
Neck pain	0	0.0	1	0.8
Neck rigidity	0	0.0	1	0.8
Pelvic pain	0	0.0	1	0.8
Face edema	1	0.8	0	0.0
Fever	1	0.8	0	0.0
Malaise	1	0.8	0	0.0
Photosensitivity	1	0.8	0	0.0
Cardiovascular System	**11**	**9.2**	**11**	**9.3**
Migraine	1	0.8	3	2.5
Chest pain	2	1.7	2	1.7
Hypertension	4	3.4	2	1.7
Arrhythmia	0	0.0	1	0.8
Cardiovascular disorder	0	0.0	1	0.8
Hemorrhage	2	1.7	1	0.8
Palpitation	0	0.0	1	0.8
Sinus bradycardia	0	0.0	1	0.8
Ventricular extrasystoles	0	0.0	1	0.8
Angina pectoris	1	0.8	0	0.0
Bundle branch block	1	0.8	0	0.0
Syncope	1	0.8	0	0.0
Digestive System	**24**	**20.2**	**20**	**16.9**
Dyspepsia	3	2.5	3	2.5
Gastrointestinal disorder	0	0.0	3	2.5
Nausea	3	2.5	3	2.5
Sore throat	3	2.5	3	2.5
Esophagitis	0	0.0	2	1.7
Tooth disorder	3	2.5	2	1.7
Diarrhea	5	4.2	1	0.8
Gastritis	0	0.0	1	0.8
Gastroenteritis	1	0.8	1	0.8
Glossitis	0	0.0	1	0.8
Mouth ulceration	1	0.8	1	0.8

Rates By Body System Irrespective of Relationship To Study Drug (continued)

	HOE 296NL		Vehicle	
	No.	%	No.	%
Tooth caries	0	0.0	1	0.8
Cholecystitis	1	0.8	0	0.0
Gum disorder	1	0.8	0	0.0
Periodontal abscess	3	2.5	0	0.0
Sore mouth	1	0.8	0	0.0
Endocrine System	**4**	**3.4**	**0**	**0.0**
Diabetes mellitis	3	2.5	0	0.0
Thyroid disorder	1	0.8	0	0.0
Injection Site Reaction	**1**	**0.8**	**0**	**0.0**
Injection Site Reaction	1	0.8	0	0.0
Metabolic & Nutritional Disorders	**4**	**3.4**	**5**	**4.2**
Gout	2	1.7	3	2.5
Bilirubinemia	0	0.0	1	0.8
Healing abnormal	0	0.0	1	0.8
Hyperuricemia	1	0.8	0	0.0
Peripheral edema	1	0.8	0	0.0
Musculo-skeletal System	**21**	**17.6**	**22**	**18.6**
Myalgia	4	3.4	6	5.1
Arthralgia	7	5.9	5	4.2
Tenosynovitis	3	2.5	4	3.4
Arthritis	0	0.0	3	2.5
Bone disorder	1	0.8	2	1.7
Joint disorder	2	1.7	2	1.7
Bone fracture (not spontaneous)	3	2.5	1	0.8
Muscle cramps	1	0.8	1	0.8
Burisitis	2	1.7	0	0.0
Nervous System	**21**	**17.6**	**18**	**15.3**
Headache	15	12.6	12	10.2
Anxiety	4	3.4	3	2.5
Depression	1	0.8	3	2.5
Reflexes decreased	0	0.0	1	0.8
Dizziness	1	0.8	0	0.0
Insomnia	1	0.8	0	0.0
Paresthesia	1	0.8	0	0.0
Reflexes increased	1	0.8	0	0.0
Respiratory System	**60**	**50.4**	**60**	**50.8**
Upper respiratory infection	38	31.9	40	33.9
Sinusitis	13	10.9	14	11.9
Bronchitis	6	5.0	9	7.6
Rhinitis	17	14.3	6	5.1
Cough increased	0	0.0	2	1.7
Asthma	1	0.8	1	0.8
Lung disorder	0	0.0	1	0.8
Laryngitis	2	1.7	0	0.0
Pharyngitis	1	0.8	0	0.0
Pleural disorder	1	0.8	0	0.0
Pneumonia	2	1.7	0	0.0