CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205175Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA #:	205175
Submission Date:	December 26, 2012
Brand Name:	Ecoza
Generic Name:	Econazole nitrate, 1%
Dosage Form:	Foam
Dosage Strength:	1%
Reviewer:	Chinmay Shukla, Ph.D.
Team Leader:	Doanh Tran, Ph.D.
Division Director:	Capt. E. Dennis Bashaw, Pharm. D.
OCP Division:	DCP-3
OND Division:	Division of Dermatology and Dental Products
Sponsor:	Amderma Pharmaceuticals LLC.
Relevant IND(s):	077,523
Submission Type:	New-submission
Indication:	Topical treatment of interdigital tinea pedis

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1. Executive Summary

This NDA submission is for econazole nitrate Foam, 1% and the Sponsor has proposed an indication for the treatment of interdigital tinea pedis (b) (4)

The Sponsor has adopted 505(b)(2) regulatory pathway and has identified Econazole nitrate Cream, 1% (NDA 018751, Spectazole®) as a listed drug. Econazole nitrate Cream, 1% is approved as a once daily application for the topical treatment of tinea pedis, tinea cruris and tinea corporis caused by *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Trichophyton tonsurans*, *Microsporum canis, Microsporum audouini, Microsporum gypseum and Epidermophyton floccosum*, in the treatment of cutaneous candidiasis and in the treatment of tinea versicolor.

The clinical program consists of four Phase 1 dermal safety trials, two Phase 2 trials which include an adult pharmacokinetic (PK) trial to support a bridge between the Foam and Cream formulations and a pediatric PK trial in subjects 12 to 17 years of age under maximal use conditions and two Phase 3 trials.

1.1 Recommendation

From a Clinical Pharmacology standpoint, this application is acceptable provided the labeling comments are adequately addressed by the Sponsor.

1.2 Post-Marketing Requirements

Conduct in-vitro assessments to evaluate the following:

1. Inhibition potential of econazole nitrate for enzymes CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4.
2. Induction potential of econazole nitrate for enzymes CYP1A2, 2B6 and 3A.

Further in-vivo assessment to address drug interaction potential may be needed based on the results of the in-vitro assessment.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

To support this NDA the Sponsor has conducted PK assessment in the following trials:

- D79-2902-07: Phase 2 safety and efficacy trial in adults with interdigital and/or moccasin type tinea pedis
- 0792951-109: Phase 2 pediatric PK trial (12-17 year old) in subjects with interdigital tinea pedis
- 0792951-303: Phase 3 safety and efficacy trial

PK results: In the adult trial (D79-2902-07), 19 subjects (male and female) with tinea pedis applied 2.4 g of econazole nitrate Foam 1% once daily to soles, toes, interdigital spaces and tops of both feet up to the ankles for 29 days. Blood samples were obtained on Day 29 at pre-dose and 1, 2, 4, 6, 8, and 12 hours after application. Results (mean ± SD) showed the time to reach peak plasma concentrations (T_{max}) was 6.8 ± 5.1 h with maximum concentration (C_{max}) of 417 ±218 pg/ml. The area under the concentration time curve for the first 12 hours post application on Day 29 (AUC_{0-12}) was 3440 ± 1920 pg-h/ml.

In the pediatric trial, 18 subjects (male and female ages 12 - 17) with interdigital tinea pedis and positive fungal cultures were treated with a mean daily amount of 3.2 g of econazole nitrate 1% Foam once daily to soles, toes, interdigital spaces and tops of both feet up to the ankles for 4 weeks. Blood samples were obtained on Day 28 at pre-dose and 7 h and 11 h post-dose. The mean ± SD econazole plasma concentration was 397 ± 289, 534 ± 745 and 575 ± 638 pg/mL at pre-dose and 7 h and 11 h post-dose, respectively.

In adult subjects, the 90% confidence interval (CI) of the ratio of geometric means of AUC (0.73 to 1.87) and C_{max} (0.74 to 1.46) of Foam vs. Cream were outside the no effect range of 0.8 to 1.25, suggesting that the Foam and the Cream are not bioequivalent. Based on ratio of geometric mean values, the C_{max} of econazole appear to be similar (observed point estimate = 1.04), however, the exposure (AUC) of econazole following administration of the Foam formulation appears to be ~ 17% higher than the Cream (observed point estimate = 1.17).

In pediatric subjects (12-17 years) limited PK samples were obtained. The systemic econazole concentrations (geometric mean) appear to be approximately 2 fold higher at 7 h and 11 h post-dose following administration of the Foam formulation compared to the Cream.

Based on cross trial comparison, the geometric mean concentrations of econazole at 7 h and 11 h post-dose in pediatric subjects was ~ 1.7 and ~ 1.2 fold higher, respectively, than the 8 h and 12 h post-dose concentrations in adults, following administration of the Foam formulation.

In the Phase 3 trial (0792951-303), blood samples were analyzed for safety purpose only in subjects with ECG abnormalities. According to the Sponsor, single blood sample was obtained on Day 29 and Day 43 (or early termination) in 2 subjects with ECG abnormalities. Measurable econazole concentration was found only in 1 subject on Day 29 and this concentration was not higher than those observed in the PK trials.

Drug metabolism: According to the Sponsor, the pre-dose, 4 h and 12 h post-dose plasma samples on Day 29 from all subjects applying either econazole nitrate Foam or Cream from Trial D79-2902-07 (PK trial in adults) were examined for the presence of metabolites of econazole. This was an exploratory study for qualitative determination of the presence of metabolites. A sample from in-vitro hepatocyte incubation with econazole at 50 μM concentration was used as a control. Both a tandem mass spectrometer and a Quadrupole time-of-flight (Q-Tof) mass spectrometer with accurate mass capabilities were used to analyze the selected plasma samples. The Sponsor claims that the tandem mass spectrometer did show peaks at retention times similar to the econazole glucuronide metabolite in the plasma samples; however, the Q-Tof showed that these peaks were either noise or not related to econazole glucuronide metabolite that was identified in the in-vitro hepatocyte incubation study. Based on these results the presence of glucuronide metabolite of econazole is unlikely to be measurable at therapeutic doses.

Drug interactions: There have been cases of drug interactions between topical econazole nitrate and anticoagulant therapy with coumarins (warfarin and acenocoumarol) reported in the FDA Adverse Event Reporting System (FAERS) and medical literature. The Division of Dermatology and Dental Products (DDDP) requested Division of Pharmacovigilance (DPV) to evaluate the case reports in association with econazole use (see review dated 07/15/2013 by Dr. Jessica Weintraub in DARRTS under NDA 018751). DVP has recommended including language in all econazole labels regarding drug-drug interaction with warfarin, resulting in an increased anticoagulant effect of

coumarins in association with topical econazole use. Clinical Pharmacology review on this issue can be found under NDA 018751 (see review by Dr. An-Chi Lu dated 08/28/2012 in DARRTS).

Formulation used: The adult PK trial (D79-2902-07) used the formulation manufactured in (b) (4) while the pediatric PK trial (0792951-109) used the formulation manufactured in USA (commercial manufacturing site). (b) (4) he overall composition of the formulation remained unchanged. The Sponsor has conducted in-vitro release test (IVRT) to bridge the formulation manufactured in (b) (4) and USA. According to Office of New Drugs Quality Assurance (ONDQA) reviewer Dr. Kelly Kitchens, the IVRT results are acceptable (for further details, see review in DARRTS by Dr. Kitchens).

QT prolongation: Based on the PK results of Trial D79-2902-07 (PK trial in adults), the Sponsor had applied for a waiver to conduct QT/QTc evaluations. Clinical Pharmacology concurred with Sponsor's justification (see review in DARRTS dated 09/23/2009 under IND 077523 by Dr. Seongeun Cho).

Reviewer comments: *Following administration of the Foam formulation, the systemic concentrations in pediatric was higher than adults, based on cross trial comparison. The highest mean (arithmetic mean) concentration in pediatrics was observed at the 11 hour post dose time point and it was 0.575 ng/mL. This concentration is ~1.5 nM (molecular weight of econazole = 381.68 g/mol), which is slightly above the sub-nanomolar threshold which is currently accepted by DDDP to waive TQT assessment for topical products. Considering the long history of econazole use and no QT related adverse events reported, the waiver for conducting TQT assessment is further justified.*

Pediatric assessment: The Sponsor has conducted a pediatric PK trial (Trial 0792951-109) under maximal use conditions in subjects 12 to 17 years of age with interdigital tinea pedis. For subjects 11 years of age and younger, the Sponsor has requested for a partial waiver of pediatric studies. At a meeting with the Pediatric Review Committee (PeRC) on 05/29/2013, PeRC agreed to the Sponsor's partial waiver request.

Clinical Pharmacology Briefing: An optional intra-division level briefing was conducted on August 26, 2013 with the following in attendance: Hae-Young Ahn, E. Dennis Bashaw, Praveen Balimane, Jing Fang, Brian Chou, Gerald Tran, An-Chi Lu, Doanh Tran and Chinmay Shukla.

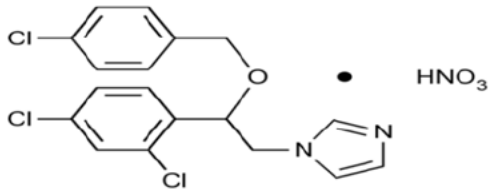
2. Question Based Review

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation?

Drug substance: Econazole nitrate is an antifungal agent with the chemical name (±)-1-[2,4-Dichloro-β-[(*p*-chlorobenzyl)oxy]phenethyl]-imidazole mononitrate. It belongs to imidazole class of antifungal agents. The molecular formula is $C_{18}H_{15}Cl_3N_2O.HNO_3$ with a molecular weight of 444.70 g/mol and the structural formula is shown in Figure 1.

Figure 1: Structure of Econazole nitrate



Formulation: The Sponsor states that supplies for the early nonclinical safety studies and clinical Phase 2 safety and efficacy PK trial in adults (D79-2902-07) were produced (b) (4)

The manufacturing was later transferred to the US (b) (4)

and the commercial process was finalized prior to Phase 3 study. Accordingly, the pediatric PK trial (0792951-109) and the two Phase 3 safety and efficacy trials (0792951-302 and 0792951-303) were conducted with the to-be-marketed formulation manufactured in USA. The Sponsor has classified (b) (4) manufacturing site change as a (b) (4) change as per SUPAC-SS guidance and have conducted an IVRT to establish a bridge between the two Foam formulations. IVRT results were reviewed by ONDQA reviewer Dr. Kelly Kitchens and according to Dr. Kitchens the results are acceptable (for further details, see review in DARRTS by Dr. Kitchens).

The composition of the bulk product is shown in Table 1. The bulk product and butane (propellant) (b) (4) and the fill weight is shown in Table 2.

Table 1: Composition of Econazole nitrate, 1% Bulk Product

Ingredients	% w/w	Function
Econazole nitrate (USP)	1.00	Active
Purified water (USP)	(b) (4)	
Stearic acid (NF)		
Povidone (b) (4) (USP)		
Propylene glycol (USP)		
Glycerin (b) (4) (USP)		
Dimethicone (b) (4) (NF)		
Trolamine (b) (4) (NF)		
Polysorbate 20 (NF)		

Table 2: Total fill weights

	10 g	70 g	(b) (4)
Econazole nitrate 1% bulk			(b) (4)
Propellant (Butane, USP)			
Total fill weight			

2.1.2 What are the proposed mechanism of action and the therapeutic indications?

Mechanism of action: Econazole is an imidazole antifungal and drugs in this class act by inhibiting the biosynthesis of ergosterol which is a constituent of fungal cell membranes. Ergosterol serves as a bioregulator of membrane fluidity and is responsible for membrane integrity of in fungal cells.

Therapeutic indication: With this application, the Sponsor is seeking an indication of topical treatment of interdigital tinea pedis (b) (4)

2.1.3 What is the proposed route of administration and dosage?

Proposed route of administration: Topical.

Proposed dosage: Once daily for 4 weeks.

2.2 General Clinical Pharmacology

2.2.1 What were the clinical trials conducted to support this NDA?

To support this application, the Sponsor has conducted four Phase 1 dermal safety trials, two Phase 2 trials which include an adult PK trial to support a bridge between the Foam and Cream and a pediatric PK trial under maximal use conditions and two Phase 3 trials. Table 3 shows a list of all clinical trials provided to support this application.

Table 3: List of all clinical trials

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Pediatric PK	0792951-109	**Module 5.3.3.5**	Compare steady state PK Foam vs. Cream	Randomized, Active-controlled	Foam 1%,; Once daily; topical Cream 1%,; Once daily; topical	50	Interdigital tinea pedis	4 weeks	Complete; Full
Phase 2 Safety and Efficacy	D79-2902-07	**Module 5.3.5.1**	Establish clinical bridge between Foam and Cream	Randomized, Placebo-controlled	Foam 1%,; Once a daily; topical Cream 1%,; Once daily; topical Vehicle Foam; once daily; topical	135	Tinea pedis (interdigital and/or moccasin type)	4 weeks	Complete; Full
Phase 3 Safety and Efficacy	0792951-302	**Module 5.3.5.1**	Determine and compare safety and efficacy of Foam vs. Placebo	Randomized, Placebo-controlled	Foam 1%,; Once a daily; topical Vehicle Foam; once daily; topical	267	Interdigital tinea pedis	4 weeks	Complete; Full
Phase 3 Safety and Efficacy	0792951-303	**Module 5.3.5.1**	Determine and compare safety and efficacy of Foam vs. Placebo. Cream comparator for safety purposes	Randomized, Placebo-controlled	Foam 1%,; Once a daily; topical Vehicle Foam; once daily; topical Cream 1%,; Once daily; topical	358	Interdigital tinea pedis	4 weeks	Complete; Full
Dermal Safety	0792951-104	**Module 5.3.3.1**	Determine irritation potential	Randomized, controlled	Econazole Nitrate Foam 1%,: Once a daily; topical Econazole Nitrate Vehicle Foam; once daily; topical Sodium Lauryl Sulfate Solution, 0.2%; once daily; topical Saline Solution, 0.9%; once daily; topical	34	Healthy Subjects	3 weeks	Complete; Full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Dermal Safety	0792951-105	**Module 5.3.3.1**	Determine potential to induce sensitization	Randomized, controlled	Econazole Nitrate Foam 1%,; 10 applications; topical Econazole Nitrate Vehicle Foam; 10 applications; topical Sodium Lauryl Sulfate Solution, 0.2%; 10 applications; topical Saline Solution, 0.9%; 10 applications topical	226	Healthy	6-8 weeks	Complete; Full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Dermal Safety	0792951-106	**Module 5.3.3.1**	Determine irritation potential after exposure to UV light	Randomized, within subject comparison	Econazole Nitrate Foam 1%,; one application; topical Econazole Nitrate Vehicle Foam; one application; topical	32	Healthy Subjects	4 days	Complete; Full
Dermal Safety	0792951-107	**Module 5.3.3.1**	Determine photosensitization potential	Randomized, within subject comparison	Econazole Nitrate Foam 1%,; seven applications; topical Econazole Nitrate Vehicle Foam; seven applications; topical	57	Healthy Subjects	6 weeks	Complete; Full

2.2.2 What are the design features of the clinical pharmacology and the clinical trials used to support dosing or claims?

Phase 2 - Design features of PK trial in adults (D79-2903-07): The primary objective of this trial was to substantiate a clinical bridge between econazole nitrate Foam, 1% and the listed drug econazole nitrate Cream, 1% based upon clinical outcome, safety, and plasma PK data. This was a multi-center, evaluator-blinded, randomized, vehicle controlled, parallel group comparison of econazole nitrate Foam, 1% with econazole nitrate Cream, 1% and the Foam vehicle. Approximately 135 subjects with tinea pedis who met the enrollment criteria with at least moderate scaling (interdigital and/or moccasin-type) and mild erythema (interdigital only) and a positive KOH finding were enrolled and randomized (1:1:1) to one of treatment arms.

The assigned study medication was applied once daily, preferably in the mornings for 4 weeks. Subjects were instructed to treat both feet by applying a thin uniform coat of the study medication over each foot in its entirety up to the inferior aspect of their ankles

once a day (i.e., soles, toes, interdigital spaces and the top surfaces of both feet up to the ankles) independent of the area of disease involvement.

At the end of 4 weeks (Day 29), at selected PK sites, blood was drawn from all subjects at prior to the application of the last dose and at 1, 2, 4, 6, 8, and 12 hours post-dose to obtain plasma drug levels of econazole to determine the extent of systemic absorption following administration of the Cream and Foam formulations.

Phase 2 - Design features of maximal use PK trial in pediatrics (0792951-109): The primary objective of this trial was to compare the PK of econazole nitrate Foam, 1% with econazole nitrate Cream, 1% in subjects with interdigital tinea pedis aged 12 years to less than 18 years who were treated under maximal use conditions. This was a multi-center, randomized, double-blind, parallel-group trial.

Approximately 42 subjects who met the entry criteria were enrolled and randomized (1:1) to econazole nitrate, Foam 1% or the econazole nitrate, Cream 1% treatment group. The enrolled subjects had to have a clinical diagnosis of interdigital tinea pedis involving at least 2 web spaces in total extending no more than approximately 1 inch proximal to the web spaces or metatarsophalangeal joints; lesions were to have at least moderate scaling and mild erythema as defined as Grade 2 and Grade 1, respectively at Baseline.

The assigned investigational product was to be applied once daily in the morning for 4 weeks and subjects were instructed to apply a thin uniform coat of the investigational product to the soles, toes, interdigital spaces, and the tops of both feet (up to the ankles). The subjects were asked to avoid washing the treatment area for at least 4 hours after each application, continue treatment regardless of symptomatic improvement, and to record their dosing in a subject diary each day.

Subjects were also instructed to record the time at which they applied investigational product on the morning of Day 27 (approximately 24 hours prior to their final dose on Day 28) and to withhold application of their final dose pending blood draw for pre-last-dose PK assessment. Subjects were then to apply their final dose (Day 28) and provide blood samples at 7 hours (±1 hour) post-last-dose and at 4 hours (±1 hour) after the 7 hour blood draw. Baseline blood sample on (Day 1) were also obtained before the start of the treatment.

2.2.3 In which trials were PK assessed and what were the results?

To support this NDA the Sponsor has conducted PK assessment in the following trials as shown in Table 4:

Table 4: List of trials with PK assessment

Trial #	Purpose	Formulation manufacturing site (b) (4)
D79-2903-07	PK trial in adult subjects with tinea pedis to establish a bridge between the Foam and Cream formulation	
0792951-109	Maximal use PK trial in pediatric subjects aged 12 to < 18 years with interdigital tinea pedis	
0792951-303	Phase 3 safety and efficacy trial – PK assessment conducted only in those subjects where ECG abnormalities were observed	

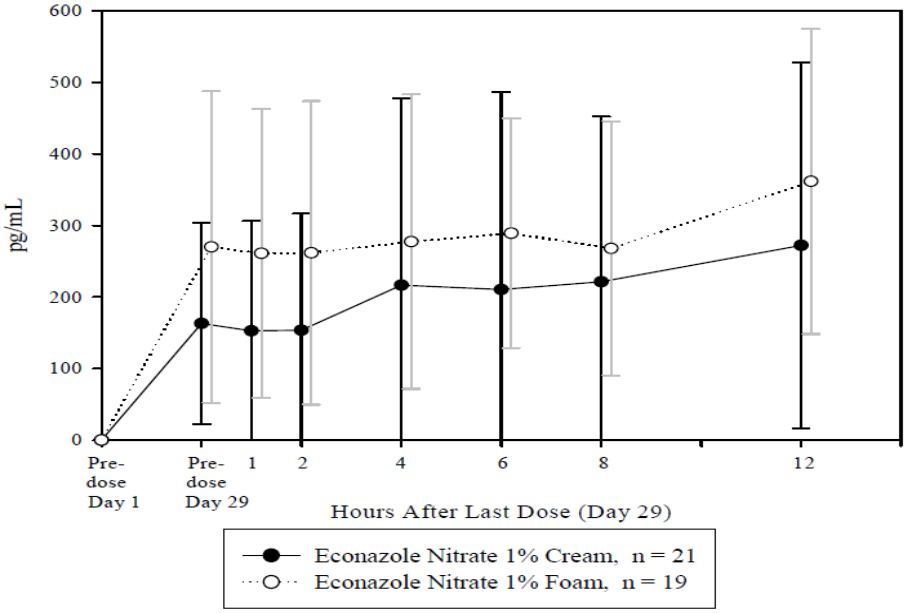
Summary of PK results of Trial D79-2903-07 (PK trial in adults): A summary of PK parameters for econazole nitrate following the administration of Cream and Foam formulation are shown in Table 5 below and the concentration versus time profile is shown in Figure 2.

Table 5: Summary of Mean ± SD PK parameters for Econazole following 29 days of once daily topical administration

PK Parameters	EN Cream 1% (N=21)	EN 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).

Figure 2: Concentration (Mean ± SD) versus time profile on Day 29 for Econazole nitrate Foam, 1% and Cream 1%



The 90% CI between the ratio of geometric means of the AUC and C_{max} of econazole following administration of the Foam versus Cream formulation for all subjects in the PK population is shown in Table 6.

Table 6: 90% CI between the ratio of geometric means of AUC and C_{max} following the administration of econazole nitrate Foam (Test) vs. Cream (Reference) for all subjects in the PK population

	Econazole Nitrate Foam 1% (N=19)		Econazole Nitrate Cream 1% (N=21)
AUC (pg*h/mL)			
Geometric Mean	2770.1		2366.1
90% Confidence Interval	(1999.0 to 3838.6)		(1662.8 to 3366.8)
Ratio of Geometric Means		1.17	
90% Confidence Interval		(0.73 to 1.87)	
Cmax (pg/mL)			
Geometric Mean	360.7		347.9
90% Confidence Interval	(286.2 to 454.6)		(266.7 to 453.8)
Ratio of Geometric Means		1.04	
90% Confidence Interval		(0.74 to 1.46)	

Reviewer comments: *The 90% CI of the geometric means of AUC and C_{max} of Foam vs. Cream were outside the no effect range of 0.8 to 1.25 suggesting that the Foam and the Cream are not bioequivalent. Based on the point estimate value, the exposure (AUC) of econazole nitrate following administration of the Foam formulation appears to be ~ 17% higher than the Cream.*

Summary of PK results of Trial 0792951-109 (Maximal use PK trial in pediatrics):
Limited PK samples were obtained in this trial and hence no PK parameters were estimated. Table 7 shows a summary of mean econazole concentrations assessed following administration of the Foam and Cream formulations and Table 8 shows geometric mean concentrations.

Table 7: Summary of Mean ± SD concentrations (pg/mL) of Econazole following Foam or Cream administrations

	Baseline/Day 1 (Prior To First Application)	Day 28 (Prior to Last Application)	Day 28 (7 Hours Post-Application)	Day 28 (4 Hours Post 7 Hour Collection)
Econazole Nitrate Foam, 1% (N=18)				
N	18	18	18	17
Mean	0.0	396.9	534.1	574.6
STD	0.00	288.89	745.33	637.63
Median	0.0	301.0	355.5	432.0
Min to Max	0 to 0	0 to 1200	0 to 3390	0 to 2690
95% CI for Mean	NC	[253.3, 540.6]	[163.4, 904.7]	[246.7, 902.4]
Difference from Econazole Nitrate Cream, 1%	0.0	187.9	358.5	401.3
95% CI for Difference	[0.0, 0.0]	[-14.5, 390.3]	[-19.8, 736.8]	[63.8, 738.7]
Econazole Nitrate Cream, 1% (N=15)				
N	15	15	15	15
Mean	0.0	209.1	175.5	173.3
STD	0.00	277.61	164.36	173.87
Median	0.0	154.0	144.0	147.0
Min to Max	0 to 0	0 to 966	0 to 515	0 to 537
95% CI	NC	[55.3, 362.8]	[84.5, 266.6]	[77.0, 269.6]

NC=Not calculated.

Table 8: Summary of Geometric mean (CV %) concentrations on Day 28

Treatment	Concentration (pg/mL) [Geometric mean (CV%)]		
	Day 28 (Prior to last application)	**Day 28 (7 h post-application)**	**Day 28 (4 h post 7 h collection)**
Econazole nitrate foam, 1%	390.15 (68)	444.13 (144)	389.22 (194)
Econazole nitrate cream, 1%	275.31 (103)	226.37 (66)	205.05 (71)

Reviewer comments: Based on the geometric mean concentrations (Table 9), on Day 28, *the systemic concentrations of econazole following administration of the Foam formulation were approximately 1.4, 2.0 and 1.9 fold higher than those observed after administration of the Cream formulation at pre-dose, 7 hours post-application and 4 hours post 7 hour collection, respectively.*

Comparing PK results from Trial D79-2903-07 (Adult PK trial) and Trial 0792951-109 (Maximal use PK trial in pediatrics): A cross-trial comparison between systemic concentrations [Geometric mean] observed in the adult PK trial (D79-2903-07) and maximal use PK trial in pediatrics (0792951-109) is made for qualitative purposes only (see Table 9).

Table 9: Geometric mean (CV %) econazole concentrations (pg/mL) from the adult trial (D79-2903-07) and pediatric trial (0792951-109).

Formulation	Trial D79-2903-07 (Adults)		Trial 0792951-109 (Pediatrics)	
	Day 29		Day 28	
	8 h post dose	***12 h post dose***	***7 h post dose***	***11 h post dose***
Foam	261.21 (61)	315.01 (68)	444.13 (144)	389.22 (194)
Cream	239.87 (86)	286.06 (79)	226.37 (66)	205.05 (71)

Reviewer Comments: *Based on Table 10 (cross trial comparison), the mean concentrations of econazole in pediatrics following administration of the Foam at 7 h and 11 h post-dose on Day 28 were approximately 1.7 and 1.2 fold higher compared to those observed at 8 h and 12 h post-dose on Day 29 in adults. In contrast, the mean systemic concentrations following Cream administration was higher (~ 1.4 fold) in adults at 12 h time point compared to pediatrics. At the time of filing this NDA, the observed increase in econazole bioavailability following administration of Foam compared to Cream formulation, was conveyed to Clinical and Pharmacology-Toxicology reviewers for the purpose of bridging. Both the reviewers concluded this to be a review issue and not a filing issue.*

Summary of PK results in the Phase 3 trial (0792951-303): In the Phase 3 trial, blood samples were analyzed for econazole concentration for safety purpose, only in subjects with ECG abnormalities. According to the Sponsor, single blood sample was obtained on Day 29 and Day 43 (or early termination) in 2 subjects with ECG abnormalities and measurable econazole concentration was found only in 1 subject on Day 29 and this

concentration was not higher than those observed in the PK trials. Specifically Subject 14-005 had Baseline, Day 29 and Day 43 blood concentrations below the level of quantification (BLQ) while Subject 03-016 had Baseline and early termination (Day 36) concentrations BLQ, but on Day 29, the systemic concentration of econazole was 216 pg/mL.

2.2.4 What information is known about drug metabolism?

According to the Sponsor, the pre-dose, 4 h and 12 h post-dose plasma samples on Day 29 from all subjects applying either econazole nitrate Foam or Cream from Trial D79-2902-07 (PK trial in adults) were examined for the presence of metabolites of econazole. This was an exploratory study for qualitative determination of the presence of metabolites. A sample from in-vitro hepatocyte incubation with econazole at 50 μM concentration was used as a control. Both a tandem mass spectrometer and a Quadrupole time-of-flight (Q-Tof) mass spectrometer with accurate mass capabilities were used to analyze the selected plasma samples. The Sponsor claims that the tandem mass spectrometer did show peaks at retention times similar to the econazole glucuronide metabolite in the plasma samples; however, the Q-Tof showed that these peaks were either noise or not related to econazole glucuronide metabolite that was identified in the in-vitro hepatocyte incubation study. Based on these results the presence of glucuronide metabolite of econazole is unlikely to be measurable at therapeutic doses.

2.2.6 What is the safety profile of econazole?

The clinical safety of econazole nitrate Foam 1% was evaluated over the course of eight clinical trials (four Phase 1 trials, two Phase 2 trials, and two Phase 3 trials). According to the Sponsor, in the Phase 1 trials, econazole nitrate Foam 1% was safe, with no dermal irritation, dermal sensitization, phototoxicity, or photosensitization observed, and a very low rate of adverse events (AEs) of mild to moderate severity, reported. The Sponsor has further reported that the two Phase 2 PK trials showed comparable safety outcomes between the Foam and the reference product Cream and no AEs or systemic toxicity were observed. In the Phase 3 trial 079-2951-303, which included an econazole nitrate Cream 1% comparator group, the Sponsor has claimed that the number of subjects reporting at least one AE was similar between all treatment groups. In the two Phase 3 trials, the Sponsor has reported the AEs to be generally mild and the most common ones were local irritation, headache and nasopharyngitis. Severe AEs have been reported in 6 subjects in the combined safety population and these include hypertension, pain associated with kidney stone, pain associated with hernia surgery, localized infection and musculoskeletal pain. All these were deemed not related to the treatment by the Sponsor. There were no deaths reported in any of the clinical trials.

Reviewer comments: *For additional information on safety, please see review by medical officer Dr. Amy Woitach in DARRTS.*

2.2.7 Has the potential for QT prolongation adequately addressed?

Based on the PK results of Trial D79-2902-07 (PK trial in adults), the Sponsor had applied for a waiver to conduct QT/QTc evaluations. Clinical Pharmacology concurred with Sponsor's justification (see review in DARRTS dated 09/23/2009 under IND 077523 by Dr. Seongeun Cho).

Reviewer comments: *Following administration of the Foam formulation, the systemic concentrations in pediatric was higher than adults, based on cross trial comparison. The highest mean (arithmetic mean) concentration in pediatrics was observed at the 11 hour post dose time point and it was 0.575 ng/mL. This concentration is ~1.5 nM (molecular weight of econazole = 381.68 g/mol), which is slightly above the sub-nanomolar threshold which is currently accepted by DDDP to waive TQT assessment for topical products. Considering the long history of econazole use and no QT related adverse events reported, the waiver for conducting TQT assessment is further justified.*

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.3.1.1 Effect of gender

The effect of gender on PK of econazole nitrate was not explored.

2.3.1.2 Effect of disease

In the adult PK trial (D79-2902-07), the Sponsor evaluated the effect of disease state on PK of econazole nitrate (see Table 10 and 11) by comparing the AUC and C_{max} obtained from subjects with healed skin and not-healed skin.

Table 10: PK parameters in healed and not-healed skin

PK Parameters (Geometric mean)	Healed Skin		Not-healed skin	
	Foam (n=2)	Cream (n=6)	Foam (n=11)	Cream (n=9)
AUC (pg*h/mL)	3184.5	1663.5	2830.6	2510.6
Cmax (pg/mL)	361.6	317.4	384.6	314.8

Table 11: Effect of disease state on PK of econazole nitrate

Ratio (Not-healed/Healed)	AUC (pg*h/mL)	Cmax (pg/mL)
Foam	0.88	1.06
Cream	1.51	0.99

Reviewer comments: *The exposure (AUC) of econazole in the Cream arm appears to be slightly higher in subjects with not-healed skin compared to healed skin. While in the Foam arm; it appears that disease resolution had minimal effect on PK. Any definitive conclusions cannot be made because of limited number of subjects.*

The Sponsor has also provided statistical analysis by calculating the 90% CI of the ratio of geometric mean of AUC and C_{max} following administration of the Foam and Cream formulation in subjects with healed and not healed skin (also included is data in subjects whose disease state is unknown) (see Table 12).

Table 12: 90% CI between the ratio of geometric means of AUC and C_{max} following the administration of econazole nitrate Foam (Test) vs. Cream (Reference) based on subgroup analysis by disease condition

	Econazole Nitrate Foam 1% (N=19)		Econazole Nitrate Cream 1% (N=21)
Subjects with Day 29 Skin = Healed[a]			
AUC (pg*h/mL)			
N	2		6
Geometric Mean	3184.5		1663.5
90% Confidence Interval	(419.5 to 24173.6)		(694.2 to 3985.9)
Ratio of Geometric Means		1.91	
90% Confidence Interval		(0.40 to 9.17)	
Cmax (pg/mL)			
N	2		6
Geometric Mean	361.6		317.4
90% Confidence Interval	(21.4 to 6121.9)		(186.8 to 539.1)
Ratio of Geometric Means		1.14	
90% Confidence Interval		(0.41 to 3.16)	
	Econazole Nitrate Foam 1% (N=19)		Econazole Nitrate Cream 1% (N=21)
Subjects with Day 29 Skin = Not Healed[a]			
AUC (pg*h/mL)			
N	11		9
Geometric Mean	2830.6		2510.6
90% Confidence Interval	(1664.5 to 4813.8)		(1684.0 to 3742.9)
Ratio of Geometric Means		1.13	
90% Confidence Interval		(0.58 to 2.17)	
Cmax (pg/mL)			
N	11		9
Geometric Mean	384.6		314.8
90% Confidence Interval	(271.0 to 545.7)		(220.0 to 450.3)
Ratio of Geometric Means		1.22	
90% Confidence Interval		(0.76 to 1.97)	
	Econazole Nitrate Foam 1% (N=19)		Econazole Nitrate Cream 1% (N=21)
Subjects with Day 29 Skin = Unknown[b]			
AUC (pg*h/mL)			
N	6		2
Geometric Mean	2541.5		5213.7
90% Confidence Interval	(1442.7 to 4477.2)		(1143.4 to 23772.9)
Ratio of Geometric Means		0.49	
90% Confidence Interval		(0.18 to 1.35)	
Cmax (pg/mL)			
N	6		2
Geometric Mean	320.5		719.0
90% Confidence Interval	(205.7 to 499.4)		(49.1 to 10533.3)
Ratio of Geometric Means		0.45	
90% Confidence Interval		(0.19 to 1.07)	

[a] Subjects with Day 29 Skin = Healed were those with no Day 29 Signs and Symptoms (Cracking/Fissuring, Maceration, Pruritus, Scaling/Hyperkeratos, and Vesiculation), with the exception of Mild Erythema.

[b] Subjects with Day 29 Skin = Unknown were discontinued at Day 29 due to Baseline negative fungal culture, and therefore, signs and symptoms were not evaluated at Day 29.

Reviewer comments: *From the data in the healed vs. not-healed skin, the systemic levels of econazole following administration of the Foam formulation appears to be higher than Cream. The same observation cannot be made in subjects with "unknown" disease state, which shows opposite effect. However, it should be noted that these observations are based on limited data, especially in the Foam arm which had only 2 subjects with healed skin.*

2.3.1.3 Pediatric subjects

The Sponsor has conducted a pediatric PK trial (Trial 0792951-109) under maximal use conditions in subjects 12 to 17 years of age with interdigital tinea pedis. For subjects 11 years of age and younger, the Sponsor has requested for a partial waiver of pediatric studies. At a meeting with the Pediatric Review Committee (PeRC) on 05/29/2013, PeRC agreed to the Sponsor's partial waiver request.

2.3.1.4 Renal impairment

The Sponsor has not evaluated PK in subjects with renal impairment.

2.3.1.5 Hepatic impairment

The Sponsor has not evaluated PK in subjects with hepatic impairment.

2.3.1.6 What pregnancy and lactation use information is there in the application?

The Sponsor has not evaluated PK in pregnant and /or lactating females.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or response and what is the impact of any differences in exposure or response?

The influence of extrinsic factors on dose-exposure and/or response was not explored.

2.4.2 Drug interactions

There have been cases of drug interactions between topical econazole nitrate and anticoagulant therapy with coumarins (warfarin and acenocoumarol) reported in the FDA Adverse Event Reporting System (FAERS) and medical literature. The Division of Dermatology and Dental Products (DDDP) requested Division of Pharmacovigilance (DPV) to evaluate the case reports in association with econazole use (see review dated 07/15/2013 by Dr. Jessica Weintraub in DARRTS under NDA 018751). DVP has recommended including language in all econazole labels regarding drug-drug interaction with warfarin, resulting in an increased anticoagulant effect of coumarins in association

with topical econazole use. Clinical Pharmacology review on this issue can be found under NDA 018751 (see review by Dr. An-Chi Lu dated 08/28/2012 in DARRTS).

Reviewer comments: *Based on the FAERS reports of drug interaction between topical econazole nitrate and coumarins and DPV review, Section 7 – Drug Interactions was added to the Sponsor proposed label (See Section 3). Since there have been no studies conducted to evaluate the drug interaction potential of econazole, the Sponsor will be recommended to assess in-vitro drug interaction potential as post marketing requirement (PMR). Based on the in-vitro results, the need for further in-vivo assessment will be evaluated.*

2.5 General Biopharmaceutics

2.5.1 Based on biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

Not Applicable

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The Proposed to-be-marketed formulation manufactured in USA was used in the pediatric PK trial (0792951-109) and the two pivotal Phase 3 trials. However, the formulation used in the adult PK trial (D79-2902-07) was manufactured (b) (4) The overall composition of the formulation remains unchanged. The Sponsor has conducted in-vitro release test (IVRT) to bridge the formulation manufactured in USA and (b) (4) and according to Office of New Drugs Quality Assurance (ONDQA) reviewer Dr. Kelly Kitchens, the IVRT results are acceptable (for further details, see review in DARRTS by Dr. Kitchens). Since to-be-marketed formulation was used in all clinical trials, in-vivo relative bioavailability assessment is not needed.

2.5.2.1 What data support or do not support a waiver of in vivo BE data?

A waiver of in-vivo BE is not necessary as the proposed to-be-marketed formulation was used in the two pivotal Phase 3 trials and the two Phase 2 PK trials.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Effect of food on the BA is not evaluated for topical formulations.

2.6 Analytical Section

2.6.1 How are the active moieties identified, and measured in the plasma and urine in the clinical pharmacology and biopharmaceutics studies?

Econazole concentrations were identified using high performance liquid chromatography (HPLC) with tandem quadrupole mass spectrometric (MS/MS) detection.

2.6.2 Which metabolites have been selected for analysis and why?

In the adult PK trial (D79-2902-07), the Sponsor had attempted to assess the presence of metabolites in selected PK samples. The Sponsor claims that since none of the metabolites were identified they were not selected for analysis. Further, this is a 505(b)(2) application and relative bioavailability of parent is usually adequate and assessment of metabolites is usually not needed.

2.6.3 For all moieties measured, is free, bound, or total measured?

Total concentrations for econazole were measured.

2.6.4 What is the range of the standard curve? How does it relate to the requirements for clinical studies?

Range: 100 pg/mL to 50,000 pg/mL.

This range was adequate as none of the plasma concentrations for econazole in the clinical trials exceeded the upper limit of 50,000 pg/mL.

Reviewer comments: *Bioanalytical work for all the clinical trials was performed by* (b) (4)

2.6.5 What are the accuracy and precision at LLOQ?

Within-run accuracy %	3.37
Between-run accuracy %	5.21
Within-run precision %	4.00
Between-run precision %	8.00

2.6.6 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler, etc.)?

Freeze/Thaw cycle stability	Stable for 3 cycles at -70 ºC
Room temperature stability	25 hours
Refrigeration stability	76 hours at 5 ºC
Long term stability	188 days at -70 ºC

Incurred sample reproducibility (ISR): For both the PK trials (D79-2902-07 and 0792951-109), ISR results indicated that more than two thirds of the selected samples were within ± 20 % of the original result.

3. Detailed Labeling Recommendations

The following changes are recommended in Sponsor's proposed labeling submitted on June 24, 2013. The **bold and underlined** text indicates insertion recommended by the reviewer and the ~~strikethrough~~ text indicates recommended deletion.

7 DRUG INTERACTIONS

Econazole nitrate should be used with caution in patients receiving warfarin treatment. Concomitant administration of econazole nitrate may increase the anticoagulant effect of warfarin. Patient's International Normalized Ratio (INR) should be monitored especially for patients who apply econazole to large percentage of body surface area or under occlusion.

8.4 Pediatric Use

Of the 173 patients treated with Econazole Nitrate Foam, 1% in the adult clinical studies, 2 patients were 12-17 years old. (b) (4)

In a pediatric (b) (4) trial Econazole (b) (4) Foam, 1% was applied **once daily** to 18 (b) (4) **-subjects** aged 12 to 17 years with **interdigital** tinea pedis for 28 days **[*see Clinical Pharmacology (12.3)*]**. (b) (4)

(b) (4)

Reviewer comments: *Additional edits in this section will be made by the Clinical team.*

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Econazole Foam is an azole antifungal [*see Clinical Pharmacology (12.4)*]. (b) (4)

(b) (4)

[redacted]

12.2 Pharmacodynamics

The pharmacodynamics of econazole nitrate foam, 1% have not been established.

12.3 Pharmacokinetics

The **systemic** [redacted] absorption of econazole [redacted] 1% foam **following topical application** was studied in one clinical **trial** [redacted] in **adults** [redacted] and one clinical **trial** [redacted] in **pediatric subjects** [redacted].

In the adult trial, 19 subjects (male and female) with tinea pedis applied econazole [redacted] **foam 1% once daily for 29 days. Subjects applied a mean daily amount of 2.4 g of econazole** [redacted] **foam 1% to soles, toes, interdigital spaces and tops of both feet up to the ankles. Blood samples were obtained on Day 29 at pre-dose and 1, 2, 4, 6, 8, and 12 hours after application. Results (mean ± SD) showed the time to reach peak plasma concentrations (T_{max}) was 6.8 ± 5.1 h-with maximum concentration (C_{max}) of 417 ±218 pg/ml. The area under the concentration time curve for the first 12 hours post application on Day 29 ($AUC_{(0-12)}$) was 3440 ± 1920 pg-h/ml**.

In the pediatric **trial** [redacted], 18 subjects (male and female ages 12 - 17) with interdigital tinea pedis and positive fungal cultures were treated with econazole [redacted] 1% foam **once** daily for 4 weeks. Subjects applied **a mean daily amount of 3.2 g of** econazole [redacted] foam 1% to soles, toes, interdigital spaces and tops of both feet up to the ankles. **Blood samples were obtained on Day 28 at pre-dose and 7 h and 11 h post-dose. The mean ± SD econazole plasma concentration was 397 ± 289, 534 ± 745 and 575 ± 638 pg/mL at pre-dose and 7 h and 11 h post-dose, respectively.** [redacted]

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)]*.


(b) (4)

4. INDIVIDUAL TRIAL REVIEW

Trial number D79-2902-07: Adult PK bridging trial

Title: A Multi-Center Randomized, Evaluator-Blinded, Vehicle Controlled, Parallel Group Comparison Study of the Safety and Efficacy of Econazole Nitrate Foam 1%, Econazole Nitrate 1% Cream and Foam Vehicle in Subjects with Tinea Pedis

Trial objectives:
Primary: To provide support in establishing a clinical bridge between Econazole Nitrate Foam 1% and the reference product based upon clinical outcome, safety, and PK data.

Secondary: To determine and compare the safety, including local tolerability, and efficacy of Econazole Nitrate Foam 1%, with Econazole Nitrate Cream 1%, and Foam vehicle in subjects with tinea pedis.

Trial drugs:
- Econazole Nitrate Foam 1% (Lot #M7036) administered once a day (QD) (Formulation manufacturing site - (b) (4))
- Econazole Nitrate Cream 1% (Fougera) (Lot #Z80) administered once a day (QD)
- Foam Vehicle (Lot #M7035) administered once a day (QD)

Primary efficacy endpoint: Complete cure indicated by negative KOH and negative fungal culture and no evidence of clinical disease at Day 43.

Secondary efficacy 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 (Week6).
- 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 zero (none) to three (severe) point scale.

Safety endpoints:
- Plasma levels of Econazole Nitrate at the end of treatment.
- Tolerability of treatment, local and systemic adverse events at each visit.
- Laboratory data: hematology, serum chemistry, and urinalyses at Baseline and Day 29.

Trial design: Subjects with tinea pedis with at least moderate scaling (Interdigital and/or Moccasin-type) and mild erythema (Interdigital only) and a positive KOH finding at the

Screening/Baseline visit and those who met the enrollment criteria were enrolled and randomized (1:1:1) to each of treatment arm.

198 subjects were screened and 135 were enrolled/randomized in the trial as follows:

- 43 subjects were randomized to Econazole Nitrate (EN) Foam, 1%
- 45subjects were randomized to Econazole Nitrate Cream, 1%
- 47 subjects were randomized to Foam Vehicle

The assigned study medication was applied once daily, preferably in the mornings for 4 weeks. Subjects were instructed to treat both feet by applying a thin uniform coat of the study medication over each foot in its entirety up to the inferior aspect of their ankles once a day (i.e., soles, toes, interdigital spaces and the top surfaces of both feet up to the ankles) independent of the area of disease involvement. Given the physical differences in the two "active" dosage forms (Foam and Cream), particular care was taken to assure the clinical evaluator was "blinded" with respect to the medication type dispensed to the subjects.

At Days 8 and 15, safety evaluation and clinical grading was performed and dermatophyte cultures taken at the Baseline visit were reviewed to ensure that subjects were eligible to continue in the trial. Subjects with negative Baseline dermatophyte cultures, exclusive of subjects participating in the PK aspect of the trial, were discontinued.

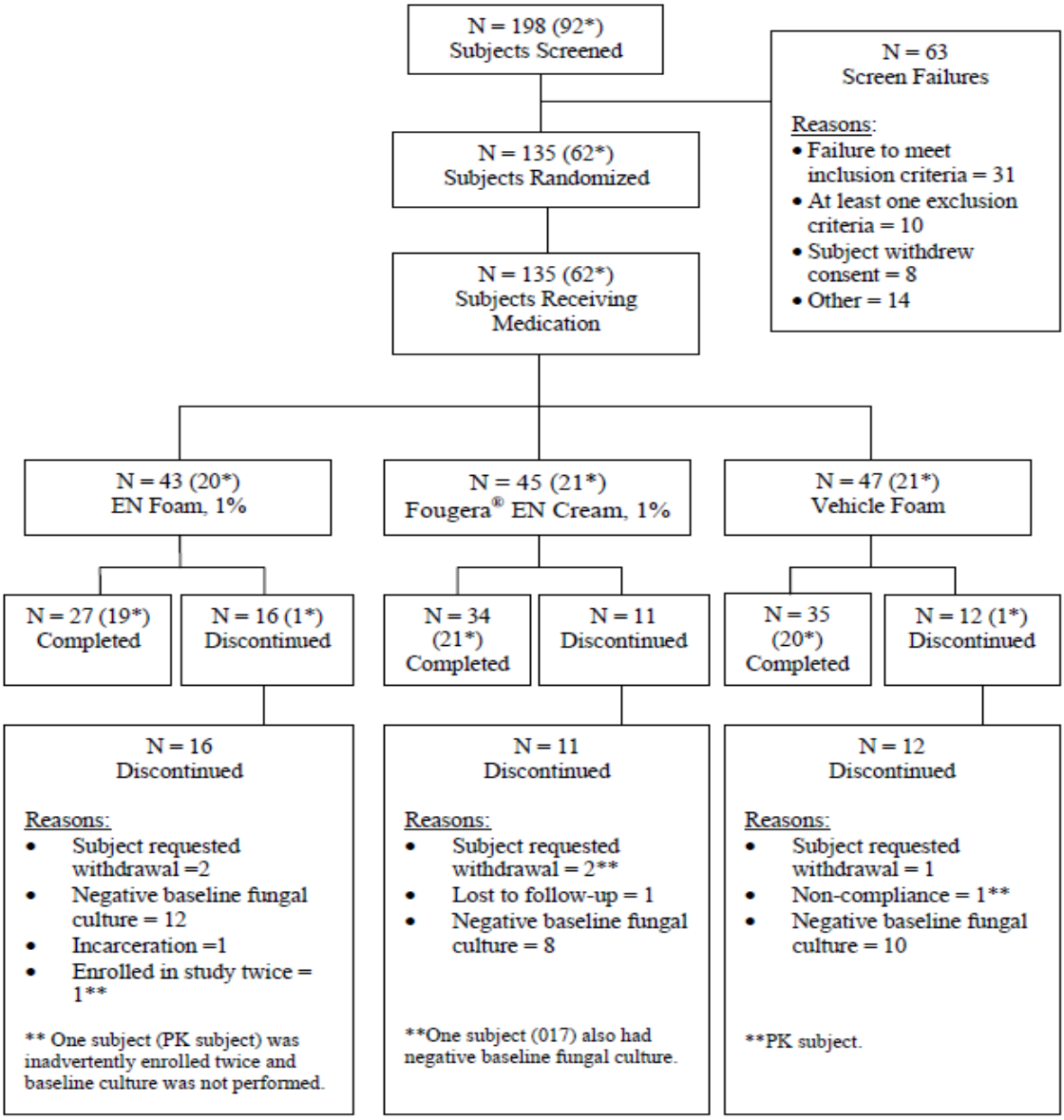
At the end-of-treatment (Day 29), safety evaluation, clinical grading and repeat KOH test and mycological culture were performed. All subjects were asked to withhold the last morning application of the study medication until after skin scrapings (specimens for KOH and cultures) had been collected. At this visit, all subjects had blood drawn to obtain end-of-treatment labs.

At the end of 4 weeks (Day 29), at selected PK sites, blood was drawn from all subjects at prior to the application of the last dose and at 1, 2, 4, 6, 8, and 12 hours post-dose to obtain plasma drug levels of Econazole nitrate to determine the extent of systemic absorption following administration of the Cream and Foam formulations.

At the end of study (Day 43), subjects with positive Baseline fungal cultures returned for the final visit for clinical evaluations and repeat KOH testing and mycological cultures were performed. At each visit, adverse reactions including local skin reactions, concurrent procedures, and changes in concomitant medications during the study were recorded.

Overall there were 63 subjects that were screen failures because of negative KOH evaluations. Figure 3 shows a schematic representation of the disposition of subjects in this trial.

Figure 3: Disposition of Subjects



*Number of PK subjects, if included in the N listed, are denoted in parentheses.

Definitions of the populations:

Intent-to-Treat Population (ITT): All subjects enrolled in the trial that were randomized, and dispensed the study medication were considered in the ITT population. ITT also includes subjects who discontinued prematurely from the trial following administration of study medication (e.g., subjects who were found to lack a positive Baseline fungal culture) were included in the ITT population. No efficacy analyses were conducted on the ITT population.

Modified Intent-to-Treat Population (MITT): All subjects enrolled in the trial who were randomized and dispensed the study medication, and who had a positive Baseline fungal culture were included in the MITT population, a subset of the ITT population.

Per-Protocol Population (PP): Subjects were included in the 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.

Amount of formulation used: In the ITT population, the average number of days of treatment was 27.5 on econazole nitrate Cream 1%, 28.2 days on econazole nitrate Foam 1%, and 28.5 days on Foam Vehicle. The mean amount of econazole nitrate Cream 1% used was 79.7, and 67.4 grams of econazole nitrate Foam 1% and 61.6 grams of Foam Vehicle were used. Hence the mean amount of formulation used per day was 2.39 grams for the Foam and 2.90 grams for the Cream.

Similar measurements were found in the MITT population. The average number of days of treatment was 27.8 on econazole nitrate Cream 1%, 28.8 days on econazole nitrate Foam 1%, and 28.2 days on Foam Vehicle. The mean amount of econazole nitrate Cream 1% used was 77.3, and 74.9 grams of econazole nitrate Foam and 66.5 grams of Foam Vehicle were used. Hence the mean amount of formulation used per day was 2.60 grams for the Foam and 2.78 grams for the Cream. The dosing summary in the PK subjects on Day 29 is shown in Table 13 below:

Table 13: Dosing summary in PK subjects on Day 29

	Econazole Nitrate Cream 1% (N=21)	**Econazole Nitrate Foam 1% (N=19)**	**Foam Vehicle (N=20)**
Number of grams applied- last dose (grams)			
Mean (SD)	3.2 (2.3)	2.9 (1.7)	3.3* (6.5)
Median	2.7	2.4	1.8
Surface Area (cm^2)			
Mean (SD)	1465.7 (198.0)	1413.3 (232.5)	1445.2 (184.2)
Median	1470.0	1358.0	1459.5
Study Medication Application Rate (mg/cm^2)			
Mean (SD)	2.2 (1.7)	2.1 (1.2)	2.5 (5.2)
Median	1.8	1.6	1.2

* The weight of medication recorded for Subject 01-112 (30.5gm) was included in this calculation. This appears to be an error at the site in recording the weight of the container after medication application. Review of the weight data for the unit of medication used at this last application (from the weight data recorded by (b) (4) the clinical supply vendor) indicates that the amount of medication applied was approximately 3.8 grams. The error was not corrected in the database. The mean grams applied of Foam vehicle would be 1.98 grams if this adjusted lower value were included in the calculation for Subject 01-112.

Demographics: MITT population demographics are shown in Table 14 below and in Table 15, population by treatment group and subject sub-group is shown.

Table 14: Demographics of the MITT population

		Econazole Nitrate Cream 1% (N=36)	Econazole Nitrate Foam 1% (N=30)	Foam Vehicle (N=37)	P-value[1]
Gender	Male	31 (86.1%)	26 (86.7%)	30 (81.1%)	0.7776
	Female	5 (13.9%)	4 (13.3%)	7 (18.9%)	
Age (years)	Mean (SD) N	45.4 (14.9) 36	45.9 (14.9) 30	43.7 (11.0) 37	0.7810
	Std Error	2.5	2.7	1.8	
	95% CI around Mean	40.5, 50.3	40.6, 51.2	40.2, 47.2	
	Median (Min, Max)	48 (18, 79)	43 (20, 82)	45 (22, 64)	
Race[2]	White	27 (75.0%)	24 (80.0%)	27 (73.0%)	0.3305
	Black/African American	8 (22.2%)	4 (13.3%)	5 (13.5%)	
	Asian	0 (0.0%)	1 (3.3%)	1 (2.7%)	
	American Indian/Alaska Native	0 (0.0%)	1 (3.3%)	0 (0.0%)	
	Other	1 (2.8%)	0 (0.0%)	4 (10.8%)	
Ethnicity	Hispanic or Latino	3 (8.3%)	5 (16.7%)	10 (27.0%)	0.1109
	Not Hispanic or Latino	33 (91.7%)	25 (83.3%)	27 (73.0%)	

[1] p-value related to the comparison of the treatment groups.
[2] More than one race could be checked thus percentages may not sum to 100%.

Table 15: MITT population by treatment and subject sub-groups

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**

Subject disposition: A summary of subject disposition for all enrolled subjects is shown in Table 16.

Table 16: Summary of subject disposition for all enrolled subjects

	Econazole Nitrate Cream 1% (N=45)	Econazole Nitrate Foam 1% (N=43)	Foam Vehicle (N=47)
Number of subjects enrolled	45 (100.0%)	43 (100.0%)	47 (100.0%)
Number of subjects randomized	45 (100.0%)	43 (100.0%)	47 (100.0%)
Number of subjects treated	45 (100.0%)	43 (100.0%)	47 (100.0%)
Number of subjects in ITT	45 (100.0%)	43 (100.0%)	47 (100.0%)
Number of subjects in MITT	36 (80.0%)	30 (69.8%)	37 (78.7%)
Number of subjects in PP	33 (73.3%)	23 (53.5%)	33 (70.2%)
Number of subjects who completed study	34 (75.6%)	27 (62.8%)	35 (74.5%)
Number of subjects with onychomycosis at BL	7 (15.6%)	9 (20.9%)	6 (12.8%)
Number of subjects withdrawn early:	11 (24.4%)	16 (37.2%)	12 (25.5%)
Subject Requested Withdrawal	2 (18.2%)	2 (12.5%)	1 (8.3%)
Lost to Follow-up	1 (9.1%)	0 (0.0%)	0 (0.0%)
Non-compliance	0 (0.0%)	0 (0.0%)	1 (8.3%)
Negative Baseline fungal culture	8 (72.7%)	12 (75.0%)	10 (83.3%)
Other	0 (0.0%)	2 (12.5%)	0 (0.0%)
Incarceration	0 (0.0%)	1 (50.0%)	0 (0.0%)
Enrolled in study twice	0 (0.0%)	1 (50.0%)	0 (0.0%)

Baseline characteristics: Description of disease sub-type and mycology at baseline in MITT population is shown in Table 17.

Table 17: Baseline characteristics of MITT population

		Randomization Group			
		Econazole Nitrate Cream 1% (N=36)	Econazole Nitrate Foam 1% (N=30)	Foam Vehicle (N=37)	P-Value[1]
Disease Sub-type					0.2398
	Interdigital Only	26 (72.2%)	20 (66.7%)	18 (48.6%)	
	Moccasin Only	4 (11.1%)	3 (10.0%)	9 (24.3%)	
	Both	6 (16.7%)	7 (23.3%)	10 (27.0%)	
KOH Results					
Interdigital	Positive	32 (100.0%)	27 (100.0%)	28 (100.0%)	1.000
	Negative	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Moccasin	Positive	10 (100.0%)	10 (100.0%)	19 (100.0%)	
	Negative	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Fungal Culture Results					1.000
Interdigital	Positive	32 (100.0%)	27 (100.0%)	28 (100.0%)	
	Negative	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Moccasin	Positive	10 (100.0%)	10 (100.0%)	19 (100.0%)	1.000
	Negative	0 (0.0%)	0 (0.0%)	0 (0.0%)	

[1] *CMH tests in conjunction with the General Association Statistic to compare the treatment groups.*
Includes only those subjects that were KOH and culture positive for a given disease subtype (Interdigital or Moccasin).

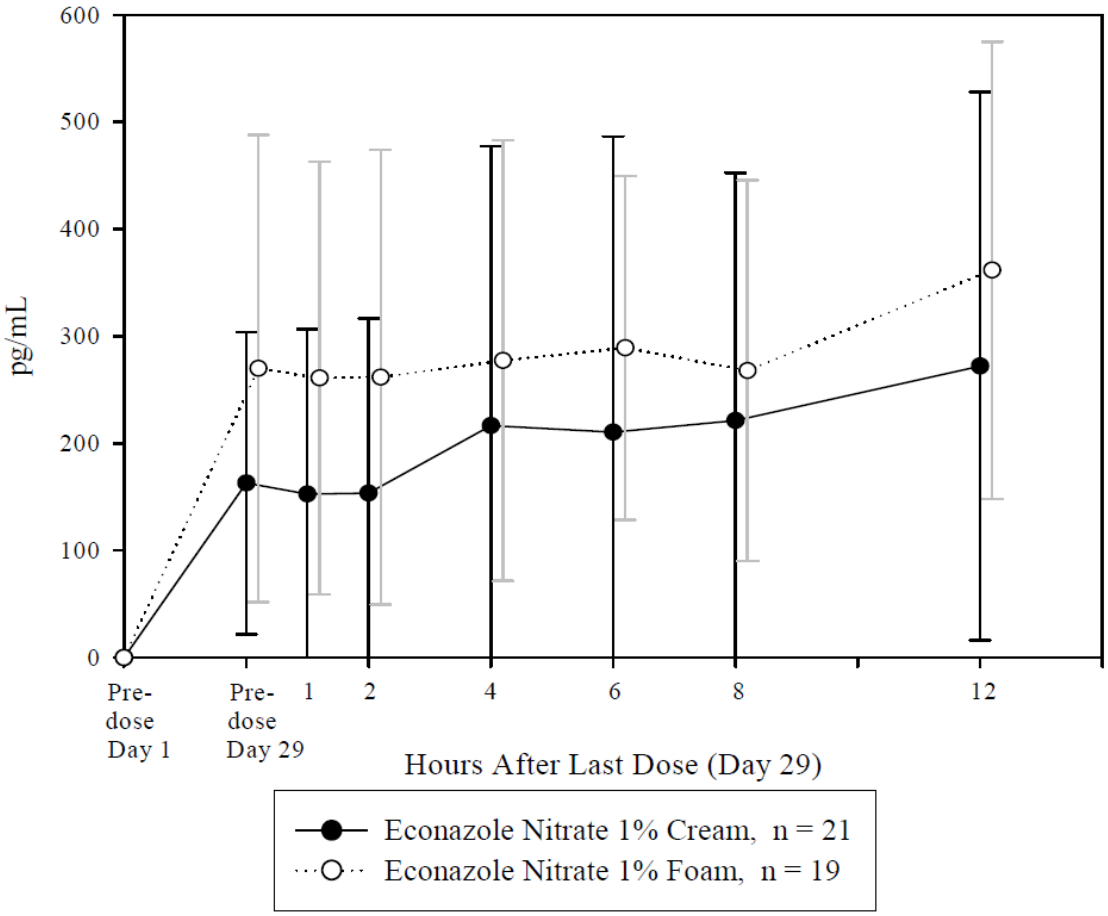
PK results: Table 18 shows the mean PK parameters of econazole following 29 Days of once-daily topical application of Foam, Cream or Foam Vehicle and the mean concentration versus time profile is shown in Figure 4

Table 18: Summary of Mean ± SD PK parameters for econazole following 29 days of once daily topical administration

PK Parameters	EN Cream 1% (N=21)	EN 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).

Figure 4: Concentration (Mean ± SD) versus time profile on Day 29 for econazole nitrate Foam, 1% and Cream 1%



The 90% confidence interval (CI) between the ratio of geometric means of the AUC and C_{max} of econazole nitrate following administration of the Foam versus Cream formulation for all subjects in the PK population is shown in Table 19. Further, the 90% CI between the ratio of geometric means of the AUC and C_{max} of econazole nitrate following administration of the Foam versus Cream formulation based on subgroup analysis by disease type is shown in Table 20.

Table 19: 90% CI between the ratio of geometric means of AUC and C_{max} following the administration of econazole nitrate Foam (Test) vs. Cream (Reference) for all subjects in the PK population

	Econazole Nitrate Foam 1% (N=19)		Econazole Nitrate Cream 1% (N=21)
AUC (pg*h/mL)			
Geometric Mean	2770.1		2366.1
90% Confidence Interval	(1999.0 to 3838.6)		(1662.8 to 3366.8)
Ratio of Geometric Means		1.17	
90% Confidence Interval		(0.73 to 1.87)	
Cmax (pg/mL)			
Geometric Mean	360.7		347.9
90% Confidence Interval	(286.2 to 454.6)		(266.7 to 453.8)
Ratio of Geometric Means		1.04	
90% Confidence Interval		(0.74 to 1.46)	

Reviewer comments: *The 90% CI of the geometric means of AUC and C_{max} of Foam vs. Cream are outside the no effect range of 0.8 to 1.25 suggesting that the Foam and the Cream are not bioequivalent. Based on the point estimate value, the exposure (AUC) of econazole nitrate following administration of the Foam formulation appears to be ~ 17% higher than the Cream.*

Table 20: 90% CI between the ratio of geometric means of AUC and C_{max} following the administration of econazole nitrate Foam (Test) vs. Cream (Reference) based on subgroup analysis by disease type

	Econazole Nitrate Foam 1% (N=19)		Econazole Nitrate Cream 1% (N=21)
Interdigital Tinea Pedis Only			
AUC (pg*h/mL)			
N	9		6
Geometric Mean	2616.4		2134.2
90% Confidence Interval	(1839.0 to 3722.4)		(889.6 to 5120.4)
Ratio of Geometric Means		1.23	
90% Confidence Interval		(0.58 to 2.58)	
Cmax (pg/mL)			
N	9		6
Geometric Mean	308.7		357.1
90% Confidence Interval	(230.0 to 414.2)		(213.5 to 597.2)
Ratio of Geometric Means		0.86	
90% Confidence Interval		(0.52 to 1.43)	

	Econazole Nitrate Foam 1% (N=19)		Econazole Nitrate Cream 1% (N=21)
Moccasin Only			
AUC (pg*h/mL)			
N	2		4
Geometric Mean	3272.0		2855.0
90% Confidence Interval	(864.3 to 12386.5)		(1197.9 to 6804.3)
Ratio of Geometric Means		1.15	
90% Confidence Interval		(0.34 to 3.85)	
Cmax (pg/mL)			
N	2		4
Geometric Mean	471.2		408.6
90% Confidence Interval	(382.9 to 580.0)		(170.5 to 978.9)
Ratio of Geometric Means		1.15	
90% Confidence Interval		(0.35 to 3.78)	

	Econazole Nitrate Foam 1% (N=19)		Econazole Nitrate Cream 1% (N=21)
Both Diseases			
AUC (pg*h/mL)			
N	8		7
Geometric Mean	2833.3		2321.6
90% Confidence Interval	(1307.0 to 6141.8)		(1314.1 to 4101.7)
Ratio of Geometric Means		1.22	
90% Confidence Interval		(0.49 to 3.05)	
Cmax (pg/mL)			
N	8		7
Geometric Mean	402.0		310.4
90% Confidence Interval	(245.0 to 659.6)		(193.3 to 498.3)
Ratio of Geometric Means		1.30	
90% Confidence Interval		(0.68 to 2.45)	

Reviewer comments: *The 90% CI of the geometric means of C_{max} and AUC of Foam vs. Cream are outside the no effect range of 0.8 to 1.25 suggesting that the Foam and the Cream are not bioequivalent in all the sub-analysis categories. Furthermore, the systemic exposure (AUC) of econazole was slightly higher following Foam administration compared to the Cream. However, due to limited number of subjects, any strong conclusions cannot be made.*

Effect of disease: The Sponsor evaluated the effect of disease state on PK of econazole (see Table 21 and 22) by comparing the AUC and C_{max} obtained from subjects with healed skin and not-healed skin.

Table 21: PK parameters in healed and not-healed skin

PK Parameters (Geometric mean)	***Healed Skin***		***Not-healed skin***	
	Foam (n=2)	***Cream (n=6)***	***Foam (n=11)***	***Cream (n=9)***
*AUC (pg*h/mL)*	*3184.5*	*1663.5*	*2830.6*	*2510.6*
Cmax (pg/mL)	*361.6*	*317.4*	*384.6*	*314.8*

Table 22: Effect of disease state on PK of econazole nitrate

Ratio (Not-healed/Healed)	***AUC (pg*h/mL)***	***Cmax (pg/mL)***
Foam	*0.88*	*1.06*
Cream	*1.51*	*0.99*

Reviewer comments: *The exposure (AUC) of econazole in the Cream arm appears to be slightly higher in subjects with not-healed skin compared to healed skin. While in the Foam arm; it appears that disease resolution had minimal effect on PK. Any definitive conclusions cannot be made because of limited number of subjects.*

The Sponsor has also provided statistical analysis by calculating the 90% CI of the ratio of geometric mean of AUC and C_{max} following administration of the Foam and Cream formulation in subjects with healed and not healed skin (also included is data in subjects whose disease state is unknown) (see Table 23).

Table 23: 90% CI between the ratio of geometric means of AUC and C_{max} following the administration of econazole nitrate Foam (Test) vs. Cream (Reference) based on subgroup analysis by disease condition

	Econazole Nitrate Foam 1% (N=19)		Econazole Nitrate Cream 1% (N=21)
Subjects with Day 29 Skin = Healed[a]			
AUC (pg*h/mL)			
N	2		6
Geometric Mean	3184.5		1663.5
90% Confidence Interval	(419.5 to 24173.6)		(694.2 to 3985.9)
Ratio of Geometric Means		1.91	
90% Confidence Interval		(0.40 to 9.17)	
Cmax (pg/mL)			
N	2		6
Geometric Mean	361.6		317.4
90% Confidence Interval	(21.4 to 6121.9)		(186.8 to 539.1)
Ratio of Geometric Means		1.14	
90% Confidence Interval		(0.41 to 3.16)	
Subjects with Day 29 Skin = Not Healed[a]			
AUC (pg*h/mL)			
N	11		9
Geometric Mean	2830.6		2510.6
90% Confidence Interval	(1664.5 to 4813.8)		(1684.0 to 3742.9)
Ratio of Geometric Means		1.13	
90% Confidence Interval		(0.58 to 2.17)	
Cmax (pg/mL)			
N	11		9
Geometric Mean	384.6		314.8
90% Confidence Interval	(271.0 to 545.7)		(220.0 to 450.3)
Ratio of Geometric Means		1.22	
90% Confidence Interval		(0.76 to 1.97)	
Subjects with Day 29 Skin = Unknown[b]			
AUC (pg*h/mL)			
N	6		2
Geometric Mean	2541.5		5213.7
90% Confidence Interval	(1442.7 to 4477.2)		(1143.4 to 23772.9)
Ratio of Geometric Means		0.49	
90% Confidence Interval		(0.18 to 1.35)	
Cmax (pg/mL)			
N	6		2
Geometric Mean	320.5		719.0
90% Confidence Interval	(205.7 to 499.4)		(49.1 to 10533.3)
Ratio of Geometric Means		0.45	
90% Confidence Interval		(0.19 to 1.07)	

[a] Subjects with Day 29 Skin = Healed were those with no Day 29 Signs and Symptoms (Cracking/Fissuring, Maceration, Pruritus, Scaling/Hyperkeratos, and Vesiculation), with the exception of Mild Erythema.
[b] Subjects with Day 29 Skin = Unknown were discontinued at Day 29 due to Baseline negative fungal culture, and therefore, signs and symptoms were not evaluated at Day 29.

Reviewer comments: *From the data in the healed vs. not-healed skin, the systemic levels of econazole following administration of the Foam formulation appears to be higher than Cream. The same observation cannot be made in subjects with "unknown" disease state, which shows opposite effect. This observation is backed by limited data especially in the Foam arm which had only 2 subjects with healed skin.*

Primary efficacy end-point: The primary efficacy endpoint was complete cure at 2 weeks after the end of the treatment (i.e. at Week 6). The complete cure rates were significantly higher than vehicle as shown in Figure 5. Table 24 shows the primacy efficacy endpoint by disease type.

Figure 5: Primary efficacy endpoint in MITT and PP population

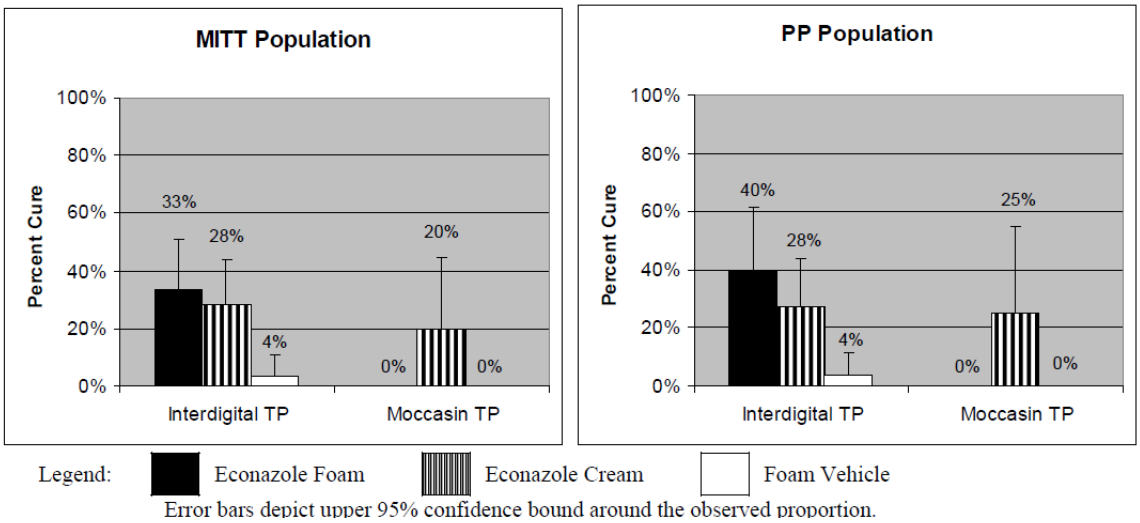


Table 24: Primary efficacy endpoint by disease sub types for the MITT population

	Econazole Nitrate Cream 1% (N = 36)	**Econazole Nitrate Foam 1% (N = 30)**	**Foam Vehicle (N = 37)**
Disease Sub-Type			
Interdigital TP	**(N = 32)**	**(N = 27)**	**(N = 28)**
	9 (28.1%)*	9 (33.3%)**	1 (3.6%)
Moccasin TP	**(N = 10)**	**(N = 10)**	**(N = 19)**
	2 (20.0%)	0 (0.0%)	0 (0.0%)
Subject Sub-Group			
Interdigital Only	**(N = 26)**	**(N = 20)**	**(N = 18)**
	7 (26.9%)	7 (35%)*	1 (5.6%)
Moccasin Only	**(N = 4)**	**(N = 3)**	**(N =9)**
	1 (25.0%)	0 (0.0%)	0 (0.0%)
Both (Interdigital + Moccasin)	**(N = 6)**	**(N =7)**	**(N =10)**
	1 (16.7%)	0 (0.0%)	0 (0.0%)

* $p<0.05$ vs. foam vehicle; ** $p=0.005$ vs. foam vehicle

Summary of safety: All subjects enrolled in the trial who were dispensed study medication (ITT population) were included in the safety analyses based on AE reporting. According to the Sponsor, 27 subjects reported at least one adverse event (AE). Most

subjects experienced AEs that were mild or moderate in severity and as per the Sponsor, the AEs were considered not related to study medication. Only two AEs were reported as severe: one in the Cream group that was not related and one in the Foam Vehicle group. AE rates were similar across the two active treatment groups with the fewest AEs being reported in the foam vehicle group. There were no deaths or SAEs that led to treatment interruption.

Reviewer comments: *For further information see review by the medical office Dr. Amy Woitach in DARRTS.*

Trial number 0792951-109: Pediatric PK trial

Title: A Multi-Center, Randomized Comparative Study of the Pharmacokinetics of Econazole Nitrate 1% Foam and Econazole Nitrate 1% Cream in Subjects with Interdigital Tinea Pedis Aged 12 Years to Less Than 18 Years

Trial objective: The primary objective of the study was to compare the PK of econazole nitrate Foam 1% with econazole nitrate Cream 1% in subjects with interdigital tinea pedis aged 12 years to less than 18 years who were treated under maximal use conditions.

Trial design: Approximately 42 subjects who met the entry criteria were enrolled and randomized (1:1) to econazole nitrate, Foam 1% or the econazole nitrate, Cream 1% treatment group. The enrolled subjects had to have a clinical diagnosis of interdigital tinea pedis involving at least 2 web spaces in total extending no more than approximately 1 inch proximal to the web spaces or metatarsophalangeal joints; lesions were to have at least moderate scaling and mild erythema as defined as Grade 2 and Grade 1, respectively at Baseline.

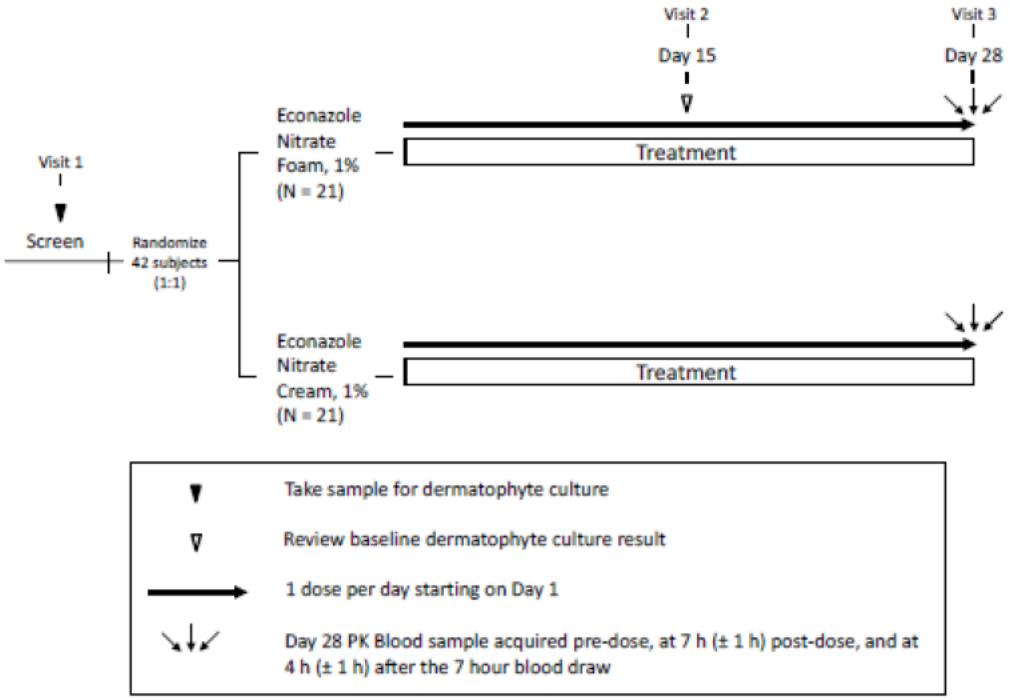
The assigned investigational product was to be applied once daily in the morning for 4 weeks and subjects were instructed to apply a thin uniform coat of the investigational product to the soles, toes, interdigital spaces, and the tops of both feet (up to the ankles). The subjects were asked to avoid washing the treatment area for at least 4 hours after each application, continue treatment regardless of symptomatic improvement, and to record their dosing in a subject diary each day.

Subjects were also instructed to record the time at which they applied investigational product on the morning of Day 27 (approximately 24 hours prior to their final dose on Day 28) and to withhold application of their final dose pending blood draw for pre-last-dose PK assessment. Subjects were then to apply their final dose (Day 28) and provide blood samples at 7 hours (±1 hour) post-last-dose and at 4 hours (±1 hour) after the 7 hour blood draw. Baseline blood sample on (Day 1) were also obtained before the start of the treatment.

At each visit, including the Screening/Baseline visit, any adverse events (AEs) including local skin reactions, concurrent procedures, and changes in concomitant medications

during the study were recorded. Figure 6 shows a schematic representation of the trial design.

Figure 6: Schematic representation of trial design



Investigational product: Details about the investigational products used is shown in Table 25.

Table 25: Investigational products used in the trial

	Econazole Nitrate Foam 1%	Econazole Nitrate Cream 1%
Active Ingredient	Econazole nitrate	Econazole nitrate
Chemical Name	1*H*-Imidazole,1-[2-[(4-chlorophenyl)methoxy-]2-(2,4-dichlorophenyl)[ethyl]-, mononitrate, (±)-	1*H*-Imidazole,1-[2-[(4-chlorophenyl)methoxy-]2-(2,4-dichlorophenyl)[ethyl]-, mononitrate, (±)-
Molecular Formula	$C_{18}H_{15}Cl_3N_2O{\cdot}HNO_3$	$C_{18}H_{15}Cl_3N_2O{\cdot}HNO_3$
Chemical Abstract Service Registry Number	68797-31-9	68797-31-9
Other Ingredients	stearic acid, propylene glycol, polysorbate 20, trolamine, PVP (povidone) , glycerol, dimethicone, water	Pegoxol 7 stearate, peglicol 5 oleate, mineral oil, benzoic acid, butylated hydroxyanisole, water
Packaging Description	(b) (4)	(b) (4)
Storage Requirements	Store at room temperature (b) (4)	Store below 86 °F (30 °C)
Appearance	White to off-white foam	White to off-white cream
Dosing Schedule	Once daily for 4 weeks	Once daily for 4 weeks
Route of Administration	Topical	Topical
Dosage Form	Foam	Cream
Batch Number	CIF-7C	361K

Subject enrollment: A total of 50 subjects were randomized (25 each in the Econazole nitrate Foam, 1% and Econazole nitrate Cream, 1% groups, respectively). All randomized subjects were included in the MITT Population. Seventeen subjects were excluded from the PK analysis (PKIN) population. Specifically 7 subjects in the Foam arm, and 9 in the Cream arm that were excluded due to a negative baseline fungal culture and 1subject in the Cream arm was excluded due to incomplete PK blood collections [Subject (08-006) moved out of the country and did not complete Day 28/Visit 3]. Summary is shown in Table 26 and 27.

Table 26: Summary of subject enrollment:

	Econazole Nitrate Foam, 1%	Econazole Nitrate Cream, 1%	Total
Number of Subjects Screened			63
Number of Subjects Randomized	25	25	50
Number of Subjects Excluded from the MITT Population	0	0	0
Number of Subjects Included in the MITT Population	25	25	50
Number of Subjects Excluded from the PKIN Population	7	10	17
Number of Subjects Included in the PKIN Population	18	15	33

Table 27: Summary of disqualified subjects from PKIN population:

	Econazole Nitrate Foam, 1%	Econazole Nitrate Cream, 1%
Number of Subjects Randomized	25	25
Number of Subjects Excluded from PKIN	7 (28.0%)	10 (40.0%)
Reason Excluded from the PKIN Population[a]		
No Documented Use of Study Medication	0 (0.0%)	0 (0.0%)
No Positive Baseline Fungal Culture	7 (100.0%)	9 (90.0%)
Incomplete PK Blood Collections	0 (0.0%)	1 (10.0%)
Non-Dosing Compliant (<80%)	0 (0.0%)	0 (0.0%)
Missed Day 28 Visit	0 (0.0%)	0 (0.0%)
Off-Schedule Day 28 (> ±2 days)	0 (0.0%)	0 (0.0%)
Other Significant Protocol Deviation(s)	0 (0.0%)	0 (0.0%)

[a] Subjects may had more than one exclusionary deviation. A primary exclusionary deviation was assigned according to the deviation that had the greatest impact on clinical evaluations, in the order listed.

Demographics: Subject demographics are shown in Table 28.

Table 28: Summary of subject demographics

	Econazole Nitrate Foam, 1% (N=25)	Econazole Nitrate Cream, 1% (N=25)	Total (N=50)
Age (years)			
N	25	25	50
Mean	14.2	14.8	14.5
SD	1.88	1.98	1.93
Median	14.0	16.0	14.5
Min to Max	12 to 17	12 to 17	12 to 17
Gender			
N	25	25	50
Male	21 (84.0%)	19 (76.0%)	40 (80.0%)
Female	4 (16.0%)	6 (24.0%)	10 (20.0%)
Ethnicity			
N	25	25	50
Hispanic or Latino	16 (64.0%)	18 (72.0%)	34 (68.0%)
Not Hispanic or Latino	9 (36.0%)	7 (28.0%)	16 (32.0%)
Race			
N	25	25	50
White	13 (52.0%)	14 (56.0%)	27 (54.0%)
Black/African American	4 (16.0%)	3 (12.0%)	7 (14.0%)
Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)
American Indian/Alaskan Native	8 (32.0%)	8 (32.0%)	16 (32.0%)
Native Hawaiian/Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)

Amount of formulation used (PKIN Subjects): The mean amount of Foam used was 3.2 g/day and the mean amount of Cream used was 3.9 g/day (see Table 29).

Table 29: Summary of the amount of formulation used

	Econazole Nitrate Foam, 1% (N=18)	Econazole Nitrate Cream, 1% (N=15)
Duration of Treatment (Days)		
N	18	15
Mean	28.6	28.7
SD	0.70	0.72
Median	29.0	29.0
Min to Max	27 to 30	27 to 30
Number of Applications		
N	18	15
Mean	28.2	28.4
SD	0.81	0.91
Median	28.0	29.0
Min to Max	27 to 29	27 to 30
Number of Grams of Medication Used During the Study		
N	18	15
Mean	91.456	111.525
SD	38.3873	71.9070
Median	85.083	102.274
Min to Max	15.94 to 160.87	7.67 to 216.78
Number of Grams of Medication Used At Last Application		
N	18	15
Mean	4.56	5.87
SD	2.394	4.492
Median	3.75	4.20
Min to Max	1.5 to 9.7	1.0 to 12.5
Compliant (≥80%)		
N	18	15
Yes	18 (100.0%)	15 (100.0%)
No	0 (0.0%)	0 (0.0%)

Analysis of Efficacy: Investigator assessment of response to treatment at Day 28 (end of treatment) is summarized in Table 30. According to the Sponsor, in the Foam and the Cream groups the majority of investigator assessments of responses to treatment were recorded as excellent or very good.

Table 30: Summary of investigator response to treatment

	Econazole Nitrate Foam, 1% (N=25)	Econazole Nitrate Cream, 1% (N=25)
Day 28 (End of treatment)		
N	19	16
Excellent	7 (36.8%)	9 (56.3%)
Very Good	7 (36.8%)	5 (31.3%)
Good	2 (10.5%)	0 (0.0%)
Fair	3 (15.8%)	1 (6.3%)
Poor	0 (0.0%)	1 (6.3%)

PK results: Since limited PK samples were obtained in this trial, no PK parameters were estimated. Table 31 shows a summary of mean econazole concentrations assessed following administration of the Foam and Cream formulations and Table 32 shows geometric mean concentrations.

Table 31: Summary of Mean ± SD concentrations (pg/mL) of Econazole following Foam or Cream administrations

	Baseline/Day 1 (Prior To First Application)	Day 28 (Prior to Last Application)	Day 28 (7 Hours Post-Application)	Day 28 (4 Hours Post 7 Hour Collection)
Econazole Nitrate Foam, 1% (N=18)				
N	18	18	18	17
Mean	0.0	396.9	534.1	574.6
STD	0.00	288.89	745.33	637.63
Median	0.0	301.0	355.5	432.0
Min to Max	0 to 0	0 to 1200	0 to 3390	0 to 2690
95% CI for Mean	NC	[253.3, 540.6]	[163.4, 904.7]	[246.7, 902.4]
Difference from Econazole Nitrate Cream, 1%	0.0	187.9	358.5	401.3
95% CI for Difference	[0.0, 0.0]	[-14.5, 390.3]	[-19.8, 736.8]	[63.8, 738.7]
Econazole Nitrate Cream, 1% (N=15)				
N	15	15	15	15
Mean	0.0	209.1	175.5	173.3
STD	0.00	277.61	164.36	173.87
Median	0.0	154.0	144.0	147.0
Min to Max	0 to 0	0 to 966	0 to 515	0 to 537
95% CI	NC	[55.3, 362.8]	[84.5, 266.6]	[77.0, 269.6]

NC=Not calculated.

Table 32: Summary of Geometric mean (CV %) concentrations on Day 28

Treatment	Concentration (pg/mL) [Geometric mean (CV %)]		
	Day 28 (Prior last application)	**Day 28 (7 h post-application)**	**Day 28 (4 h post 7 h collection)**
Econazole nitrate foam, 1%	390.15 (68)	444.13 (144)	389.22 (194)
Econazole nitrate cream, 1%	275.31 (103)	226.37 (66)	205.05 (71)

Reviewer comments: Based on the geometric mean concentrations (Table 9), on Day 28, *the systemic concentrations of econazole following administration of the Foam formulation were approximately 1.4, 2.0 and 1.9 fold higher than those observed after administration of the Cream formulation at pre-dose, 7 hours post-application and 4 hours post 7 hour collection, respectively.*

Summary of safety: No AEs, SAEs, or deaths were reported and no subject discontinued treatment.

Reviewer comments: *For further information see review by the medical office Dr. Amy Woitach in DARRTS.*

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

/s/

CHINMAY SHUKLA
08/28/2013

DOANH C TRAN
08/28/2013

EDWARD D BASHAW
08/29/2013
Concur with proposed PMR

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**205175**	**Brand Name**	**Ecoza (Proposed)**
OCP Division (I, II, III, IV, V)	**III**	**Generic Name**	**Econazole nitrate, 1%**
Medical Division	**DDDP**	**Drug Class**	**Antifungal**
OCP Reviewer	**Chinmay Shukla, Ph.D.**	**Indication(s)**	**Topical treatment of interdigital tinea pedis**
OCP Team Leader	**Doanh Tran, Ph.D.**	**Dosage Form**	**Foam**
Pharmacometrics Reviewer	**NA**	**Dosing Regimen**	**Apply once daily for 4 weeks**
Date of Submission	**December 26, 2012**	**Route of Administration**	**Topical**
Estimated Due Date of OCP Review	**August 30, 2013**	**Sponsor**	**Amderma Pharmaceuticals LLC**
Medical Division Due Date	**September 10, 2013**	**Priority Classification**	**Standard**
PDUFA Due Date	**December 26, 2013**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

single dose:				
multiple dose:	**X**	**2**		*** Trial D79-2902-07 (Adults) (Formulation manufactured in (b) (4)) * Trial 079-2951-109 (12-18 yr old) (Formulation manufactured in USA)**
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	**X**			**Max use PK trial 079-2951-109 (12 to 18 yr old)**
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**1**		**Trial D79-2902-07 was conducted in adults with the purpose of supporting a clinical bridge between the proposed Foam formulation and the listed drug Econazole nitrate Cream, 1%**
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				

Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**8**		**Phase 1: Four dermal safety trials** **Phase 2: Two maximal use PK trials (One to support clinical bridge and other one in pediatrics)** **Phase 3: Two safety and efficacy trials**

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			**The manufacturing site was transferred (b) (4) to USA. Sponsor has conducted in-vitro release test to bridge the 2 formulations. Trial D79-2902-07 used the formulation manufactured in (b) (4) and was conducted in adults with the purpose of supporting a clinical bridge between the proposed Foam formulation and the listed drug Econazole nitrate Cream, 1%.**
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			

19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	**All reports are in English**

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? __ __Yes____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.
- N.A. -

Chinmay Shukla, Ph.D.
Reviewing Clinical Pharmacologist Date

Doanh Tran, Ph.D.
Team Leader Date

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Filing Memorandum

Clinical Pharmacology Review

NDA: 205175
Compound: Econazole nitrate foam, 1%
Indication: Topical treatment of interdigital tinea pedis
Sponsor: Amderma Pharmaceuticals, LLC
Date: 12/22/2012
Reviewer: Chinmay Shukla
Related IND: 77523

Background: This NDA submission is for econazole nitrate Foam, 1% and the Sponsor has proposed an indication for the treatment of interdigital tinea pedis (b) (4) The Sponsor has adopted 505(b)(2) regulatory pathway and has identified econazole nitrate cream, 1% (NDA 018751, *Spectazole®*) (based on patent information in Section 1.3.5.1) as a listed drug. Econazole nitrate Cream, 1% is approved as a once daily application for the topical treatment of tinea pedis, tinea cruris and tinea corporis caused by *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Trichophyton tonsurans*, *Microsporum canis, Microsporum audouini, Microsporum gypseum and Epidermophyton floccosum*, in the treatment of cutaneous candidiasis and in the treatment of tinea versicolor.

Dosing regimen: The Sponsor is proposing topical administration, once a day for 4 weeks.

Formulation: The Sponsor states that supplies for the early nonclinical safety studies and clinical Phase 2 safety and efficacy trial (D79-2902-07) were produced (b) (4) The manufacturing was later transferred to the USA (b) (4) and the commercial process was finalized prior to Phase 3 study. Accordingly, the pediatric PK trial (0792951-109) and the two Phase 3 safety and efficacy trials (0792951-302 and 0792951-303) were conducted with the to-be-marketed formulation. The Sponsor has classified the (b) (4) manufacturing site change as a (b) (4) change as per SUPAC-SS guidance and have conducted an in-vitro release test (IVRT) with the purpose of establishing a bridge between the 2 Foam formulations. IVRT will be reviewed by Office of New Drugs Quality Assurance (ONDQA).

Reviewer comment: *This reviewer checked with CMC lead Dr. Shulin Ding* (b) (4) *but CMC will require more information to make such determination. Accordingly, CMC plans to ask the Sponsor for further clarification.*

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Clinical trials: To support this application, the Sponsor has conducted four Phase 1 dermal safety trials, two Phase 2 trials which include pediatric PK trial under maximal use conditions and adult PK trial under maximal use conditions to support a bridge between the Foam and Cream and two Phase 3 trials. A list of all clinical trials is provided in Table 1 below.

Table 1: List of clinical trials

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Pediatric PK	0792951-109	**Module 5.3.3.5**	Compare steady state PK Foam vs. Cream	Randomized, Active-controlled	Foam 1%,; Once daily; topical Cream 1%,; Once daily; topical	50	Interdigital tinea pedis	4 weeks	Complete; Full
Phase 2 Safety and Efficacy	D79-2902-07	**Module 5.3.5.1**	Establish clinical bridge between Foam and Cream	Randomized, Placebo-controlled	Foam 1%,; Once a daily; topical Cream 1%,; Once daily; topical Vehicle Foam; once daily; topical	135	Tinea pedis (interdigital and/or moccasin type)	4 weeks	Complete; Full
Phase 3 Safety and Efficacy	0792951-302	**Module 5.3.5.1**	Determine and compare safety and efficacy of Foam vs. Placebo	Randomized, Placebo-controlled	Foam 1%,; Once a daily; topical Vehicle Foam; once daily; topical	267	Interdigital tinea pedis	4 weeks	Complete; Full
Phase 3 Safety and Efficacy	0792951-303	**Module 5.3.5.1**	Determine and compare safety and efficacy of Foam vs. Placebo. Cream comparator for safety purposes	Randomized, Placebo-controlled	Foam 1%,; Once a daily; topical Vehicle Foam; once daily; topical Cream 1%,; Once daily; topical	358	Interdigital tinea pedis	4 weeks	Complete; Full
Dermal Safety	0792951-104	**Module 5.3.3.1**	Determine irritation potential	Randomized, controlled	Econazole Nitrate Foam 1%,; Once a daily; topical Econazole Nitrate Vehicle Foam; once daily; topical Sodium Lauryl Sulfate Solution, 0.2%; once daily; topical Saline Solution, 0.9%; once daily; topical	34	Healthy Subjects	3 weeks	Complete; Full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Dermal Safety	0792951-105	**Module 5.3.3.1**	Determine potential to induce sensitization	Randomized, controlled	Econazole Nitrate Foam 1%,; 10 applications; topical Econazole Nitrate Vehicle Foam; 10 applications; topical Sodium Lauryl Sulfate Solution, 0.2%; 10 applications; topical Saline Solution, 0.9%; 10 applications topical	226	Healthy	6-8 weeks	Complete; Full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Dermal Safety	0792951-106	**Module 5.3.3.1**	Determine irritation potential after exposure to UV light	Randomized, within subject comparison	Econazole Nitrate Foam 1%,; one application; topical Econazole Nitrate Vehicle Foam; one application; topical	32	Healthy Subjects	4 days	Complete; Full
Dermal Safety	0792951-107	**Module 5.3.3.1**	Determine photosensitization potential	Randomized, within subject comparison	Econazole Nitrate Foam 1%,; seven applications; topical Econazole Nitrate Vehicle Foam; seven applications; topical	57	Healthy Subjects	6 weeks	Complete; Full

Pharmacokinetic assessment: The Sponsor has assessed blood concentrations in the following trials:

- 0792951-109: Phase 2 pediatric PK trial (12-18 year old) with interdigital tinea pedis
- D79-2902-07: Phase 2 safety and efficacy trial in adults with interdigital and/or moccasin type tinea pedis
- 0792951-303: Phase 3 trial

Serial PK sampling was done in trial D79-2902-07 while sparse sampling was done in the pediatric PK trial (0792951-109). The exposure with the Foam appears to be approximately 30 to 40% higher compared to the Cream (listed drug) in adults and approximately 2 to 3 fold higher in pediatrics. In the Phase 3 trial (0792951-303), blood samples were analyzed for safety purpose

only in subjects with ECG abnormalities. According to the Sponsor, blood samples in 2 subjects with ECG abnormalities were analyzed and measurable econazole nitrate concentration was found only in 1 subject.

Reviewer comments: *The observed increase in bioavailability following Foam administration compared to Cream was conveyed to Clinical and Pharm-Tox for the purpose of bridging. Both Clinical and Pharm-Tox have concluded this to be a review issue and not a filing issue. Further, according to Clinical Pharmacology review dated 09/23/2009 (see review in DARRTS), based on results of Trial D79-2902-07 the Sponsor provided justification for not conducting additional QT/QTc evaluations and Clinical Pharmacology concurred with Sponsor's justification. This will be re-considered during the NDA review.*

Bioanalytical method validation reports and bioanalysis reports: For the two Phase 2 trials (D79-2902-07 and 0792951-109) the bioanalytical reports are submitted. The bioanalytical method appears to be validated however further clarification with regard to long term storage stability of PK samples will be required (see comments for the Sponsor). Also stability data of internal standard miconazole is not provided and will be requested. The method validation report and the bioanalysis report have not been submitted for the Phase 3 trial (0792951-303) and will be requested from the Sponsor.

Proposed labeling: In the Clinical Pharmacology section (Section 12) of the label, the Sponsor has not included results from the maximal use trials conducted with their Foam formulation. Also Section 12 has not been divided in to sub-sections as requested during the Pre-NDA meeting (see meeting minutes in DARRTS dated 09/19/2012). This will be considered at the time of labeling review of this NDA.

Recommendation: The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Human Pharmacokinetics and Bioavailability section for NDA 205175 is fileable.

Comments to be sent to the Sponsor:

1. Provide storage stability data of internal standard miconazole to support the duration of bioanalysis.
2. According to your reports, Trial 0792951-109 (Pediatric PK) was initiated on September 21, 2011 (first informed consent) and as per your bioanalytical study report (MC11B-0109) the sample analysis was completed on May 16, 2012, i.e. a total duration of 238 days. The extended stability of econazole in human plasma (as per report MC08B-088) of 188 days will be inadequate to support the stability of PK samples for the entire duration from initiation of the trial to completion of bioanalysis. Provide additional stability data to support storage stability of at least 238 days or provide detailed data to support that all samples were analyzed within 188 days of sample collection.
3. According to the report for Trial D79-2902-07 the trial completion date provided is September 25, 2008 and according to your pharmacokinetics report (MC08B-0089 – Appendix A), the bioanalysis project completion date is stated as September 8, 2008. Clarify how the bioanalysis project completion date is before the trial completion date.
4. For Trial D79-2902-07, add a column to provide identification of the treatment administered for each subject (Foam or Cream) in your raw data set file pc.xpt.

5. For Trial D79-2902-07 provide the relative bioavailability data between foam and cream as ratio of the geometric mean as well as 90% confidence interval of the ratio of the geometric mean for AUC and C_{max} for the entire population. In addition, provide descriptive statistics and statistical analysis comparing the Foam and the Cream formulation by calculating 90% confidence interval for the geometric mean of Cmax and AUC stratified by subject disease type (i.e. interdigital only, moccasin only and subjects having both interdigital and moccasin).
6. We note that PK following drug administration was assessed only on the final day of the study after 4 weeks of drug application in Trial D79-2902-07 and 0792951-109. We also note that the proposed treatment duration with your product is 4 weeks. Hence, the systemic exposure information obtained on the final day of treatment could be from subjects that have healed skin and this may not represent maximal use conditions. For Trial D79-2902-07, provide a sub-group analysis (both descriptive statistics and relative bioavailability analyses) of your PK data by categorizing the data from subjects with healed skin and data from subjects that have not yet healed. For Trial 0792951-109, provide comparative systemic concentrations by categorizing the data from subjects with healed skin and data from subjects that have not yet healed. Also provide a table for each of these 2 trials showing information on disease severity at baseline and on the day of PK assessment for each subject.
7. For your Phase 3 trial (0792951-303), provide bioanalytical method validation and bioanalysis reports.

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/s/

CHINMAY SHUKLA
02/12/2013

DOANH C TRAN
02/12/2013