CLINICAL REVIEW

Application Type	NDA
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Priority or Standard	Standard
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Division / Office	DDDP/ ODE III
Reviewer Name(s)	Amy Sakulich Woitach, D.O., M.S.
Review Completion Date	September 23, 2016
Established Name	Naftifine hydrochloride
(Proposed) Trade Name	Naftin Cream, 2%
Therapeutic Class	allylamine antifungal
Applicant	Merz Pharmaceuticals
Formulation(s)	2% cream
Dosing Regimen	Daily for 14 days
Indication(s)	Tinea corporis
Intended Population(s)	Ages 2 years and older

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends approval of NDA 19599/ Supplement 13 for the use of naftifine hydrochloride cream, 2% in the treatment of tinea corporis in patients ≥ 2 years of age. This reviewer also concludes that postmarketing requirement 1857-2 is fulfilled and recommends that labeling changes are warranted based on the data derived from these studies. This recommendation is predicated upon the applicant's acceptance of revised labeling.

1.2 Risk Benefit Assessment

One study in tinea corporis is acceptable as evidence of effectiveness for the indication of tinea corporis in children 2 years of age and older. In the Phase 4 trial, Naftin cream 2% was superior to vehicle at Day 21 for the primary endpoint of complete cure which was defined as having negative mycology results (dermatophyte culture and KOH) and absence of erythema, induration, and pruritus ($p=0.01$ at a one-sided significance level of 0.025) as well as for the secondary endpoints of (i) effective treatment defined as negative KOH, negative culture sampled from the target lesions defined at baseline with erythema, induration, and pruritus sign/symptom scores of 0 or 1 on all lesions identified at baseline ($p=0.001$) and for (ii) mycological cure defined as negative KOH result and negative dermatophyte culture sampled from the site cultured at baseline or last site cultured most representative of overall severity from lesions present at baseline ($p=0.001$).

In support of safety in children 2 to 11 years of age, adverse event reporting was assessed at each evaluation. Standard safety laboratory and vital sign assessments were performed at baseline and on Day 21. There were no serious adverse events (SAEs) or deaths that occurred during the studies. Very few adverse events (AEs) were reported in the trial and there were no clinically significant laboratory or vital sign changes. Additionally, in a second open-labelled, PK trial, all subjects showed low but measurable levels of naftifine in plasma after topical application of Naftin Cream, 2%. No AEs or clinically significant laboratory changes were reported in this trial.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No additional safety issues were identified in these studies. No postmarketing REMS are recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

2.1 Product Information

Naftifine is a synthetic, broad spectrum, antifungal agent and allylamine derivative for the topical treatment of tinea pedis, tinea cruris, and tinea corporis caused by the organisms Trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton tonsurans and Epidermophyton floccosum.

Naftin Cream 2% (NAFT-500) was approved on January 13, 2012 for the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organism Trichophyton rubrum in adult patients ≥18 years of age based on studies conducted in tinea pedis and tinea cruris in subjects 12 years of age and older.

Naftifine HCl is also currently available in the U.S. in a 1% cream and 1% gel formulation. Naftin Cream 1% was approved on February 29, 1988; Naftin Gel 1% was approved June 18, 1990.

The studies contained in this submission were conducted to fulfill the following PREA PMR in the approval letter dated January 13, 2012 (NDA 019599 S-011) for Naftifine Cream 2%:

> *PMR 1857-2 PK/safety/efficacy study in pediatric subjects aged 2 years to 17 years 11 months with tinea corporis*

2.2 Tables of Currently Available Treatments for Proposed Indications

Topical Antifungal Agents (Tinea Pedis)	NDA	Dosage (Tinea Pedis)	Dosage (Tinea Corporis/Cruris)	Date of Approval	INDICATIONS AND USAGE (LABEL)
Econazole (Spectazole)	NDA 018-751	QD for 4 weeks	QD for 2 weeks	December 23, 1982	Spectazole Cream is indicated for the topical application in the treatment of tinea pedis, tiena cruris, and tinea corporis caused by *Tichophyton rubrum, Trichophyton mentagrophytes, Tricophyton tonsurans, Microsporum canis, Microsporum audouini, Microsporum gypseum,* and *Epidermophyton floccosum,* in the treatment of cutaneous candidiasis, and in the treatment of tinea versicolor (2001).
Ciclopirox (Loprox)	NDA 018-748	BID 4 weeks	NA	December 30, 1982	Loprox Cream is indicated for the topical treatment of the following dermal infections: tinea pedis, tinea cruris, and tinea corporis due to *Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum, and Microsporum canis*, candidiasis (moniliasis) due to *Candida albicans*, and tinea (pityriasis) versicolor due to *Malassezia furfur (2003)*.
Sulconazole (Exelderm)	NDA 018-737	BID 4 weeks	QD or BID for 3 weeks	August 30, 1985	EXELDERM (sulconazole nitrate) CREAM, 1.0% is an antifungal agent indicated for the treatment of tinea pedis (athlete's foot), tinea cruris, and tinea corporis caused by *Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum*, and *Microsporum canis*, and for the treatment of tinea versicolor (2003).
Oxiconazole (Oxistat)	NDA 019-828	QD or BID 1 month	QD or BID for 2 weeks	December 30, 1988	OXISTAT Cream and Lotion are indicated for the topical treatment of the following dermal infections: tinea pedis, tinea cruris, and tinea corporis due to *Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum*. OXISTAT Cream is indicated for the topical treatment of tinea (pityriasis) versicolor due to *Malassezia furfur* (2004)
(OTC) Clotrimazole (Lotrimin AF)	NDA 020-888	BID 4 weeks	BID 2-4 weeks	October 27, 1989	LOTRIMIN AF CREAM cures athelet's foot (tinea pedis), jock itch (tinea cruris) and ringworm (tinea corporis). For effective relief of the itching, cracking, burning and discomfort which can accompany these conditions (2001)
(OTC) Terbinafine (Lamisil Cream)	NDA 020-192	BID 1-2 weeks	QD 1 week	March 9, 1999	Uses: cures most athlete's foot (tinea pedis), cures most jock itch (tinea cruris) and ringworm (tinea corporis), relieves itching, burning, cracking, and scaling which accompany these conditions (2007)

Butenafine (Mentax)	NDA 020-524	Once daily for 4 weeks	combined label	October 18, 1996	Mentax® (butenafine HCl cream), 1%, is indicated for the topical treatment of the following dermatologic infections: tinea (pityriasis) versicolor due to *M. furfur* (formerly *P. orbiculare*), interdigital tinea pedis (athlete's foot), tinea corporis (ringworm) and tinea cruris (jock itch) due to *E. floccosum, T. mentagrophytes, T. Rubrum, and T tonsurans* (2002).
Butenafine (Mentax)	NDA 020-663	combined label	Once daily for two weeks	December 31, 1996	Mentax® (butenafine HCl cream), 1%, is indicated for the topical treatment of the following dermatologic infections: tinea (pityriasis) versicolor due to *M. furfur* (formerly *P. orbiculare*), interdigital tinea pedis (athlete's foot), tinea corporis (ringworm) and tinea cruris (jock itch) due to *E. floccosum, T. mentagrophytes, T. Rubrum, and T tonsurans* (2002).
(OTC) Butenafine (Lotrimin Ultra)	NDA 021-307	BID 1 week	QD 2 weeks	December 7, 2001	Uses: cures most athlete's foot between the toes, jock itch and ringworm. Revlieves itching, burning, cracking, and scaling which accompany these conditions (2001)
Sertaconazole (Ertaczo)	NDA 021-385	BID 4 weeks	No indication for tinea corporis or cruris	December 10, 2003	ERTACZO (sertaconazole nitrate) Cream, 2%, is indicated for the treatment of interdigital tinea pedis in immunocompetent patients 12 years of age an dolder, caused by: *Trichophyton rubrum, Trichophyton mentagrophytes*, and *Epidermophyton floccosum*.
Ketoconazole (Generic)	ANDA 075-581 and 076-294	QD 6 weeks	QD 2 weeks	75-581: April 25, 2000 76-294: April 28, 2004	Ketoconazole Cream 2% is indicated for the topical treatment of tinea corporis, tinea cruris and tinea pedis caused by Trichophyton rubrum, T. mentagrophytes and Epidermophyton floccsum; in the treatment of tinea (pityriasis) versicolog caused by Malassezia furfur (Pityrosporum orbiculare); in the treatment of cutaneous candidasis caused by Candida spp. and in the treatment of seborrheic dermatitis (2002).
Naftifine (Naftin)	NDA 019-599	QD for 2 weeks	QD for 2 weeks	January 13, 2012	NAFTIN Cream, 2% is an allylamine antifungal indicated for the treatment of interdigital tinea pedis, tinea, cruris, and tinea coporis caused by the organism *Trichophyton rubrum* in adults ≥ 18 years of age.
Naftifine (Naftin) Gel	NDA 204-286	QD for 2 weeks	NA	June 27, 2013	NAFTIN (naftifine hydrochloride) Gel, 2% is an allylamine antifungal indicated for the treatment of interdigital tinea pedis caused by the organisms Trichophyton rubrum, Trichophyton mentagrophytes, and Epidermophyton floccosum in patients 18 years of age and older.
Lotrisone 1% cream; lotion	NDA 18827; 20010	BID for 4 weeks	BID for 2 weeks	July 10, 1984; December 8, 2000	LOTRISONE Cream and Lotion are indicated in patients 17 years and older for the topical treatment of symptomatic inflammatory tinea pedis, tinea cruris, and tinea corporis due to Epidermophyton floccosum, Trichophyton mentagrophytes, and Trichophyton rubrum. Effective treatment without the risks associated with topical corticosteroid use may be obtained using a topical antifungal agent that does not contain a corticosteroid, especially for noninflammatory tinea infections. The efficacy of LOTRISONE Cream or Lotion for the treatment of infections caused by zoophilic dermatophytes (eg, Microsporum canis) has not been established. Several cases of treatment failure of LOTRISONE Cream in the treatment of infections caused by Microsporum canis have been reported.
ECOZA (econazole nitrate) topical foam, 1%,	NDA 205175	QD for 4 weeks	No indication for tinea corporis or cruris	October 24, 2013	Ecoza is an azole antifungal indicated for the treatment of interdigital tinea pedis caused by Trichophyton rubrum, Trichophyton mentagrophytes, and Epidermophyton fl

					Occosum in patients 12 years of age and older.
LUZU (luliconazole) Cream, 1%	NDA 204153	QD for 2 weeks	QD for 1 week	November 14, 2013	LUZU (luliconazole) Cream, 1% is an azole antifungal indicated for the topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organisms Trichophyton rubrum and Epidermophyton floccosum, in patients 18 years of age and older.

Source: Internal DDDP database and FDA approved labeling

2.3 Availability of Proposed Active Ingredient in the United States

In the U.S., naftifine HCl is currently available in 1% and 2% strengths as cream and gel formulations. The 2% cream product is available in a generic formulation.

2.4 Important Safety Issues With Consideration to Related Drugs

Naftifine hydrochloride is a topical allylamine antifungal and since initial approval of the 1% formulation in 1988, the most common adverse reactions were local skin reactions. Although not likely applicable here, the oral administration of terbinafine, a systemic allylamine antifungal, has been reported to be associated with liver failure, taste and smell disturbance, depressive symptoms, neutropenia and Stevens-Johnson's syndrome. These adverse events were not observed with topical terbinafine or with naftifine hydrochloride.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Naftin Cream 2% (NAFT-500) was approved on January 13, 2012 for the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organism Trichophyton rubrum in adult patients ≥18 years of age. The approval was granted in adults because only three pediatric patients exposed to active study drug completed treatment in the clinical development program for tinea pedis and tinea cruris and the Naftin Cream, 1% product is not approved for use in pediatric patients. Dr. Brenda Vaughan completed the clinical review of application 19-599/S011 for the approval. See Dr. Vaughan's October 21, 2011 clinical review and December 23, 2011 addendum for details.

At the time of approval, studies to evaluate pediatric subjects under the age of 2 were waived. A deferral of studies evaluating pediatric subjects above the age of 2 was granted and these were incorporated into PREA postmarketing requirements as follows:

> **1857-1** PK/Safety/Tolerability study under maximal use conditions in subjects ages 12 years to 17 years 11 months with a minimum of at least 18 evaluable

subjects with tinea pedis and tinea cruris towards the upper end of disease severity in the patient population.

1857-2 PK/Efficacy/Safety study in pediatric subjects ages 2 years to 17 years 11 months with tinea corporis.

PMR 1857-1 was fulfilled as Supplement 12 on October 10, 2014. A supplement for the submitted pediatric study removed the adult restriction in labeling.

The studies submitted with this supplement, MUS90200_4024_1 and MUS90200_4025_1 (hereinafter denoted as Trial 4024 and 4025, respectively) are to address PMR 1857-2 and the submission includes proposed labeling changes.

2.6 Other Relevant Background Information

It should be noted that historically, prior to passage of PREA requirements, the indication of tinea corporis was included in labeling for products that had adequately demonstrated safety and efficacy for tinea pedis and tinea cruris. No additional tinea corporis trials were required. Most older products indicated for tinea corporis did not conduct trials specifically for adults or children with tinea corporis.

The Pediatric Research Equity Act is the law that requires pediatric studies in certain situations. PREA became law in December 2003 and was reauthorized in September 2007. PREA requires that all new drug and biologic applications that trigger the law contain a pediatric assessment, unless this requirement has been waived or deferred.

PREA is triggered when an application or supplement for a drug or a biological product is submitted for:

- a new indication
- new dosing regimen (any change in a single dose, maximum daily dose or dosing interval)
- new active ingredient (including a new combination)
- new dosage form (e.g., tablet to suspension)
- a new route of administration (e.g., subcutaneous to intramuscular, etc.)

The studies must include data to support pediatric dosing and administration and age-appropriate formulations must be used in the studies. Hence, upon approval of the 2% formulations of Naftin, the sponsor was required to address PREA and conducted PK and safety/efficacy studies to address the use in pediatric populations.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The sponsor conducted 2 studies to fulfill the PREA PMR in pediatric subjects aged 2 years to 17 years and 11 months. Trials 4024 and 4025 enrolled 231 and 27 subjects, respectively. Study sites were both within and outside of the US.

The review team did not recommend study site inspections as the product has been previously approved, and it would provide a low yield for this application. The efficacy in the single trial in tinea corporis in the pediatric population is supported by extrapolation from the adult studies in tinea pedis and tinea cruris indications. Thus, inspection of sites for the purpose of assessing impact of trial conduct on efficacy outcome would not provide a substantial contribution. Additionally, the safety profile for the active moiety is reasonably well characterized; the data collected in the trials is supportive of safe use in the pediatric population. Again, conducting inspections to assess the impact of trial conduct on safety would not likely provide a substantial contribution.

3.2 Compliance with Good Clinical Practices

The applicant reports that clinical trials 4024 and 4025 were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and its amendments and that are consistent with Good Clinical Practice (GCP), the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and the applicable regulatory requirements.

An IRB reviewed and approved the protocol, informed consent, and any other study related documentation as appropriate. All subjects were required to give written informed consent prior to participation in the study.

3.3 Financial Disclosures

The applicant reports that none of the financial interests or arrangements described in 21 CFR § 54.4(a)(3) exists. See appended Clinical Investigator Financial Disclosure Review Template

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There are no new CMC data contained in this efficacy supplement. The CMC team reviewed the proposed revision of the CMC portion of the drug label.

4.2 Clinical Microbiology

Clinical information in the original submission was insufficient to include other organisms beyond T. rubrum in labeling. See clinical microbiology and supervisory reviews from original submission. The clinical studies in this submission do not support expansion of the indication to include the treatment of other dermatophytes.

4.3 Preclinical Pharmacology/Toxicology

There are no new nonclinical data contained in this efficacy supplement. The pharmacology/toxicology team reviewed the proposed revision of the pharmacology/toxicology portion of the drug label.

4.4 Clinical Pharmacology

The sponsor submitted results of the trial 4025, which evaluated the systemic exposure of naftifine following once daily topical application of Naftin Cream 2% for 2 weeks in 27 pediatric subjects (2 to < 12 years) with tinea corporis affecting at least 1% of body surface area (BSA). A total of 27 pediatric subjects all had measurable levels of naftifine in plasma. In this study, the geometric mean values of Cmax and AUC0-24 were lower than those observed in previous trials based on cross-study comparisons with the trials for tinea pedis and cruris in subjects ≥13 years of age who received higher daily doses of Naftin Cream, 2%.

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds NDA 019599/S013 acceptable pending agreement on recommended labeling changes. The team also finds that efficacy supplement also satisfies the PREA requirements 1857-2 as outlined in the approval letter for NDA 19599/S011 dated 1/13/2012.

4.4.1 Mechanism of Action

See reviews of the original submission. This supplement does not provide additional information.

4.4.2 Pharmacodynamics

See reviews of the original submission. This supplement does not provide additional information.

4.4.3 Pharmacokinetics

With this submission, the results of results of trial 4025 will be added to approved labeling.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Clinical Trials for this review cycle:	Number of Subjects	Number of Sites	First subject enrolled; last subject completed
MUS90200-4024-1: A Phase 4, Double-Blind, Randomized, Vehicle-Controlled, Multicenter, Parallel Group Evaluation of the Efficacy and Safety of Naftin® (naftifine hydrochloride) Cream, 2% in Pediatric Subjects with Tinea Corporis	A total of 259 subjects were screened to obtain 231 subjects that were randomized, 116 to Naftin Cream, 2% group and 115 to vehicle. The primary analysis population was the FAS (subjects with positive culture at baseline for whom the primary efficacy endpoint is available). N=181 FAS subjects(Naftin cream 88; vehicle 93)	18 sites in the US, Dominican Republic, Panama, and Honduras. The majority of the ITT population is non-US	20 August 2014; 27 October 2015
MUS90200-4025-1: An Open-Label, Multi-Center, Multiple-Application Pharmacokinetic Study of Naftin® (naftifine hydrochloride) Cream, 2% in Pediatric Subjects with Tinea Corporis	A total of 27 subjects were enrolled and received Naftin Cream, 2% in this study: 17 younger pediatric subjects (i.e., those 2 to <6 years of age) and 10 older pediatric subjects (i.e., those 6 to <12 years of age	two (2): one each in Honduras and the Dominican Republic	08 June 2015; 23 September 2015

5.2 Review Strategy

Trial 4024, a randomized control trial, was reviewed for a demonstration of safety and efficacy in the treatment of tinea corporis in children.

Trial 4025, an open-labeled, PK trial was reviewed to determine bioavailability in pediatric subjects with tinea corporis. Data obtained was also evaluated by cross-study comparisons with PK data from other naftifine HCl products/ indications/ populations. Safety and Efficacy were reported by the applicant and was considered for supportive evidence only.

5.3 Discussion of Individual Studies/Clinical Trials

4024
The study objective was to evaluate the safety and efficacy of Naftin cream, 2% applied once daily for 2 weeks, each compared to its vehicle in the treatment of pediatric subjects aged 2 to 17 years and 11 months with positive KOH, positive dermatophyte culture, and clinical signs and symptoms of tinea corporis.

A total of 259 subjects were screened to obtain 231 subjects that were randomized in a 1:1 ratio, 116 to Naftin (naftifine hydrochloride) Cream, 2% group and 115 to vehicle.

Subjects applied the assigned investigational product once daily to all affected areas plus a half-inch margin around each lesion for two weeks and returned to the study center for a follow-up visit at Days 14 and 21. Subjects were evaluated at Day 1 (screening/baseline), Day 14 (end of treatment), and Day 21 (1-week post-treatment, end of study).

Efficacy assessments included KOH and culture evaluation, and clinical signs and symptoms (erythema, induration, and pruritus). The primary efficacy endpoint was the complete cure at Day 21 where complete cure was defined as negative mycology results (dermatophyte culture, KOH) and absence of erythema, induration and pruritus on all lesions identified at baseline.

Safety assessments included physical examination and laboratory assessment at Day1 (baseline) and Day 21 and adverse event assessment at each visit.

Major inclusion criteria included:

- Males or non-pregnant females ≥2 years <18 years of any race. Females of child bearing potential must have a negative urine pregnancy test.
- Presence of tinea corporis characterized by clinical evidence of a tinea infection of at least moderate erythema, moderate induration, and mild pruritus.

- KOH positive and culture positive baseline skin scrapings obtained from the site with the most severely affected lesion or a representative site of the overall severity (active border).

Major exclusion criteria included:

- Major medical illness (e.g. autoimmune deficiency syndrome, cancer, diabetes mellitus, renal failure, immunocompromised state)
- Abnormal physical or laboratory findings as per the investigator
- Pregnancy or lactating females
- Tinea infection of the face, scalp, groin, and/or feet
- Current evidence of compromised skin, atopic or contact dermatitis, eczema, impetigo, lichen planus, pityriasis rosea, pityriasis versicolor, psoriasis, seborrheic dermatitis and syphilis.
- Severe dermatophytoses, mucocutaneous candidiasis, or bacterial skin infection
- Patients with tinea corporis who have concurrent dermatophytosis of the scalp, beard or nails
- Concomitant use of topical anti-fungal or steroid therapy within 14 days
- Concomitant use of oral anti-fungal therapy within 3 months
- Concomitant use of systemic antibiotic or steroid therapy within 1 month

18 centers (U.S., Puerto Rico, Dominican Republic, Belize, Honduras, Panama, and El Salvador) participated in the study and are listed in the following table:

Table 1: Investigators for Trial 4204

Site Number	Investigator First Name	Investigator Last Name	Institution	Specialty	Address	Phone
001310	Francisco	Flores, MD	FXM Research Miramar	Dermatology	14601 SW 29th Street Suite 208 Miramar, FL 33027	954-430-1097
001311	Hector	Wiltz, MD	FXM Research Corp	Dermatology	11760 Bird Road Suite 452 Miami, FL 33175	305-220-5222
180001	Daisy	Blanco, MD	Instituto Dermatológico	Dermatology	Calle Federico Velásquez Esq. Albert Thomas Ensanche Maria Auxiliadora Santo Domingo, República Dominicana	809-684-3257 ext. 262

180002	Ynca Nina	Vasquez, MD	Instituto Dermatológico y Cirugía de Piel	Dermatology	Calle Prolongación Sanchez Esquina Luperón #1 San Cristóbal, Republica Dominicana	809-528-4848
507001	Charles	McKeever, MD	Hospital Punta Pacifica	Dermatology	Blvd. Pacifica y Via Punta Darien Suite 5-27 Panama City, Panama	507-204-8466
504001	Nelly	Paz, MD	Hospital y ClinicaBendana	Dermatology	Ave. Circunvalación 3 Piso, Local 312 San Pedro Sula, Honduras	504-2516-2902
001312	Javier	Alonso-LLamazares, MD	International Dermatology Research, Inc.	Dermatology	8370 West Flagler Street Suite 200 Miami, FL 33144	305-225-0400
001279	Amaury	Roman, MD	Advanced Medical Concepts PSC	Dermatology	4 Balldorioty Street Cidra, PR 00739	787-739-3376
001313	Sunil	Dhawan, MD	Center for Dermatology Clinical Research, Inc.	Dermatology	2557 Mowry Avenue Suite 25 and 34 Fremont, CA 94538	510 797-4111 Ext.3
001097	Michael	Gold, MD	Tennessee Clinical Research Center	Dermatology	2000 Richard Jones Road Suite 223 Nashville, TN 37215	615-383-9660
001293	William	Huang, MD, MPH	Wake Forest Baptist Health	Dermatology	Department of Dermatology 4618 Country Club Road Winston Salem, NC 27104	336-716-3926
001126	Adnan	Nasir, MD	Wake Research	Dermatology	3100 Duraleigh Road Suite 304 Raleigh, NC 27612	919-781-2514
001307	Melody	Stone, MD	MediSearch Clinical Trials	Dermatology	1419 Village Drive Saint Joseph, MO 64506	816-364-1507

001314	Johnnie	Woodson, MD	J. Woodson Dermat ology & Associat	Dermatology	229 N. Pecos Road Suite 100 Henderson, NV 89074	702-485-5300
001309	Herschel	Stoller, MD	Quality Clinical Research, Inc.	Dermatology	10040 Regency Cr Suite 375 Omaha, NE 68114	402-934-0044
001316	Norman	Bystol, MD	Radiant Research	Dermatology	6290 E. Grant Rd. Tucson AZ 85712	520-885-6793 Ext. 4007
001301	Oscar	De La Mora, MD	Khruz Biotechnology Research Institute	Dermatology	995 Gateway Center Way Suite 202 San Diego, CA 92102	619-264-3107
0010319	John	Calcagno, MD	Cyn3rgy Research & Development	Dermatology	24850 SE Stark Suite #180 Gresham, OR 97030	503-907-2179

The original protocol was finalized on 23 September 2015; it was subsequently amended three times as follows:

Amendment 1.0, dated 02 May 2014, made the following substantive changes:

- Removal of the Naftin® (naftifine hydrochloride) Gel, 2% [NAFT-600] arm and its respective comparator vehicle arm.
- Incorporate Food and Drug Administration (FDA) recommendations based on the review of the protocol.
    - Elaboration on handling of missing data, especially the specification for the primary imputation method for handling missing data. Additionally, a plan for sensitivity analysis was included to ensure that efficacy results were not driven by the method of handling missing data.
    - Adjustments to produce an adequate sample size for the proposed trial to demonstrate efficacy and safety of tinea corporis.
    - Pre-specify statistical analyses in the protocol in order to be able to establish adequate efficacy claims.
    - Modification to the narrative regarding the percentage of baseline positive cultures being monitored and how the number of subjects randomized were accounted for or adapted.
    - Addition of antimicrobial susceptibility testing was performed on all isolates collected at baseline and at the end of the study. The methods used for in vitro susceptibility testing were performed using standardized

methods recommended by the Clinical Laboratory Standards Institute (CLSI).
- Addition of the use of a central laboratory for all microbiologic testing.

Amendment 2.0, dated 27 June 2014, made the following substantive changes:
- Elaboration of packaging and labelling.
- Modification to the subject diary instructions
- Addition of on-site dipstick urinalysis in children and adolescents in order to minimize the effects of poor clean-catch urine techniques.

Amendment 3.0, dated 20 August 2014 made the following substantive changes:
- Additional clarification was provided for assessing lesions at baseline and at the end of the study.
- Specification that all lesions assessed at baseline are the lesions that need to be assessed at the end of the study for efficacy; as opposed to assessing all lesions present at the end of the study including those that may have developed post baseline.
- Updates to the statistical sections and further clarification on missing data imputation methods.

4025

The study objective was to evaluate the systemic exposure of naftifine following topical application of Naftin Cream 2% in pediatric subjects (2 to < 12 years) with tinea corporis affecting at least 1% of body surface area (BSA). The secondary objectives were to evaluate subject efficacy, tolerability, and safety after 2 weeks of once-daily applications of Naftin (naftifine HCl) Cream, 2%.

This was an open-label, multi-center, repeat-application study designed to evaluate the systemic exposure (PK profile) of once-daily topical application of Naftin (naftifine HCl) Cream, 2% for 2 weeks in subjects 2 to < 12 years of age with tinea corporis. The trial was conducted under maximal clinical use conditions where Naftin Cream, 2% were to be applied ≥ 0.5 g but ≤ 3 g in subjects aged 2 to < 6 years and ≥ 1 g but ≤ 4 g in subjects 6 to < 12 years, once daily to all affected areas plus a ½-inch margin excluding the groin, hands, scalp, and feet. The plasma PK on Day 1 and urinary excretion of naftifine (Days 1 and 14) were determined only in the older age group. Both age groups had plasma PK samples collected on Day 14.

The study planned to enroll approximately 30 pediatric subjects to obtain at least 10 evaluable subjects in each of the two age cohorts (2 to < 6 years and 6 to < 12 years).

The main inclusion/exclusion criteria were as follows:

Subjects were males or females 2 to < 12 years, of any race with tinea corporis characterized by clinical evidence of a tinea infection (at least marked erythema, marked induration, and moderate pruritus) at multiple sites covering a total of at least 1% of BSA and potassium hydroxide (KOH)-positive and culture-positive baseline skin scrapings obtained from the site most severely affected or a representative site of the overall severity (active border). Subjects were not permitted to have tinea infection of the scalp, face, groin, and/or feet.

Efficacy was assessed as complete cure at Day 21. Complete cure was defined as a negative mycology results from the central laboratory (negative dermatophyte culture and KOH) and absence of erythema, induration, and pruritus (score of 0 on each sign/symptom on all lesions identified at baseline).

Summarized safety variables were

- Occurrences, severity, and relationship of adverse events (AEs) and serious adverse events (SAEs)
- Significant clinical laboratory findings and vital signs.

This study was conducted at two investigational sites, one each in Honduras and the Dominican Republic as shown in the table below:

Table 2: Investigators for Trial 4025

Site Number	Investigator First Name	Investigator Last Name	Institution	Specialty	Address	Phone
504001	Nelly	Paz, MD	Hospital y ClinicaBendana	Dermatology	Ave. Circunvalación 3 Piso, Local 312 San Pedro Sula, Honduras	504-2516-2902
180001	Daisy	Blanco, MD	Instituto Dermatológico	Dermatology	Calle Federico Velásquez Esq. Albert Thomas Ensanche Maria Auxiliadora Santo Domingo, República Dominicana	809-684-3257 ext. 262

001261	Terry	Jones, MD	J & S Studies, Inc.	Dermatology	1710 Crescent Pointe Parkway College Station, TX 77845	979-774-5933

The original protocol was finalized on 19 September 2012; it was subsequently amended four times.

Amendment 1, dated 02 May 2014, made the following substantive changes:

- Removal of the NAFT-600 arm and its respective comparator vehicle arm as well as the removal of the vehicle arm in the Naftin Cream, 2% group to avoid unnecessary blood draws in this group, given this is only a safety study of Naftin Cream, 2% (i.e., a 1-arm study).
- Incorporate Food and Drug Administration (FDA) recommendations based on their review of the protocol. These changes included the following:
    - Stratification of enrollment by age to ensure that there was an approximately even distribution of subjects within the proposed age ranges to ensure there was adequate enrollment at the lowest ages.
    - The study design was revised to minimize blood volumes drawn.
    - To limit blood loss due to testing, the number of blood draws for clinical labs was reduced to 2 (baseline and Day 21) across all age groups.

Amendment 2, dated 03 July 2014, made the following substantive changes:

- Added on-site dipstick urinalysis in children and adolescents to minimize the effects of poor clean-catch urine techniques.

Amendment 3, dated 11 September 2014, made the following substantive changes:

- Dosing stratifications were made based on age cohort where subjects aged 2 to <6 years used 3g of product versus subjects aged 6 to <12 years used 4g of product. The doses were based on data from previous pediatric studies conducted using Naftin (naftifine HCl) Cream, 2% and the doses also ensured the appropriateness for maximum use conditions relative to a subject's age and weight stature.
- Inclusion criteria were modified to include a minimum percent BSA of involved skin. At least 1% of the skin was required to have tinea corporis involvement.
- Specification of the size of the area of drug application (i.e., percent BSA for application). The total application area involved ≥10% of a subject's BSA, which included the affected area(s) plus a ½-inch margin, as well as application to any surrounding skin to make up the remainder of the ≥10% BSA. This approach simulates maximum use conditions.
- Addition of a data safety monitoring board (DSMB) to meet periodically (as outlined in the DSMB charter).

Amendment 4, dated 16 March 2015, made the following substantive changes:

- The protocol no longer instructed that IP be applied to additional areas of healthy skin beyond the ½-inch margin. Thus, subjects were enrolled and treated if they had at least 1% BSA affected; however, they were no longer required to have a total application criteria of ≥10% BSA (unless a subject presented with disease totaling ≥10% BSA) since only the affected areas plus a ½-inch margin was now to be treated.
- Based on the prior protocol (dated 11 September 2014), FDA suggested that the applied dose could have been less than the maximum dose of 3 to 4g as stated in the protocol. It was recommended to record the estimated surface areas being treated and the actual amount of applied drug product for each subject and also that the sponsor set a minimum applied dose to help ensure that the dose applied would be representative of the upper end of the range expected in clinical use. Based on these recommendations, the amended protocol stated that subjects enrolled must have at least 1% BSA affected and the doses were stratified by age cohorts as follows: (1) pediatric subjects aged 2 to <6 years were to use at least 0.5g but no more than 3g of Naftin to all affected areas plus a ½-inch margin of health skin and (2) pediatric subjects aged 6 to <12 years were to use at least 1 gram but no more than 4g of Naftin to all affected areas plus a ½-inch margin of healthy skin.
- Adjustments to the sample size narrative and stratification of sample size by age group were made. Approximately 30 subjects were planned for enrollment in the study including at least 10 evaluable subjects, but no more than 20 evaluable subjects in the 2 to <6 years age group and at least 10 evaluable but no more than 20 evaluable subjects in the 6 to <12 years age group. This sample size was considered to be sufficient to detect differences in pharmacokinetics in pediatric subjects without exposing too large a number of subjects to undue risk and discomfort.
- Modifications and/or clarification to the PK variables as well as to the analysis of the variables based on study design changes were made. Additional clarification was provided regarding the definitions of the PK variables especially as they related to analyses accounting for dose, age, and body weight.
- Given the changes regarding dose stratification by age cohort, where a minimum and maximum dose threshold was set (per the judgment of the treating physician) as opposed to a maximum use application study, the DSMB was removed from the planned study.

6 Review of Efficacy

Efficacy Summary

Efficacy was determined based on data from trial 4024 and the results from this study will be described in section 6. Efficacy in tinea corporis is also supported by the demonstration of efficacy in the other tinea indications. The additional trial submitted

with this supplement, 4025, is an open-labelled PK study that also evaluated the proportion of subjects achieving each efficacy endpoint. This data is summarized in section 6.1.10 and is supportive of efficacy for tinea corporis.

- Primary endpoint of Complete Cure [negative mycology results (dermatophyte culture and KOH) and absence of erythema, induration, and pruritus] at Day 21 **(Naftin 46% vs. vehicle 28%)**

- Secondary endpoints

    - Effective Treatment (negative KOH, negative culture, and erythema, induration, and pruritus grades of 0 or 1) at Day 21**(Naftin 58% vs. vehicle 34%)**

    - Mycological Cure (negative KOH and negative culture) at Day 21 **(Naftin 63% vs. vehicle 39%)**

The results from Trial 4024 showed that the Naftin cream 2% was superior to vehicle at Day 21 for the primary endpoint of complete cure which was defined as having negative mycology results (dermatophyte culture and KOH) and absence of erythema, induration, and pruritus (p=0.01 at a one-sided significance level of 0.025) as well as for the secondary endpoints of (i) effective treatment defined as negative KOH, negative culture sampled from the target lesions defined at baseline with erythema, induration, and pruritus sign/symptom scores of 0 or 1 on all lesions identified at baseline (p=0.001) as well as for (ii) mycological cure defined as negative KOH result and negative dermatophyte culture sampled from the site cultured at baseline or last site cultured most representative of overall severity from lesions present at baseline (p=0.001).

Table 3: Primary and Secondary Efficacy Endpoint Analysis

Trial 4024				
Endpoint		Naftin N=91	Vehicle N=93	p-value
Primary	Complete Cure (1) at Day 21	42 (46%)	26 (28%)	0.01
Secondary	Effective Treatment (2) at Day 21	53 (58%)	32 (34%)	0.001
	Mycological Cure (3) at Day 21	57 (63%)	36 (39%)	0.001

Source: biostatistics review table 1
Source: P-values were from the Chi-square test with a one-sided significance level of 0.025; the protocol-specified primary imputation method for handling missing data was to impute missing as treatment failure (MVTF).

(1) Complete Cure was defined as negative mycology results (dermatophyte culture and KOH) and absence of erythema, induration, and pruritus (scores of 0 on each),
(2) Effective Treatment was defined as negative KOH, negative culture, and erythema, induration, and pruritus grades of 0 or 1,

(3) Mycological Cure was defined as negative KOH and negative culture.

6.1 Indication

Naftin cream 2% was approved on 1/13/2012 for the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organism Trichophyton rubrum in adults ≥ 18 years of age. To fulfill a PREA postmarketing requirement, the applicant conducted a Phase 4 Evaluation of the Efficacy and Safety in Pediatric Subjects with Tinea Corporis (Trial 4024), and a PK study in children 2 to 12 years of age (Trial 4025) and submitted the results in this supplemental NDA application. With this submission, the sponsor requests approval for use in patients 2 years of age and older.

6.1.1 Methods

This submission was submitted in eCTD format and was entirely electronic. Both SDTM and analysis datasets were submitted. The applicant's clinical study reports, clinical summaries, and proposed labeling were reviewed with analysis and input from the statistical review team. The following data sets were defined by the sponsor and used in the analyses:

- Full Analysis Set (FAS): subset of SES with positive culture at baseline for whom the primary efficacy endpoint is available (which the sponsor notes in the protocol is the case for all subjects, because dropouts and cases with missing information will be considered as not complete cures). The primary analysis population was the FAS.

- Per Protocol Set (PPS): subset in the FAS without major protocol violations, and major protocol violations are defined as subjects with insufficient baseline signs and symptoms, unmet inclusion/exclusion criteria, treatment with forbidden concomitant medications, enrollment prior to study determined wash-out of concomitant medications, Visit 3 occurring outside of the visit window, missing or unknown Visit 3 KOH and dermatophyte result, missing or unknown erythema, scaling and pruritus scores at Visit 3.

The sponsor conducted a one-sided hypothesis tests. For handling of missing data, the sponsor used missing value treated as failure (MVTF) as the primary imputation method, and used the last observation carried forward (LOCF) as a sensitivity analysis. See Dr. Carin Kim's statistical review for full details.

6.1.2 Demographics

The baseline demographics were generally balanced across the treatment arms. Approximately 61% of the subjects were male, 44% were white and 55% were black, and the mean age of the subjects was 8.8 years of age.

Table 4: Baseline demographic characteristics in FAS population

	Trial 4024	
	Naftin, 2%	Vehicle
FAS	91	93
Sex		
Female	35 (38%)	37 (40%)
Male	56 (62%)	56 (60%)
Race		
White	39 (43%)	42 (45%)
Black	51 (56%)	51 (55%)
Other	1 (1%)	0 (0%)
Age		
Mean ± SD	8.8 ± 4.2	8.8 ± 4.4
range	2, 17	2, 17
Median	9	8

Source: Statistical review Table 4

A majority of the subjects in both the Naftin (naftifine hydrochloride) Cream, 2% group and the vehicle group were Hispanic or Latino (92.2% versus 90.4%, respectively). This is expected since the majority of subjects in the full analysis set were from foreign sites due to a high failure rate of positive cultures at US sites. From a clinical perspective, it is unlikely that a response to the treatment of tinea corporis with Naftin cream, 2% in a Hispanic population would be significantly different than in a non- Hispanic population.

6.1.3 Subject Disposition

Trial 4024 randomized a total of 231 subjects (116 Naftin 2%; 115 vehicle), and after excluding 47 subjects that had negative mycology at baseline and 3 subjects that did not have any post-baseline assessments, the applicant considered a total of 181 subjects for their full analysis set (FAS) for efficacy analyses. The review team did not agree with the sponsor's exclusion. Following the intent-to-treat (ITT) principle, the statistical reviewer included those 3 subjects that did not have any post-baseline efficacy data (3 subjects). Therefore, the Agency's FAS included 91 and 93 subjects for Naftin cream, 2% and vehicle, respectively.

Table 5: Subject Disposition Trial 4024

	Trial 4024	
	Naftin, 2%	Vehicle
Randomized; Safety	116	115
Applicant's Full Analysis Set (FAS[1])	88	93
Reasons excluded from FAS		
Negative mycology at baseline	25	22
No post-baseline efficacy data	3 [2]	0
Discontinued	4 (3%)	0 (0%)
Adverse Events	0	0
Withdrawal by subject	2	0
Lack of Efficacy	0	0
Loss to Followup	1	0
Protocol violation	0	0
Physician Decision	1	0
Other	0	0

Source: Statistical review Table 3 Applicant's Study Report, (1) FAS defined as subjects with positive culture at baseline for whom the primary efficacy endpoint is available; (2) subjects MUS90200_4024_1-S0402; MUS90200_4024_1-S0763; MUS90200_4024_S0764

A total of 4 randomized subjects discontinued the trial, and they were considered to be treatment failures per the protocol-specified primary imputation method.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint was the complete cure at Day 21 where complete cure was defined as negative mycology results (dermatophyte culture, KOH) and absence of erythema, induration and pruritus on all lesions identified at baseline.

Naftin cream 2% was superior to vehicle (46% vs. 28%) at Day 21 for the primary endpoint of complete cure which was defined as having negative mycology results (dermatophyte culture and KOH) and absence of erythema, induration, and pruritus (p=0.01). See Table 3 above.

This endpoint of complete cure has been used to support approval of other types of cutaneous fungal skin infections and in this reviewer's opinion is a clinically relevant endpoint for assessing the treatment of tinea corporis.

6.1.5 Analysis of Secondary Endpoints(s)

The secondary endpoints are as follows:

- Treatment effectiveness at Day 21 defined as negative KOH, negative culture sampled from the target lesions defined at baseline with erythema, induration, and pruritus sign/symptom scores of 0 or 1 on all lesions identified at baseline.

- Mycological cure at Day 21 defined as negative KOH result and negative dermatophyte culture sampled from the site cultured at baseline or last site cultured most representative of overall severity from lesions present at baseline.

Naftin cream 2% was superior to vehicle at Day 21 for the secondary endpoints of effective treatment (58% vs. 34% p=0.001) as well as mycological cure (63% vs 39%, p=0.001). See Table 3 above.

These secondary endpoints have been used to support efficacy in other types of cutaneous fungal skin infections and in this reviewer's opinion are clinically relevant endpoints for supporting efficacy in the treatment of tinea corporis.

6.1.6 Other Endpoints

Not applicable for this indication.

6.1.7 Subpopulations

The primary efficacy endpoint of complete cure was analyzed by sex, race and age group (<9 vs. ≥9 years of age) and are shown in the table below. Analyses by sex and race subgroups were generally consistent across the treatment arms. The treatment effect in the younger age group (≥2 and <9 years of age) was larger than those of the older age group (≥9 and <18 years of age). This appears to be due to a larger treatment effect in the vehicle arm in the older children. Given that naftifine has demonstrated efficacy in older children and adults for other infections with the same dermatophytes, this difference does not appear to be clinically significant.

Table 6: Analysis of the Primary Efficacy Endpoint by Sex, Race and Age

	Trial 4024	
	Naftin, 2%	Vehicle
FAS	91	93
Sex		
Female	16/35 (46%)	11/37 (30%)
Male	26/56 (46%)	15/56 (27%)
Race		

White	20/39 (51%)	13/42 (31%)
Black	22/51 (43%)	13/51 (25%)
Other	0/1 (0%)	0 (0%)
Age		
< mean (9 years of age)	19/44 (43%)	9/47 (19%)
≥ mean age (9 years of age)	23/47 (49%)	17/46 (37%)

Source:Statistical reviewer's table 6

The treatment effects for the primary endpoint of complete cure at Day 21 by study center were analyzed and are presented in the table below.

Table 7: Analysis of the Primary Efficacy Endpoint by Study Center

Trial 4024			
Efficacy by Site		Naftin N=91	Vehicle N=93
By site	Primary Endpoint	42 (46%)	26 (28%)
	001126	0	1
	001279	0	1
	001293	1	0
	001307	1	0
	180001	16/29 (55%)	8/28 (29%)
	180002	8/28 (29%)	6/28 (21%)
	504001	17/32 (53%)	12/35 (34%)

Source: Statistics reviewer table 7

4 of the 7 sites had a single FAS subject for analysis. Baseline/Visit1 dermatophyte culture failure rates were very high in these countries. Among subjects in the FAS, the USA contributed only three subjects. Dominican Republic and Honduras contributed the majority of the FAS subjects. Of the remaining non-US sites, 2 show consistency in regard to treatment effect. It is not clear as to why site 180002 demonstrated a lower treatment effect.

Reviewer comment: The primary analysis population is non-US. Clinical extrapolation to a US population seems reasonable to this reviewer especially given that naftifine has demonstrated efficacy in other clinical studies for infections with the same dermatophytes. Therefore, relying on foreign data is acceptable.

Findings of Trial 4024 were not reproduced in a second study. Until recently, sponsors were granted the indication of tinea corporis if the product was studied in both tinea pedis and tinea cruris. It is this reviewer's opinion that the efficacy demonstrated in this single trial along with the efficacy of Naftin cream, 2% demonstrated in the other tinea indications supports the indication of tinea corporis.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Only one dose was assessed in this single trial.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of Efficacy and Tolerance were not assessed.

6.1.10 Additional Efficacy Issues/Analyses

A treatment effect of Naftin Cream, 2% was evaluated for tinea corporis in pediatric subjects in Trial 4025, a maximal use PK study. The efficacy measures (complete cure, effective treatment and mycological cure) were the same as the primary and secondary endpoints used in Trial 4024. The data is supportive of the results seen in Trial 4024. The outcome for Trial 4025 is shown below:

Table 8: Treatment Effectiveness in Open-labelled Trial 4025

Efficacy Parameter	**2 to <6 years (N=17) n (%) [90% CI]**	**6 to <12 years (N=10) n (%) [90% CI]**
Complete cure	16 (100.0) [82.9, 100.0]	9 (90.0) [60.6, 99.5]
Effective treatment	16 (100.0) [82.9, 100.0]	10 (100.0) [74.1, 100.0]
Mycological cure	16 (100.0) [82.9, 100.0]	10 (100.0) [74.1, 100.0]

Source: Applicant's CSR Table 22

7 Review of Safety

Safety Summary

Subjects were assessed for safety based on adverse event reporting at each evaluation. Standard safety laboratory and vital sign assessments were performed at baseline and on Day 21. There were no SAEs or deaths that occurred during the studies. Few adverse events were reported and no new safety signals were identified.

In the open-labelled, PK study, all subjects showed low but measurable levels of naftifine in plasma after topical application of Naftin Cream, 2%. No adverse events were reported in this 14 day trial.

No clinically meaningful trends were observed with respect to laboratory or vital signs findings in either trial.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety analysis for this supplemental application was primarily based on one randomized, controlled trial. The safety Evaluation Set (SES) includes all subjects exposed to the study medication at least once. The sponsor did not provide an integrated summary of safety for randomized control clinical trial 4024 and open-labelled clinical 4025. This did not impact safety analysis of adverse events because no adverse events were reported for the 27 subjects in trial 4025. All AE analysis is from the single study 4024.

Clinically meaningful trends were assessed in both trials with respect to laboratory or vital signs findings. Notable values for either trial will be discussed in the respective section below.

7.1.2 Categorization of Adverse Events

The incidence of AEs during the study period were coded and tabulated using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.0. Treatment-emergent adverse events (TEAEs) were defined as AEs with onset or a worsening of a pre-existing AE after the first administration of investigational product up to and including 14 days after last administration. Incidences of TEAEs were summarized based on the system organ class level and on the preferred term level (i.e., total and in percent, by intensity and by relationship). Incidence of TEAEs were summarized overall as well as after stratification by age group (2 <6 years and 6 to <12 years).

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

No pooling was conducted.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Subjects applied study drug topically to all affected areas plus a half-inch of surrounding skin affected by tinea corporis. The extent of exposure by treatment groups is in the table below.

Table 9: Exposure in Trial 4024 SES Population

Parameter	Naftin® Cream, 2% N=116	Vehicle N=115	Total N=231
Duration of Exposure (Days)			
N	116	115	231
Mean (SD)	14.7 (3.02)	15.3 (0.71)	15.0 (2.21)
Median	15.0	15.0	15.0
Min, Max	1, 20	14, 18	1, 20
Classified Duration of Exposure (Days), n (%)			
≤7 Days	5 (4.3)	0	5 (2.2)
>7 Days to ≤ 14 Days	1 (0.9)	2 (1.7)	3 (1.3)
>14 Days	110 (94.8)	113 (98.3)	223 (96.5)

N= Number of subjects in the treatment group and analysis set, SD = Standard Deviation, Min = minimum, Max = maximum, n = number of observations
Duration of Exposure [days] = (date of last study medication - date of first study medication) + 1
Source: Applicants CSR Table 15

The majority of subjects completed the 14 days of treatment and were exposed to Naftin cream, 2% at the proposed labeled dose and duration.

Trial 4025 demonstrated that systemic exposure in this pediatric population was lower than those observed in previous PK trials with Naftin Cream, 2% in pediatric subjects 13 to < 18 years of age or adults. See section 7.7. Thus, systemic safety can be supported by the previous clinical trials with Naftin, 2% cream

7.2.2 Explorations for Dose Response

See reviews of the original submission. This supplement does not provide additional information.

7.2.3 Special Animal and/or In Vitro Testing

See reviews of the original submission. This supplement does not provide additional information.

7.2.4 Routine Clinical Testing

Clinical laboratory assessments were performed at screening/baseline and on Day 21 and were to include the following parameters:

- Chemistry profile, including the following: total protein, albumin, blood urea nitrogen (BUN), creatinine, alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin, sodium, potassium, chloride, bicarbonate, calcium, magnesium, glucose, triglycerides, total cholesterol
- Complete blood count (CBC), including the following: hemoglobin, hematocrit, red blood cells (RBC), mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, total white blood cells (WBC), neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count
- Urinalysis (on-site dipstick), including: glucose, bilirubin, ketones, blood, pH, protein, urobilinogen, nitrite, and leucocytes. Abnormal on-site urine dipstick results will require a urinalysis, including microscopy, by the central laboratory
- Urine pregnancy (on-site kit) only on females of child-bearing potential (who started menarche)

7.2.5 Metabolic, Clearance, and Interaction Workup

See reviews of the original submission. This supplement does not provide additional information.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There were no TEAEs of special interest in this study.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported.

7.3.2 Nonfatal Serious Adverse Events

There were no serious adverse events reported.

7.3.3 Dropouts and/or Discontinuations

There were no significant TEAEs that led to study discontinuation.

7.3.4 Significant Adverse Events

There were no significant adverse events reported.

7.3.5 Submission Specific Primary Safety Concerns

There were no TEAEs of special interest in this study.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

There were a total of 17 AEs reported by 14 subjects. Adverse events reported were for common ailments like upper respiratory infections, fever, cough, dysmenorrhea, headache and abdominal pain. All TEAEs reported during the study were considered not related to study drug.

Table 10: Number (%) of subjects with TEAEs by SOC (≥ 1%) and PT

MedDRA System Organ Class Preferred Term	Naftin® Cream, 2% (N=116)		Vehicle (N=115)	
	n	(%)	n	(%)
Subjects with at least one TEAE	4	(3.4)	10	(8.7)
Infections and infestations	3	(2.6)	5	(4.3)
Nasopharyngitis	2	(1.7)	2	(1.7)
Upper respiratory tract infection	1	(0.9)	2	(1.7)
Pharyngitis bacterial	0	(0)	1	(0.9)
Nervous system disorders	0	(0)	2	(1.7)
Headache	0	(0)	2	(1.7)

Treatment emergent adverse events are defined as adverse events with on set or worsening on or after date of first dose of study treatment up to and including 30 days after the last dose is taken.
A subject with more than one TEAE within a SOC/Preferred Term was counted once in the SOC/Preferred Term.
Source: Sponsor's CSR Table 17

Reviewer's comment: No new adverse reactions were identified in the trial. The product is currently labeled for irritation, but there were no reports of irritation in the study. This reviewer concurs with the sponsor's assessment that the reported AEs are unlikely to be related to the study drug.

7.4.2 Laboratory Findings

Samples for safety laboratory were obtained at Screening/Baseline and Day 21. Lab values were considered based on comparison to the normal reference range provided. No clinically significant changes were seen at day 21. No TEAEs associated with laboratory abnormalities were reported after administration of Naftin (naftifine hydrochloride) Cream, 2%.

Hematology
Changes in hematology parameters were not clinically significant. There were no large decreases in hemoglobin (Hb)/ hematocrit (Hct) from baseline to Day 21. One naftin-treated subject, 180002-S1164, had an increase of Hb/Hct from 12.6/40.8 at baseline to 14.8/48 at Day 21. The reason for this increase is not clear, but similar increases were not seen in other subjects treated with Naftin cream. One vehicle-treated subject had an increase of Hb/Hct from 16.2/50.1 at baseline to 17.5/52.2 at Day 21.

Platelets counts were variable between baseline and Day 21, but the majority of subjects remained within the normal range. There were no clinically significant changes.

Although the protocol planned on an assessment of white blood cells, the data is not reported. Reversible agranulocytosis has been reported with the oral allylamine antifungal terbinafine. Naftin labeling includes agranulocytosis in the post-marketing section of labeling. While it may be useful to evaluate the effect that Naftin cream, 2% has on white blood cells in pediatric subjects, agranulocytosis was not reported in the original clinical trials and there were no reports of serious infections in this trial. Additionally, it would be unlikely to see a rare event like agranulocytosis in this small clinical trial.

Chemistry
No significant shifts in serum creatinine with the exception of subject180002-S1164, who had an increase from 0.57 mg/dL to 0.78 mg/dL at Day 21. Medical history for this 12 year old, black/ Hispanic male, who also had increases in his red cell count, was not reported.

Mild elevations in alkaline phosphate (ALP) were seen in subjects in both treatment arms. This is not unexpected in children as elevated levels of ALP are normally seen during growth spurts.

Transaminases did not show clinically significant increases >2x the upper limit of normal (ULN), with the exception of naftin-treated subject18001-S0066, who had an elevated ALT 3X ULN at both baseline and Day 21. Thus, the elevation is not related to treatment.

Urinalysis/ Pregnancy testing
No clinically relevant trends were noted on urinalysis. All urine pregnancy tests for women of childbearing potential were negative

7.4.3 Vital Signs

Vital signs, including pulse, systolic blood pressure (BP), and diastolic BP, were recorded at Screening/Baseline and Day 21. No clinically relevant trends were noted in the mean changes from baseline in pulse or blood pressure following treatment.

7.4.4 Electrocardiograms (ECGs)

ECGs were not performed.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

See reviews of the original submission. This supplement does not provide additional information.

7.5.2 Time Dependency for Adverse Events

The maximum exposure was 14 days and time dependency for AEs was not addressed. Other indications for which this product is approved have provided for a longer duration of exposure of Naftin cream, 2%.

7.5.3 Drug-Demographic Interactions

Too few AEs occurred in the trial to make any assessment regarding drug-demographic interactions.

7.5.4 Drug-Disease Interactions

Drug disease interaction was not explored.

7.5.5 Drug-Drug Interactions

See reviews of the original submission. This supplement does not provide additional information.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

See reviews of the original submission. This supplement does not provide additional information.

7.6.2 Human Reproduction and Pregnancy Data

This supplement does not provide additional pregnancy data. No pregnancies occurred in the submitted trials. A literature search to address the Pregnancy and Lactation Labeling Rule (PLLR) format in labeling was submitted and Merz found that there was no available nonclinical or clinical literature pertaining to the use of Naftin Cream, 2% in pregnant women. Additionally, a search of the sponsor's pharmacovigilance database shows that there are no reports of pregnant or lactating women who have been treated with Naftin Cream, 2%.The Division of Pediatrics and Maternal Health (DPMH) was consulted to review the PLLR proposed labeling. DPMH also conducted a search of published literature and found no reports of adequate and well-controlled studies of naftifine use in pregnant women.

7.6.3 Pediatrics and Assessment of Effects on Growth

Studies to evaluate pediatric subjects under the age of 2 were waived and this information was communicated in the 1/13/2012 approval letter which states the following:

- We are waiving the pediatric study requirement for ages 0 to 11 years 11 months for tinea pedis and tinea cruris, because too few children with the condition exist.
- We are waiving the pediatric study requirements for ages 0 to 1 year 11 months for tinea corporis, because too few children with the condition exist.

Deferral of studies evaluating pediatric subjects above the age of 2 were granted and these were incorporated into PREA postmarketing requirements as follows:

> **1857-1** PK/Safety/Tolerability study under maximal use conditions in subjects ages 12 years to 17 years 11 months with a minimum of at least 18 evaluable subjects with tinea pedis and tinea cruris towards the upper end of disease severity in the patient population.
>
> **1857-2** PK/Efficacy/Safety study in pediatric subjects ages 2 years to 17 years 11 months with tinea corporis.

PMR 1857-1 was fulfilled as Supplement 12 on 10/10/2014 and modifications were included in labeling.

The studies submitted with this supplement are to address PMR 1857-2. This product triggers PREA as a new indication and a partial waiver/ assessment was discussed at the Pediatric Review Committee (PeRC) on September 7, 2016.

Labeling was discussed at the meeting. See section 9 for additional information. PeRC Recommendations are as follows:

- The PeRC agreed with the plan for a partial waiver in pediatric patients < 2 years of age because studies are impossible or highly impractical and to the assessment of pediatric patients 2 to < 18 years of age.
- The PeRC recommended that the division consider whether the data from this study of tinea corporis in patients 2-11 years provides sufficient information to approve the product for use in patients with tinea pedis and tinea cruris in this age range as well.
- The PeRC recommended the division revise the waiver section of the PeRC template to represent all three indications or remove tinea pedis and tinea cruris from this section if the division would only be approving use for tinea corporis.

Reviewer comment: It is this reviewer's opinion that the data from the studies of tinea corporis in patients 2-11 years old in addition to the prior characterization of the product supports safe and effective use of Naftin cream, 2% in patients with tinea pedis and tinea cruris in this age range as well. Studies were conducted in children down to age 12 for approval of these indications. There were few young subjects due to lack of disease in these populations. Tinea pedis is more common in adolescents but rare in prepubertal children; adults and adolescents are affected by tinea cruris much more commonly than are children. Of these three tinea infections, tinea pedis is often the most difficult to treat and tinea cruris is likely to be associated with higher systemic levels due to increased absorption in the crural folds. It is unlikely that should tinea pedis occur in a pubertal 8 or 9 year old child, the product would be ineffective. Thus,

efficacy could be extrapolated into this younger population. Regarding safety, because systemic levels in the 2-11 year olds with tinea corporis treated under maximum use conditions was lower than the other indications, these studies do not provide data to support the potentially increased systemic levels achieved with treatment for tinea corporis. However, based on the safety profile for the product and the low likelihood of young children with the disease, it is reasonable to conclude that Naftin cream, 2% could be used safely in the treatment of tinea cruris in younger children.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

This was not assessed in this submission.

7.7 Additional Submissions / Safety Issues

The sponsor submitted results of the trial 4025, which evaluated the systemic exposure of naftifine following topical application of Naftin Cream 2% in 27 pediatric subjects (2 to < 12 years) with tinea corporis affecting at least 1% of body surface area (BSA).

The age demographics for the 27 subjects included 17 subjects in the 2 to < 6 years of age cohort (mean 4.1 years, range 2-5 years); and 10 subjects in the 6 to < 12 years of age cohort (mean 9.2 years, range 7-11 years). All subjects were of Hispanic ethnicity and all were classified as either of white (63%) or black (37%) race.

Naftin Cream, 2% was to be applied once daily under maximal use conditions for 14 days. The mean (standard deviation) actual dose amount of Naftin Cream, 2% applied in the younger and older cohorts was 1.6 (0.67) gram/day and 2.5 (0.61) gram/day, respectively. Pre-dose plasma PK samples were collected on Days 1, 12, 13, and 14. Only the older cohort had plasma PK assessment following the dose application on Day 1. Both cohorts had PK assessment following the dose application on Day 14.

Dr. Yanhui Lu reviewed the trial from a clinical pharmacology perspective and provides a cross-study comparison to other Naftin PK trials in her review. Dr. Lu's findings on the study are as follows:

> All subjects had measurable levels of naftifine in plasma. Steady-state was reached within the study period for both groups. Following a single dose on Day 1 in subjects 6 to < 12 years of age, the geometric mean (coefficient of variation or CV%) values of peak plasma concentration (Cmax) and area under the plasma concentration-time curve from time 0 to 24 hours (AUC0-24) were 3.60 (76.6%) ng/mL and 49.8 (64.4%) ng*h/mL, respectively. On Day 14 in this group, the Cmax and AUC0-24 were 3.31 (51.2%) ng/mL and 52.4 (49.2%) ng*h/mL, respectively. For the subjects 2 to < 6 years of age on Day 14, the Cmax and AUC0-24 were 3.98 (186%) ng/mL and 54.8 (150%) ng*h/mL, respectively. In the

older age group of patients 6 to < 12 years, the systemic exposures (both Cmax and AUC0-24) on Days 1 and 14 were similar. Although the dose applied in the younger group was less than that in the older group (mean(SD) dose of 1.6 (0.67) g/day versus 2.5 (0.61) g/day), the geometric mean plasma naftifine concentration-time profiles in the two groups were comparable on Day 14. The geometric mean values of Cmax and AUC0-24 were lower than those observed in previous trials where Naftin Cream, 2% was investigated with different skin conditions at higher daily doses in pediatric subjects 13 to < 18 years of age or adults. The cross-study comparison is shown in the table below.

Table 11: Cross-study Comparison of PK Results from Naftin cream, 2% Trials

Trial		**Previous Trial MUS90200/1023/0**		**Previous trial**	**Current Trial 4025**	
Age Group Name		***≥ 18***	***13- <18 yr***	***≥ 18***	***2 - <6 yr***	***6 - <12 yr***
Number of Evaluable Subjects		*6*	*22*	*21*	*17*	*10*
Mean Dose (SD), g/day		*7.5 (0.6)*	*8.2 (0.6)*	*6.4 (0.73)*	*1.6 (0.67)*	*2.5 (0.61)*
Day 1	**AUC_{0-24} (ng*h/mL)**	68.6 (95.4%)	138.3 (50.2%)	117 (41.2%)	-	49.8 (64.4%)
	C_{max} (ng/mL)	3.98 (83.0%)	9.21 (48.4%)	7 (55.6%)	-	3.60 (76.6%)
	T_{max} (h)	12.0 (8-24)	7.0 (2-24)	8.0 (4-24)	-	8.0 (4.0-24)
	Median (range) fe (%)	0.00143 (0.0003-0.0159)	0.00300 (0.0005-0.0648) (n=12)	0.0016 (0.00038-0.09080)	-	0.0029 (0.00073-0.0085)
Day 14	**AUC_{0-24} (ng*h/mL)**	124.6 (49.9%)	192.5 (74.9%)	204 (28.5%)	54.8 (150	52.4 (49.2%)
	C_{max} (ng/mL)	6.83 (51.3)	12.7 (67.2%)	11 (29.3%)	3.98 (186	3.31 (51.2%)
	T_{max} (h)	7.0 (6-24)	6.0 (2-12)	6.0 (0-16)	8.0 (4.0-24)	8.0 (4.0-12)
	Median (range) fe (%)	0.0025 (0.0006-0.0045)	0.0033 (0-0.041) (n=20)	0.0020 (0.00047-0.038)	-	0.0014 (0.000054-0.0062)

Safety was assessed by adverse event reporting and laboratory analyses in Trial 4025. None of the subjects experienced an adverse event. Samples for safety laboratories were obtained at Screening, Baseline, Day 14, and Day 21.

No clinically meaningful trends were observed with respect to laboratory or vital signs findings.

8 Postmarket Experience

There have been no issues identified in the sponsor's post-marketing reporting regarding the safety or effectiveness of naftifine HCl.

9 Appendices

9.1 Literature Review/References

1. Hurwitz Clinical Pediatric Dermatology: A Textbook of Skin Disorders of Childhood and Adolescence, Paller AS and Mancini A.J. Elsevier Health Sciences 5th edition Sep 25, 2015 p402-414.
2. Lesher JL. Tinea corporis. eMedicine from WebMD [Internet]. 2016 Aug 8. Available at: http://www.emedicine.com/derm/topic421.htm.

9.2 Labeling Recommendations

1 Indications and Usage
The sponsor proposes the following expansion of the indication (bold):

> *NAFTIN Cream is indicated for the treatment of: interdigital tinea pedis, tinea cruris, and tinea corporis caused by* ***dermatophytes such as*** *Trichophyton rubrum* ***in patients 2 years of age and older*****.**

These studies do not support treatment of other dermatophytes as implied in the sponsor's proposed language. The language should be similar to the currently approved indication:

> *NAFTIN Cream is indicated for the treatment of: interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organism Trichophyton rubrum.*

The patient labeling team is requesting that the division include the age range in the indication section. The PeRC also stated that the policy is changing to include the age range in the indication and given the absence of new safety concerns in the 2-11 year old patients, PeRC considered it reasonable to consider labeling naftifine cream for all three types of tinea in this age group.

The Division has determined that the indication will be kept consistent with the other naftifine HCl products that are approved for use in children and not prescribe the age in the indication section. Section 8 will provide additional information on the data available for the pediatric population and is recommended to be revised as follows:

> **8.4 Pediatric Use**
> The safety and effectiveness of NAFTIN Cream have been established in pediatric patients age 12 and above with with interdigital tinea pedis and tinea cruris and ages 2 and above with tinea corporis [see Clinical Studies (14)].

Use of NAFTIN Cream in theses age groups is supported by evidence from adequate and well controlled studies in adults and children, and with additional safety and PK data from two open label trials, conducted in 49 pediatric subjects ≥2 years of age who were exposed to NAFTIN Cream [see Clinical Studies (14) and Clinical Pharmacology (12.3)].

Safety and effectiveness of Naftin Cream in the treatment of tinea cruris and interdigital tinea pedis in pediatric patients less than 12 years of age have not been established. Safety and effectiveness of Naftin Cream in the treatment of tinea corporis in pediatric patients less than 2 years of age have not been established.

DPMH revised sections 8.1 and 8.2 of Naftin (naftifine) labeling for compliance with the PLLR and this reviewer concurs with the recommendations as follows:

8 Use in Specific Populations
8.1 Pregnancy
Risk Summary
There are no available data with NAFTIN Cream in pregnant women to inform the drug associated risk for major birth defects and miscarriage. In animal reproduction studies with pregnant rats, there were no adverse developmental effects observed with oral administration of naftifine hydrochloride during organogenesis at doses up to 18-times the maximum recommended human dose (MRHD). In animal reproduction studies with pregnant rats and rabbits, there were no adverse developmental effects with subcutaneous administration of naftifine hydrochloride during organogenesis at doses up to 2- and 4- times, respectively, the MRHD [see Data]. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15- 20%, respectively.

Data
Animal Data
Systemic embryofetal development studies were conducted in rats and rabbits. For the comparison of animal to human doses based on body surface area comparison (mg/m2), the MRHD is set at 8 g of NAFTIN 2% cream per day (2.67 mg/kg/day for a 60 kg individual). Oral doses of 30, 100 and 300 mg/kg/day naftifine hydrochloride were administered during the period of organogenesis to pregnant female rats. No treatment-related effects on embryofetal development were noted at doses up to 300 mg/kg/day (18- times MRHD). Subcutaneous doses of 10 and 30 mg/kg/day naftifine hydrochloride were administered during

the period of organogenesis to pregnant female rats. No treatment-related effects on embryofetal development were noted at 30 mg/kg/day (2-times MRHD). Subcutaneous doses of 3, 10 and 30 mg/kg/day naftifine hydrochloride were administered during the period of organogenesis to pregnant female rabbits. No treatment related effects on embryofetal development were noted at 30 mg/kg/day (4-times MRHD). A peri- and post-natal development study was conducted in rats. Oral doses of 30, 100 and 300 mg/kg/day naftifine hydrochloride were administered to female rats from gestational day 14 to lactation day 21. Reduced body weight gain of females during gestation and of the offspring during lactation was noted at 300 mg/kg/day (18-times MRHD). No developmental toxicity was noted at 100 mg/kg/day (6-times MRHD).

8.2 Lactation

Risk Summary

There is no information available on the presence of NAFTIN Cream in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. The lack of clinical data during lactation precludes a clear determination of the risk of NAFTIN Cream to an infant during lactation; therefore, the development and health benefits of breastfeeding should be considered along with the mother's clinical need for NAFTIN cream and any potential adverse effects on the breastfed infant from NAFTIN cream or from the underlying maternal condition.

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/s/

AMY S WOITACH
09/25/2016

DAVID L KETTL
09/26/2016