CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205175Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

Division of Anti-Infective Products
Clinical Microbiology Consult Review

NDA: 205175
(SDN-001 and eCTD 0000; SDN-007 and eCTD 0007; SDN-011 and eCTD 0005; SDN-012 and eCTD 0009; SDN-016 and eCTD 0012)
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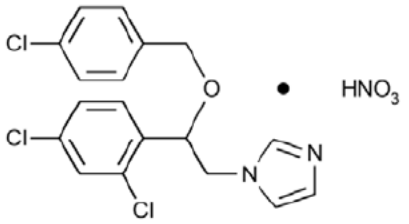
Date Review Completed: 08/01/2013
Reviewer: Shukal Bala

APPLICANT
Amderma Pharmaceuticals LLC
440 US Hwy 22 East
Bridgewater, New Jersey 08807

DRUG PRODUCT NAME
Proprietary name: Ecoza
Non-proprietary name: Econazole nitrate
Chemical name: 1-[2-{(4-chloro-phenyl)methoxy}-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole mononitrate
Molecular/Structural formula: $C_{18}H_{15}Cl_3N_2O.HNO_3$



Molecular weight: 444.7

PROPOSED INDICATION
Treatment of interdigital tinea pedis (b) (4)

PROPOSED DOSAGE FORM, STRENGTH, ROUTE OF ADMINISTRATION AND DURATION OF TREATMENT
Dosage form: Foam
Route of administration: Topical
Dosage: 1%
Duration of treatment: Once daily for 4 weeks

DISPENSED
Rx

RELATED DOCUMENTS
IND 77,523; Fougera® package insert as the reference listed drug (RLD)

REMARKS
The subject of this 505(b)(2) NDA is Ecoza [econazole nitrate foam (1%)] for the treatment of interdigital tinea pedis (b) (4) The applicant has evaluated the efficacy of econazole nitrate foam 1% (Ecoza) in one phase 2 and two phase 3 clinical trials in patients with interdigital tinea pedis. The safety and efficacy was compared with econazole nitrate cream 1% (Fougera®) as the RLD. Overall, the results show comparable activity between Ecoza® and Fougera®.

(b) (4) The RLD is approved for the treatment of indications other than interdigital tinea pedis. As Ecoza will be approved for the treatment of interdigital tenia pedis only, the pathogens associated with interdigital tenia pedis only should be listed in the labeling. (b) (4)

Based on current practice, some changes in the organization of microbiology information in Sections 12.1 and 12.4 of the labeling are recommended.

CONCLUSIONS AND COMMENTS
The NDA supplement is approvable pending an accepted version of the labeling. The changes proposed in the section 12.1 and 12.4 of the labeling are as follows (additions marked as double-underlined and deletions as striked out):

12.1 Mechanism of Action

(b) (4)

Econazole nitrate is an antifungal agent [see *Clinical Pharmacology, Microbiology (12.4)*].

12.4 Microbiology

Mechanism of Action
Econazole nitrate, an azole antifungal agent, inhibits fungal cytochrome P-450-mediated 14 alpha-lanosterol demethylase enzyme. This enzyme functions to convert lanosterol to ergosterol. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell wall and may be responsible for the fungistatic activity of econazole. Mammalian cell demethylation is less sensitive to econazole inhibition.

Activity *in vitro* and in clinical infections

Econazole nitrate has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE section**.

(b) (4)

Epidermophyton floccosum

(b) (4)

(b) (4)

(b) (4)

Trichophyton mentagrophytes

Trichophyton rubrum

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Table of Contents

1. Executive Summary

The subject of this 505(b)(2) NDA is econazole nitrate foam (1%) for the treatment of interdigital tinea pedis (b) (4)

Econazole nitrate, an azole, is known to exhibit anti-fungal activity against dermatophytes that include *Trichophyton rubrum*, *T. mentagrophytes*, *T. tonsurans, E. floccosum*, and *Microsporum* species. The applicant has evaluated the efficacy of econazole nitrate foam 1% in patients with interdigital tenia pedis in one phase 2 trial and two phase 3 trials. The efficacy was compared with econazole nitrate cream 1% (Fougera®) currently approved for treatment of tinea pedis, tinea cruris, tinea corporis, cutaneous candidiasis, and *Tinea versicolor*. This is a 505(b)(2) NDA and the applicant has cross-referenced the Fougera® package insert as the reference listed drug (RLD).

Overall, the results of the three clinical trials show econazole nitrate foam to be effective in improving clinical and mycological cure rates compared to the vehicle group; the cure rates were comparable to the RLD. The mycological cure rates were higher than either the effective treatment or complete cure rates at the end of treatment (Day 29) and at follow-up visit (Day 43). *T. rubrum* was the most common dermatophyte isolated. Econazole nitrate was effective in patients with infections due to *T. rubrum*, *T. mentagrophytes*, and *E. floccosum*; MICs of all baseline isolates were ≤0.5 µg/mL with a MIC_{90} of ≤0.016 µg/mL. There was no correlation between MICs of baseline isolates and clinical or mycological response. There does not appear to be any change in MIC values of isolates collected after treatment compared to the baseline isolates.

2. Introduction and Background

The subject of this 505(b)(2) NDA is econazole nitrate foam (1%) for the treatment of interdigital tinea pedis (b) (4) Tinea pedis, a common superficial skin disease, is commonly known as athlete's foot.

Several topical antifungal products that contain econazole nitrate are available for the treatment of interdigital tinea pedis. The applicant has cross-referenced econazole nitrate cream (1%) – the Fougera® package insert as the reference listed drug (RLD) for several sections of the proposed labeling including the microbiology section. Fougera® is approved for the treatment of

- tinea pedis, tinea cruris, and tinea corporis caused by *T. rubrum*, *T. mentagrophytes*, *T. tonsurans*, *M. canis*, *M. audouini*, *M. gypseum*, *and Epidermophyton floccosum*,
- cutaneous candidiasis, and
- tinea versicolor.

3. Nonclinical Microbiology

3.1. Mechanism of action

Econazole, like other azoles, is known to inhibit the cytochrome P-450-dependent enzyme lanosterol demethylase (14α-sterol demethylase), an enzyme that is important for ergosterol

biosynthesis from lanosterol. This may be responsible for the antifungal activity of econazole.[1, 2, 3, 4, 5] The accumulation of lanosterol correlates with the subsequent loss of ergosterol, an essential component for maintaining fungal cell wall integrity and function. Econazole may also inhibit endogenous respiration, interact with membrane phospholipids, inhibit the transformation of yeasts to mycelial forms, inhibit purine uptake, and impair triglyceride and/or phospholipid biosynthesis.[2]

The enzyme 14α-sterol demethylase is also present in mammalian cells and plays an important role in cholesterol synthesis. However, azoles have greater affinity for the enzyme in fungal cells compared to those in mammalian cells.

Comments:

- *In the original NDA submission, the applicant had not proposed to include mechanism of action of econazole in the Ecoza labeling nor does the RLD package insert include any information on mechanism of action. Upon request from the Division, the applicant has reformatted the package insert in accordance with the PLR format.* (b) (4) *For antimicrobial products, the mechanism of action should be summarized under section 12.4* (b) (4)
- *Some changes to the proposed text are recommended (for details see Section 6 'The Labeling" of this review).*

3.2. Activity *in vitro*

The *in vitro* susceptibility of clinical isolates collected from patients with tinea pedis in the one phase 2 trial (Study D79-2902-07) and two phase 3 clinical trials (Study 079-2951-302 and 079-2951- 303) was determined by Clinical Laboratory Standards Institute (CLSI) method (M38-A2[6]). All testing was performed (b) (4) Briefly, isolates were subcultured onto Potato Dextrose Agar (PDA) slants, frozen at -80ºC, and batched for susceptibility testing in RPMI-1640 as the test medium; the inoculum concentration was 1-3 x 10^3 CFU/ml, and the incubation time was 4 days at 35°C. The minimum inhibitory concentrations (MICs) were read at the 80% inhibition endpoint based on a comparison with the growth control.

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[1] Ghannoum MA and Rice LB. Antifungal agents: mode of action, mechanisms of resistance, and correlation of these mechanisms with bacterial resistance. J. Clin Microbiol. (1999) 12; 501-517.

[2] http://www.drugbank.ca/drugs/DB01127

[3] Econazole nitrate PRODUCT DATA SHEET issue date 04/11/2013

[4] Sheehan DJ, Hitchcock CA and Sibley CM. (1999) Current and emerging azole antifungal agents. Clin. Microbiol. Rev. 12:40–79.

[5] Fromtling, RA. Overview of medically important antifungal azole derivatives. Clin Microbiol Rev 1988; 1(2): 187-217.

[6] Clinical and Laboratory Standards Institute (CLSI). Reference Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi; Approved Standard- Second Edition. CLSI document M38-A2. Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, PA 19087 USA, 2008.

Appropriate quality control (QC) was performed on each day of testing. The QC strains included for each day testing were *Trichophyton rubrum* MYA 4438 and *T. mentagrophytes* MYA 4439. Comparator drugs included for testing were ciclopirox (CIC), and terbinafine (TER), fluconazole (FLU), and/or itraconazole (ITR).

The dermatophyte isolates tested include *T. rubrum*, *T. mentagrophytes*, *E. floccosum,* and *T. tonsurans*. Econazole MIC_{90s} and MIC_{50s} (concentration at which 90% and 50% of isolates tested were inhibited, respectively) were lower than CIC, ITR, and FLU for all *T. rubrum, T. mentagrophytes* and *E. floccosum* isolates tested. Econazole MICs were similar to TER (Table 1).

Table 1: MIC data summary (µg/ml) for econazole (ECO) and comparators ciclopirox (CIC), fluconazole (FLU), itraconazole (ITR), and terbinafine (TER)

Study D79-2902-07:

	ECO	CIC	FLU	ITR	TER
T. rubrum					
Range (n=86)	0.002-0.016	0.12-0.5	0.5-4.0	0.016-0.12	0.002-8.0
MIC50	0.008	0.25	2	0.06	0.008
MIC90	0.016	0.25	4	0.12	0.016
T. mentagrophytes					
Range n = 10	0.001-0.12	0.12-0.25	0.06-32	0.016-0.06	0.004-0.016
MIC50	0.004	0.25	4	0.016	0.004
MIC90	0.016	0.25	16	0.03	0.008
E. floccosum					
Range (n=5)	0.002-0.008	0.12-0.5	2	0.016-0.03	0.008-0.06
MIC50	0.004	0.25	2	0.016	0.016
MIC90	0.004	0.5	2	0.03	0.016

Note that calculation of MIC_{90} values for antifungals against *E. floccosum* is inappropriate since less than 10 isolates were tested

Study 079-2951-302:

	Econazole	Ciclopirox	Terbinafine
T. rubrum (n=139)			
Range	0.001-0.125	0.06-1.0	0.001-0.03
MIC_{50}	0.008	0.25	0.008
MIC_{90}	0.03	0.5	0.016
E. floccosum (n=14)			
Range	0.001-0.03	0.125-0.5	0.001-0.06
MIC_{50}	0.004	0.25	0.016
MIC_{90}	0.016	0.5	0.03
T. mentagrophytes (n=9)			
Range	0.004-0.06		0.004-0.016
T. tonsurans (n=1)			
Range	0.008	0.25	0.016

MIC_{50} and MIC_{90} not determined on $n<10$

Study 079-2951-303:

	Econazole	Ciclopirox	Terbinafine
T. rubrum (n=231)			
Range	0.001-0.5	0.03-1.0	0.001-8.0
MIC_{50}	0.008	0.25	0.004
MIC_{90}	0.016	0.5	0.008
T. mentagrophytes (n=12)			
Range	0.002-0.125	0.06-1.0	0.001-8.0
MIC_{50}	0.016	0.125	0.004
MIC_{90}	0.06	0.5	0.008
E. floccosum (n=9)			
Range	0.004-0.03	0.25-1.0	0.004-0.016

MIC_{50} and MIC_{90} not determined on $n<10$

Minimum fungicidal concentrations (MFC) were also determined for econazole; testing was performed according to the modifications published by Canton *et al*. (2003)[7] and Ghannoum and Isham (2007)[8]. Specifically, the total contents of each clear well from the

[7] Canton E, Peman J, Viudes A, Quindos G, Gobernado M, Espinel-Ingroff A. Minimum fungicidal concentrations of amphotericin B for bloodstream Candida species. Diagn Microbiol Infect Dis. (2003) **45:** 203-206.

[8] Ghannoum MA, Isham N. Voriconazole and caspofungin cidality against non- albicans Candida Species. Infectious Diseases in Clinical Practice (2007) **15** (4):250-253.

MIC assays were subcultured onto potato dextrose agar. To avoid antifungal carryover, the aliquots were allowed to soak into the agar and then were streaked for isolation once dry, thus removing the cells from the drug source. Cidal activity was defined as an MFC/MIC ratio ≤ 4. The MFCs were 15 to 500-fold higher than MICs for a majority (over 90 %) of the isolates tested thereby suggesting fungistatic activity (Table 2).

Table 2: MIC/MFC (µg/ml) for *T. mentagrophytes* and *E. floccosum* isolates*

T. mentagrophytes isolates

Subject No.	Site No.	CMM #	Treatment Arm	Visit	ECO MIC	ECO MFC	CIC	FLU	ITR	TER
022	03	179	C	Baseline	0.004	>.5	0.25	16	0.016	0.004
027	04	6	V	Baseline	0.008	>.5	0.25	8	0.03	0.004
031	04	21	C	Baseline	0.12	>.5	0.25	16	0.016	0.004
035	04	33	V	Baseline	0.002	>.5	0.25	4	0.016	0.008
051	05	146	C	Baseline	0.002	>.5	0.12	4	0.016	0.004
066	01	61	C	Baseline	0.001	>.5	0.25	2	0.03	0.004
067	01	88	C	Baseline	0.016	0.25	0.25	32	0.03	0.016
085	04	68	V	Baseline	0.016	>.5	0.25	0.06	0.06	0.004
091	04	77	C	Baseline	0.008	>.5	0.12	2	0.016	0.004
124	01	193	C	Baseline	0.001	0.5	0.12	0.5	0.016	0.008

***E. floccosum* isolates**

Subject No.	Site No.	CMM #	Treatment Arm	Visit	ECO MIC	ECO MFC	CIC	FLU	ITR	TER
047	05	91	V	Baseline	0.004	>.5	0.5	2	0.016	0.016
062	01	62	V	Baseline	0.002	0.12	0.12	2	0.016	0.008
068	01	93	F	Baseline	0.008	>.5	0.5	2	0.03	0.06
089	02	270	F	Baseline	0.004	0.06	0.25	2	0.03	0.016
143	02	267	V	Baseline	0.004	0.5	0.12	2	0.016	0.016

Treatment arms: C = econazole nitrate cream 1%, F = econazole nitrate foam 1%, V = vehicle
* None of the subjects had isolates at the Week 4 (End of Treatment) or Week 6 (End of Study)

MFC summary

T. rubrum	Range (n=86)	.008- >0.5
	MFC_{50}	>0.5
	MFC_{90}	>0.5
T. mentagrophytes	Range (n=10)	0.25- >0.5
	MFC_{50}	>0.5
	MFC_{90}	>0.5
E. floccosum	Range (n=5)	0.06- >0.5
	MFC_{50}	0.5
	MFC_{90}	>0.5

Source: Study D79-2902-07

Comments:

- *The activity of econazole nitrate was similar to terbinafine and better than other comparator drugs tested.*
- *T. mentagrophytes MYA 4439 QC strain used by the applicant is appropriate. T. rubrum MYA 4438 strain used for testing of isolates from patients in phase 2 trial is*

also appropriate. For testing of isolates from patients in phase 3 trials, the applicant had stated in the original NDA submission that the T. rubrum MYA 4498 strain was tested which is not listed in the CLSI M38-A2 document. The applicant has clarified that this was a typographical error and that MYA 4438 strain was used for testing of all isolates from phase 2 and phase 3 trials.

3.3. Drug Resistance

Development of drug resistance to azoles is common and has been principally studied in yeasts (*Candida albicans*); resistance may occur by a variety of mechanisms, including target modification (expression of low-affinity 14α-demethylases), overexpression of targets, alteration of membrane permeability to the azoles, and active efflux of the antifungal (Balkis *et al*., 2002).[9] Treatment failure in cases of tinea pedis and other dermal infections is common and can be particularly problematic in cases of *T. rubrum* infection (Kwon-Chung 1992[10]).

MICs of clinical isolates collected prior to initiation of therapy, in the phase 2 and phase 3 clinical trials performed by the applicant, were shown to be same as MICs of isolates collected after 4 weeks of treatment and 2 weeks follow up (for details see section 5 of this review).

4. Overview of Clinical Pharmacology

The pharmacokinetics (PK) of econazole nitrate foam 1% was measured in a subset of patients in a phase 2 trial in subjects aged ≥ 18 years with a clinical diagnosis of tinea pedis (Study D79-2902-07). Econazole nitrate foam (1%) or cream (1%) was applied once daily, for 4 weeks to the feet of subjects. Plasma samples collected prior to the application of the last dose and at 1, 2, 4, 6, 8, and 12 hours after the last dose were qualitatively analyzed to characterize and compare the PK profile of the two econazole nitrate products. The extent of econazole systemic exposure following administration of foam or cream formulations of econazole nitrate was similar (Table 3). The concentrations are expected to be much lower compared to skin; the concentrations in the skin were not measured (for details see Clinical Pharmacology review).

[9] Balkis MM, Leidich SD, et al. Mechanisms of fungal resistance: an overview. Drugs (2002) **62**: 1025-1040.

[10] Kwon-Chung KJ, Bennett JE. Medical Mycology. Lea & Febiger, Philadelphia (1992).

Table 3: Plasma concentrations (pg/mL) and PK parameters of econazole following 29 days of once-daily topical application of econazole* (Study D79-2902-07)

PK Parameters	Econazole Nitrate Cream 1% (N=21)	Econazole Nitrate Foam 1% (N=19)
T_{max} (h)	8.40 ± 4.31	6.82 ± 5.07
C_{max} (pg/mL)	344 ± 320	417 ± 218
AUC(0-12) (pg h/mL)	2520 ± 2330	3440 ± 1920

*20 subjects in the Foam Vehicle group were analyzed for plasma econazole levels. All were found to be below the quantifiable limit (BQL <100pg/mL).

Source: **Table 1** and **Table 2** of the D79-2902-07 Pharmacokinetics Report (D79-2902-07 Clinical Study Report Appendix 16.1.13.1).

The Fougera® (RLD) package insert states the following:

> After topical application to the skin of normal subjects, systemic absorption of econazole nitrate was extremely low. Although most of the applied drug remained on the skin surface, drug was found in the stratum corneum which, by far, exceeded the minimum inhibitory concentration for dermatophytes. Inhibitory concentrations were achieved in the epidermis and as deep as the middle region of the dermis. Less than 1% of the applied dose was recovered in the urine and feces.

Comments:

- *Econazole nitrate foam 1% will be applied topically. The concentration of the drug at the site of infection will be several-fold higher than the MICs of the pathogens associated with tenia pedis.*

5. Clinical Microbiology

The clinical microbiology evaluations were performed in one phase 2 trial in patients with tenia pedis (both interdigital and moccasin subtype) and two phase 3 trials in patients with interdigital tenia pedis and are summarized below.[11]

5.1. Phase 2 trial

This was a 3-arm, multi-center, randomized, evaluator-blinded, vehicle controlled, parallel group comparison trial to evaluate the safety and efficacy of econazole nitrate foam 1%, econazole nitrate cream 1% (Fougera®; RLD), and foam vehicle in subjects with tinea pedis with either interdigital and moccasin involvement or both (Study D79-2902-07). Male and female subjects ≥ 18 years of age with clinical [Grade 1 (mild erythema) and grade 2 (moderate scaling)] and microbiological diagnosis were enrolled.

Microbiological diagnosis included positive microscopic evidence of hyphae of a skin scraping taken from the most infected areas on the feet and mounted in 10-20% potassium hydroxide (KOH). For KOH examination, the specimen(s) were mounted in Chlorazol Black E containing KOH and the sample(s) examined at the site laboratory for presence or absence of hyphal elements by microscopy. If KOH positive, skin scrapings were sent to a central laboratory (b) (4) for fungal culture; evaluable subjects had a

[11] About 1.4% of the isolates in all trials were stated to be non-viable and therefore microbiological testing could not be performed.

positive KOH and were fungal culture positive for a dermatophyte in the skin scrapings collected at the baseline visit.

Subjects on topical antifungals or topical corticosteroids within 30 days prior to the start of the study or systemic antifungal therapy within 12 weeks prior to the start of the study medication were not eligible to participate. Subjects with concurrent tinea infection were not enrolled; however, subjects with concurrent onychomycosis were eligible to participate in the study (about 22 subjects with onychomycosis patients were enrolled; the details were not included in the microbiology datasets). Treatment was administered daily for 4-weeks and patients followed for 2-weeks post-treatment. The subjects were evaluated for clinical response, laboratory parameters, and safety endpoints for the 6-week study period (Table 4). Mycological evaluations (KOH and cultures) were performed at the end of treatment (Visit 4, Day 29) and end of the study (Visit 5, Day 43).

Efficacy was based on clinical grading of tinea pedis for each affected region (moccasin and interdigital) and mycological evaluations. For each sub-type of tinea pedis (with confirmed presence of fungal hyphae by KOH test and culture), the severity of erythema, scaling/hyperkeratosis, cracking/fissuring, maceration, vesiculation, and pruritus were evaluated by the investigator using a 4-point scale from 0 = None to 3 = Severe for each sign or symptom.

Primary Endpoint:

- Complete cure: negative KOH and negative fungal culture and no evidence of clinical disease as indicated by scores of 0 = none for each sign and symptom at Day 43.

Secondary Endpoints:

- Effective treatment: negative KOH, negative fungal culture, no or mild (a score of 0 or 1) erythema and/or scaling with all other signs or symptoms being absent (score = 0) at Day 43 (Week 6).
- Mycological cure: negative KOH and negative culture at Day 43 (Week 6).
- Clinical improvement defined as responses of good, very good, or excellent as determined from Investigator and Subject Assessments at Day 29 (Week 4) and Day 43 (Week 6).
- Changes from baseline in individual and cumulative signs and symptoms of disease (erythema, scaling/hyperkeratosis, cracking/fissuring, maceration, vesiculation and pruritus) for each type of tinea pedis at each visit on a scale of zero (none) to three (severe) points.

Table 4: Study D79-2902-07- Study schedule

Event	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5€
	Screen/Baseline (Day 1)	Day 8 (± 2 days)	Day 15 (± 3 days)	Day 29 (± 4 days)	Day 43 (± 4 days)
Written Informed Consent	X				
Medical History	X				
Brief Physical Examination	X				
Inclusion/Exclusion Criteria	X	X*	X*	X*	
Urine pregnancy testing	X			X	
Mycology (KOH/Fungal cultures)	X			X	X
Lab Tests (CBC, serum chemistry, UA)	X±			X	
Lab Test: Plasma (Drug levels) (Selected sites)	X**			X***	
Randomization to study products	X				
Clinical Evaluations (Signs and Symptoms)	X	X	X	X	X
Investigator and Subject Assessment of Response to Treatment)				X	X
Dispense Subject Instruction Sheet, Instructions for Use	X				
Dispense and/or Review Subject Diary	X	X	X	X	
Dispense Drug	X	X	X		
Apply study medications	X	X†	X†	X†	
Concomitant Medications	X	X	X	X	X
Adverse Events	X	X	X	X	X
Collect study medications		X	X	X	X

* Subjects who did not meet the inclusion/exclusion criteria (i.e., negative Visit 1 culture) were discontinued from the study when the dermatophyte culture results were available.
** Blood samples for plasma drug levels were collected prior to dosing on Day 1.
*** On Day 29, just prior to drug application, and at 1 hour (± 2 minutes), 2 hours (± 3 minutes), 4 and 6 hours (± 5 minutes), 8 and 12 hours (± 10 minutes), after the application of the last dose, blood for plasma drug levels were collected from all subjects at the PK sites.
€ Only subjects with positive Baseline fungal cultures were required to complete this visit.
± Subjects had to be fasting (had not eaten for approximately 8 hours) for the Baseline laboratory tests.
† Subjects were instructed not to apply study medications on visit days until after clinical evaluations (and laboratory specimens) had been completed.

All subjects enrolled in the study who were randomized and dispensed study medication, and who had a positive baseline fungal culture were included in the modified intent-to-treat (MITT) population. Subjects were included in the per protocol (PP) efficacy analyses if they were dispensed and applied the study medication and met all of the following conditions:

- Positive baseline KOH evaluation and positive fungal culture.
- Week 6 (Visit 5), was within protocol-specified windows: Day 43 ± 4 days.
- Received drug as randomized.
- Minimum number of doses received was defined as 80% of doses based on start and stop dates of study medication application.
- Blinded clinical review found no significant violations of eligibility criteria including no use of prohibited medications/therapies during the study.

Of the 135 subjects enrolled at six sites within the US, 103 were in the MITT population and 89 in the PP population (Table 5). About 38% of the subjects had moccasin tenia pedis of which approximately 58% had both interdigital and moccasin subtype.

Table 5: Study D79-2902-07 - number of subjects in MITT and PP population

MITT

Subject Sub-Groups	Treatment Group			Sub-Total
	Econazole Nitrate 1% Cream	Econazole Nitrate 1% Foam	Foam Vehicle	
Interdigital Only	26	20	18	**64**
Moccasin Only	4	3	9	**16**
Both (Interdigital & Moccasin)	6	7	10	**23**
Total	**36**	**30**	**37**	**103**

Information obtained from Table 14.2.1b.

PP

Subject Sub-Groups	Treatment Group			Sub-Total
	Econazole Nitrate 1% Cream	Econazole Nitrate 1% Foam	Foam Vehicle	
Interdigital Only	25	14	16	**55**
Moccasin Only	4	3	8	**15**
Both (Interdigital & Moccasin)	4	6	9	**19**
Total	**33**	**23**	**33**	**89**

Information obtained from Appendices 16.2.1.1 and 16.2.6.1.

Number of subjects enrolled by site within the United States

Site	Investigator	Subjects Enrolled & Randomized ITT	MITT Subjects	PP Subjects
01	Smith	36	27	23
02	Stewart	14	12	11
03	Gold	12	9	8
04	Jarratt	42	35	30
05	Kempers	22	17	14
06	Swinyer	9	3	3
Total		**135**	**103**	**89**

Table information obtained from Appendix 16.2.1.1

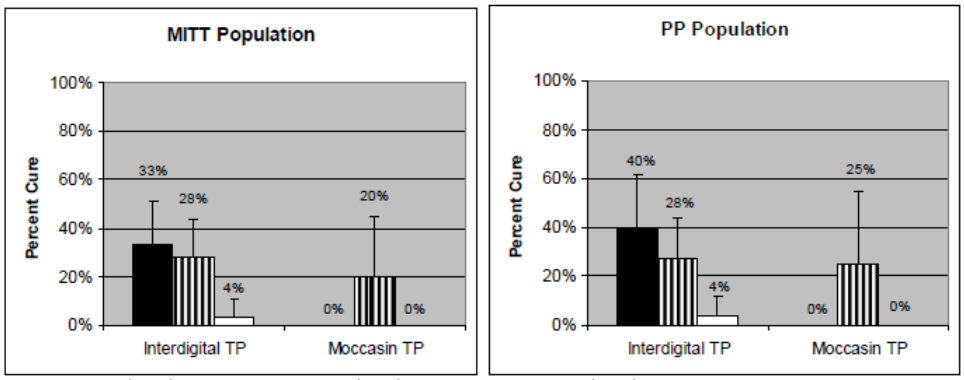
In both MITT and PP population, the complete cure rates were similar in interdigital tenia pedis patients treated with econazole nitrate foam 1% or econazole nitrate cream 1% and superior than the vehicle group (Figure 1A). Similarly, effective treatment and mycological cure rates were similar in patients treated with cream or foam formulations of econazole nitrate and superior to those in the foam vehicle group in the MITT and PP populations (Figures 1B and 1C).

Both formulations (foam and cream) of econazole nitrate were less effective against moccasin tenia pedis compared to interdigital tenia pedis (Figure 1).

Overall, the results suggest that the mycological cure rates were higher than either the effective treatment or complete cure rates in all the groups at the end of treatment (Day 29) and at follow-up (Day 43) visits; fungal cultures were negative at the Day 29 and Day 43 time points for the majority of subjects treated with either the econazole nitrate foam or cream formulations.

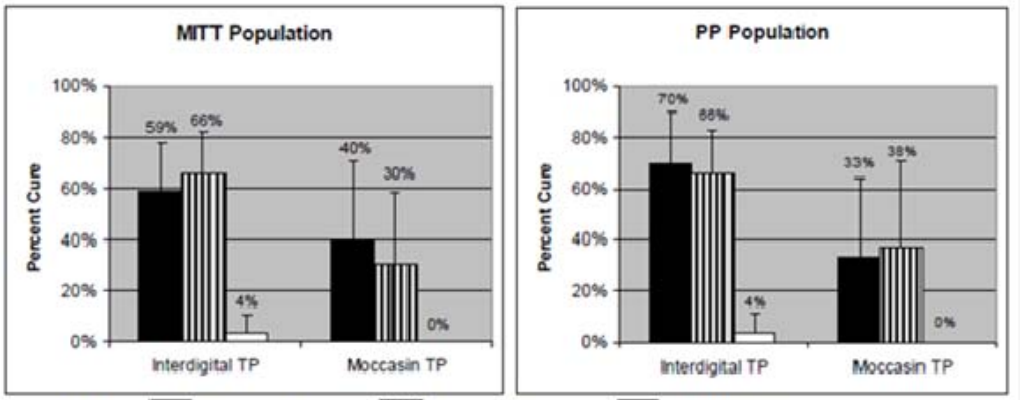
Figure 1: Study D79-2902-07 – Clinical and mycological cure rates at Day 43 (TOC) by treatment group and disease sub-type in MITT and PP populations

A: Complete cure – primary endpoint:



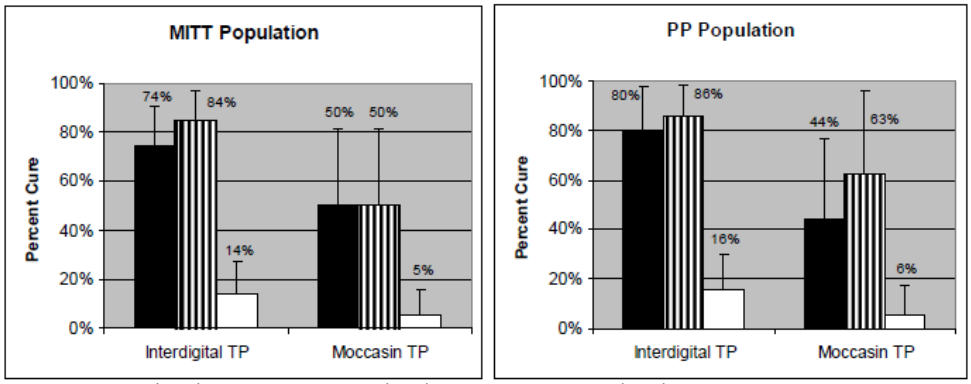
Error bars depict upper 95% confidence bound around the observed proportion.
Information obtained from Figure 14.2.41. See Table 11.4.1.1.2 below for N in each treatment group.

B: Effective treatment – secondary efficacy endpoint:



Error bars depict upper 95% confidence bound around the observed proportion.
Information obtained from Figure 14.2.42. See Table 11.4.1.2.2 below for N in each treatment group.

C: Mycological cure rates – secondary endpoint:



Error bars depict upper 95% confidence bound around the observed proportion.
Information obtained from Figure 14.2.43. See Table 11.4.1.2.4 below for N in each treatment group.

The most common dermatophyte identified in the study for all treatment groups, independent of disease subtype, was *T. rubrum* (Tables 6 and 7); there were few isolates of *T. mentagrophytes* and *E. floccosum*.

In vitro susceptibility of 101 isolates was measured by the CLSI method (M38-A2[6]) and MIC determined. Control strains included ATCC dermatophyte QC strains (*T. rubrum* MYA 4438 and *T. mentagrophytes* MYA 4439). Of the 101 isolates tested, 98 were baseline isolates; one isolate was collected from a patient at Day 29 and 2 at Day 43 time points. Comparator drugs included for testing were CIC, FLU, ITR, and TER for *in vitro* testing. MFCs were also determined for econazole and testing was performed as describe above (see section 3.2). The MIC of all baseline isolates were ≤0.0125 µg/mL with a MIC_{90} of 0.016 µg/mL. There was no correlation between MICs of baseline isolates with clinical or mycological response.

The MICs of the isolates from 3 patients (2 treated with foam and 1 with cream formulations of econazole nitrate) at the end of treatment (n=1) or follow-up (n=2) visits were similar to that of MICs of isolates collected at baseline (Table 8).

Table 6: Study D79-2902-07 - clinical and mycological response by fungal species in MITT population

Treatment Group/ Species	Day 29 n/ N (%) Clinical Success	Proven Mycological Eradication	Presumed Mycological Eradication*	Negative KOH	Day 43 n/ N (%) Clinical Success	Proven Mycological Eradication	Presumed Mycological Eradication*	Negative KOH
MITT								
Econazole Foam								
Interdigital Tinea Pedis								
T. rubrum	7/24 (29.2%)	15/23 (65.2%)	22/23 (95.7%)	15/23 (65.2%)	8/22 (36.4%)	17/22 (77.3%)	22/22 (100.0%)	17/22 (77.3%)
E. floccosum	1/2 (50.0%)	2/2 (100.0%)	2/2 (100.0%)	2/2 (100.0%)	1/2 (50.0%)	2/2 (100.0%)	2/2 (100.0%)	2/2 (100.0%)
Moccasin								
T. rubrum	1/10 (10.0%)	2/9 (22.2%)	9/9 (100.0%)	2/9 (22.2%)	1/9 (11.1%)	4/8 (50.0%)	8/9 (88.9%)	4/8 (50.0%)
Total	9/36 (25.0%)	19/34 (55.9%)	33/34 (97.1%)	19/34 (55.9%)	10/33 (30.3%)	23/32 (71.9%)	32/33 (97.0%)	23/32 (71.9%)
Econazole Cream								
Interdigital Tinea Pedis								
T. rubrum	7/24 (29.2%)	19/24 (79.2%)	23/24 (95.8%)	20/24 (83.3%)	7/24 (29.2%)	21/24 (87.5%)	24/24 (100.0%)	21/24 (87.5%)
T. mentagrophytes	2/6 (33.3%)	5/6 (83.3%)	5/6 (83.3%)	6/6 (100.0%)	2/6 (33.3%)	5/6 (83.3%)	6/6 (100.0%)	5/6 (83.3%)
Moccasin								
T. rubrum	1/9 (11.1%)	3/9 (33.3%)	8/9 (88.9%)	3/9 (33.3%)	2/9 (22.2%)	5/9 (55.6%)	8/9 (88.9%)	5/9 (55.6%)
Total	10/39 (25.6%)	27/39 (69.2%)	36/39 (92.3%)	29/39 (74.4%)	11/39 (28.2%)	31/39 (79.5%)	38/39 (97.4%)	31/39 (79.5%)
Vehicle								
Interdigital Tinea Pedis								
T. rubrum	0/23 (0.0%)	3/23 (13.0%)	10/23 (43.5%)	5/23 (21.7%)	1/22 (4.5%)	3/22 (13.6%)	8/22 (36.4%)	3/22 (13.6%)
T. mentagrophytes	0/2 (0.0%)	1/2 (50.0%)	2/2 (100.0%)	1/2 (50.0%)	1/2 (50.0%)	1/2 (50.0%)	1/2 (50.0%)	1/2 (50.0%)
E. floccosum	0/2 (0.0%)	0/2 (0.0%)	1/2 (50.0%)	0/2 (0.0%)	0/2 (0.0%)	0/2 (0.0%)	0/2 (0.0%)	0/2 (0.0%)
Moccasin								
T. rubrum	0/17 (0.0%)	1/17 (5.9%)	7/17 (41.2%)	3/17 (17.6%)	0/17 (0.0%)	1/17 (5.9%)	4/17 (23.5%)	4/17 (23.5%)
T. mentagrophytes	0/0 (0.0%)	0/0 (0.0%)	0/0 (0.0%)	0/0 (0.0%)	0/0 (0.0%)	0/0 (0.0%)	0/0 (0.0%)	0/0 (0.0%)
E. floccosum	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)
Total	0/45 (0.0%)	5/45 (11.1%)	20/45 (44.4%)	9/45 (20.0%)	2/44 (4.5%)	5/44 (11.4%)	13/44 (29.5%)	8/44 (18.2%)

* Negative Mycological Culture.

SOURCE: TDARE\Quinnova\D79-2902-07\Analysis\IT2 (Mar 22, 2013 16:48)

Note:
Clinical success represents no signs/symptoms

Table 7: Study D79-2902-07 - clinical and mycological response by fungal species in PP population

Treatment Group/ Species	Day 29 n/ N (%) Clinical Success	Proven Mycological Eradication	Presumed Mycological Eradication*	Negative KOH	Day 43 n/ N (%) Clinical Success	Proven Mycological Eradication	Presumed Mycological Eradication*	Negative KOH
PP								
Econazole Foam								
Interdigital Tinea Pedis								
T. rubrum	7/19 (36.8%)	12/18 (66.7%)	18/18 (100.0%)	12/18 (66.7%)	7/19 (36.8%)	15/19 (78.9%)	19/19 (100.0%)	15/19 (78.9%)
E. floccosum	1/1 (100.0%)	1/1 (100.0%)	1/1 (100.0%)	1/1 (100.0%)	1/1 (100.0%)	1/1 (100.0%)	1/1 (100.0%)	1/1 (100.0%)
Moccasin								
T. rubrum	1/9 (11.1%)	1/8 (12.5%)	8/8 (100.0%)	1/8 (12.5%)	1/9 (11.1%)	4/8 (50.0%)	8/9 (88.9%)	4/8 (50.0%)
Total	9/29 (31.0%)	14/27 (51.9%)	27/27 (100.0%)	14/27 (51.9%)	9/29 (31.0%)	20/28 (71.4%)	28/29 (96.6%)	20/28 (71.4%)
Econazole Cream								
Interdigital Tinea Pedis								
T. rubrum	7/23 (30.4%)	19/23 (82.6%)	22/23 (95.7%)	20/23 (87.0%)	6/23 (26.1%)	20/23 (87.0%)	23/23 (100.0%)	20/23 (87.0%)
T. mentagrophytes	2/6 (33.3%)	5/6 (83.3%)	5/6 (83.3%)	6/6 (100.0%)	2/6 (33.3%)	5/6 (83.3%)	6/6 (100.0%)	5/6 (83.3%)
Moccasin								
T. rubrum	1/8 (12.5%)	2/8 (25.0%)	7/8 (87.5%)	2/8 (25.0%)	2/8 (25.0%)	5/8 (62.5%)	7/8 (87.5%)	5/8 (62.5%)
Total	10/37 (27.0%)	26/37 (70.3%)	34/37 (91.9%)	28/37 (75.7%)	10/37 (27.0%)	30/37 (81.1%)	36/37 (97.3%)	30/37 (81.1%)
Vehicle								
Interdigital Tinea Pedis								
T. rubrum	0/21 (0.0%)	3/21 (14.3%)	10/21 (47.6%)	4/21 (19.0%)	1/21 (4.8%)	3/21 (14.3%)	8/21 (38.1%)	3/21 (14.3%)
T. mentagrophytes	0/2 (0.0%)	1/2 (50.0%)	2/2 (100.0%)	1/2 (50.0%)	1/2 (50.0%)	1/2 (50.0%)	1/2 (50.0%)	1/2 (50.0%)
E. floccosum	0/2 (0.0%)	0/2 (0.0%)	1/2 (50.0%)	0/2 (0.0%)	0/2 (0.0%)	0/2 (0.0%)	0/2 (0.0%)	0/2 (0.0%)
Moccasin								
T. rubrum	0/16 (0.0%)	1/16 (6.3%)	6/16 (37.5%)	3/16 (18.8%)	0/16 (0.0%)	1/16 (6.3%)	4/16 (25.0%)	4/16 (25.0%)
E. floccosum	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)
Total	0/42 (0.0%)	5/42 (11.9%)	19/42 (45.2%)	8/42 (19.0%)	2/42 (4.8%)	5/42 (11.9%)	13/42 (31.0%)	8/42 (19.0%)

* Negative Mycological Culture.

SOURCE: TDARE\Quinnova\D79-2902-07\Analysis\IT2 (Mar 22, 2013 16:48)

Table 8: Study D79-2902-07 - econazole MIC range and MIC_{90} (µg/mL) at different visits by fungal species

Organism	US/ Non-US Site	Econazole MIC Range (MIC_{90})		
		Baseline	**Day 29**	**Day 43**
		(*n*=84)	(*n*=1)	(*n*=2)
Trichophyton rubrum	US	0.002-0.03 (MIC_{90}=0.016)	0.004 (MIC_{90} ND)*	0.004-0.008 (MIC_{90} ND)
	non-US	–	–	–
		Baseline	**Day 29**	**Day 43**
		(*n*=10)	(*n*=0)	(*n*=0)
Trichophyton mentagrophytes	US	0.001-0.125 (MIC_{90} = 0.016)	–	–
	non-US	–	–	–
		Baseline	**Day 29**	**Day 43**
		(*n*=5)	(*n*=0)	(*n*=0)
Epidermophyton floccosum	US	0.002-0.008 (MIC_{90} ND)	–	–
	non-US	–	–	–

* ND = Not Determined (*n*=<10)

MIC for *T. rubrum* isolates from subjects with baseline and Week 4 or Week 6 fungal cultures

Subject No.	Isolate Location (I or M*)	Site No.	Tx Arm**	Visit	ECO MIC	ECO MFC	CIC	FLU	ITR	TER
095	I	04	F	Baseline	0.008	>.5	0.25	2	0.12	0.008
095	I	04	F	Week 4	0.004	>.5	0.25	2	0.06	0.008
126	M	01	F	Baseline	0.008	>.5	0.25	4	0.03	0.004
126	M	01	F	Week 6	0.008	>.5	0.5	2	0.12	0.016
119	M	01	C	Baseline	0.008	>.5	0.25	2	0.06	0.004
119	M	01	C	Week 6	0.004	0.5	0.25	1	0.06	0.002

*I = Interdigital; M=Moccasin (Appendix 16.2.6.1).
**Treatment (Tx) arms: C = Econazole Nitrate Cream 1%, F = Econazole Nitrate Foam 1%
Information obtained from Table 2 of the *In Vitro* Susceptibility Report (Appendix 16.1.13.2).

Source: SDN-012

Comments:

- *Clinical and mycological cure rates in econazole nitrate foam (Ecoza®) and Fougera® cream (RLD) treated patients were similar and better than those in the foam vehicle group.*
- *Both cream and foam formulations of econazole nitrate were less effective against the moccasin tenia pedis compared to interdigital tenia pedis.*
- *The mycological cure rates were higher than either the effective treatment or complete cure rates in all treated patients at the end of treatment (Day 29) and at follow-up (Day 43) visits.*
- *T. rubrum was the most common dermatophyte isolated.*
- *MICs of all baseline isolates were ≤0.0125 µg/mL with a MIC_{90} of 0.016 µg/mL. There was no correlation between MICs of baseline isolates and clinical or mycological response.*
- *The MICs of isolates collected at week 4 or 6 from the three econazole-treated (foam or cream) subjects were similar to that of the baseline isolates.*

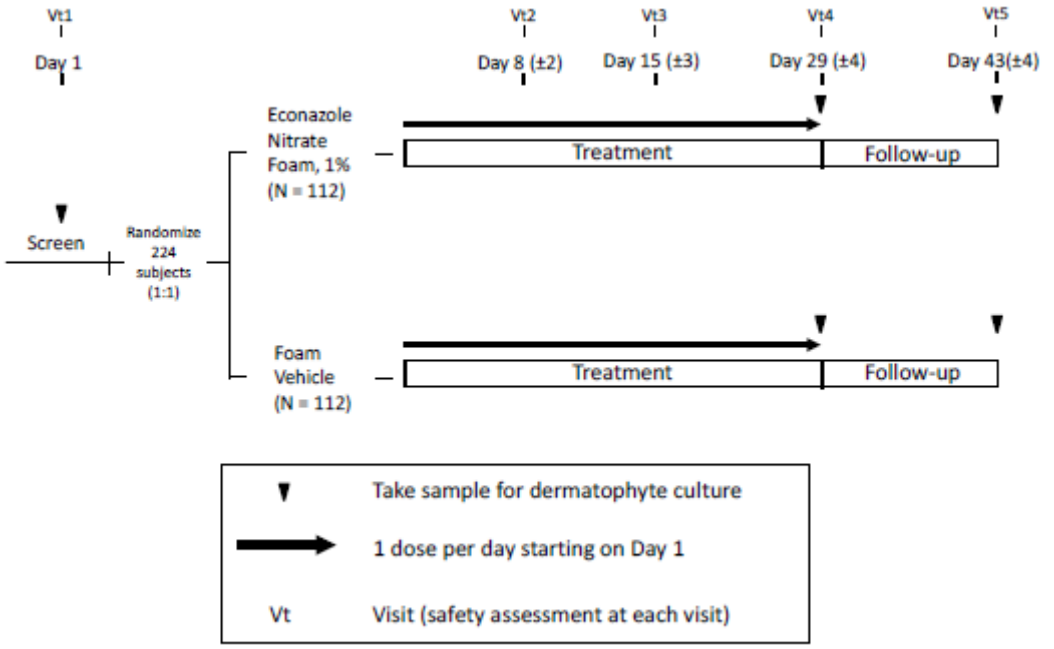
5.2. Phase 3 trials

5.2.1. Study 079-2951-302

This was a multi-center, randomized, double-blind, vehicle controlled, parallel group comparison study to evaluate the safety and efficacy of econazole nitrate foam 1% and foam vehicle in subjects with interdigital tinea pedis. Treatment was administered daily for 4-weeks and patients followed for 2-weeks post-treatment. Study design was same as the phase 2 study summarized above except that subjects ≥ 12 years with clinical [grade 1 (mild erythema) and grade 2 (moderate scaling)] and microbiological (positive microscopic evidence of hyphae by KOH examination) diagnosis of interdigital tinea pedis were enrolled. If the KOH was positive, the skin scrapings were sent to the (b) (4) laboratory (b) (4) for fungal culture. Subjects with concurrent tinea infection e.g., tinea versicolor, tinea cruris, moccasin-type tinea pedis or onychomycosis were not enrolled. The clinical, safety, and mycological evaluations were performed at different time intervals during the 6-week study period (Figure 2). Mycological evaluations were performed at the end of treatment (Visit 4, Day 29) and end of the study (Visit 5, Day 43). *In vitro* susceptibility testing of clinical isolates, collected at either of the visits (baseline, end of treatment, and follow-up) was performed by the CLSI method[6].

The primary and secondary endpoints were same as summarized above for the phase 2 trial.

Figure 2: Study 079-2951-302 - Schedule of events



Event	Visit 1 Screen/Baseline[1] (Day 1)	Visit 2 Day 8 (± 2 days)	Visit 3 Day 15 (± 3 days)	Visit 4 End of Treatment Day 29 (± 4 days)	Visit 5 Two Weeks Post Treatment Day 43 (± 4 days)
	TREATMENT PHASE[2]				
Written Informed Consent[1,3]	X				
Medical History	X				
Brief Physical Examination	X				
Inclusion/Exclusion Criteria[7]	X				
Confirm Baseline Fungal Culture Results		X[5]	X[5]	X[5]	
Urine Pregnancy Testing[4, 5, 6]	X	For discontinued subjects only	For discontinued subjects only	X	
Clinical Evaluations (Signs and Symptoms)[10]	X	X	X	X	X
Mycology (KOH/Fungal cultures)	X			X	X
Lab Tests (CBC, serum chemistry, UA)[8]	X			X	X[9]
Randomization to Study Products	X				
Investigator & Subject Assessment of Response to Treatment				X	X
Dispense Subject Instruction Sheet	X				
Dispense, Collect and/or Review Subject Diary	X	X	X	X	
Dispense Drug	X	X	X		
Concomitant Medications	X	X	X	X	X
Adverse Events	X	X	X	X	X
Collect Study Medications		X	X	X	X
Selected Sites Only:					
Photographs of Interdigital TP (selected sites only)	X				X

1. Screening visit and Baseline visit may be combined for qualified subjects that do not require washout of any prohibited medications. Subjects with a screening visit should have their consent to participate reaffirmed and females are required to have a negative pregnancy test at Baseline within 72 hours prior to medication being dispensed.
2. Subjects will be instructed not to apply study medications on visit days until after clinical evaluations have been completed.
3. Consent may be signed up to 45 days prior to the Baseline visit to allow qualified subjects to washout of a prohibited therapy if required.
4. Urine pregnancy tests must have a minimum sensitivity of 25 mIU ß-hCG/ml of urine and must be performed at screening and within 72 hours prior to the start of study medication at Baseline.
5. Subjects determined to have a negative Baseline fungal culture at this visit will be discontinued from the study after completing End of Study activities as defined in Section 13.
6. UPT must be performed within 72 hours prior to the start of the study
7. If screening and baseline activities cannot be completed on the same day but can be completed within 48 hours, the KOH does not have to be repeated prior to treatment assignment.
8. Subjects must have fasted for at least 8 hours prior to all laboratory tests.
9. Laboratory tests will be repeated for subjects with a clinically significant lab test (as assessed by the investigator) at the EOT visit. Subjects who terminate prematurely will have laboratory tests performed.
10. Perform Clinical Evaluations before scraping for Mycology (KOH/Culture).

Sixteen investigators (14 in the United States and 2 in Central America) participated in the study. Two investigational sites in the US (Investigational Sites 07 and 15) were closed due to lack of enrollment. A total of 267 study subjects were randomized (135 and 132 in the foam vehicle and econazole nitrate foam 1% groups, respectively). Of the 267 subjects

enrolled, 165 were in the MITT population and 150 in the PP population (Table 9). All PP subjects completed treatment and the study.

Table 9: Study 079-2951-302 - Summary of subject enrollment and evaluability (all subjects)

	Foam Vehicle	Econazole Nitrate Foam 1%	Total
Number of subjects enrolled[a]			345
Number of subjects who failed screening			78
Number of subjects randomized	135	132	267
Number of subjects excluded from MITT analyses	52 (38.5%)	50 (37.9%)	102 (38.2%)
Number of subjects included in MITT analyses	83 (61.5%)	82 (62.1%)	165 (61.8%)
Number of subjects excluded from PP analyses	60 (44.4%)	57 (43.2%)	117 (43.8%)
Number of subjects included in PP analyses	75 (55.6%)	75 (56.8%)	150 (56.2%)
Number of subjects excluded from Safety analyses	1 (0.7%)	2 (1.5%)	3 (1.1%)
Number of subjects included in Safety analyses	134 (99.3%)	130 (98.5%)	264 (98.9%)

[a] Enrolled subjects are those subjects who signed an informed consent.

The results showed that complete cure rates were superior in the econazole nitrate foam group compared to the vehicle group in both MITT and PP population (Table 10). Similarly, effective treatment and mycological cure rates were higher in econazole foam treated subjects compared to the placebo group (Table 11). The mycological cure rates were higher than either the effective treatment or complete cure rates in the treated patients at the end of treatment (Day 29) and at follow-up (Day 43) visits.

Table 10: Study 079-2951-302 Primary endpoint - analysis of complete cure at two weeks post-treatment (Day 43)

(A) MITT

	Foam Vehicle (N=83)	Econazole Nitrate Foam 1% (N=82)	P-value[a]
Two Weeks Post-treatment (Day 43)			
Complete cure[b]			
No	81 (97.6%)	63 (76.8%)	
Yes	2 (2.4%)	19 (23.2%)	<0.001
95% confidence interval	[0.0%, 5.7%]	[14.0%, 32.3%]	

[a] P-value from CMH test, stratified by analysis center.
[b] A subject has a complete cure if both KOH and fungal culture results are negative and no erythema, scaling, fissuring, maceration, vesiculation, and pruritus.

Note: Last observation carried forward was used to impute missing observations.

(B) PP

	Foam Vehicle (N=75)	Econazole Nitrate Foam 1% (N=75)	P-value[a]
Two Weeks Post-treatment (Day 43)			
Complete cure[b]			
No	73 (97.3%)	57 (76.0%)	
Yes	2 (2.7%)	18 (24.0%)	<0.001
95% confidence interval	[0.0%, 6.3%]	[14.3%, 33.7%]	

[a] P-value from CMH test, stratified by analysis center.
[b] A subject has a complete cure if both KOH and fungal culture results are negative and no erythema, scaling, fissuring, maceration, vesiculation, and pruritus.

Note: Last observation carried forward was used to impute missing observations.

Table 11: Study 079-2951-302 Secondary endpoints - mycological cure and effective treatment at two weeks post-treatment (Day 43)

(A) MITT

	Foam Vehicle (N=83)	Econazole Nitrate Foam 1% (N=82)	P-value[a]
Two Weeks Post-treatment (Day 43)			
Mycological cure[b]			
No	70 (84.3%)	26 (31.7%)	
Yes	13 (15.7%)	56 (68.3%)	<0.001
95% confidence interval	[7.8%, 23.5%]	[58.2%, 78.4%]	
Effective treatment[c]			
No	74 (89.2%)	42 (51.2%)	
Yes	9 (10.8%)	40 (48.8%)	<0.001
95% confidence interval	[4.2%, 17.5%]	[38.0%, 59.6%]	
Negative KOH			
No	59 (71.1%)	26 (31.7%)	
Yes	24 (28.9%)	56 (68.3%)	
95% confidence interval	[19.2%, 38.7%]	[58.2%, 78.4%]	
Negative fungal culture			
No	54 (65.1%)	7 (8.5%)	
Yes	29 (34.9%)	75 (91.5%)	
95% confidence interval	[24.7%, 45.2%]	[85.4%, 97.5%]	
No/mild erythema, No/mild scaling; and No fissuring, maceration, vesiculation, and pruritus			
No	57 (68.7%)	33 (40.2%)	
Yes	26 (31.3%)	49 (59.8%)	
95% confidence interval	[21.3%, 41.3%]	[49.1%, 70.4%]	

[a] P-value from CMH test, stratified by analysis center.
[b] A subject has a mycological cure if both KOH and fungal culture results are negative.
[c] A subject has a effective treatment if both KOH and fungal culture results are negative, no/mild erythema or scaling, and no fissuring, maceration, vesiculation, and pruritus.

Note: Last observation carried forward was used to impute missing observations.

(B) PP

	Foam Vehicle (N=75)	Econazole Nitrate Foam 1% (N=75)	P-value[a]
Two Weeks Post-treatment (Day 43)			
Mycological cure[b]			
No	63 (84.0%)	22 (29.3%)	
Yes	12 (16.0%)	53 (70.7%)	<0.001
95% confidence interval	[7.7%, 24.3%]	[60.4%, 81.0%]	
Effective treatment[c]			
No	67 (89.3%)	37 (49.3%)	
Yes	8 (10.7%)	38 (50.7%)	<0.001
95% confidence interval	[3.7%, 17.7%]	[39.4%, 62.0%]	
Negative KOH			
No	52 (69.3%)	22 (29.3%)	
Yes	23 (30.7%)	53 (70.7%)	
95% confidence interval	[20.2%, 41.1%]	[60.4%, 81.0%]	
Negative fungal culture			
No	48 (64.0%)	4 (5.3%)	
Yes	27 (36.0%)	71 (94.7%)	
95% confidence interval	[25.1%, 46.9%]	[89.6%, 99.8%]	
No/mild erythema, No/mild scaling; and No fissuring, maceration, vesiculation, and pruritus			
No	52 (69.3%)	28 (37.3%)	
Yes	23 (30.7%)	47 (62.7%)	
95% confidence interval	[20.2%, 41.1%]	[51.7%, 73.6%]	

[a] P-value from CMH test, stratified by analysis center.
[b] A subject has a mycological cure if both KOH and fungal culture results are negative.
[c] A subject has a effective treatment if both KOH and fungal culture results are negative, no/mild erythema or scaling, and no fissuring, maceration, vesiculation, and pruritus.

Note: Last observation carried forward was used to impute missing observations.

The most common dermatophyte identified in the study was *T. rubrum* (see Tables 12 and 13). There were very few patients with *T. mentagrophytes* (≤4 in the econazole nitrate foam group and ≤3 in the vehicle group in the MITT or PP populations) and *E. floccosum* (n=8 in the econazole nitrate group and ≤6 in the vehicle group in MITT and PP populations); one patient had a mixed infection with *T. rubrum* and *T. mentagrophytes* and another patient had *T. tonsurans* in the placebo group (Tables 12 and 13). Econazole nitrate foam was effective in improving clinical and mycological cure rates in both MITT and PP population on day 29 and day 43.

Subjects from the non-US sites infected with *T. rubrum* and treated with econazole nitrate showed a trend towards decreased clinical cure rates (14% in either MITT or PP population) compared to those from the US sites (~25% in either MITT or PP population); however, mycological cure rates were similar (Tables 12 and 13). The baseline MIC_{90}s for *T. rubrum* isolates from US and non-US sites were 0.016 µg/mL (range 0.001 to 0.125 µg/mL) and 0.03 µg/mL (0.002 to 0.06 µg/mL) (Table 14). There was no difference in MICs of isolates collected at baseline compared to those collected at Day 29 or Day 43.

The number of dermatophyte isolates other than *T. rubrum* were small (<10).

Overall, the MIC of all baseline isolates were ≤0.0125 µg/mL with a MIC_{90} of 0.016 µg/mL. There was no correlation between MICs of baseline isolates and clinical or mycological response.

Table 12: Study 079-2951-302 - Clinical and mycological response by fungal species in MITT population

Treatment Group/Species	Day 29 n/N (%) Clinical Success	Proven Mycological Eradication	Presumed Mycological Eradication*	Negative KOH	Day 43 n/N (%) Clinical Success	Proven Mycological Eradication	Presumed Mycological Eradication*	Negative KOH
MITT								
Econazole Foam								
US sites								
T. rubrum	7/44 (15.9%)	24/44 (54.5%)	39/44 (88.6%)	26/44 (59.1%)	11/44 (25.0%)	30/43 (69.8%)	40/43 (93.0%)	31/44 (70.5%)
T. mentagrophytes	0/3 (0.0%)	3/3 (100.0%)	3/3 (100.0%)	3/3 (100.0%)	2/4 (50.0%)	3/4 (75.0%)	4/4 (100.0%)	3/4 (75.0%)
E. floccosum	1/7 (14.3%)	3/6 (50.0%)	7/7 (100.0%)	3/6 (50.0%)	3/7 (42.9%)	4/7 (57.1%)	7/7 (100.0%)	4/7 (57.1%)
Non-US sites								
T. rubrum	1/22 (4.5%)	14/22 (63.6%)	19/22 (86.4%)	14/22 (63.6%)	3/22 (13.6%)	16/22 (72.7%)	21/22 (95.5%)	16/22 (72.7%)
T. mentagrophytes	0/1 (0.0%)	1/1 (100.0%)	1/1 (100.0%)	1/1 (100.0%)	0/1 (0.0%)	1/1 (100.0%)	1/1 (100.0%)	1/1 (100.0%)
E. floccosum	0/1 (0.0%)	0/1 (0.0%)	1/1 (100.0%)	0/1 (0.0%)	0/1 (0.0%)	1/1 (100.0%)	1/1 (100.0%)	1/1 (100.0%)
Total	9/78 (11.5%)	45/77 (58.4%)	70/78 (89.7%)	47/77 (61.0%)	19/79 (24.1%)	55/78 (70.5%)	74/78 (94.9%)	56/79 (70.9%)
Placebo Foam								
US sites								
T. rubrum	4/55 (7.3%)	9/55 (16.4%)	27/55 (49.1%)	20/55 (36.4%)	3/55 (5.5%)	10/55 (18.2%)	20/55 (36.4%)	15/55 (27.3%)
T. mentagrophytes	0/2 (0.0%)	1/2 (50.0%)	2/2 (100.0%)	1/2 (50.0%)	0/2 (0.0%)	1/2 (50.0%)	1/2 (50.0%)	2/2 (100.0%)
E. floccosum	0/4 (0.0%)	1/4 (25.0%)	2/4 (50.0%)	1/4 (25.0%)	0/4 (0.0%)	0/4 (0.0%)	1/4 (25.0%)	0/4 (0.0%)
Non-US sites								
T. rubrum	3/14 (21.4%)	3/14 (21.4%)	3/14 (21.4%)	10/14 (71.4%)	1/14 (7.1%)	1/13 (7.7%)	5/12 (41.7%)	3/13 (23.1%)
T. mentagrophytes	0/1 (0.0%)	1/1 (100.0%)	1/1 (100.0%)	1/1 (100.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	1/1 (100.0%)
E. floccosum	0/2 (0.0%)	1/2 (50.0%)	2/2 (100.0%)	1/2 (50.0%)	0/2 (0.0%)	1/2 (50.0%)	2/2 (100.0%)	1/2 (50.0%)
T. tonsurans	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	1/1 (100.0%)	0/1 (0.0%)	0/0	0/0	1/1 (100.0%)
T. mentag/T. rubrum	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	1/1 (100.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	1/1 (100.0%)
Total	7/80 (8.8%)	16/80 (20.0%)	37/80 (46.3%)	36/80 (45.0%)	4/80 (5.0%)	13/78 (16.7%)	29/77 (37.7%)	24/79 (30.4%)

* Negative Mycological Culture.

SOURCE: KGLYNN\QUINNOVA\079-2951-302\ANALYSIS\IT2 (Mar 18, 2013 09:17)

Source: SDN -12

Table 13: Study 079-2951-302 - Clinical and mycological response by fungal species in PP population

Treatment Group/Species	Day 29 n/N (%) Clinical Success	Proven Mycological Eradication	Presumed Mycological Eradication*	Negative KOH	Day 43 n/N (%) Clinical Success	Proven Mycological Eradication	Presumed Mycological Eradication*	Negative KOH
PP								
Econazole Foam								
US sites								
T. rubrum	7/43 (16.3%)	23/43 (53.5%)	38/43 (88.4%)	25/43 (58.1%)	11/43 (25.6%)	29/42 (69.0%)	39/42 (92.9%)	30/43 (69.8%)
T. mentagrophytes	0/2 (0.0%)	2/2 (100.0%)	2/2 (100.0%)	2/2 (100.0%)	1/2 (50.0%)	2/2 (100.0%)	2/2 (100.0%)	2/2 (100.0%)
E. floccosum	1/7 (14.3%)	3/6 (50.0%)	7/7 (100.0%)	3/6 (50.0%)	3/7 (42.9%)	4/7 (57.1%)	7/7 (100.0%)	4/7 (57.1%)
Non-US sites								
T. rubrum	1/21 (4.8%)	14/21 (66.7%)	19/21 (90.5%)	14/21 (66.7%)	3/21 (14.3%)	15/21 (71.4%)	20/21 (95.2%)	15/21 (71.4%)
T. mentagrophytes	0/1 (0.0%)	1/1 (100.0%)	1/1 (100.0%)	1/1 (100.0%)	0/1 (0.0%)	1/1 (100.0%)	1/1 (100.0%)	1/1 (100.0%)
E. floccosum	0/1 (0.0%)	0/1 (0.0%)	1/1 (100.0%)	0/1 (0.0%)	0/1 (0.0%)	1/1 (100.0%)	1/1 (100.0%)	1/1 (100.0%)
Total	9/75 (12.0%)	43/74 (58.1%)	68/75 (90.7%)	45/74 (60.8%)	18/75 (24.0%)	52/74 (70.3%)	70/74 (94.6%)	53/75 (70.7%)
Placebo Foam								
US sites								
T. rubrum	4/51 (7.8%)	9/51 (17.6%)	25/51 (49.0%)	20/51 (39.2%)	3/51 (5.9%)	9/51 (17.6%)	19/51 (37.3%)	14/51 (27.5%)
T. mentagrophytes	0/2 (0.0%)	1/2 (50.0%)	2/2 (100.0%)	1/2 (50.0%)	0/2 (0.0%)	1/2 (50.0%)	1/2 (50.0%)	2/2 (100.0%)
E. floccosum	0/3 (0.0%)	1/3 (33.3%)	1/3 (33.3%)	1/3 (33.3%)	0/3 (0.0%)	0/3 (0.0%)	0/3 (0.0%)	0/3 (0.0%)
Non-US sites								
T. rubrum	3/14 (21.4%)	3/14 (21.4%)	3/14 (21.4%)	10/14 (71.4%)	1/14 (7.1%)	1/13 (7.7%)	5/12 (41.7%)	3/13 (23.1%)
T. mentagrophytes	0/1 (0.0%)	1/1 (100.0%)	1/1 (100.0%)	1/1 (100.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	1/1 (100.0%)
E. floccosum	0/2 (0.0%)	1/2 (50.0%)	2/2 (100.0%)	1/2 (50.0%)	0/2 (0.0%)	1/2 (50.0%)	2/2 (100.0%)	1/2 (50.0%)
T. tonsurans	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	1/1 (100.0%)	0/1 (0.0%)	0/0	0/0	1/1 (100.0%)
T. mentag/T. rubrum	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	1/1 (100.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	1/1 (100.0%)
Total	7/75 (9.3%)	16/75 (21.3%)	34/75 (45.3%)	36/75 (48.0%)	4/75 (5.3%)	12/73 (16.4%)	27/72 (37.5%)	23/74 (31.1%)

* Negative Mycological Culture.

SOURCE: KGLYNN\QUINNOVA\079-2951-302\ANALYSIS\IT2 (Mar 18, 2013 09:17)

Source: SDN -12

Table 14: Study 079-2951-302 - Econazole MIC range and MIC_{90} at different visits by fungal species*

Organism	US/ Non-US Site	Econazole MIC range (MIC_{90})		
Trichophyton rubrum	US	**Baseline** (*n*=104) 0.001-0.125 (MIC_{90} = 0.016)	**Day 29** (*n*=34) 0.004-0.03 (MIC_{90} = 0.016)	**Day 43** (*n*=35) 0.001-0.03 (MIC_{90} = 0.016)
	non-US	**Baseline** (*n*=35) 0.002-0.06 (MIC_{90} = 0.03)	**Day 29** (*n*=19) 0.001-0.03 (MIC_{90} = 0.03)	**Day 43** (*n*=9) 0.002-0.016 (MIC_{90} ND)*
Trichophyton mentagrophytes	US	**Baseline** (*n*=6) 0.008-0.06 (MIC_{90} ND)	**Day 29** (*n*=0) --	**Day 43** (*n*=1) 0.001 (MIC_{90} ND)
	non-US	**Baseline** (*n*=3) 0.004-0.03 (MIC_{90} ND)	**Day 29** (*n*=0) --	**Day 43** (*n*=1) 0.016 (MIC_{90} ND)
Epidermophyton floccosum	US	**Baseline** (*n*=11) 0.001-0.016 (MIC_{90} = 0.016)	**Day 29** (*n*=4) 0.008-0.016 (MIC_{90} ND)	**Day 43** (*n*=6) 0.002-0.008 (MIC_{90} ND)
	non-US	**Baseline** (*n*=3) 0.004-0.03 (MIC_{90} ND)	**Day 29** (*n*=1) 0.016 (MIC_{90} ND)	**Day 43** (*n*=0) --
Trichophyton tonsurans	US	**Baseline** (*n*=0) --	**Day 29** (*n*=0) --	**Day 43** (*n*=0) --
	non-US	**Baseline** (*n*=1) 0.008 (MIC_{90} ND)	**Day 29** (*n*=0) --	**Day 43** (*n*=0) --

* ND = Not Determined (*n*=<10)

* MIC (µg/mL) values represent testing performed on all isolates at different visits regardless of treatment arm.

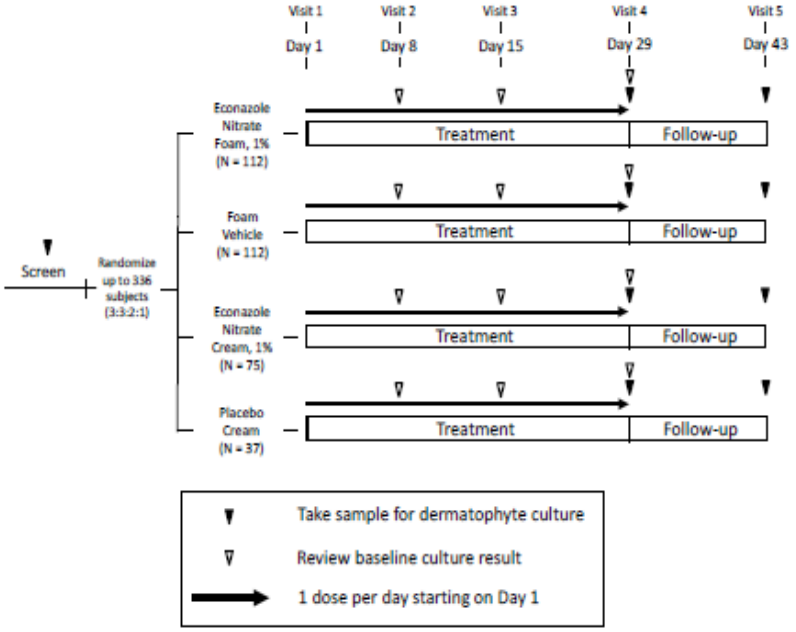
Comments:

- *Econazole nitrate foam was effective in improving clinical and mycological cure rates compared to the vehicle. The mycological cure rates were higher than either the effective treatment or complete cure rates in the econazole treated patients at both the end of treatment (Day 29) and at follow-up (Day 43) visits.*
- *Clinical cure rates in subjects, infected with T. rubrum, from non-US sites show a trend towards decrease compared to the US sites. However, there were a small number of patients from the non-US sites compared to the US sites. There was no difference in mycological cure rates or in vitro susceptibility of isolates from US vs. non US sites.*
- *T. rubrum was the most common dermatophyte isolated.*
- *MICs of all baseline isolates were ≤0.0125 µg/mL with a MIC_{90} of 0.016 µg/mL. There was no correlation between MICs of baseline isolates and clinical or mycological response.*
- *There was no change in MICs of isolates collected during or after treatment compared to the baseline isolates.*

5.2.2. Study 079-2951-303

This was a multi-center, randomized, double-blind, vehicle-controlled, parallel group trial to compare the efficacy and safety of econazole nitrate foam 1% and the foam vehicle in subjects with interdigital tinea pedis. Econazole nitrate cream 1% (RLD) was included as an evaluator blinded comparator to support a clinical bridge with the foam dosage form; placebo cream was included for blinding purposes. The subjects were randomized 3:3:2:1 to the econazole nitrate foam 1%, foam vehicle, econazole nitrate cream 1%, or placebo cream treatment groups, respectively. The enrollment criteria, treatment duration, primary and secondary endpoints, and study evaluations were similar to the Phase 2 Study D79-2902-07 and Phase 3 Study 079-2951-302 summarized above. Briefly, the assigned investigational product was to be applied once daily for 4 weeks. The clinical and mycological evaluations were performed at different time intervals during the 6-week study period (Figure 3). Mycological evaluations were performed at the end of treatment (Visit 4, Day 29) and end of the study (Visit 5, Day 43). *In vitro* susceptibility testing of clinical isolates was performed once the identification of dermatophyte was confirmed. For culture positive specimens at different visits (baseline, end of treatment, and follow-up), dermatophyte isolates were tested for *in vitro* susceptibility by the CLSI method[6].

Figure 3: Study 079-2951-303 - Schematic representation of study design



Event	Study Phase				
	Treatment[2]				Follow-up
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	Screen[1] (Day 1)	Day 8 (± 2)	Day 15 (± 3)	Day 29 (± 4)	Day 43 (± 4)
Written informed consent[1, 3]	X				
Medical history	X				
Brief physical examination	X				
Inclusion/exclusion criteria[4]	X				
Confirm inclusion/exclusion criteria		X[5]	X[5]	X[5]	
Urine pregnancy test[5, 6, 7]	X	X[8]	X[8]	X	
Clinical evaluations (signs and symptoms)[9]	X	X	X	X	X
Mycology (KOH/fungal cultures)	X			X	X
Hematology, chemistry, urinalysis[10]	X			X	X[11]
Randomization	X				
Assess treatment response				X	X
Dispense subject instruction sheet	X				
Dispense and/or review subject diary	X	X	X	X	
Dispense drug	X	X	X		
Concomitant medications	X	X	X	X	X
Adverse events	X	X	X	X	X
Collect investigational products		X	X	X	X
12-lead ECG and plasma sample (selected sites only)	X			X	X

[1] Screening visit and baseline visit may have been combined for qualified subjects who did not require washout of any prohibited medications. Subjects with a screening visit should have had their consent to participate reaffirmed and females were required to have a negative pregnancy test at baseline within 72 hours prior to medication being dispensed.
[2] Subjects were instructed not to apply investigational products on visit days until after clinical evaluations had been completed.
[3] Consent may have been signed up to 45 days prior to the baseline visit to allow qualified subjects to washout of a prohibited therapy if required.
[4] If screening and baseline activities could not be completed on the same day but could be completed within 48 hours, the KOH did not have to be repeated prior to treatment assignment.
[5] Subjects determined to have a negative baseline fungal culture at this visit were discontinued from the study after completing End-of-Study activities as defined in Section 13 of the protocol (Section 16.1.1).
[6] Urine pregnancy test (minimum sensitivity of 25 mIU ß-hCG/mL of urine) was to be performed at screening and within 72 hours prior to the start of investigational product at baseline.
[7] Urine pregnancy test must have been performed within 72 hours prior to the start of the study.
[8] For discontinued subjects only.
[9] Clinical evaluations were to be performed before scraping for mycology (KOH/culture).
[10] Subjects were to have fasted (had not eaten for approximately 8 hours) in preparation for all laboratory tests.
[11] Laboratory tests were repeated for subjects who had a clinically significant laboratory test (as assessed by the investigator) at the End-of-Treatment visit. Subjects who terminated prematurely had laboratory tests performed. Clinical evaluations were performed before scraping for mycology (KOH/fungal cultures).

Of the 457 subjects enrolled at 18 sites within the US, 256 were in the MITT population and 197 in the PP population (Table 15).

Table 15: Study 079-2951-303 - Summary of subject enrollment and evaluability

	Placebo Cream	Econazole Nitrate Cream 1%	Foam Vehicle	Econazole Nitrate Foam 1%	Total
Number of subjects enrolled*					457
Number of subjects who failed screening					99
Number of subjects randomized	40	80	119	119	358
Number of subjects excluded from MITT analyses	10 (25.0%)	28 (35.0%)	36 (30.3%)	28 (23.5%)	102 (28.5%)
Number of subjects included in MITT analyses	30 (75.0%)	52 (65.0%)	83 (69.7%)	91 (76.5%)	256 (71.5%)
Number of subjects excluded from PP analyses	18 (45.0%)	35 (43.8%)	52 (43.7%)	56 (47.1%)	161 (45.0%)
Number of subjects included in PP analyses	22 (55.0%)	45 (56.3%)	67 (56.3%)	63 (52.9%)	197 (55.0%)
Number of subjects excluded from Safety analyses	0 (0.0%)	1 (1.3%)	4 (3.4%)	3 (2.5%)	8 (2.2%)
Number of subjects included in Safety analyses	40 (100.0%)	79 (98.8%)	115 (96.6%)	116 (97.5%)	350 (97.8%)

* Enrolled subjects are those subjects who signed an informed consent.

The results showed that the complete cure rates at 2 weeks post-treatment (Day 43) in patients treated with econazole nitrate foam or cream in the MITT and PP populations were better than the placebo groups (Table 16). The complete cure rates were 25% in both the MITT and PP populations in patients treated with econazole nitrate foam; approximately one third of the patients in the econazole nitrate cream in the MITT and PP populations were clinically cured; such differences in clinical cure rates between the two formulations could be due to less number of patients in econazole nitrate cream arm compared to the foam group.

Table 16: Study 079-2951-303 - Primary endpoint: analysis of complete cure at two weeks post-treatment (Day 43)

(A) MITT

	Placebo Cream (N=30)	Econazole Nitrate Cream 1% (N=52)	Foam Vehicle (N=83)	Econazole Nitrate Foam 1% (N=91)	P-value[a]
Two Weeks Post-treatment (Day 43)					
Complete cure[b]					
No	29 (96.7%)	35 (67.3%)	79 (95.2%)	68 (74.7%)	
Yes	1 (3.3%)	17 (32.7%)	4 (4.8%)	23 (25.3%)	<0.001
95% confidence interval	[0.0%, 9.8%]	[19.9%, 45.4%]	[0.2%, 9.4%]	[16.3%, 34.2%]	

[a] P-value from CMH test, stratified by analysis center. Econazole Nitrate Cream 1% and Placebo Cream excluded from analyses.
[b] A subject has a complete cure if both KOH and fungal culture results are negative and no erythema, scaling, fissuring, maceration, vesiculation, and pruritus.

Note: Last observation carried forward was used to impute missing observations.

(B) PP

	Placebo Cream (N=22)	Econazole Nitrate Cream 1% (N=45)	Foam Vehicle (N=67)	Econazole Nitrate Foam 1% (N=63)	P-value[a]
Two Weeks Post-treatment (Day 43)					
Complete cure[b]					
No	21 (95.5%)	29 (64.4%)	63 (94.0%)	47 (74.6%)	
Yes	1 (4.5%)	16 (35.6%)	4 (6.0%)	16 (25.4%)	0.001
95% confidence interval	[0.0%, 13.2%]	[21.6%, 49.5%]	[0.3%, 11.6%]	[14.6%, 36.1%]	

[a] P-value from CMH test, stratified by analysis center. Econazole Nitrate Cream 1% and Placebo Cream excluded from analyses.
[b] A subject has a complete cure if both KOH and fungal culture results are negative and no erythema, scaling, fissuring, maceration, vesiculation, and pruritus.

Note: Last observation carried forward was used to impute missing observations.

Similarly, effective treatment and mycological cure rates at Day 43, in subjects treated with econazole nitrate foam or cream were higher than the placebo groups in both MITT and PP populations (Tables 17 and 18). Similar observations were made at Day 29 (EOT). The mycological cure rates were higher than the clinical cure rates in the treated subjects.

Table 17: Study 079-2951-303- Secondary endpoints: analysis of mycological cure and effective treatment at two weeks post-treatment (Day 43) in MITT population

	Placebo Cream (N=30)	Econazole Nitrate Cream 1% (N=52)	Foam Vehicle (N=83)	Econazole Nitrate Foam 1% (N=91)	P-value[a]
Two Weeks Post-treatment (Day 43)					
Mycological cure[b]					
No	29 (96.7%)	19 (36.5%)	68 (81.9%)	30 (33.0%)	
Yes	1 (3.3%)	33 (63.5%)	15 (18.1%)	61 (67.0%)	<0.001
95% confidence interval	[0.0%, 9.8%]	[50.4%, 76.5%]	[9.8%, 26.4%]	[57.4%, 76.7%]	
Effective treatment[c]					
No	29 (96.7%)	25 (48.1%)	74 (89.2%)	47 (51.6%)	
Yes	1 (3.3%)	27 (51.9%)	9 (10.8%)	44 (48.4%)	<0.001
95% confidence interval	[0.0%, 9.8%]	[38.3%, 65.5%]	[4.2%, 17.5%]	[38.1%, 58.6%]	

[a] P-value from CMH test, stratified by analysis center. Econazole Nitrate Cream 1% and Placebo Cream excluded from analyses.
[b] A subject has a mycological cure if both KOH and fungal culture results are negative.
[c] A subject has a effective treatment if both KOH and fungal culture results are negative, no/mild erythema or scaling, and no fissuring, maceration, vesiculation, and pruritus.

Note: Last observation carried forward was used to impute missing observations.

	Placebo Cream (N=30)	Econazole Nitrate Cream 1% (N=52)	Foam Vehicle (N=83)	Econazole Nitrate Foam 1% (N=91)	P-value[a]
Two Weeks Post-treatment (Day 43)					
Negative KOH					
No	25 (83.3%)	18 (34.6%)	54 (65.1%)	29 (31.9%)	
Yes	5 (16.7%)	34 (65.4%)	29 (34.9%)	62 (68.1%)	<0.001
95% confidence interval	[3.3%, 30.0%]	[52.5%, 78.3%]	[24.7%, 45.2%]	[58.6%, 77.7%]	
Negative fungal culture					
No	24 (80.0%)	4 (7.7%)	52 (62.7%)	12 (13.2%)	
Yes	6 (20.0%)	48 (92.3%)	31 (37.3%)	79 (86.8%)	<0.001
95% confidence interval	[5.7%, 34.3%]	[85.1%, 99.6%]	[26.9%, 47.8%]	[79.9%, 93.8%]	
No/mild erythema, No/mild scaling; and No fissuring, maceration, vesiculation, and pruritus					
No	26 (86.7%)	21 (40.4%)	58 (69.9%)	42 (46.2%)	
Yes	4 (13.3%)	31 (59.6%)	25 (30.1%)	49 (53.8%)	0.001
95% confidence interval	[1.2%, 25.5%]	[46.3%, 73.0%]	[20.3%, 40.0%]	[43.6%, 64.1%]	

[a] P-value from CMH test, stratified by analysis center. Econazole Nitrate Cream 1% and Placebo Cream excluded from analyses.
[b] A subject has a mycological cure if both KOH and fungal culture results are negative.
[c] A subject has a effective treatment if both KOH and fungal culture results are negative, no/mild erythema or scaling, and no fissuring, maceration, vesiculation, and pruritus.

Note: Last observation carried forward was used to impute missing observations

Table 18: Study 079-2951-303- Secondary endpoints: analysis of mycological cure and effective treatment at two weeks post-treatment (Day 43) in PP population

	Placebo Cream (N=22)	Econazole Nitrate Cream 1% (N=45)	Foam Vehicle (N=67)	Econazole Nitrate Foam 1% (N=63)	P-value[a]
Two Weeks Post-treatment (Day 43)					
Mycological cure[b]					
No	21 (95.5%)	16 (35.6%)	54 (80.6%)	18 (28.6%)	
Yes	1 (4.5%)	29 (64.4%)	13 (19.4%)	45 (71.4%)	<0.001
95% confidence interval	[0.0%, 13.2%]	[50.5%, 78.4%]	[9.9%, 28.9%]	[60.3%, 82.6%]	
Effective treatment[c]					
No	21 (95.5%)	21 (46.7%)	58 (86.6%)	31 (49.2%)	
Yes	1 (4.5%)	24 (53.3%)	9 (13.4%)	32 (50.8%)	<0.001
95% confidence interval	[0.0%, 13.2%]	[38.8%, 67.9%]	[5.3%, 21.6%]	[38.4%, 63.1%]	

[a] P-value from CMH test, stratified by analysis center. Econazole Nitrate Cream 1% and Placebo Cream excluded from analyses.
[b] A subject has a mycological cure if both KOH and fungal culture results are negative.
[c] A subject has a effective treatment if both KOH and fungal culture results are negative, no/mild erythema or scaling, and no fissuring, maceration, vesiculation, and pruritus.

Note: Last observation carried forward was used to impute missing observations.

	Placebo Cream (N=22)	Econazole Nitrate Cream 1% (N=45)	Foam Vehicle (N=67)	Econazole Nitrate Foam 1% (N=63)	P-value[a]
Two Weeks Post-treatment (Day 43)					
Negative KOH					
No	18 (81.8%)	15 (33.3%)	41 (61.2%)	17 (27.0%)	
Yes	4 (18.2%)	30 (66.7%)	26 (38.8%)	46 (73.0%)	<0.001
95% confidence interval	[2.1%, 34.3%]	[52.9%, 80.4%]	[27.1%, 50.5%]	[62.1%, 84.0%]	
Negative fungal culture					
No	17 (77.3%)	3 (6.7%)	42 (62.7%)	3 (4.8%)	
Yes	5 (22.7%)	42 (93.3%)	25 (37.3%)	60 (95.2%)	<0.001
95% confidence interval	[5.2%, 40.2%]	[86.0%, 100.0%]	[25.7%, 48.9%]	[90.0%, 100.0%]	
No/mild erythema, No/mild scaling; and No fissuring, maceration, vesiculation, and pruritus					
No	19 (86.4%)	17 (37.8%)	44 (65.7%)	27 (42.9%)	
Yes	3 (13.6%)	28 (62.2%)	23 (34.3%)	36 (57.1%)	0.001
95% confidence interval	[0.0%, 28.0%]	[48.1%, 76.4%]	[23.0%, 45.7%]	[44.9%, 69.4%]	

[a] P-value from CMH test, stratified by analysis center. Econazole Nitrate Cream 1% and Placebo Cream excluded from analyses.
[b] A subject has a mycological cure if both KOH and fungal culture results are negative.
[c] A subject has a effective treatment if both KOH and fungal culture results are negative, no/mild erythema or scaling, and no fissuring, maceration, vesiculation, and pruritus.

Note: Last observation carried forward was used to impute missing observations.

The most common dermatophyte isolated was *T. rubrum* (Tables 19 and 20). There were very few isolates of *T. mentagrophytes* (n=12) and *E. floccosum* (n=6); one patient had a mixed infection with *T. rubrum* and *E. floccosum* (Tables 19 and 20). Econazole nitrate foam was more effective than vehicle in improving clinical and mycological cure rates, in both MITT and PP population, on day 29 and day 43.

In vitro susceptibility results of clinical isolates showed no difference in MICs of isolates collected at baseline compared to those at Day 29 or Day 43 (Table 21). The MIC values were in the same range as those reported for isolates from patients in the Phase 2 (Study 79-2902-07) and Phase 3 (Study 079-2951-302) studies summarized above.

There was no correlation between MICs of baseline isolates and clinical or mycological response.

Table 19: Study 079-2951-303 - Clinical and mycological response by fungal species in MITT population

Treatment Group/Species	Day 29 n/N (%) Clinical Success	Proven Mycological Eradication	Presumed Mycological Eradication*	Negative KOH	Day 43 n/N (%) Clinical Success	Proven Mycological Eradication	Presumed Mycological Eradication*	Negative KOH
MITT (US sites)								
Econazole Foam								
T. rubrum	16/73 (21.9%)	50/72 (69.4%)	64/72 (88.9%)	54/72 (75.0%)	22/74 (29.7%)	57/73 (78.1%)	71/73 (97.3%)	58/73 (79.5%)
T. mentagrophytes	0/1 (0.0%)	0/1 (0.0%)	1/1 (100.0%)	0/1 (0.0%)	1/2 (50.0%)	1/2 (50.0%)	2/2 (100.0%)	1/2 (50.0%)
E. floccosum	2/4 (50.0%)	2/4 (50.0%)	3/4 (75.0%)	3/4 (75.0%)	2/4 (50.0%)	2/4 (50.0%)	3/4 (75.0%)	2/4 (50.0%)
E. floc/T. rubrum	0/1 (0.0%)	0/1 (0.0%)	1/1 (100.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)
Total	18/79 (22.8%)	52/78 (66.7%)	69/78 (88.5%)	57/78 (73.1%)	25/81 (30.9%)	60/80 (75.0%)	76/80 (95.0%)	61/80 (76.3%)
Placebo Foam								
T. rubrum	4/70 (5.7%)	15/70 (21.4%)	27/70 (38.6%)	29/70 (41.4%)	5/69 (7.2%)	13/69 (18.8%)	26/70 (37.1%)	26/69 (37.7%)
T. mentagrophytes	0/6 (0.0%)	0/5 (0.0%)	2/4 (50.0%)	1/6 (16.7%)	1/6 (16.7%)	2/6 (33.3%)	4/6 (66.7%)	2/6 (33.3%)
E. floccosum	0/2 (0.0%)	0/2 (0.0%)	0/2 (0.0%)	2/2 (100.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)
Total	4/78 (5.1%)	15/77 (19.5%)	29/76 (38.2%)	32/78 (41.0%)	6/76 (7.9%)	15/76 (19.7%)	30/77 (39.0%)	28/76 (36.8%)
Econazole Cream								
T. rubrum	8/44 (18.2%)	29/44 (65.9%)	40/44 (90.9%)	30/44 (68.2%)	16/42 (38.1%)	27/42 (64.3%)	39/42 (92.9%)	28/42 (66.7%)
T. mentagrophytes	0/4 (0.0%)	3/4 (75.0%)	4/4 (100.0%)	3/4 (75.0%)	1/4 (25.0%)	3/4 (75.0%)	4/4 (100.0%)	3/4 (75.0%)
E. floccosum	1/2 (50.0%)	2/2 (100.0%)	2/2 (100.0%)	2/2 (100.0%)	0/2 (0.0%)	2/2 (100.0%)	2/2 (100.0%)	2/2 (100.0%)
Total	9/50 (18.0%)	34/50 (68.0%)	46/50 (92.0%)	35/50 (70.0%)	17/48 (35.4%)	32/48 (66.7%)	45/48 (93.8%)	33/48 (68.8%)
Placebo Cream								
T. rubrum	1/29 (3.4%)	1/29 (3.4%)	2/29 (6.9%)	11/29 (37.9%)	2/27 (7.4%)	1/28 (3.6%)	6/28 (21.4%)	5/28 (17.9%)
Total	1/29 (3.4%)	1/29 (3.4%)	2/29 (6.9%)	11/29 (37.9%)	2/27 (7.4%)	1/28 (3.6%)	6/28 (21.4%)	5/28 (17.9%)

* Negative Mycological Culture.

SOURCE: BARMSTRONG\QUINNOVA\079-2951-303\ANALYSIS\IT2 (Mar 15, 2013 16:06)

Source: SDN-12

Table 20: Study 079-2951-303 - Clinical and mycological response by fungal species in PP population

Treatment Group/Species	Day 29 n/N (%) Clinical Success	Proven Mycological Eradication	Presumed Mycological Eradication*	Negative KOH	Day 43 n/N (%) Clinical Success	Proven Mycological Eradication	Presumed Mycological Eradication*	Negative KOH
PP (US sites)								
Econazole Foam								
T. rubrum	11/58 (19.0%)	41/58 (70.7%)	51/58 (87.9%)	45/58 (77.6%)	16/58 (27.6%)	44/57 (77.2%)	56/57 (98.2%)	45/57 (78.9%)
T. mentagrophytes	0/1 (0.0%)	0/1 (0.0%)	1/1 (100.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	1/1 (100.0%)	0/1 (0.0%)
E. floccosum	1/3 (33.3%)	1/3 (33.3%)	2/3 (66.7%)	2/3 (66.7%)	1/3 (33.3%)	1/3 (33.3%)	2/3 (66.7%)	1/3 (33.3%)
E. floc/T. rubrum	0/1 (0.0%)	0/1 (0.0%)	1/1 (100.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)
Total	12/63 (19.0%)	42/63 (66.7%)	55/63 (87.3%)	47/63 (74.6%)	17/63 (27.0%)	45/62 (72.6%)	59/62 (95.2%)	46/62 (74.2%)
Placebo Foam								
T. rubrum	3/61 (4.9%)	15/62 (24.2%)	23/62 (37.1%)	29/62 (46.8%)	5/62 (8.1%)	12/62 (19.4%)	23/62 (37.1%)	25/62 (40.3%)
T. mentagrophytes	0/4 (0.0%)	0/4 (0.0%)	1/3 (33.3%)	0/4 (0.0%)	1/4 (25.0%)	1/4 (25.0%)	2/4 (50.0%)	1/4 (25.0%)
E. floccosum	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	1/1 (100.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)
Total	3/66 (4.5%)	15/67 (22.4%)	24/66 (36.4%)	30/67 (44.8%)	6/67 (9.0%)	13/67 (19.4%)	25/67 (37.3%)	26/67 (38.8%)
Econazole Cream								
T. rubrum	7/40 (17.5%)	26/40 (65.0%)	36/40 (90.0%)	27/40 (67.5%)	15/40 (37.5%)	25/40 (62.5%)	37/40 (92.5%)	26/40 (65.0%)
T. mentagrophytes	0/3 (0.0%)	2/3 (66.7%)	3/3 (100.0%)	2/3 (66.7%)	1/3 (33.3%)	2/3 (66.7%)	3/3 (100.0%)	2/3 (66.7%)
E. floccosum	1/2 (50.0%)	2/2 (100.0%)	2/2 (100.0%)	2/2 (100.0%)	0/2 (0.0%)	2/2 (100.0%)	2/2 (100.0%)	2/2 (100.0%)
Total	8/45 (17.8%)	30/45 (66.7%)	41/45 (91.1%)	31/45 (68.9%)	16/45 (35.6%)	29/45 (64.4%)	42/45 (93.3%)	30/45 (66.7%)
Placebo Cream								
T. rubrum	1/22 (4.5%)	1/22 (4.5%)	2/22 (9.1%)	10/22 (45.5%)	2/21 (9.5%)	1/22 (4.5%)	5/22 (22.7%)	4/22 (18.2%)
Total	1/22 (4.5%)	1/22 (4.5%)	2/22 (9.1%)	10/22 (45.5%)	2/21 (9.5%)	1/22 (4.5%)	5/22 (22.7%)	4/22 (18.2%)

* Negative Mycological Culture.

SOURCE: BARMSTRONG\QUINNOVA\079-2951-303\ANALYSIS\IT2 (Mar 15, 2013 16:06)

Source: SDN-12

Table 21: Study 079-2951-303 - Econazole MIC range and MIC_{90} at different visits by fungal species

Organism	US/ Non-US Site	Econazole MIC range (MIC_{90})		
Trichophyton rubrum		**Baseline (*n*=231)**	**Day 29 (or ET*) (*n*=91)**	**Day 43 (*n*=70)**
	US	0.001-0.5 (MIC_{90} = 0.016)	0.001-0.06 (MIC_{90} = 0.016)	0.001-0.03 (MIC_{90} = 0.016)
	non-US	--	--	--
Trichophyton mentagrophytes		**Baseline (*n*=12)**	**Day 29 (or ET) (*n*=2)**	**Day 43 (*n*=2)**
	US	0.002-0.125 (MIC_{90} = 0.06)	0.016-0.03 (MIC_{90} ND)**	0.004-0.008 (MIC_{90} ND)
	non-US	--	--	--
Epidermophyton floccosum		**Baseline (*n*=10)**	**Day 29 (or ET) (*n*=1)**	**Day 43 (*n*=2)**
	US	0.004-0.03 (MIC_{90} = 0.016)	0.016 (MIC_{90} ND)	0.004-0.008 (MIC_{90} ND)
	non-US	--	--	--

* ET = Early Termination

**ND = Not Determined (*n*=<10)

Source: SDN-12
Note: MIC results represent testing of all isolates collected at different visits regardless of treatment arm.

Comments:

- *Econazole nitrate foam was effective in improving clinical and mycological cure rates compared to the vehicle group; the cure rates in the econazole nitrate foam or cream treated subjects were similar. The mycological cure rates were higher than either the effective treatment or complete cure rates at the end of treatment (Day 29) and at follow-up visit (Day 43).*
- *Econazole nitrate was active against all of the three dermatophyte strains tested.*
- *T. rubrum was the most common dermatophyte isolated.*
- *MICs of all baseline isolates were ≤0.5 µg/mL with a MIC_{90} of ≤0.016 µg/mL. There was no correlation between MICs of baseline isolates and clinical or mycological response.*
- *There does not appear to be any change in MIC values of isolates collected after treatment compared to the baseline isolates.*

6. The labeling

Applicant's version of the microbiology section of the labeling:

12.1 Mechanism of Action

Econazole is a highly selective inhibitor of fungal cytochrome P450 dependent enzyme lanosterol 14-α-demethylase. This enzyme functions to convert lanosterol to ergosterol. The subsequent loss of normal sterols correlates with the accumulation of 14-α-methyl sterols in fungi and may be responsible for the fungistatic activity of econazole. Mammalian cell demethylation is much less sensitive to econazole inhibition *(Sheehan et al. 1999, Ghannoum 1999, Fromtling 1988).*

12.4 Microbiology

Econazole nitrate has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections *[see Indications and Usage (1)]*.

Dermatophytes	**Yeasts**
Epidermophyton floccosum	*Candida albicans*
Microsporum audouini	*Malassezia furfur*
Microsporum canis	
Microsporum gypseum	
Trichophyton mentagrophytes	
Trichophyton rubrum	
Trichophyton tonsurans	

Econazole nitrate exhibits broad-spectrum antifungal activity against the following organisms *in vitro*, but **the clinical significance of these data is unknown**.

Dermatophytes	**Yeasts**
Trichophyton verrucosum	*Candida guillermondii*
	Candida parapsilosis
	Candida tropicalis

15 REFERENCES

Fromtling, RA. Overview of medically important antifungal azole derivatives. *Clin Microbiol Rev* 1988; 1(2): 187-217.

Ghannoun MA and Rice LB. Antifungal agents: Mode of action, mechanisms of resistance and correlation of the mechanism with bacterial resistance. *Clin Microbiol Rev* 1999; 12(4); 501-517.

Sheehan, DJ, Hitchcock, CA and Sibley, CM. Current and Emerging Azole Antifungal Agents. Clin Microbiol Rev 1999, 12(1): 40-79.

Comments:

1. *The* (b) (4) *following should be stated in section 12.1:*

   12.1 "Mechanism of action"
   - *Econazole nitrate is an azole antifungal drug (see Clinical pharmacology, Microbiology 12.4).*

2. (b) (4) *The RLD is approved for the treatment of following indications:*

- *Tinea pedis, tinea cruris, and tinea corporis caused by Trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton tonsurans, Microsporum canis, Microsporum audouini, Microsporum gypseum, and Epidermophyton floccosum,*
- *Cutaneous candidiasis, and*
- *Tinea versicolor.*

Ecoza® will be approved for the treatment of tenia pedis only. The applicant has performed bridging studies that support efficacy of econazole nitrate foam to be similar to the RLD. Therefore, the pathogens associated with interdigital tenia pedis only should be listed in the Microbiology section of the labeling. (b) (4)

3. *The applicant has proposed* (b) (4)

[See appended electronic signature page]
Shukal Bala, Ph.D.
Microbiologist, DAIP

CONCURRENCE:
DAIP/Acting Microbiology Team Leader/ Kerry Snow MS, MT (ASCP)

CC:
NDA # 205175
DAIP/PM/Frances LeSane
DDDP/PM/Cristina Attinello and Matthew White

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/s/

SHUKAL BALA
08/01/2013

KERRY SNOW
08/01/2013

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 25 June 2013

TO: NDA 205175

FROM: Erika Pfeiler, Ph.D.
Microbiologist

THROUGH: John Metcalfe, Ph.D.
Senior Microbiology Reviewer

cc: Catherine Tran-Zwanetz
Regulatory Health Project Manager
CDER/OPS/ONDQA

SUBJECT: Product Quality Microbiology assessment of Microbial Limits for Econazole Nitrate Foam 1% [Submission Date: 29 January 2013]

The microbial limits (b) (4) specifications for Econazole Nitrate Foam 1% are acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

Econazole Nitrate Foam 1% is for cutaneous use.

The drug product is tested for microbial limits at release using a method consistent with USP Chapter <61> (Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests) and <62> (Microbiological Examination of Non-sterile Products: Tests for Specified Microorganisms).

The microbial limits acceptance criteria include a total aerobic microbial count (b) (4) and total yeast and mold count (TYMC) (b) (4) as well as the absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa* per gram. The TYMC limit is (b) (4) recommended in USP Chapter <1111> (Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use). The microbial limits test methods were verified to be appropriate for use with the drug product following procedures consistent with those in USP Chapter <61> and <62>.

M E M O R A N D U M

[redacted] (b) (4) . The test method was verified to be appropriate for use with the drug product.

The drug product will also be tested [redacted] (b) (4) as part of the post-approval stability protocol.

ADEQUATE

Reviewer Comments – The microbiological quality of the drug product is controlled via a suitable testing protocol. The proposed specification for total yeast and mold count is [redacted] (b) (4) An information request was sent to the applicant on 13 May 2013 to clarify whether microbial limits testing would be performed at product release. The applicant responded (DARRTS Date 24 June 2013) with information that was adequate to complete the review.

END

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/s/

ERIKA A PFEILER
06/25/2013

JOHN W METCALFE
06/25/2013
I concur.

CLINICAL MICROBIOLOGY FILING CHECKLIST

NDA Number: 205175 (Original) **Applicant:** AmDerma Pharmaceuticals, LLC **Stamp Date:** 1/14/ 2013

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

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comments
1	Is the microbiology information (preclinical/nonclinical and clinical) described in different sections of the NDA organized in a manner to allow substantive review to begin?	X		For preclinical microbiology information Fougera® (econazole nitrate Cream, 1%) has been used as the reference listed drug (RLD)
2	Is the microbiology information (preclinical/nonclinical and clinical) indexed, paginated and/or linked in a manner to allow substantive review to begin?	X		No new preclinical studies included; see comment no.1
3	Is the microbiology information (preclinical/nonclinical and clinical) legible so that substantive review can begin?	X		
4	On its face, has the applicant submitted *in vitro* data in necessary quantity, using necessary clinical and non-clinical strains/isolates, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling?	X		No new preclinical studies included; see comment no.1
5	Has the applicant submitted any required animal model studies necessary for approvability of the product based on the submitted draft labeling?			N/A
6	Has the applicant submitted all special/critical studies/data requested by the Division during pre-submission discussions?			N/A
7	Has the applicant submitted the clinical microbiology datasets in a format which intents to correlate baseline pathogen with clinical and microbiologic outcome?		X	• Microbiology results are included in MB dataset files • Microbiology analysis datasets not found; the information was requested from the applicant in a teleconference held on 2/6/13.
8	Has the applicant submitted draft/proposed interpretive criteria/breakpoint along with quality control (QC) parameters and interpretive criteria, if applicable, in a manner consistent with contemporary standards, which attempt to correlate criteria with clinical results of NDA/BLA studies, and in a manner to allow substantive review to begin?			N/A

MICROBIOLOGY FILING CHECKLIST

	Content Parameter	Yes	No	Comments
9	Has the applicant submitted a clinical microbiology dataset in an appropriate/standardized format which intents to determine resistance development by correlating changes in the phenotype (such as *in vitro* susceptibility) and/or genotype (such as mutations) of the baseline pathogen with clinical and microbiologic outcome?		X	See comment no. 7
10	Has the applicant used standardized or nonstandardized methods for measuring microbiologic outcome? If nonstandardized methods were used, has the applicant included complete details of the method, the name of the laboratory where actual testing was done and performance characteristics of the assay in the laboratory where the actual testing was done?	Yes		Standardized methods for microbiologic testing used; all testing performed (b) (4) (b) (4)
11	Has the applicant submitted draft labeling consistent with current regulation, divisional and Center policy, and the design of the development package?	X		The microbiology section of the labeling is same as the RLD but not consistent with the current policy.
12	Has the applicant submitted annotated microbiology draft labeling consistent with current divisional policy, and the design of the development package?	X		
13	Have all the study reports, published articles, and other references been included and cross-referenced in the annotated draft labeling or summary section of the submission?	X		
14	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	X		

IS THE MICROBIOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA is not fileable from the microbiology perspective, state the reasons and provide comments to be sent to the Applicant.

N/A

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

The following comments were communicated to the applicant on 2/8/13:

1. In the mycology study report the results of *in vitro* susceptibility testing of clinical isolates performed (b) (4) were summarized as the range of minimum inhibitory concentration (MIC), MIC_{50} and MIC_{90} values irrespective of the fungal species and the time of collection of the isolate. It is unclear if these include results of patients who failed therapy. The results by different fungal species and isolates collected from patients enrolled at different sites and at different

visits could not be found. Please clarify if these results (summary tables and analysis datasets) have been submitted. If yes, then please let us know where to find. If these results have not been submitted, then please provide us with the following:

i. Summary tables that include MIC_{50}, MIC_{90}, and MIC range by fungal species, different sites, and different visits (e.g., baseline, day 29, and day 43).

ii. Analysis data sets that include subject and site identifiers, treatment arm, and fungal species identified at different visits (e.g., baseline, day 29, and day 43), as well as clinical cure, mycological response, and antifungal susceptibility test results.

The results of each of the clinical trial should be presented separately. We encourage you to share examples of Tables with us using sham datasets for our comment and feedback.

2. You state that the Clinical and Laboratory Standards Institute (CLSI) method was used for *in vitro* susceptibility testing. Please provide a reference to the CLSI method used; any deviations from the CLSI method should also be specified. Additionally, please provide results of the quality control strains included for testing.

Shukal Bala	*2/11/13*
Reviewing Microbiologist Division of Antiinfective Products	Date

Kerry Snow	*2/11/13*
Acting Microbiology Team Leader Division of Antiinfective Products	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHUKAL BALA
02/11/2013

KERRY SNOW
02/11/2013