CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

019599Orig1s011

Trade Name:	NAFTIN
Generic or Proper Name:	naftifine hydrochloride
Sponsor:	Sebela Ireland LTD
Approval Date:	January 13, 2012
Indication:	NAFTIN (naftifine hydrochloride) Cream, 2 % is an allylamine antifungal indicated 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.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019599Orig1s011

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 019599/S-011

SUPPLEMENT APPROVAL

Merz Pharmaceuticals
Attention: Bhushan Hardas, MD, MBA
Vice President and Head of US Research and Development
4215 Tudor Lane
Greensboro, NC 27410

Dear Dr. Hardas:

Please refer to your Supplemental New Drug Application (sNDA) dated and received December 16, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for NAFTIN® (naftifine hydrochloride) Cream, 2%.

We acknowledge receipt of your amendments dated January 12, February 2, and 25, May 27, June 2, July 8, 12, 18, 27, and 29, August 1, 15, and 16, September 6, 21, and 22, October 3, 5, and 20, November 9, December 14, 22, and 28, 2011, and January 9, 10(2) and 11(2), 2012.

This "Prior Approval" supplemental new drug application provides for a change in strength and dosage.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container.

Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved NDA 019599/S-011**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

WAIVED

1. 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.

2. 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.

DEFERRED

1. We are deferring submission of your pediatric study for ages 12 years to 17 years 11 months for this application because the products is ready for approval in adults for the indications of tinea pedis and tinea cruris.

2. We are deferring submission of your pediatric study for ages 2 years to 17 years 11 months for this application because the product is ready for approval in adults for the indication of tinea corporis.

PREA POSTMARKETING REQUIREMENTS

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

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.

The timetable you submitted on December 22, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	07/2012
Study/Trial Completion:	07/2013
Final Report Submission:	12/2013

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

The timetable you submitted on December 22, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2012
Study/Trial Completion:	09/2013
Final Report Submission:	02/2014

Submit the protocol(s) to your IND 077530, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of carcinogenesis.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1857-3 A 2-year dermal rat carcinogenicity study.

The timetable you submitted on December 22, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/2012
Study Completion:	07/2015
Final Report Submission:	09/2016

Submit the protocol to your IND 077530, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

> Collect viscosity data from all available manufactured batches up to 24 months.
>
> The timetable you submitted on December 22, 2011 states that you will conduct this study according to the following schedule:
>
> Final Report Submission: 04/2013

Submit clinical protocols to your IND 077530 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

> Food and Drug Administration
> Center for Drug Evaluation and Research
> Division of Drug Marketing, Advertising, and Communications
> 5901-B Ammendale Road
> Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling

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

/s/

SUSAN J WALKER
01/13/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019599Orig1s011

<u>LABELING</u>

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NAFTIN® Cream, 2% safely and effectively.
See full prescribing information for NAFTIN (naftifine hydrochloride) Cream, 2%.

NAFTIN (naftifine hydrochloride) Cream, 2% for topical use
Initial U.S. Approval: 1988

----------INDICATIONS AND USAGE----------
NAFTIN (naftifine hydrochloride) Cream, 2% is an allylamine antifungal indicated 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. (1)

----------DOSAGE AND ADMINISTRATION----------
For topical use only. NAFTIN (naftifine hydrochloride) Cream, 2% is not for ophthalmic, oral, or intravaginal use. (2)

Appy a thin layer of NAFTIN (naftifine hydrochloride) Cream, 2% once-daily to the affected areas plus a ½ inch margin of healthy surrounding skin for 2 weeks. (2)

----------DOSAGE FORMS AND STRENGTHS----------
Cream: 2% (3)

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
If redness or irritation develops with the use of NAFTIN Cream, 2% treatment should be discontinued. (5.1)

----------ADVERSE REACTIONS----------
The most common adverse reaction (≥1%) is pruritus. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merz Pharmaceuticals, LLC at 877-743-8454 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 01/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

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Reference ID: 3070857

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NAFTIN (naftifine hydrochloride) Cream, 2% is indicated 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.

2 DOSAGE AND ADMINISTRATION

For topical use only. NAFTIN (naftifine hydrochloride) Cream, 2% is not for ophthalmic, oral or intravaginal use. Apply a thin layer of NAFTIN Cream, 2% once-daily to the affected areas plus a ½ inch margin of healthy surrounding skin for 2 weeks.

3 DOSAGE FORMS AND STRENGTHS

Cream: 2%, white to off-white cream

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Local Adverse Reactions

If irritation or sensitivity develops with the use of NAFTIN (naftifine hydrochloride) Cream, 2% treatment should be discontinued. Patients should be directed to contact their physician if these conditions develop following use of NAFTIN (naftifine hydrochloride) Cream, 2%.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

During clinical trials, 760 subjects were exposed to naftifine 1% and 2% cream formulations. A total of 421 subjects with tinea pedis and/or tinea cruris were treated with NAFTIN (naftifine hydrochloride) Cream, 2%. In two randomized, vehicle-controlled trials (400 patients were treated with NAFTIN (naftifine hydrochloride) Cream, 2%). The population was 12 to 88 years old, primarily male (79%), 48% Caucasian, 36% Black or African American, 40% Hispanic or Latino and had either predominantly interdigital tinea pedis or tinea cruris. Most subjects received doses once-daily, topically, for 2 weeks to cover the affected skin areas plus a ½ inch margin of surrounding healthy skin. In the two vehicle-controlled trials, 17.5% of NAFTIN (naftifine hydrochloride) Cream, 2% treated subjects experienced an adverse reaction compared with 19.3% of vehicle subjects. The most common adverse reaction (≥1%) is pruritus. Most adverse reactions were mild in severity. The incidence of Adverse Reactions in the NAFTIN Cream, 2% treated population were not significantly different than the vehicle treated population.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postmarketing use of (naftifine hydrochloride): redness/irritation, inflammation, maceration, swelling, burning, blisters, serous drainage, crusting, headache, dizziness, leukopenia, agranulocytosis. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. There are no adequate and well-controlled studies of NAFTIN (naftifine hydrochloride) Cream, 2% in pregnant women. Because animal reproduction studies are not always predictive of human response, NAFTIN (naftifine hydrochloride) Cream, 2% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The animal multiples of human exposure calculations were based on daily dose body surface area comparison (mg/m^2) for the reproductive toxicology studies described in this section and in Section 13.1. The Maximum Recommended Human Dose (MRHD) was set at 8 g 2% cream per day (2.67 mg/kg/day for a 60 kg individual).

Systemic embryofetal development studies were conducted in rats and rabbits. Oral doses of 30, 100 and 300 mg/kg/day naftifine hydrochloride were administered during the period of organogenesis (gestational days 6 – 15) to pregnant female rats. No treatment-related effects on embryofetal toxicity or teratogenicity were noted at doses up to 300 mg/kg/day (18.2X MRHD). Subcutaneous doses of 10 and 30 mg/kg/day naftifine hydrochloride were administered during the period of organogenesis (gestational days 6 – 15) to pregnant female rats. No treatment-related effects on embryofetal toxicity or teratogenicity were noted at 30 mg/kg/day (1.8X MRHD). Subcutaneous doses of 3, 10 and 30 mg/kg/day naftifine hydrochloride were administered during the period of organogenesis (gestational days 6 – 18) to pregnant female rabbits. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 30 mg/kg/day (3.6X 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 (18.2X MRHD). No developmental toxicity was noted at 100 mg/kg/day (6.1X MRHD).

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NAFTIN (naftifine hydrochloride) Cream, 2% is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. The number of pediatric patients ≥12 years of age studied were too small to adequately assess safety and efficacy.

8.5 Geriatric Use

Clinical studies of NAFTIN (naftifine hydrochloride) Cream, 2% did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Reference ID: 3070857

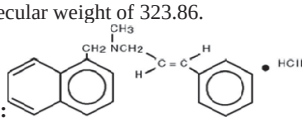
11 DESCRIPTION

NAFTIN (naftifine hydrochloride) Cream, 2% is a white to off-white cream for topical use only. Each gram of (naftifine hydrochloride) Cream contains 20 mg of naftifine hydrochloride, a synthetic allylamine antifungal compound.

Chemically, naftifine HCl is (E)-N-Cinnamyl-N-methyl-1-napthalenemethylamine hydrochloride.

The molecular formula is $C_{21}H_{21}N \cdot HCl$ with a molecular weight of 323.86.

The structural formula of naftifine hydrochloride is:



NAFTIN (naftifine hydrochloride) Cream, 2% contains the following inactive ingredients: benzyl alcohol, cetyl alcohol, cetyl esters wax, isopropyl myristate, polysorbate 60, purified water, sodium hydroxide, sorbitan monostearate, stearyl alcohol, and hydrochloric acid.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

NAFTIN (naftifine hydrochloride) Cream, 2% is a topical antifungal drug *[see Clinical Pharmacology(12.4)]*

12.2 Pharmacodynamics

The pharmacodynamics of NAFTIN (naftifine hydrochloride) Cream, 2% have not been established**.**

12.3 Pharmacokinetics

In vitro and *in vivo* bioavailability studies have demonstrated that naftifine penetrates the stratum corneum in sufficient concentration to inhibit the growth of dermatophytes.

The pharmacokinetics of NAFTIN Cream, 2% was evaluated following once-daily topical application for 2 weeks to twenty one adult subjects, both males and females, with both tinea pedis and tinea cruris. The median total amount of cream applied was 6.4 g (range 5.3-7.5 g) per day. The results showed that the systemic exposure (i.e. maximum concentration (Cmax) and area under the curve (AUC)) to naftifine increased over the 2 week treatment period in all the 21 subjects. Geometric Mean (CV%) AUC0-24 was 117 (41.2) ng*hr/mL on Day 1, and 204 (28.5) ng*hr/mL on Day 14. Geometric Mean (CV %) Cmax was 7 ng/mL (55.6) on Day 1 and 11 ng/mL (29.3) on day 14. Median Tmax was 8.0 hours on Day 1 (range: 4 to 24) and 6.0 hours on Day 14 (range: 0 to 16). Accumulation after 14 days of topical application was less than two fold. Trough concentrations generally increased throughout the 14 day study period. Naftifine continued to be detected in plasma in 13/21 (62%) subjects on day 28, the mean (SD) plasma concentrations were 1.6 ± 0.5 ng/mL (range below limit of quantitation (BLQ) to 3 ng/mL).

In the same pharmacokinetic study conducted in patients with tinea pedis and tinea cruris, median fraction of the dose excreted in urine during the treatment period was 0.0016% on Day 1 versus 0.0020% on Day 14.

12.4 Microbiology

Although the exact mechanism of action against fungi is not known, naftifine hydrochloride appears to interfere with sterol biosynthesis by inhibiting the enzyme squalene 2, 3-epoxidase.This inhibition of enzyme activity results in decreased amounts of sterols, especially ergosterol, and a corresponding accumulation of squalene in the cells.

Naftifine has been shown to be active against most isolates of the following fungi, both in vitro and in clinical infections, as described in the INDICATIONS AND USAGE section:

Trichophyton rubrum

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies to evaluate the carcinogenic potential of NAFTIN (naftifine hydrochloride) Cream, 2% have not been performed.

Naftifine hydrochloride revealed no evidence of mutagenic or clastogenic potential based on the results of two *in vitro* genotoxicity tests (Ames assay and Chinese hamster ovary cell chromosome aberration assay) and one *in vivo* genotoxicity test (mouse bone marrow micronucleus assay).

Oral administration of naftifine hydrochloride to rats, throughout mating, gestation, parturition and lactation, demonstrated no effects on growth, fertility or reproduction, at doses up to 100 mg/kg/day (6.1X MRHD).

Reference ID: 3070857

14 CLINICAL STUDIES

14.1 Tinea Cruris

NAFTIN (naftifine hydrochloride) Cream, 2% has been investigated for safety and efficacy in a randomized, double-blind, vehicle-controlled, multi-center study in 146 subjects with symptomatic and dermatophyte culture positive tinea cruris. Subjects were randomized to receive (naftifine hydrochloride)Cream or vehicle. Subjects applied the study agent (naftifine hydrochloride) Cream or vehicle) to the affected area plus a ½-inch margin of healthy skin surrounding the affected area once-daily for 2 weeks. Signs and symptoms of tinea cruris (presence or absence of erythema, pruritus, and scaling) were assessed, and KOH examination and dermatophyte culture were performed at the primary efficacy endpoint at week 4.

The mean age of the study population was 47 years and 87% were male and 43% were white. At baseline, subjects were confirmed to have signs and symptoms of tinea cruris, positive KOH exam, and confirmed dermatophyte presence based on culture results from a central mycology laboratory. The analysis of the intent-to-treat population was a comparison of the proportions of subjects with a complete cure at the week 4 visit (see Table 2). Complete cure was defined as both clinical cure (absence of erythema, pruritus, and scaling) and mycological cure (negative KOH and dermatophyte culture).

The percentage of subjects experiencing clinical cure and the percentage of subjects experiencing mycological cure at week 4 are presented individually in Table 1 below

Table 1 Efficacy Results for Pivotal Tinea Cruris Trial (Week 4 Assessment)

Endpoint	NAFTIN (naftifine hydrochloride) Cream, 2% N=75	VehicleN=71
Complete Cure[a]	19(25%)	2(3%)
Effective Treatment [b]	45(60%)	7(10%)
Mycological Cure[c]	54(72%)	11(16%)

a Complete cure is a composite endpoint of both mycological cure and clinical cure
Clinical cure is defined as the absence of erythema, pruritus, and scaling (grade of 0)
b Effective treatment is a negative KOH preparation and negative dermatophyte culture, erythema, scaling, and pruritus grades of 0 or 1 (absent or nearly absent)
c Mycological cure is defined as negative KOH and dermatophyte culture

14.2 Interdigital Tinea Pedis

NAFTIN (naftifine hydrochloride)Cream, 2% has been investigated for efficacy in a randomized, double-blind, vehicle-controlled, multi-center study in 216 subjects with symptomatic and dermatophyte culture positive tinea pedis. Subjects were randomized to receive NAFTIN (naftifine hydrochloride)Cream, 2% or vehicle. Subjects applied the study agent (naftifine hydrochloride)cream or vehicle) to the affected area of the foot plus a ½-inch margin of healthy skin surrounding the affected area once-daily for 2 weeks. Signs and symptoms of tinea pedis (presence or absence of erythema, pruritus, and scaling) were assessed and KOH examination and dermatophyte culture was performed at the primary efficacy endpoint at week 6.

The mean age of the study population was 42 years and 71% were male and 57% were white. At baseline, subjects were confirmed to have signs and symptoms of tinea pedis, positive KOH exam, and confirmed dermatophyte culture. The primary efficacy endpoint was the proportions of subjects with a complete cure at the week 6 visit (see Table 3). Complete cure was defined as both a clinical cure (absence of erythema, pruritus, and scaling) and mycological cure (negative KOH and dermatophyte culture).

The efficacy results at week 6, four weeks following the end of treatment, are presented in Table 3 below. Naftin Cream demonstrated complete cure in subjects with interdigital tinea pedis, but complete cure in subjects with only moccasin type tinea pedis was not demonstrated.

Table 2 Efficacy Results for Pivotal Tinea Pedis Trial (Week 6 Assessment)

Endpoint	NAFTIN (naftifine hydrochloride) Cream, 2% N=147	Vehicle N=70
Complete Cure[a]	26(18%)	5(7%)
Effective Treatment [b]	83(57%)	14(20%)
Mycological Cure[c]	99(67%)	15(21%)

a Complete cure is a composite endpoint of both mycological cure and clinical cure
Clinical cure is defined as absence of erythema, pruritus, and scaling (grade of 0)
b Effective treatment is a negative KOH preparation and negative dermatophyte culture, erythema, scaling, and pruritus grades of 0 or 1 (absent or near absent)
c Mycological cure is defined as negative KOH and dermatophyte culture

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

NAFTIN (naftifine hydrochloride) Cream, 2% is a white to off-white cream supplied in collapsible tubes in the following sizes:
30g – NDC 0259-1102-30
45g – NDC 0259-1102-45
60g – NDC 0259-1102-60

Storage
Store NAFTIN (naftifine hydrochloride) Cream, 2% at 25 C (77 F); excursions permitted to 15-30 C (59-86 F) *[see USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION

Reference ID: 3070857

- Inform patients that NAFTIN (naftifine hydrochloride) Cream, 2% is for topical use only. NAFTIN (naftifine hydrochloride) Cream, 2% is not intended for intravaginal or ophthalmic use.
- If irritation or sensitivity develops with the use of NAFTIN (naftifine hydrochloride) Cream, 2% treatment should be discontinued and appropriate therapy instituted. Patients should be directed to contact their physician if these conditions develop following use of NAFTIN (naftifine hydrochloride) Cream, 2%.

NAFTIN (naftifine hydrochloride) Cream, 2% is manufactured for Merz Pharmaceuticals, LLC, Greensboro, NC 27410
NAFTIN (naftifine hydrochloride) Cream, 2% is a registered trademark of Merz Pharmaceuticals, LLC

Reference ID: 3070857

Reference ID: 3070857

CAP END
OPEN END
4 7/8" TUBE LENGTH
NDC 0259-1102-30
NAFTIN®
(Naftifine Hydrochloride) Cream, 2%
For Topical Use Only
Not for Ophthalmic Use, Oral or Intravaginal Use
30g
Rx Only
Active Ingredient: naftifine hydrochloride
Inactive Ingredients: benzyl alcohol; cetyl alcohol; cetyl esters wax; isopropyl myristate; polysorbate 60; purified water; sodium hydroxide; sorbitan monostearate; and stearyl alcohol. Hydrochloric acid may be added to adjust pH. Dosage: Refer to accompanying package insert for complete prescribing information. Storage: Store Naftin (naftifine hydrochloride) Cream at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Manufactured for:
Meiji Pharmaceuticals, LLC
Greensboro NC 27410
Expiration date 00 00
Lot Number 0000000000
FPO

(b) (4)

Aluminum / Die Line

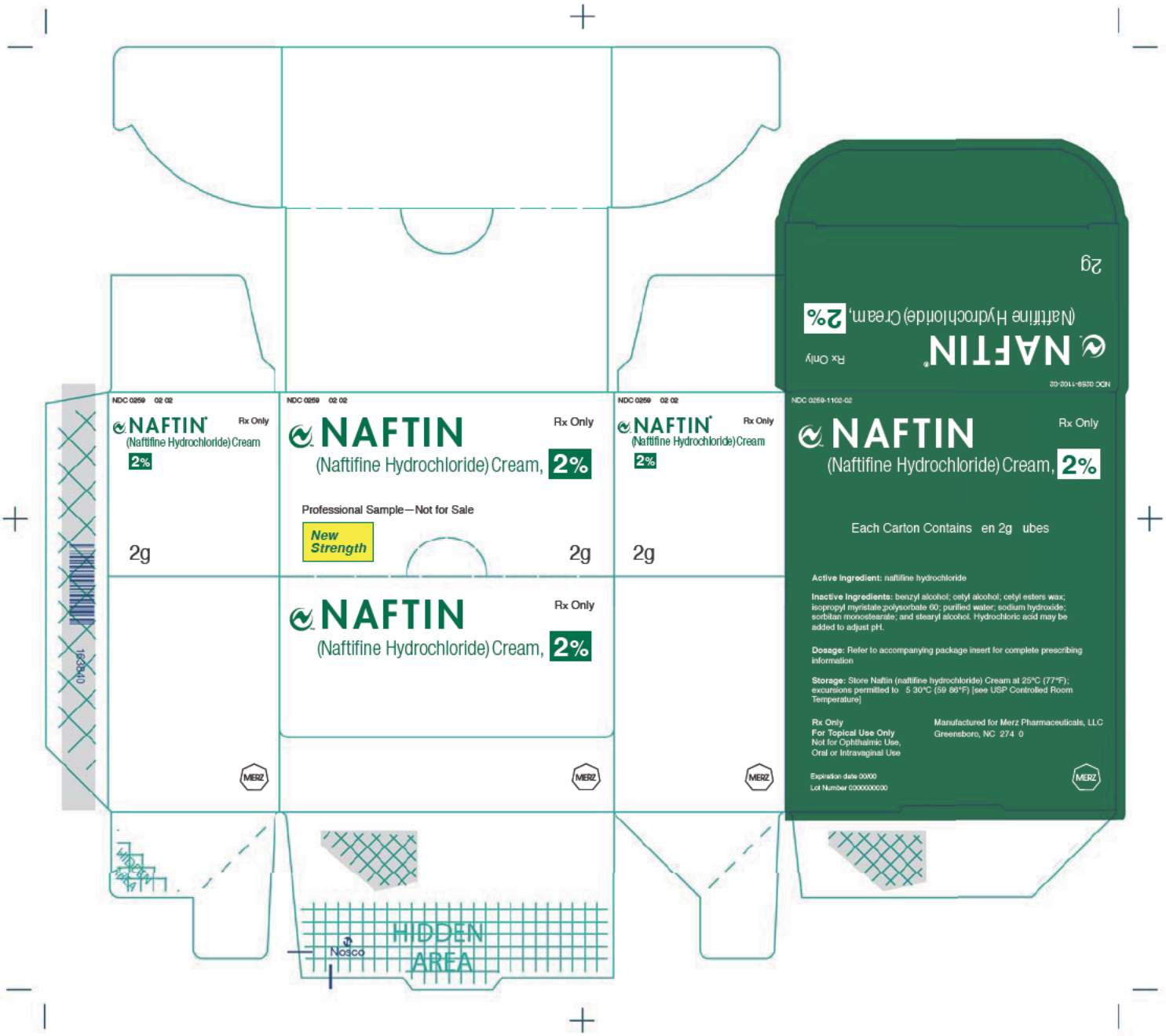
Customer Name – Product Name – (b) (4)
July 29, 2011 – Dimensions: 1 1/8" x 5"

Please Note:
Free Copy Area for Crimp, Eyemark Location/Colour and Bare Metal, are most common values supplied, please verify with your filler for accurate dimensions/location.

Colours - Plates

PMS XXX	PMS XXX	PMS XXX	PMS XXX	PMS XXX

CAP END
SHOULDER
FREE COPY AREA
5 1/2"
TUBE
LENGTH
FREE COPY AREA OR CRIMP
EYE MARK LOCATION
SEAL WELL
OPEN END
NDC 0259-1102-60
NAFTIN®
60g
(Naftifine Hydrochloride) Cream, 2%
R Only
For Topical Use Only
Not for Ophthalmic Use, Oral or Intravaginal Use
MERZ
Active Ingredient: naftifine hydrochloride
Inactive Ingredients: benzyl alcohol; cetyl a cohol; cetyl esters wax; isopropyl myristate; polysorbate 60; purified water; sodium hydroxide; sorb tan monostearate; and stearyl alcohol. Hydrochloric acid may be added o adjust pH.
Dosage: Refer to accompanying package insert for complete prescribing information.
Storage: Store Naftin (naftifine hydrochloride) Cream at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
FPO
Manufactured for
Merz Pharmaceuticals, LLC
Greensboro NC 27410
Expiration date 00/00
Lot Number 0000000000


NDC 0259 02 02
NAFTIN
Rx Only
(Naftifine Hydrochloride) Cream
2%
2g
NDC 0259 02 02
NAFTIN
Rx Only
(Naftifine Hydrochloride) Cream, 2%
Professional Sample—Not for Sale
New Strength
2g
NDC 0259 02 02
NAFTIN
Rx Only
(Naftifine Hydrochloride) Cream
2%
2g
NAFTIN
Rx Only
(Naftifine Hydrochloride) Cream, 2%
MERZ
MERZ
MERZ
HIDDEN AREA
Nosco
NDC 0259-1102-02
NAFTIN
Rx Only
(Naftifine Hydrochloride) Cream, 2%
2g
NDC 0259-1102-02
NAFTIN
Rx Only
(Naftifine Hydrochloride) Cream, 2%
Each Carton Contains en 2g ubes
Active Ingredient: naftifine hydrochloride
Inactive Ingredients: benzyl alcohol; cetyl alcohol; cetyl esters wax; isopropyl myristate;polysorbate 60; purified water; sodium hydroxide; sorbitan monostearate; and stearyl alcohol. Hydrochloric acid may be added to adjust pH.
Dosage: Refer to accompanying package insert for complete prescribing information
Storage: Store Naftin (naftifine hydrochloride) Cream at 25°C (77°F); excursions permitted to 5 30°C (59 86°F) [see USP Controlled Room Temperature]
Rx Only
For Topical Use Only
Not for Ophthalmic Use, Oral or Intravaginal Use
Manufactured for Merz Pharmaceuticals, LLC
Greensboro, NC 274 0
Expiration date 00/00
Lot Number 0000000000
MERZ

Reference ID: 3070857

NDC 0259-1102-30

NAFTIN®

(Naftifine Hydrochloride) Cream, 2%

For Topical Use Only
Not for Ophthalmic Use, Oral or Intravaginal Use

New Strength

30g
Rx Only

NDC 0259-1102-30

NAFTIN®
(Naftifine Hydrochloride) Cream, 2%

Active Ingredient: naftifine hydrochloride
Inactive Ingredients: benzyl alcohol; cetyl alcohol; cetyl esters wax; isopropyl myristate; polysorbate 60; purified water; sodium hydroxide; sorbitan monostearate; and stearyl alcohol. Hydrochloric acid may be added to adjust pH.
Dosage: Refer to accompanying package insert for complete prescribing information.
Storage: Store Naftin (naftifine hydrochloride) Cream at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

NDC 0259-1102-30

NAFTIN®

(Naftifine Hydrochloride) Cream, 2%

For Topical Use Only
Not for Ophthalmic Use, Oral or Intravaginal Use

New Strength

30g
Rx Only

NDC 0259-1102-30

3 02594 77090 2

Manufactured for Merz Pharmaceuticals, LLC, Greensboro, NC 27410

NDC 0259-1102-30
NAFTIN®
(Naftifine HCl) Cream, 2%
30g

NDC 0259-1102-30
NAFTIN®
(Naftifine HCl) Cream, 2%
Expiration date 00/00
Lot Number 0000000000
30g

NDC 0259-1102-45

NAFTIN®

(Naftifine Hydrochloride) Cream, 2%

New Strength

45g

Rx Only

For Topical Use Only

Not for Ophthalmic Use, Oral or Intravaginal Use

MERZ

NDC 0259-1102-45

NAFTIN®

(Naftifine Hydrochloride) Cream, 2%

Active Ingredient: naftifine hydrochloride

Inactive Ingredients: benzyl alcohol; cetyl alcohol; cetyl esters wax; isopropyl myristate; polysorbate 60; purified water; sodium hydroxide; sorbitan monostearate; and stearyl alcohol. Hydrochloric acid may be added to adjust pH.

Dosage: Refer to accompanying package insert for complete prescribing information.

Storage: Store Naftin (naftifine hydrochloride) Cream at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

MERZ

NDC 0259-1102-45

NAFTIN®

(Naftifine Hydrochloride) Cream, 2%

New Strength

45g

Rx Only

For Topical Use Only

Not for Ophthalmic Use, Oral or Intravaginal Use

MERZ

NDC 0259-1102-45

3 02594 77090 2

MERZ

Manufactured for Merz Pharmaceuticals, LLC, Greensboro, NC 27410

NDC 0259-1102-45

NAFTIN®

(Naftifine HCl) Cream, 2%

45g

MERZ

NDC 0259-1102-45

NAFTIN®

(Naftifine HCl) Cream, 2%

45g

MERZ

Expiration date 00/00

Lot Number 0000000000

Reference ID: 3070857

NDC 0259-1102-60

NAFTIN®

(Naftifine Hydrochloride) Cream, 2%

New Strength

60g

Rx Only

For Topical Use Only

Not for Ophthalmic Use, Oral or Intravaginal Use

MERZ

NDC 0259-1102-60

NAFTIN®

(Naftifine Hydrochloride) Cream, 2%

Active Ingredient: naftifine hydrochloride

Inactive Ingredients: benzyl alcohol; cetyl alcohol; cetyl esters wax; isopropyl myristate; polysorbate 60; purified water; sodium hydroxide; sorbitan monostearate; and stearyl alcohol. Hydrochloric acid may be added to adjust pH.

Dosage: Refer to accompanying package insert for complete prescribing information.

Storage: Store Naftin (naftifine hydrochloride) Cream at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

NDC 0259-1102-60

NAFTIN®

(Naftifine Hydrochloride) Cream, 2%

New Strength

60g

Rx Only

For Topical Use Only

Not for Ophthalmic Use, Oral or Intravaginal Use

NDC 0259-1102-60

3 02594 77090 2

Manufactured for Merz Pharmaceuticals, LLC, Greensboro, NC 27410

NDC 0259-1102-60

NAFTIN®

(Naftifine HCl) Cream, 2%

60g

Expiration date 00/00

Lot Number 0000000000

NDC 0259-1102-60

NAFTIN®

(Naftifine HCl) Cream, 2%

60g

Reference ID: 3070857

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019599Orig1s011

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	January 12th, 2012
From	Susan J. Walker, M.D., F.A.A.D.
Subject	Division Director Summary Review
NDA/Supplement #	NDA 19-599/ S-011
Applicant Name	Merz Pharmaceuticals
Date of Submission	December 16th, 2011
PDUFA Goal Date	January 16th, 2012
Proprietary Name / Established (USAN) Name	Naftifine hydrochloride/Naftin Cream
Dosage Forms / Strength	Cream 2%
Proposed Indication(s)	1. Tinea Pedis 2. Tinea Corporis 3. Tinea Cruris
Action	**Approval**

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Cross Discipline Team Leader	David Kettl, MD
Medical Officer Review	Brenda Vaughan, MD
Statistical Review	Carin Kim, PhD
Pharmacology Toxicology Review	Jianyong Wang, PhD
CMC Review/OBP Review	Jean Salemme, PhD
Microbiology Review	Kerry Snow, PhD
Clinical Pharmacology Review	Abimbola Adebowale, PharmD
DDMAC	Lynn Panholzer, PharmD
DSI	Roy Blay, PhD
CDTL Review	David Kettl, MD
OSE/DMEPA	Loretta Holmes, BSN, PharmD
ONDQA/Biopharmaceutics	Deepika Arora Lakhani, PhD
QT/IRT	Joanne Zhang, PhD

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Reference ID: 3071813

Signatory Authority Review

1. Introduction

Naftifine hydrochloride is the active ingredient of Naftin 1% Cream, approved in February 1988 under NDA 19599, and Naftin 1% Gel, approved in June 1990 under NDA 19356, for the treatment of tinea pedis, tinea cruris, and tinea corporis.

The applicant, Merz Pharmaceuticals, submitted this NDA supplement for a new 2% cream formulation, and proposes a shorter dosing regimen for naftifine hydrochloride cream 2% (b) (4) (b) (4) to provide a shorter treatment compared to the currently marketed Naftin 1% Cream product. Naftifine Cream, 2% is proposed to be applied once-daily in patients aged 12 years and older for 2 weeks.

This review documents my concurrence with the recommendation of the review team for approval. The Cross Discipline Team Leader, Dr David Kettl, has summarized the team conclusions and recommendations in his review, and this review will borrow extensively from his document.

2. Background

Naftifine hydrochloride is a synthetic allylamine derivative. The exact mechanism of antifungal action of naftifine is unknown, but investigations suggest the antifungal activity of naftifine hydrochloride is related to its inhibition of squalene epoxidase in dermatophytes, leading to an accumulation of intracellular lipids that ultimately results in irreversible damage to the fungal cell wall. The applicant has performed no new studies regarding the mechanism of action of naftifine.

Reference ID: 3071813

When Naftin Cream 1% was developed in the 1980's, applicants were not required to separately assess the various types of tinea pedis. Distinctions between interdigital and moccasin type tinea pedis were not generally made in clinical trials in that era. This applicant was advised of the need to specify definitive inclusion/exclusion criteria for different types of tinea pedis in their development program as early as the preIND meeting on November 6, 2007, and the need to provide a pre-specified statistical analysis plan for the different tinea pedis types.

3. CMC/Device

The applicant's proposed viscosity acceptance criterion, (b) (4) cps, was deemed acceptable as an interim specification. The applicant will be asked to collect viscosity data from all available manufactured batches during the first 12 months after the supplement (S011) approval date. Within 15 months after the S-011 approval date, the applicant will be required to submit the final viscosity report, with complete viscosity information/data and a proposal for their final viscosity specification. The January 11th, 2012 CMC review refers to the December 22nd 2011 amendment providing for final agreement on this postmarketing commitment.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were determined to be acceptable. Stability testing supports an expiry of 24 months.

The carton and container labeling is recommended as acceptable and the supplement is recommended for Approval.

4. Nonclinical Pharmacology/Toxicology

The application includes information necessary for approval. Data that describe the carcinogenicity of the drug substance are appropriate in support of labeling of products that are intended for chronic use (see the ICH S1A document, "The Need for Long-term Rodent Carcinogenicity Studies of Pharmaceuticals"). These data may be submitted post-approval, and will be incorporated into the label at that time.
I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Reference ID: 3071813

The primary conclusion of the clinical microbiology review, by Dr. Kerry Snow, is that [redacted] (b) (4) current labeling standards should be observed regarding the mechanism of action section. I concur with the recommendations and conclusions reached by the clinical microbiology reviewer.

7. Clinical/Statistical-Efficacy

The applicant has provided adequate information to support the approval of naftifine 2% for use as described in the final approved labeling.

Tinea Cruris

NAFTIN (naftifine hydrochloride) Cream, 2% has been investigated for safety and efficacy in a randomized, double-blind, vehicle-controlled, multi-center study in 146 subjects with symptomatic and dermatophyte culture positive tinea cruris. Subjects were randomized to receive (naftifine hydrochloride) Cream or vehicle. Subjects applied the study agent (naftifine hydrochloride) Cream or vehicle) to the affected area plus a ½-inch margin of healthy skin surrounding the affected area once-daily for 2 weeks. Signs and symptoms of tinea cruris (presence or absence of erythema, pruritus, and scaling) were assessed and KOH and dermatophyte culture were performed at the primary efficacy endpoint at week 4.

The mean age of the study population was 47 years and 87% were male and 43% were white. At baseline, subjects were confirmed to have signs and symptoms of tinea cruris, positive KOH exam, and confirmed dermatophyte presence based on culture results from a central mycology laboratory. The analysis of the intent-to-treat population was a comparison of the proportions of subjects with a complete cure at the week 4 visit (see Table 1). Complete cure was defined as both clinical cure (absence of erythema, pruritus, and scaling) and mycological cure (negative KOH and dermatophyte culture).

The percentage of subjects experiencing clinical cure and the percentage of subjects experiencing mycological cure at week 4 are presented individually in Table 1 below.

Table 1 Efficacy Results for Tinea Cruris Trial (Week 4 Assessment)

Endpoint	NAFTIN (naftifine hydrochloride) Cream, 2% N=75	Vehicle N=71
Complete Cure (a)	19(25%)	2(3%)
Effective Treatment (b)	45(60%)	7(10%)
Mycological Cure (c)	54(72%)	11(16%)

a. Complete cure is a composite endpoint of both mycological cure and clinical cure. Clinical cure is defined as the absence of erythema, pruritus, and scaling (grade of 0).
b. Effective treatment is a negative KOH preparation and negative dermatophyte culture, erythema, scaling, and pruritus grades of 0 or 1 (absent or nearly absent).
c. Mycological cure is defined as negative KOH and dermatophyte culture.

Reference ID: 3071813

Interdigital Tinea Pedis

NAFTIN (naftifine hydrochloride) Cream, 2% has been investigated for efficacy in a randomized, double-blind, vehicle-controlled, multi-center study in 216 subjects with symptomatic and dermatophyte culture positive tinea pedis. Subjects were randomized to receive NAFTIN (naftifine hydrochloride) Cream, 2% or vehicle. Subjects applied the study agent (naftifine hydrochloride) cream or vehicle) to the affected area of the foot plus a ½-inch margin of healthy skin surrounding the affected area once-daily for 2 weeks. Signs and symptoms of tinea pedis (presence or absence of erythema, pruritus, and scaling) were assessed and dermatophyte culture was performed at the primary efficacy endpoint at week 6.

The mean age of the study population was 42 years and 71% were male and 57% were white. At baseline, subjects were confirmed to have signs and symptoms of tinea pedis, positive KOH exam, and confirmed dermatophyte culture. The primary efficacy endpoint was the proportions of subjects with a complete cure at the week 6 visit (see Table 3). Complete cure was defined as both a clinical cure (absence of erythema, pruritus, and scaling) and mycological cure (negative KOH and dermatophyte culture).

The efficacy results at week 6, four weeks following the end of treatment, are presented in Table 2 below. Naftin Cream demonstrated complete cure in subjects with interdigital tinea pedis, but complete cure in subjects with only moccasin type tinea pedis was not demonstrated.

Table 2 Efficacy Results for Pivotal Tinea Pedis Trial (Week 6 Assessment)

Endpoint	NAFTIN (naftifine hydrochloride) Cream, 2% N=147	Vehicle N=70
Complete Cure (a)	26(18%)	5(7%)
Effective Treatment (b)	83(57%)	14(20%)
Mycological Cure ©	99(67%)	15(21%)

a. Complete cure is a composite endpoint of both mycological cure and clinical cure. Clinical cure is defined as absence of erythema, pruritus, and scaling (grade of 0).
b. Effective treatment is a negative KOH preparation and negative dermatophyte culture, erythema, scaling, and pruritus grades of 0 or 1 (absent or near absent).
c. Mycological cure is defined as negative KOH and dermatophyte culture.

8. Safety

A total of 421 patients were exposed to naftifine 2% cream during the clinical development program. Naftifine cream has been approved at the 1% concentration since 1988, and risks associated with its use have been low. There were no deaths in the naftifine cream 2% trials, and I concur that the serious adverse event of “influenza” is unlikely to be related to study drug. The incidence of adverse reactions in the naftifine 2% cream treated population was not significantly different than the vehicle treated population.

Reference ID: 3071813

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

The Pediatric Research Equity Act requires all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens to contain an assessment of the safety and effectiveness of the pediatric patients across all relevant populations unless this requirement is waived or deferred. The pediatric plan is lacking in this application, and the Pediatric Review Committee (PeRC) provided the following recommendations.

Waivers and Deferrals:

- The pediatric study requirement for ages 0 to 11 years 11 months for tinea pedis and tinea cruris are waived, because too few children with the condition exist.
- The pediatric study requirements for ages 0 to 1 year 11 months for tinea corporis are waived because too few children with the condition exist.
- The pediatric study for ages 12 years to 17 years 11 months for this application are deferred because the products is ready for approval in adults for the indications of tinea pedis and tinea cruris
- The pediatric study for ages 2 years to 17 years 11 months for this application are deferred because the product is ready for approval in adults for the indication of tinea corporis.

PREA Postmarketing Requirements:

• PREA post-marketing requirement for a PK/Efficacy/Safety study in pediatric patients 2 years and above with tinea corporis.

• PREA post-marketing requirement for a pharmacokinetic study of NAFT-500 cream in adolescents aged 12-17 years old with tinea pedis and tinea cruris.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

Reference ID: 3071813

Labeling discussion including proprietary name, physician's labeling, carton/container labeling and patient labeling have been concluded.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action
  - The product will be approved with final labeling as concurred by the agency and applicant.

- Risk Benefit Assessment
  - The benefits of this product outweigh the risk when used as recommended in the prescribing information.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  - None

- Recommendation for other Postmarketing Requirements and Commitments

  - Postmarketing Commitment:

1. Collect viscosity data from manufactured batches up to 24 months. Provide a report with complete viscosity information/data and a proposal for final viscosity specifications by April 2013.

  - Postmarketing Requirements

1. Conduct a pharmacokinetic (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.

The timetable submitted on December 22, 2011 provides the following schedule:

Final Protocol Submission: 07/2012
Study/Trial Completion: 07/2013
Final Report Submission: 12/2013

2. Conduct a pharmacokinetic (PK)/Efficacy/Safety study in pediatric subjects ages 2 years to 17 years 11 months with tinea corporis.

The timetable submitted on December 22, 2011 provides the following schedule:

Final Protocol Submission: 09/2012
Study/Trial Completion: 09/2013

Reference ID: 3071813

Final Report Submission: 02/2014

3. Conduct a 2-year dermal rat carcinogenicity study. The timetable submitted on December 22, 2011 provides the following schedule:

Final Protocol Submission: 12/2012
Study Completion: 07/2015
Final Report Submission: 09/2016

Reference ID: 3071813

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

/s/

SUSAN J WALKER
01/13/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019599Orig1s011

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application 019599/011

The following officers or employees of FDA participated in the decision to approve this application and consent to be identified:

Abimbola Adebowale
Bashaw, Edward
Bates, Doris
Chan, Irene
David, Jeannie
Delasko, Jeanne
Fiszman, Monica
Hill, Barbara
Holmes, Loretta
Kettl, David
Kim, Carin
Marsik, Frederic
Salemme, Jean
Snow, Kerry
Stockbridge, Norman
Tran, Doanh
Walker, Susan
Wang, Jianyong
Zhang, Joanne
Zhu, Hao

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019599Orig1s011

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	November 10, 2011
From	David Kettl, MD, FAAP
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 19-599 Supplement S-011
Applicant	Merz Pharmaceuticals
Date of Submission	December 16, 2011
PDUFA Goal Date	January 16, 2012
Proprietary Name / **Established (USAN) names**	Naftifine hydrochloride Naftin Cream
Dosage forms / Strength	Cream
Proposed Indication(s)	1. Tinea pedis 2. Tinea cruris 3. Tinea corporis
Recommended:	*Approval*

1. Introduction

Naftifine hydrochloride is the active ingredient of Naftin 1% Cream, approved in February 1988 under NDA 19599, and Naftin 1% Gel, approved in June 1990 under NDA 19356, for the treatment of tinea pedis, tinea cruris, and tinea corporis.

The applicant, Merz Pharmaceuticals, submitted this NDA supplement for a new 2% cream formulation, and proposes a shorter dosing regimen for naftifine hydrochloride cream 2% (b) (4) (b) (4) to provide a shorter treatment compared to the currently marketed Naftin 1% Cream product. Naftifine Cream, 2% is proposed to be applied once-daily in patients aged 12 years and older for 2 weeks.

The proposed indication for Naftifine Cream, 2 % is for "the topical treatment of tinea pedis, tinea cruris, and tinea corporis in patients 12 years and older. Naftin Cream 2% is proposed to be applied topically onto affected areas plus a ½ inch margin of healthy surrounding skin once-daily for 2 weeks."

The applicant stated that production of Naftin Cream, 1% will be discontinued upon approval of this application for naftifine cream, 2%.

The sponsor is also developing NAFT-600 (naftifine hydrochloride) 2% *gel* for the treatment of tinea pedis under IND 105603. An NDA application is expected in 2012 for this gel product.

Reference ID: 3043289

The clinical review, by Dr. Brenda Vaughan, recommends an approval action for the treatment (b) (4) of interdigital tinea pedis, tinea cruris, and tinea corporis in adults, (b) (4), and safety and efficacy in pediatric subjects was not demonstrated due to limited enrollment of pediatric subjects in the development program. This application has not yet been reviewed by the Pediatric Review Committee (PERC), but the submitted pediatric plan is likely to be deemed inadequate and additional clinical trial information across all relevant pediatric populations is expected to be recommended.

No new safety concerns were indentified in the trials conducted with naftifine cream 2%, and the product was noted to be slightly more irritating than the currently approved 1% formulation. Naftifine has a long history of marketed use, since 1988, and has not been associated with serious adverse events. There are no expected adverse events beyond the currently labeled local irritation, burning/stinging, dryness, itching, and erythema noted in the current prescribing information for the 1% gel and cream.

Outstanding issues from other review disciplines include acceptance of an interim standard for viscosity from the CMC review by Dr. Selemme, with recommendation for a post-marketing commitment/requirement for additional viscosity information to be submitted through 36 month stability test points post approval.

The clinical pharmacology review by Dr. Abi Adebowale concluded that there is insufficient PK information for the adolescent population, and recommends a post marketing requirement (PMR) for a pediatric (ages 12-17 years old) pharmacokinetic (PK) study in patients with tinea pedis and tinea cruris. If a trial in tinea corporis is deemed necessary, PK information should be collected in that trial as well.

This CDTL review concurs with the recommendation of approving naftifine cream 2% for the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis in adults, and concurs with the post marketing requirements discussed below.

2. Background

The proposed product, naftifine cream 2%, is intended for the treatment of superficial fungal infections of the skin, including tinea pedis (fungal infection of the foot and also known as "athlete's foot"), tinea cruris (groin and surrounding tissue), and tinea corporis (body).

Naftifine hydrochloride is a synthetic allylamine derivative. The exact mechanism of antifungal action of naftifine is unknown, but investigations suggest the antifungal activity of naftifine hydrochloride is related to its inhibition of squalene epoxidase in dermatophytes, leading to an accumulation of intracellular lipids that ultimately results in irreversible damage to the fungal cell wall. The applicant has performed no new studies regarding the mechanism of action of naftifine.

Reference ID: 3043289

When Naftin Cream 1% was developed in the 1980's, applicants were not required to separately assess the various types of tinea pedis. Distinctions between interdigital and moccasin type tinea pedis were not generally made in clinical trials in that era. This applicant was advised of the need to specify definitive inclusion/exclusion criteria for different types of tinea pedis in their development program as early as the preIND meeting on November 6, 2007, and the need to provide a pre-specified statistical analysis plan for the different tinea pedis types.

Like most meeting advice provided to sponsors for antifungal products prior to PREA, this applicant was advised that safety and efficacy for tinea corporis could be assumed following successful development programs for tinea pedis and tinea cruris, and that separate studies in tinea corporis were not required.

The Pediatric Research Equity Act now requires all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens to contain an assessment of the safety and effectiveness of the pediatric patients across all relevant populations unless this requirement is waived or deferred. This issue will be addressed by Pediatric Review Committee (PeRC), which has not convened for this application at the time of this review. The pediatric plan is lacking in this application, and the PeRC is likely to make recommendations for at least one additional clinical trial. Since tinea corporis occurs with some frequency in younger children, it is likely that the PREA requirements will necessitate completion of a study for pediatric subjects with tinea corporis as part of a complete pediatric plan prior to allowing a pediatric indication for this product.

3. CMC/Device

Naftin Cream is a white to off-white cream containing naftifine hydrochloride 2% as the active ingredient and the excipients benzyl alcohol, cetyl alcohol, cetyl esters wax, isopropyl myristate, polysorbate 60, purified water, sodium hydroxide, sorbitan monostearate, and stearyl alcohol, hydrochloric acid.

The composition of the proposed naftifine 2% cream differs from the approved Naftin 1% cream in the amount of active, 2% compared to 1%, [redacted] (b) (4). Most of the chemistry, manufacturing and controls approved for the 1% cream are proposed for the 2% cream in this application.

Two issues affecting product quality arose in the early stages of review of this product: degradation products and specifications for viscosity.

At the pre-NDA meeting, the applicant was informed by ONDQA that the approved drug product specification was not acceptable for the proposed 2% cream in that the specification has no test for viscosity and degradation products. Values obtained for degradation products have been provided in this efficacy supplement to support the addition of tests and acceptance

Reference ID: 3043289

criteria to the drug product specification. The evaluation of the proposed limits for individual and total degradants was determined by ONDQA following submissions of additional information by the applicant to be acceptable.

During the pre-NDA meeting, the ONDQA Chemistry Lead, Dr. Shulin Ding informed the applicant that the drug product specification should have a test for viscosity. As the applicant had not been aware of this issue prior to the clinical trial, the sponsor tested the clinical batch for viscosity at 32 months and at 36 months at 25 C/60% RH conditions, but at no earlier time points.

The applicant complied with the Agency request to add a viscosity test and acceptance criteria to the drug product specification. Viscosity values obtained for the clinical batch and the time (b) (4) for the three registration batches were obtained at (b) (4) rpm, and that all future viscosity measurements will be obtained at (b) (4) rpm.

However, the viscosity data provided do not allow a correlation to be made between the clinical batch and the commercial batches in that a side-by-side evaluation has not been conducted. In consideration that the viscosity test can be used as a quality control test, and that data have been provided for the proposed commercial batches, Dr. Selemme, the ONDQA reviewer, concluded, with concurrence by the ONDQA team, that the presented viscosity data was acceptable as an interim specification without the correlation to the clinical batch.

The applicant's proposed viscosity acceptance criterion, (b) (4) cps, was deemed acceptable as an interim specification. The applicant will be asked to collect viscosity data from all available manufactured batches during the first 12 months after the supplement (S-011) approval date. Within 15 months after the S-011 approval date, the applicant will be required to submit the final viscosity report, with complete viscosity information/data and a proposal for their final viscosity specification.

Following multiple interactions between ONDQA and the applicant, the ONDQA review team recommends the following the following Post-Marketing Commitment/Requirement:

> As limited data have been provided for registration batches, the viscosity characteristic of the product throughout stability is not known. Additionally, the viscosity test acceptance range of (b) (4) cPs may not be appropriate once the viscosity of the product at the end of shelf-life is known. The following comments, therefore, should be conveyed to the sponsor:
>
> *For the Viscosity test acceptance range, the proposed acceptance criteria of (b) (4) (b) (4) cPs is acceptable as an interim specification. To demonstrate the viscosity characteristic during stability studies, and to support the acceptance range, provide viscosity data obtained at 24 month or 36 month stability test points, once these data are obtained.*

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The stability data for the three registration batches show that the batches met the acceptance criteria of all tests up to 9 months at 25 C/60% RH. Values show little change from initial values. The stability data was concluded to be acceptable by the ONDQA review.

(b) (4) month expiry dating was proposed by the applicant, (b) (4) the current 24 month expiry approved for the Naftin Cream 1%. (b) (4) a 24 month expiry is recommended by the ONDQA review.

The Establishment Evaluation Request concluded an overall recommendation of "acceptable" on February 24, 2011, for the two manufacturing sites for the product.

The drug product will be available in 2g physician sample, 30 g, 45 g, and 60 g tubes. The 45 g size has been proposed in this submission as an additional size for the commercial product, though Naftin 1% Cream is currently available in 30 g, 60g, and 90 g trade sizes. All container/closure tube materials are identical to the approved container, and are manufactured by (b) (4) according to DMF (b) (4)

Upon acceptance of the PMC/PMR for viscosity specifications listed above, and completion of acceptable labeling, the ONDQA review recommends approval of this application. There are no other outstanding product quality issues that would impact an approval action.

4. Nonclinical Pharmacology/Toxicology

General toxicology studies have been conducted extensively with various formulations of naftifine HCl in rats, rabbits, guinea pigs, dogs, monkeys, and minipigs.

To date, there is no carcinogenicity data available for naftifine. The applicant was informed during the March 12, 2010 preNDA meeting that the carcinogenicity potential of naftifine 2% cream product should be evaluated. However, in consideration of the historical use of naftifine HCl, it was deemed by Dr. Jianyong Wang, the nonclinical reviewer, to be acceptable to conduct the carcinogenicity testing as a postmarketing requirement.

A two year carcinogenicity study is recommended as a post-marketing requirement. The proposed timeline, with the study to begin in July, 2013, and submission of the study report in September, 2016, is acceptable to the nonclinical review team.

Nonclinical findings in oral toxicity studies included reduction in body weight gain and increases in serum bilirubin, creatinine, and urea levels. Findings in dermal toxicity studies included very slight erythema and reduction in body weight gain.

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In genetic toxicology studies, naftifine was negative in a bacterial mutagenicity test, an *in vitro* chromosome aberration test, and an *in vivo* micronucleus test. There is no concern for the genotoxicity of naftifine.

Reproductive and developmental toxicology studies have been conducted with naftifine in rats and rabbits. Naftifine did not affect fertility in rats at oral doses up to 100 mg/kg/day. Naftifine did not show a teratogenic effect in rats at oral doses up to 300 mg/kg/day or in rabbits at subcutaneous doses up to 30 mg/kg/day. The NOAEL for embryo-fetal developmental effects was considered to be 30 mg/kg/day in this study. Naftifine had no adverse effects on peri- and postnatal development in rats at oral doses up to 100 mg/kg/day.

Naftifine solutions up to 10% were not irritating to rabbit skin. Naftifine 1% cream was slightly irritating to rabbit skin. Naftifine 1% and 3% creams were slightly irritating to the conjunctiva, but not toxic to the cornea of rabbit eye. Naftifine 5% solution was not a contact sensitizer in guinea pigs.

Naftifine and naftifine 2% cream exhibited minimal UVB absorbance. The extent of UVB absorbance does not trigger the need for a nonclinical photoirritation study.

Overall the toxicity profile of naftifine 2% cream drug product has been well characterized. The proposed daily topical dosage of 2% cream applied once daily would be comparable to the approved dosage of Naftin® Gel 1% (applied twice daily). From a pharmacology/toxicology perspective, the proposed clinical doses do not elicit a significant safety concern.

This efficacy supplement is approvable from a pharmacology/toxicology perspective, as the proposed clinical doses do not elicit any significant safety concerns, pending acceptance of the dermal rat carcinogenicity study as a post marketing requirement, and completion of final labeling.

5. Clinical Pharmacology/Biopharmaceutics

Systemic bioavailability of naftifine hydrochloride or its metabolites is not necessary for therapeutic effect against dermatophytes, as the topical cream product is thought to act locally against specific fungal organisms.

The bioavailability of naftifine cream, 2% under maximal use conditions was evaluated in study MRZ 90200/FI/1002. This study was designed as an open label, single-center, multiple application study following once-daily topical application for 2 weeks. The plasma and urine concentrations of naftifine was determined in 21 adult subjects (Age range 18-63 years old) with tinea cruris (all subjects) and tinea pedis (all subjects had tinea pedis on both feet with 18

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subjects having both interdigital and moccasin-type infections). Maximal use condition was defined as having both feet and bikini area affected to which the cream was applied.

A total of 8 grams per day were to be applied as follows: 2 grams to each foot and 4 grams to the bikini area. However, the total amount applied during the study was actually somewhat less than 8g (ranging from 5.3 -7.5g) per day.

The results showed that the systemic exposure as Cmax and area under the curve (AUC) to naftifine increased over the 2 week treatment period in all 21 subjects. It does not appear that steady state was achieved during the 14 day duration of this study. Trough concentrations (Ctrough) generally increased throughout the 14 day study period. The plasma concentrations obtained on Day 28 were lower than the plasma concentrations observed on Day 1 and Day 14 indicating that an increase in systemic exposure after the last application on Day 14 was not observed, and no further PK assessments were recommended.

The applicant provided additional information on the metabolism and excretion of naftifine from published literature in this submission. The currently approved label for Naftin 1 % gel and cream has the following information on the metabolism and excretion of naftifine:

> "Naftifine and/or its metabolites are excreted via urine and feces with a half-life of approximately two to three days".

The information provided in the published literature below supports the language in the currently approved label for the Naftin 1 % cream and gel formulations. Recommended additions to Section 12 of the prescribing information will be communicated to the sponsor for concurrence and reflect the maximal use PK study discussed above.

The treatment duration proposed for the NAFT-500 2% cream product is 2 weeks. The proposed daily dosage of naftifine 2% cream is comparable to the approved daily dosage of Naftin 1% gel (once daily for 2% cream vs. twice daily for 1% gel). The topical daily dose of NAFT-500 under maximum clinical use conditions is 8 g/day, which would result in an exposure of 2.67 mg/kg/day to the active ingredient naftifine HCl for a 60 kg individual.

In July, 2011, the applicant submitted their final QT-QTc study report "Merz Protocol No. MUS 90200/1018/1" to support cardiovascular safety with use of topical naftifine hydrochloride (HCl) 2% cream. The late submission of this report and associated ECG waveforms necessitated an extension of the review clock by three months. This study report has been reviewed by the Interdisciplinary Review Team for QT Studies (IRT-QT) (review dated 09/09/2011).

According to the IRT-QT team overall summary of findings: "No significant QTc prolongation effect of naftifine HCl (600 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between naftifine HCl (600 mg)

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and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines."

(b) (4)

The pharmacodynamics of naftifine hydrochloride has not been established.

From a clinical pharmacology perspective, this application is acceptable pending agreements on the recommended labeling changes, the Post Marketing Requirement (PMR) for a pediatric/adolescent (ages 12-17 years old) Pharmacokinetic (PK) study in patients with tinea pedis and tinea cruris and, a possible recommendation by Pediatric Review Committee (PeRC) for a Post Marketing Commitment (PMC)/PMR clinical study for the treatment of tinea corporis in pediatric patients aged ≥ 2 years of age. If a clinical study needs to be conducted for the treatment of tinea corporis in pediatric patients aged ≥ 2 years of age as a PMC/PMR, then collection of PK data from this population would also be recommended.

6. Clinical Microbiology

The 1% naftifine gel and cream formulations were approved for the treatment of *Trichophyton rubrum*, *T. mentagrophytes*, and *Epidermophyton floccosum*. In addition, the 1% gel formulation was approved for the treatment of *Trichophyton tonsurans*. (b) (4) .

The applicant has provided data from recent *in vitro* studies that demonstrate the antifungal activity of naftifine against fungal isolates commonly associated with tinea pedis and tinea cruris, including *Trichophyton rubrum*, *T. mentagrophytes*, and *Epidermophyton floccosum*. MIC_{90} values, as determined in three *in vitro* studies, against all of the above pathogens, were ≤ 1 mcg/mL. Fungicidal activity, defined by the investigators as "a ≥ 99.9% reduction in the number of CFU/mL from the starting inoculum count" was demonstrated against 100% of *T. rubrum* isolates tested (n = 50). Fungicidal activity against isolates of *T. mentagrophytes* (n = 50), as determined in this investigation, was less robust, with only 78% of isolates identified as inhibited at the stated criteria.

(b) (4) .

Data from the two pivotal clinical trials supports the applicant's claim of mycological cure

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associated with naftifine cream, 2% treatment in cases of tinea pedis and tinea cruris caused by isolates of *Trichophyton rubrum*, compared to treatment with placebo, and of naftifine cream, 2% (2 week treatment) in cases of tinea pedis caused by isolates of *T. rubrum*, compared to the currently marketed product (4 week treatment). (b) (4) .

The applicant did not attempt an analysis of antifungal resistance observed during the clinical trials. Susceptibility results obtained for selected isolates indicated that naftifine was active, *in vitro*, against all isolates of *T. rubrum* tested.

The other primary change in labeling from the existing approved naftifine 1% products is the change in language regarding mechanism of action. The statement, "The inhibition of ergosterol synthesis and the accumulation of toxic concentrations of squalene in the cell may result in death of the fungal cell" is proposed, but not adequately supported. The clinical microbiology review recommends, and is concurred by the clinical team, that "a mechanism of resistance to naftifine has not been described."

There are no outstanding clinical microbiology issues beyond agreement on final labeling.

7. Clinical/Statistical- Efficacy

At the Pre-IND meeting (11/6/2007) the applicant was advised that at least one study in tinea pedis and one study in tinea cruris would be needed to obtain the indications of tinea pedis, corporis and cruris. Safety and efficacy is assumed for the tinea corporis indication at the same treatment regimen and duration in adult patients once safety and efficacy is successfully demonstrated for tinea pedis and cruris. The Agency also stated that safety and efficacy studies should separately analyze efficacy for interdigital and moccasin type tinea pedis. The Agency's advice was reiterated at the preNDA meeting on May 12, 2010.

To support the sNDA for naftifine cream, 2%, 6 clinical studies were conducted. Two phase 3 clinical studies were conducted, one for the treatment of tinea pedis and one for the treatment of tinea cruris. In addition, a phase 1 maximal-use, pharmacokinetic study in patients, and three provocative phase 1 dermal safety studies (irritation/sensitization, phototoxicity, and photoallergenicity) were conducted.

The primary objective of the tinea cruris trial was to evaluate the efficacy and safety of naftifine cream applied once daily (QD) for 2 weeks, compared to vehicle in the treatment of subjects with KOH and culture positive symptomatic tinea cruris. The protocol-specified endpoint was the proportion of subjects with complete cure at week 4 where complete cure is defined as negative mycology results (dermatophyte culture and KOH), and absence of

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erythema, scaling and pruritus (grade 0 on each) using a 4-point scale (0=absent, 1=mild, 2=moderate, 3=marked).

For enrollment, eligible subjects were to be ≥12 years of age with clinical signs and symptoms of tinea cruris of at least moderate erythema, moderate scaling, mild pruritus, and a positive KOH.

The tinea pedis trial was a 4-arm study of naftifine cream, 2% (2-week treatment), 2-week vehicle treatment, naftifine 1% (4-week treatment), and 4-week placebo. The primary objective was to evaluate the efficacy and safety of naftifine cream, 2% vs. 2-week vehicle treatment. The protocol-specified endpoint was the proportion of subjects with complete cure at week 6 where complete cure is defined as negative mycology results (dermatophyte culture and KOH), and absence of erythema, scaling and pruritus (grade 0 for each) on the 4-point scale (0=absent, 1=mild, 2=moderate, 3=marked, 4=not done).

The applicant stated that "exploratory analyses for descriptive purposes only" were used in comparing the naftifine 2% cream to Naftin 1% Cream.

The Tinea Cruris study demonstrated statistical significance (p<0.001) with response rates of 25.3% and 2.8% for NAFT-500 and vehicle, respectively; and the Tinea Pedis study demonstrated statistical significance (p=0.01) with response rates of 17.7% and 7.1% for naftifine 2% cream and vehicle, respectively:

Table 1. Complete Cure Rate for Tinea Cruris and Tinea Pedis trials

	NAFT-500 N=75	Vehicle N=71	p-value
Tinea Cruris (1)	19 (25.3%)	2 (2.8%)	<0.001
Tinea Pedis (2)	26 (17.7%)	5 (7.1%)	0.01

Complete Cure is defined as having negative mycology results (dermatophyte culture and KOH) and absence of erythema, scaling and pruritus at Week 4 (1) and Week 6 (2).
P-value is calculated from a one-sided CMH test stratified by pooled sites (FAS, LOCF)

Source: Agency Biostatistics review by Dr. Carin Kim

The study populations are not large, but are in line with precedent approvals, the most recent of which was Ertaczo in December, 2003.

The Agency Biostatistics reviewer, Dr. Carin Kim, evaluated the complete cure rates of the approved Naftin 1% vs. 4-week vehicle, and the naftifine 2% cream vs. 2-week vehicle to compare the relative risk-benefit determinations from the tinea pedis trial. The complete cure rate is slightly higher for the NAFT-500 arm when compared to that of Naftin 1% arm, however, it should be noted that the complete cure rate for the vehicle (treatment duration of 2 weeks) arm is twice as high compared to that of the Naftin 1% vehicle (treatment duration of 4 weeks) arm:

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Complete Cure Rate at Week 6

	Tinea Pedis			
	NAFT-500 N=147	Vehicle[1] N=70	Naftin 1% N=143	Vehicle[2] N=65
Complete Cure Rate[3]	26 (17.7%)	5 (7.1%)	23 (16.1%)	2 (3.1%)
Complete Cure Rate[4]	23 (15.7%)	5 (7.1%)	22 (15.4%)	2 (3.3%)

One-sided CMH test stratified by pooled sites.
(1) Treatment duration of 2 weeks to match that of NAFT-500
(2) Treatment duration of 4 weeks to match that of Naftin 1%
(3) Sponsor's analysis: FAS, LOCF. P-value=0.001 for Naftin vs. 4-week vehicle; p-value =0.01 for NAFT-500 vs. 2-week vehicle.
(4) Reviewer's analysis: FAS, missing imputed as failure. P-value =0.0015 for Naftin 1% vs. 4-week vehicle; p-value= 0.02 for NAFT-500 vs. 2-week vehicle.

Issues regarding approvability of the submitted application:

1. [redacted] (b) (4)

While the applicant conducted two studies with naftifine cream 2%, one in tinea cruris, and one in tinea pedis, in accordance with the minimal requirements outlined at the preIND meeting, and both studies demonstrated significance for the primary efficacy endpoint of complete cure, the application cannot be approved in its current form [redacted] (b) (4) [redacted] (b) (4).

In the tinea pedis study, while the Agency previously advised that the applicant separately analyze efficacy and safety for each type of tinea pedis, the study's inclusion criteria did not accurately or adequately specify the specific types of tinea pedis, and included subjects with all types of tinea pedis (i.e., interdigital, moccasin, and others). Further, the protocol did not pre-specify a way of analyzing the distinct types of tinea pedis.

To address the Agency's concerns regarding separate analyses based on tinea pedis types, the applicant re-classified each subject to interdigital, moccasin or both. However, the applicant's method of reclassification was found on Agency review to be inconsistent and somewhat subjective. [redacted] (b) (4) [redacted] The Agency statistical review by Dr. Kim illustrates that only 12 subjects likely had moccasin tinea pedis and none achieved complete cure. [redacted] (b) (4) [redacted]

2. Age indication

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The applicant is seeking an indication for subjects 12 years and older; however, only 1 subject in the tinea pedis trial and two subjects in the tinea cruris trial exposed to naftifine 2% cream were between the ages of 12 and 17 years.

Despite the age indication of 12 years sought by the applicant, insufficient data has been provided that safety and efficacy in the adolescent population has been demonstrated. Labeling should be limited to patients aged 18 years and older.

As discussed below, the tinea corporis indication may need clinical trial data to support its use in children and adolescents, as PREA requirements may amend the previous advice for the pediatric population.

No Special Protocol Assessment was submitted for Agency review. The Statistical Analysis Plan (SAP) was amended three times (effective dates: 8/10/2009, 10/7/2009, and 12/23/2009), however, the amended SAPs were not submitted to the Agency for comments.

8. Safety

Naftifine cream has been approved at the 1% concentration since 1988, and risks associated with its use have been low. The phase 3 tinea pedis trial included the 1% marketed formulation as a comparator arm, so some limited comparative safety data is available. Although the numbers are small, the 2% formulation appears more irritating than the 1% drug product. Overall application site reactions were twice that for the 2 % formulation (i.e., application site pruritus 7 (1.8) vs. 1 (0.4), application site dryness 3 (0.8) vs. 1 (0.4), and contact dermatitis 2 (0.5) vs. 0 for naftifine 2% and naftifine 1%, respectively.

There were no deaths in the naftifine cream 2% trials. One serious adverse event of “influenza” was reported in the tinea pedis trial, but was considered mild in intensity, and deemed unlikely to be related to study drug by the applicant or Agency review.

Three subjects on naftifine cream 2% reported severe treatment emergent adverse events: application site pruritus, skin exfoliation, and genital erythema. Common treatment emergent adverse events greater than placebo included headache, and application site pruritus and irritation. There were no clinically significant changes in chemistry or hematology parameters. Electrocardiograms were not performed during the clinical development program.

Provocative dermal safety study results demonstrated a mild risk for irritation, and little risk as a primary sensitizer. However, “contact dermatitis” leading to discontinuation was reported in as an adverse reaction in the clinical phase 3 trials. This will be captured in section 6 of the prescribing information. No evidence of phototoxicity or photosensitivity was observed.

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The primary clinical review by Dr. Brenda Vaughan recommends the conduct of a long term safety study based on the ICH E1a guidance recommendations. She notes that only 421 patients were exposed to the 2% formulation during clinical development while 236 patients were exposed to the lower 1% concentration in the submitted pivotal trials.

The proposed daily dosage of naftifine 2% cream is comparable to the approved daily dosage of Naftin 1% gel (once daily for 2% cream vs. twice daily for 1% gel) for which there is long term usage history. Given the fact that the currently approved labeling for Naftin 1% Cream specifies dosage and administration instructions that are not specific amounts ("A sufficient quantity of Naftin Cream 1% should be gently massaged into the affected and surrounding skin areas once per day), this CDTL review concludes that this PMC/PMR recommendation by the primary clinical reviewer can be waived based on the long term historical use of Naftin Cream and Gel 1% since 1988. It appears to this reviewer that the information gained from a long term safety study would not be particularly useful for labeling, in that patients will self limit application amounts in the face of local irritative side effects, and that no significant pattern of adverse events have been reported over two decades of use for the 1% cream and gel formulations.

9. Advisory Committee Meeting

No Advisory Committee meetings were required, nor held for this application.

10. Pediatrics

Naftifine hydrochloride is currently marketed as 1 % cream and 1 % gel formulations (NDA 19-599 (Approved February 29, 1988) and 19-356 (Approved June 18, 1990), respectively) for the topical treatment of tinea pedis, tinea cruris and tinea corporis. It is noted that the approved label for Naftin1 % Cream and Gel state that "safety and effectiveness in pediatric patients have not been established."

The pediatric plan is inadequate and does not address the use of the proposed 2% cream across all relevant populations for all indications. The application did not address the indication of tinea corporis at all, requesting that the pediatric plan be "assumed for tinea corporis."

A partial waiver request of the requirement to provide information on pediatric patients under the Pediatric Research Equity Act (PREA) for patients 0 – 11 years of age (<12 years) was submitted. The applicant, Merz, specifically requested a waiver of the requirement to conduct studies in pediatric subjects younger than 12 years of age on the basis that naftifine cream 2% does not represent a significant therapeutic alternative for this age group and is unlikely to be used in a substantial number of patients younger than 12 years of age. Tinea pedis and tinea

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cruris occur less frequently in children than in adults, and less frequently in children less than 12 years of age than in adolescents.

However, tinea corporis occurs with reasonable frequency in younger children, though, as noted above, the PeRC has not provided specific advice on this issue as of the date of this review. It is likely that a clinical trial in pediatric subjects with tinea corporis will need to be conducted to satisfactorily address PREA and gain labeling for the pediatric population.

(b) (4)

The review team recommends that the applicant evaluate the PK of naftifine cream 2% in adolescents aged 12-17 years old as part of a pediatric plan to meet the Pediatric Research Equity Act (PREA) PMR . The PK information obtained in the adolescent population will be important for evaluating systemic safety. (b) (4)

(b) (4)

As of the date of this review, the PeRC review of this application is scheduled for November 16, 2011.

11. Other Relevant Regulatory Issues

Two study sites were selected for DSI inspection due to the relatively high treatment responders and large numbers of subjects enrolled. According to the DSI review finalized 08/05/2011, no regulatory violations were noted. The studies appear to have been conducted adequately, and the data generated appear acceptable in support of the respective indication.

There were no issues identified with financial disclosures or GCP guidelines.

12. Labeling

Review of the proposed label submitted by the applicant was based on evaluation of the clinical study for the NDA as well as DMEPA, DRISK, and DDMAC consultative reviews.

The proposed name Naftin Cream, is being reviewed by DMEPA following rejection of the [redacted] (b) (4) Carton and container labeling has been accepted by the CMC reviewer and clinical team. DRISK has provided comments for the carton and container sections of the label which have been incorporated into the proposed labeling which is to be forwarded to the applicant for concurrence.

As noted above, the applicant will be presented with prescribing information that differs from their proposal [redacted] (b) (4) of interdigital tinea pedis as well as limitation of the population to adults.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The clinical team leader concurs with the primary clinical reviewer that this product should be approved for the indication of interdigital tinea pedis, tinea cruris, and tinea corporis in adults pending successful completion of labeling negotiations with the applicant and acceptance of post-marketing informational requirements discussed in this review.

- Risk Benefit Assessment

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Efficacy for interdigital tinea pedis and tinea cruris has been demonstrated, and it is reasonable, based on historical precedents, to assume efficacy for tinea corporis in adults.

The safety findings are largely limited to local adverse events, with no serious adverse events deemed related to the study product. The local adverse events are expected given the marketing experience of 1% Naftin products since 1988, and are not dissimilar in scope and severity.

The benefits of this product outweigh the risks when used as the prescribing information recommends for adults, and this CDTL review concurs that this application should be approved for adults. The conclusion that this application should be approved is shared by each review discipline, and there are no outstanding approvability issues beyond agreement on final product labeling and acceptance of the recommended post marketing requirements.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

REMS is neither required nor recommended for this topical antifungal product. Labeling is adequate to inform prescribers and patients of expected adverse events and risks.

- Recommendation for other Postmarketing Requirements and Commitments

The rationale for three recommended PMC/PMR's is described above. Discussions with the applicant are pending clearance of proposed labeling to be sent for concurrence.

- For the Viscosity test acceptance range, the proposed acceptance criteria of (b) (4) (b) (4) cPs is acceptable as an interim specification. To demonstrate the viscosity characteristics during stability studies, and to support the acceptance range, provide viscosity data obtained at 24 month or 36 month stability test points, once these data are obtained.
- Maximum use PK safety study in pediatric subjects ≥ 12 years to 17 years, 11 months of age is recommended. (Note that the marketed Naftin Cream, 1% product, is not approved for use in pediatric patients.)
- Conduct of a multicenter, randomized, blinded, vehicle-controlled study with use of naftifine hydrochloride 2% cream for treatment of tinea corporis in pediatric patients ≥2 years of age is needed as a PMC/PMR. As of the date of this review, the applicant has not submitted a Pediatric Plan that covers all relevant pediatric populations (i.e., study of tinea corporis which has the highest prevalence in preadolescents (Lesher, 2010)). Pediatric Review Committee (PeRC) recommendations are pending as of the date of this review.

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- Recommended Comments to Applicant

There are no other recommended comments exclusive of agreed upon labeling in PLR format. Labeling discussions have not been initiated with the sponsor as of the date of this review. Post marketing commitments/requirements are discussed above and also require agreement by the applicant as labeling discussions proceed.

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/s/

DAVID L KETTL
11/10/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019599Orig1s011

MEDICAL REVIEW(S)

Addendum to CLINICAL REVIEW

Application Type	NDA
Application Number(s)	19-599/S011
Priority or Standard	Standard
Submit Date(s)	
Received Date(s)	December 16, 2010
PDUFA Goal Date	January 16, 2012
Division / Office	DDDP/OND
Reviewer Name(s)	Brenda E. Vaughan, M.D.
Review Completion Date	
Established Name	Naftifine hydrochloride
(Proposed) Trade Name	Naftin® (b) (4)
Therapeutic Class	
Applicant	Merz Pharmaceuticals LLC
Formulation(s)	Cream
Dosing Regimen	Apply topically onto affected areas plus ½ inch margin of healthy surrounding skin once-daily for 2 weeks
Indication(s)	Tinea pedis, Tinea cruris, & Tinea corporis
Intended Population(s)	Age ≥12 and above

Reference ID: 3063608

The purpose of this addendum is to address the following six issues:1) clarify half life and systemic exposure through day 28 for naftifine hydrochloride 2% cream, 2) (b) (4) [redacted], 3) recommend inclusion of the 1 % Naftin arm data into the text and tables of the clinical studies section of the label although only one comparative study was conducted, 4) provide Pediatric Review Committee's (PeRC) recommendations for study of pediatric patients , 5) provide additional clarification for the clinical recommendation to use the applicant's baseline post hoc classification of the types of tinea pedis studied to assess efficacy, and 6) include clinical concurrence for PMC/PMR's for viscosity, and dermal carcinogenicity in rats in the clinical review.

1. Clinical Pharmacology reviewer indicates that although steady state was not achieved during the 14 day duration of this study, sampling at day 28 indicates that concentration was not increasing after the last applied dose on day 14. According to an 11/22/2011 email from the clinical pharmacology reviewer, the applicant provided plasma concentrations data obtained on day 28 which was lower than the plasma concentrations observed on Day 1 and Day 14 indicating that an increase in systemic exposure was not observed after the last application on Day 14.

2. According to the Clinical Microbiology Consultation completed July 22, 2011, (b) (4) [redacted]. In labeling review, Section 1 (Indications and Usage): deletion of (b) (4) [redacted] was recommended with the following rationale provided: (b) (4) [redacted] The majority of the clinical team concurs with the Microbiology Reviewer's conclusion.

From a clinical perspective, (b) (4) [redacted]:

- Advice provided by the Agency at the PreIND Meeting regarding pathogens. According to the minutes, "Since *T. rubrum* is considered one of the most common organisms found in tinea pedis as well as <u>one of the most difficult to eradicate</u>, greater than 50% of the clinical cases should be culture positive for *T. rubrum* from the initial visit."
- The Clinical Microbiology review indicating that the applicant provided data from recent in vitro studies that demonstrate the antifungal activity of naftifine against fungal isolates commonly associated with tinea pedis and

tinea cruris, including *Trichophyton rubrum*, *T. mentagrophytes*, and *Epidermophyton floccosum*.

- [redacted] (b) (4) that 1% naftifine gel and cream formulations are approved for the treatment of *Trichophyton rubrum*, *T. mentagrophytes*, and *Epidermophyton floccosum* indicating efficacy of the moiety in eradicating *T. mentagrophytes*, and *Epidermophyton floccosum*. If indeed it is the Agency's position as recorded in the preIND meeting minutes that *T. rubrum* is one of the most difficult to eradicate and unless there is known development of resistance, [redacted] (b) (4)
- Duration of therapy is 2 weeks and fungal culture results may not be available for up to one week or more. It is the opinion of this reviewer that [redacted] (b) (4)

3. The 1% study arm may not be included in the label; however, it is the recommendation of this reviewer to include the 1 % Naftin arm data into the text and tables of the clinical studies section. Study details and results for the 1% formulation should be disclosed based on one study due to the fact that the applicant is the owner of both drug products; therefore, comparative data are acceptable for labeling based on results of one vs. two comparative study requirements. The applicant submitted data from a 6-week, double-blind, randomized, placebo-controlled, multicenter, parallel group Phase 3 study of naftifine hydrochloride 2% cream compared to vehicle (placebo) and to commercially available Naftin® I% (positive control) in the treatment of tinea pedis.

4. The Applicant's pediatric plan was presented to the Pediatric Review Committee (PeRC) on November 9, 2011. The committee recommended the following:

- PREA PMR for a PK/Efficacy/Safety study in pediatric patients 2 years and above with tinea corporis. It was suggested that the PK component could be conducted using the Population Pharmacokinetics approach with limited PK sampling from the subjects to confirm that the systemic exposure in patients with tinea corporis (smaller surface area with no occlusion) would not be higher than that of the patients with tinea cruris (higher surface area with occlusion) or tinea pedis.
- PREA PMR PK study of NAFT-500 cream in adolescents aged 12-17 years old with tinea pedis and tinea cruris.

5. Classification of tinea pedis studied. As noted in the 10/18/2011 review, an approval recommendation is being made for treatment of interdigital type tinea pedis [redacted] (b) (4) . According to the applicant (ISE pg. 45 of 58), subjects randomized to treatment with NAFT-500 Cream, 2% or placebo in the Phase 3 tinea pedis study presented at Screening (Visit 1) with different types of infection.

The post hoc assessment schemata and methodology used provided by the applicant (ISE, Section 8.3) follows:

"In the Phase 3 tinea pedis study (MUS 90200-0736/1), subjects who were randomized to NAFT-500 Cream, 2% or placebo for 2 weeks or Naftin 1% Cream or placebo for 4 weeks presented at Screening (Visit 1) with both interdigital- and moccasin-type tinea pedis (41.0%, 45.8%, 40.3%, and 35.3%, respectively), interdigital-type tinea pedis only (44.0%, 40.7%,41.9%, and 44.5%, respectively), moccasin-type tinea pedis only (7.7%, 5.9%, 8.5%, and 13.4%, respectively), or Other (7.3%, 7.6%, 9.3%, and 6.7%, respectively) (see Table 7–6 in Section 7.2.2).
The tinea pedis study was not designed to treat a specific type of tinea pedis; rather, subjects were instructed to treat the affected area recorded at Baseline and Investigators were instructed to evaluate the worst site at each visit. Therefore, clinical sites assessed for efficacy were treated and evaluated for either interdigital- or moccasin-type tinea pedis, or both, in the following manner (Table 8–1):
- Subjects diagnosed with interdigital tinea pedis at Screening (Visit 1) and assessed for treatment of the same type at the Terminal Visit were classified as having interdigital tinea pedis.
- Subjects diagnosed with moccasin-type tinea pedis at Screening and assessed for treatment of the same type at the Terminal Visit were classified as having moccasin-type tinea pedis.
- Subjects diagnosed with interdigital tinea pedis at Screening and assessed for treatment of moccasin-type tinea pedis at the Terminal Visit, or vice versa, were classified as having both interdigital- and moccasin-type tinea pedis.
- Subjects who were not diagnosed or assessed for a specific type of tinea pedis at the Screening and/or Terminal Visit were classified as having either interdigital- or moccasin type tinea pedis on a subject-by-subject basis using the recorded "site of assessment." The most frequently encountered sites of assessment for the affected subjects included "left foot between 1st and 2nd toe" (classified as interdigital) and "right heel" (classified as moccasin)."

For the ISE analysis (ISE, pg 97), the primary efficacy endpoints (complete cure at Week 6) and most important secondary efficacy endpoints (treatment effectiveness and mycological cure at Week 6) were evaluated in subgroups treated for interdigital- or moccasin-type tinea

pedis or both types of tinea pedis using post-hoc analyses of the FAS and PPS populations.

It is the opinion of this reviewer that disease assignment and re-assignment based on the most clinically involved target area as proposed above by the applicant is arbitrary as tinea pedis is clinically diagnosed by global inspection. Whereas the applicant's baseline classification as recorded on the Case Report Form (CRF) into interdigital, plantar (moccasin) or both (e.g., interdigital and moccasin) and moccasin is understandable from a clinical perspective, the "Other" classification was not defined in the protocol and thus the type of tinea pedis this represents is unknown.

Given that a specific type of tinea pedis was not specified for enrollment and classification is being made post hoc, use of the applicant's baseline classification appears to be most logical classification to use. Inclusion of the end of study visit site of inspection is inconsistent with the primary endpoint, complete cure, since all clinical signs and symptoms of tinea pedis should have resolved and there would not be any clinically involved areas.

6. This reviewer concurs with the following CMC PMC and pharmacology/toxicology PMR recommendations:

- To collect viscosity data from all available manufactured batches during the first 12 months after the supplement (S-011) approval date. Within 15 months after the S-011 approval date, the applicant will be required to submit the final viscosity report, with complete viscosity information/data and a proposal for their final viscosity specification. According to verbal communication with the CMC reviewer's a PMR is not needed as the applicant has agreed to provide the needed data and the 1% formulation has been approved for a number of years.
- To conduct a 2-year dermal rat carcinogenicity study as a postmarketing requirement. The agreed upon proposed timeline is for the study to begin in July 2013 with submission of the study report in September 2016. These dates are currently under negotiation and may vary.

Brenda Vaughan, M.D.
Medical Officer, Dermatology

Reference ID: 3063608

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/s/

BRENDA E VAUGHAN
12/23/2011

DAVID L KETTL
12/23/2011

(b) (4)

Applicant has concurred with post marketing studies and provided acceptable timelines.

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	19-599/S011
Priority or Standard	Standard
Submit Date(s)	
Received Date(s)	December 16, 2010
PDUFA Goal Date	January 16, 2012
Division / Office	DDDP/OND
Reviewer Name(s)	Brenda E. Vaughan, M.D.
Review Completion Date	
Established Name	Naftifine hydrochloride
(Proposed) Trade Name	Naftin® (b) (4)
Therapeutic Class	
Applicant	Merz Pharmaceuticals LLC
Formulation(s)	Cream
Dosing Regimen	Apply topically onto affected areas plus ½ inch margin of healthy surrounding skin once-daily for 2 weeks
Indication(s)	Tinea pedis, Tinea cruris, & Tinea corporis
Intended Population(s)	Age ≥12 and above

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical prospective, an approval recommendation is being made for use of 2% naftifine hydrochloride cream applied topically onto affected areas plus a ½ inch margin of healthy surrounding skin once-daily for 2 weeks in treatment of interdigital tinea pedis, tinea cruris, and tinea corporis due to *Trichophyton rubrum* [redacted] (b) (4) in adults ≥ 18 years old; however, this recommendation is predicated upon the applicant's acceptance of revised labeling and commitment to conduct phase 4 studies listed in Section 1.4. One study in tinea pedis is being accepted as substantial evidence of effectiveness for that indication since statistical superiority of active study drug was demonstrated over vehicle and based on an agreement made by the Agency at the 2007 PreIND meeting that one study in tinea pedis would be acceptable. Safety and efficacy was demonstrated for treatment of tinea cruris with use of 2% naftifine hydrochloride cream in adults; therefore as previously agreed upon, safety and efficacy is being assumed for the tinea corporis indication at the same treatment regimen and duration in adult patients.

The approval recommendation is being made for treatment of interdigital type tinea pedis [redacted] (b) (4) . (b) (4) [redacted] (b) (4) interdigital is that complete cure, the primary efficacy endpoint, was achieved in a numerically higher number of patients diagnosed at baseline with interdigital tinea pedis and interdigital/moccasin-type while no patients obtained complete cure in the moccasin-type only subset of patients. [redacted] (b) (4) . The applicant made a post hoc reclassification of the types of tinea pedis studied. According to the Agency's statistical review, it is difficult to draw conclusions regarding the complete cure rates for each subset due to small numbers of patients with complete cure for each type of tinea pedis. Compete Cure rates based on the Agency's assessment of the "original baseline type of tinea pedis" for Phase 3 tinea pedis study (MUS 90200-0736/1) are as follows: 13/65 (20%), 12/57 (21.1%) , 0/12 (0%), 0/3 (0%), and 1/13 (7.7%) for both interdigital and moccasin-type, interdigital-type only, moccasin-type only, and Other, respectively (Source: Statistical Table 18).

1.2 Risk Benefit Assessment

The applicant included study of an already approved drug product, Naftin® (naftifine hydrochloride) Cream, 1% in the Phase 3 clinical tinea pedis development program. Risks associated with treatment with both naftifine hydrochloride 1% and the 2% cream appear to be low in patients treated in the pivotal trials. According to the Agency's Statistical Reviewer the complete cure rate is slightly higher for the NAFT-500 arm when compared to that of Naftin Cream, 1% arm; however, the difference in treatment effect between the 2% formulation and its vehicle is much smaller than the difference between the approved 1% formulation and its vehicle study arm. Complete cure rates for the 2% formulation and the already

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approved Naftin 1% cream formulation for treatment of tinea pedis are: 23 (15.7%) vs. 5 (7.1%) and 22 (15.4%) vs. 2 (3.3%); respectively (Statistical Table 11. Complete Cure rate at Week 6).

Although the numbers are small, the 2% formulation appears more irritating than the 1% drug product with exception of application site irritation 2 (0.5 %) vs. 4 (1.7 %) for naftifine 2% and naftifine 1%, respectively. Overall application site reactions were twice that for the 2 % formulation (i.e., application site pruritus 7 (1.8) vs. 1 (0.4), application site dryness 3 (0.8) vs. 1 (0.4), and contact dermatitis 2 (0.5) vs. 0 for naftifine 2% and naftifine 1%, respectively.

At the PreIND meeting the applicant was advised as follows: "…you will need to provide information to clarify the reason for proceeding with the development plan for a 2% product. It is unclear what the clinical public health advantage would be for a 2% product dosed in the same manner as the 1% product. You proposed shortened duration of treatment and increased efficacy over the current product, and you need to provide information to support that position. You need to provide a development program for Naftin that optimizes its treatment profile". Treatment regimen studied for the 2% drug product and vehicle is 2 weeks, whereas the treatment regimen studied for the 1% drug product and vehicle is 4 weeks. However, the labeled treatment regimen for the 1% product is vague and states that if no clinical improvement is seen after four weeks of treatment with Naftin® Cream, 1%, the patient should be re-evaluated.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None needed.

1.4 Recommendations for Postmarket Requirements and Commitments

- Maximum use PK safety study in pediatric subjects ≥ 12 years to 17 years, 11 months of age is recommended. Only three pediatric patients were exposed to active study drug and completed weeks 4 and 6 in the applicant's tinea pedis and tinea cruris clinical development program. The marketed Naftin® Cream, 1% product, is not approved for use in pediatric patients.
- Conduct of a multicenter, randomized, blinded, vehicle-controlled study with use of naftifine hydrochloride 2% cream for treatment of tinea corporis in pediatric patients ≥2 years of age may be needed as a PMC/PMR. As of the date of this review, the applicant has not submitted a Pediatric Plan that covers all relevant pediatric populations (i.e., study of tinea corporis which has the highest prevalence in preadolescents (Lesher, 2010)). Prior to Pediatric Research Equity Act (PREA), the Division did not recommend conduct of separate studies in tinea corporis and Pediatric Review Committee (PeRC) recommendations are pending.
- Conduct of a long term safety study is needed based on ICH E1a guidance document. As noted in the PreIND meeting minutes between the applicant and the Agency, the proposed indications of tinea pedis, cruris, and corporis are considered chronic since patients often require repeated treatment over multiple years. Only 421 patients were exposed to the 2% formulation during clinical development while 236 patients were exposed to the lower concentration. The applicant

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was referred to the ICH E1a guidance in terms of numbers of patients needed on drug product for long-term safety given the potential for recurrence of tinea infections.

2 Introduction and Regulatory Background

The majority of superficial fungal infections in the United States are tinea infections, which are primarily caused by three types of dermatophytes: *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum* [Foster et al, 2004]. The most common tineas are defined by the location of the infection as follows: tinea pedis (foot and also known as "athlete's foot"), tinea cruris (groin and surrounding tissue), and tinea corporis (body). Tinea pedis is most commonly associated with infection manifesting between the toes (interdigital) or with widespread erythema, hyperkeratosis, and scaling on the sole and heel of the foot (moccasin or plantar) and other types of tinea pedis infections (vesicular and ulcerative) [Weinstein and Berman, 2002; Noble et al,1998].

Adults and adolescents are affected by tinea cruris much more commonly than are children. Tinea corporis is a superficial fungal infection of the glabrous skin (i.e., skin regions except the scalp, groin, palms, and soles) and affects persons of all age groups, but the prevalence is highest in preadolescents [Lesher, 2010].

According to the PreIND meeting minutes, in order to obtain the desired indications of tinea pedis, corporis, and cruris, at least one study in tinea pedis and one study in tinea cruris were recommended. Sufficient numbers of subjects will need to be assessed from tinea pedis studies *and* separate tinea cruris studies in order to gain an additional indication for tinea corporis. When efficacy is demonstrated for tinea pedis, then efficacy at the same dosage and duration may be assumed for tinea cruris, but safety for tinea cruris may not be assumed. Efficacy and safety of the study medication may be assumed for tinea corporis at the same dosage and duration. Since *T. rubrum* is considered one of the most common organisms found in tinea pedis as well as one of the most difficult to eradicate, greater than 50% of the clinical cases should be culture positive for *T. rubrum* from the initial visit.

2.1 Product Information

- Description of the product
  Naftin Cream is a white to off-white cream containing naftifine hydrochloride 2% as the active ingredient and the excipients benzyl alcohol, cetyl alcohol, cetyl esters wax, isopropyl myristate, polysorbate 60, purified water, sodium hydroxide, sorbitan monostearate, and stearyl alcohol, hydrochloric acid.

- Established name and proposed trade name

The established name is naftifine HCl. DMEPA completed a proprietary name review for the proposed name, Naftin [redacted] (b) (4) 2%, under IND 77530. The proposed name was rejected and the applicant has since submitted a reconsideration request under that same IND. According to an 08/17/2011 email from DMEPA, since the proprietary name review was never submitted to the NDA, the applicant cannot use an unapproved proprietary name in any of their labels or labeling that are

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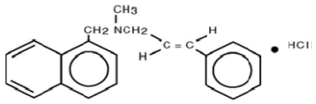
under review in S-011 of NDA 19-599. Therefore, (b) (4) cannot be represented in any of their labels and labeling unless DMEPA approves the name under the NDA. The applicant should submit the name request to the NDA.

Throughout the clinical review, the terms NAFT-500 (naftifine hydrochloride) Cream, 2%, NAFT-500 Cream, 2%, NAFT-500, naftifine hydrochloride 2%, TRADENAME, and 2% formulation are used interchangeably.

- Chemical class

Naftifine HCl is an allylamine antifungal. Chemically, Naftifine HCl is (E)-N-Cinnamyl-N-methyl-1-napthalenemethylamine hydrochloride. Naftifine hydrochloride has an empirical forumula of $C_{21}H_{21}N{\bullet}HCl$ and a molecular weight of 323.86. Its structural formula is:



2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1. Currently Approved Topical Antifungal Cream Formulations (b) (4) (b) (4)

Topical Antifungal Established /Tradename	**Application #**	**Date of Approval**
Econazole (Spectazole)	NDA 018-751	December 23, 1982
Ciclopirox (Loprox)	NDA 018-748	December 30, 1982
Sulconazole (Exelderm)	NDA 018-737	August 30, 1985
Nafifine (Naftin)	NDA 019-599	February 29, 1988
Oxiconazole (Oxistat)	NDA 019-828	December 30, 1988
Clotrimazole (Lotrimin AF)	NDA 020-888	October 27, 1989
Terbinafine (Lamisil Cream)	NDA 020-980	March 9, 1999
Butinafine (Mentax)	NDA 020-524	October 18, 1996
Butinafine (Mentax)	NDA 020-663	December 31,1996
Ketoconazole	ANDA 075-581 & ANDA 076-294	April 25, 2000 April 28, 2004
Sertaconazole (Ertczo)	NDA 021-385	December 10, 2003

Source: Gary Chang, M.D. (FDA Medical Officer) and Drugs @ FDA database)

2.3 Availability of Proposed Active Ingredient in the United States

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

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2.4 Important Safety Issues With Consideration to Related Drugs

Naftifine hydrochloride is a synthetic allylamine derivative. Other allylamine antifungals include terbinafine, and butenafine. The applicant provided assessment of adverse events of special interest that included assessment of liver, kidney, and cardiac parameters.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

- November 6, 2007 - PIND 77,530 meeting
- January 6, 2009 – IND Advice/Information Request
- March 12, 2010 - Pre-NDA meeting
- October 1, 2010 – email correspondence

2.6 Other Relevant Background Information

The applicant is developing NAFT-600 2% gel formulation under IND 105,603.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Two study sites were selected for DSI inspection due to the relatively high treatment responders and large number of subjects enrolled.

Table 2

Site # (Name, Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
#25, Amaury A. Roman, MD Advanced Medical Concepts, PSC Cidra, PR 00739	Study MRZ 90200/FI/3001	25	Tinea Cruris
#06, Zoe Draelos 2444 N. Main Street High Point, NC 27262	Study MUS 90200-0736/1	12	Tinea Pedis

According to DSI conclusion finalized 08/05/2011, no regulatory violations were noted. The clinical investigator sites of Drs. Roman and Draelos were inspected in support of this NDA. No regulatory violations were observed during these inspections, and they are classified No Action Indicated (NAI).
It is noted that the observation notes for Dr. Roman are based on the preliminary communications provided by the FDA field investigator. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIR. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

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3.2 Compliance with Good Clinical Practices

According to the applicant, studies were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki, and in compliance with all International Conference on Harmonization Good Clinical Practice (GCP) guidelines. In addition, all local regulatory requirements were followed; in particular, those affording greater protection to the safety of study participants.

3.3 Financial Disclosures

Merz Pharmaceutical, LLC stated the following: "As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)."

4 Significant Efficacy/Safety Issues **Related to Other Review Disciplines**

4.1 Chemistry Manufacturing and Controls

According to October 4, 2011 CMC review, "deficiencies identified with the degradation method have been resolved. The method is validated for the analysis of degradants in the drug product. Additionally, deficiencies with the viscosity method and data have been resolved. The applicant's proposed viscosity acceptance criterion, (b) (4) cps, is acceptable as an interim specification. The applicant will be asked to collect viscosity data from all available manufactured batches during the first 12 months after the supplement (S-011) approval date. Within 15 months after the S-011 approval date, the applicant will be required to submit the final viscosity report, with complete viscosity information/data and a proposal for their final viscosity specification."

4.2 Clinical Microbiology

The Clinical Microbiology Consultant concluded the following:
"applicant has provided data from recent in vitro studies that demonstrate the antifungal activity of naftifine against fungal isolates commonly associated with tinea pedis and tinea cruris, including *Trichophyton rubrum*, *T. mentagrophytes*, and *Epidermophyton floccosum*. MIC90 values, as determined in three in vitro studies, against all of the above pathogens, were ≤ 1 mcg/mL. Fungicidal activity, defined by the investigators as "a ≥ 99.9% reduction in the number of CFU/mL from the starting inoculum count" was demonstrated against 100% of *T. rubrum* isolates tested (n = 50). Fungicidal activity against isolates of *T. mentagrophytes* (n = 50), as determined in this investigation, was less robust, with only 78% of isolates identified as inhibited at the stated criteria."

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According to the Clinical Micro Reviewer, data from the two pivotal clinical trials supports the applicant's claim of mycological cure associated with NAFT-500 Cream, 2% treatment in cases of tinea pedis and tinea cruris caused by isolates of *Trichophyton rubrum*, compared to treatment with placebo, and of NAFT-500 Cream, 2% (2 week treatment) in cases of tinea pedis caused by isolates of *T. rubrum*, compared to the currently marketed product (4 week treatment). (b) (4) .

4.3 Preclinical Pharmacology/Toxicology

The Pharm/Tox reviewer concluded that NDA 19-599 Supplement-11 is approvable from a pharmacological/toxicological perspective, provided that the recommended changes in the label are incorporated into the NAFT-500 2% cream label. The applicant was advised at the PreIND Meeting that for a drug product intended to be used chronically in humans, the potential to induce carcinogenicity should be evaluated. To date there is no carcinogenicity data available for naftifine HCl. The carcinogenicity potential of NAFT-500 cream product should be evaluated; therefore, a 2-year dermal rat carcinogenicity study will be conducted as a post-marketing requirement.

4.4 Clinical Pharmacology

The Clinical Pharmacology reviewer concluded that the application is acceptable pending agreements on the recommended labeling changes and the Post Marketing Requirement (PMR) for a pediatric (ages 12-17 years old) Pharmacokinetic (PK) study and Agency.

Mechanism of Action

According to the label, the exact mechanism of action against fungi is not known; however, naftifine hydrochloride appears to interfere with sterol biosynthesis by inhibiting the enzyme squalene 2, 3-epoxidase.This inhibition of enzyme activity results in decreased amounts of sterols, especially ergosterol, and a corresponding accumulation of squalene in the cells. The inhibition of ergosterol synthesis and the accumulation of toxic concentrations of squalene in the cell may result in death of the fungal cell.

4.4.2 Pharmacodynamics

The pharmacodynamics of naftifine hydrochloride have not been established

4.4.3 Pharmacokinetics

Systemic bioavailability of naftifine hydrochloride or its metabolites is not necessary for therapeutic effect against dermatophytes. The pharmacokinetics of TRADENAME Cream was evaluated following once-daily topical application for 2 weeks to 21 adult males and females subjects, with both tinea pedis and tinea cruris. The median total amount of cream applied was 6.4 g (range 5.3-7.5 g) per day. The results showed that the systemic exposure (i.e. maximum concentration (Cmax) and area under the curve (AUC)) to naftifine increased over the 2 week treatment period in all the 21 subjects. Geometric Mean (CV%) AUC0-24hr was 117 (41.2) ng*hr/mL on Day 1, and 204 (28.5) ng*hr/mL on Day 14. Geometric Mean (CV %) Cmax was 7 ng/mL (55.6) on Day 1 and 11 ng/mL (29.3) on day 14. Median Tmax was 8.0 hours on Day 1

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(range: 4 to 24) and 6.0 hours on Day 14 (range: 0 to 16). Accumulation after 14 days of topical application was less than two fold. Trough concentrations generally increased throughout the 14 day study period. Naftifine continued to be detected in plasma in 13/21 (62%) subjects on day 28, the mean (SD) plasma concentrations were 1.6 ± 0.5 ng/mL (range below limit of quantitation (BLQ) to 3 ng/mL).

In the same pharmacokinetic study conducted in patients with tinea pedis and tinea cruris, median fraction of the dose excreted in urine during the treatment period was 0.0016% on Day 1 versus 0.0020% on Day 14.

5 Sources of Clinical Data

Clinical trials sponsored by the applicant are the source of clinical data used in this review.

5.1 Tables of Studies/Clinical Trials

5.2 Table 4 (Applicant's Tabular Listing of all Clinical Studies (Module 5 – Clinical Study Reports)

Phase 1	MRZ 90200/FI/1003	5.3.3.1	Evaluate the sensitization potential and degree of skin irritation on intact skin	Single-site, randomized, single-blind, controlled study	NAFT-500; 21 occluded applications during the irritation phase and one occluded application during the challenge phase	250	Healthy subjects ages 18-65 years	21 days of occluded patches followed by a 14-day rest phase followed by a 48-hour challenge phase	Complete Full

Study Type	Study Protocol/ Identifier	Study Report Location	Study Objectives	Study Design and Type of Control	Test Product(s): Dose, Route, and Regimen;	Subject Number	Subject Description	Treatment Duration	Study Status/ Type of Report
Phase 1	MUS 90200/1013/1	5.3.3.1	Evaluate the potential to produce phototoxicity reactions	Controlled, open-label, blinded evaluator, single dose	NAFT-500; single, occluded 24 hour application	34	Healthy subjects ages 18 -70 years	Single occluded 24 hour application	Complete Full
Phase 1	MUS 90200/1014/1	5.3.3.1	Evaluate the potential to produce photoallergenicity reactions	Controlled, open-label, blinded evaluator, single dose	NAFT-500; 6 occluded applications during the induction phase and one occluded application during the challenge phase	57	Healthy Subjects ages 18 -70 years	6 days of occluded patches followed by a 14-day rest phase followed by a 24-hour challenge phase	Complete Full
Phase 1	MRZ 90200/FI/1002	5.3.3.2	To quantify the pharmacokinetics under maximal clinical use conditions	Open-label, single-center, multiple-application	NAFT-500; 8g applied topically	21	Subjects with tinea pedis and tinea cruris	14 days	Complete Full

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Study Type	Study Protocol/ Identifier	Study Report Location	Study Objectives	Study Design and Type of Control	Test Product(s): Dose, Route, and Regimen;	Subject Number	Subject Description	Treatment Duration	Study Status/ Type of Report
Phase 3	MUS 90200/076/1	5.3.5.1	To evaluate the efficacy and safety of NAFT-500 compared to placebo	Double-blind, randomized, placebo-controlled, multicenter, parallel group	NAFT-500; applied topically once a day to affected areas and a ½ inch margin of adjacent healthy skin	709	Subjects with tinea pedis	14 days	Complete Full
Phase 3	MRZ 90200/FI/3001	5.3.5.1	To evaluate the efficacy and safety of NAFT-500 compared to placebo	Double-blind, randomized, placebo-controlled, multicenter, parallel group	NAFT-500; applied topically once a day to affected areas and a ½ inch margin of adjacent healthy skin	334	Subjects with tinea cruris	14 days	Complete Full

Abbreviation: NA = not applicable.

5.2 Review Strategy

Data from two Phase 3 clinical trials, one each conducted in tinea pedis and tinea cruris were submitted and reviewed in support of safety and efficacy for three indications: tinea pedis, tinea cruris, and tinea corporis.

5.3 Discussion of Individual Studies/Clinical Trials

The applicant conducted two Phase 3 multicenter, randomized, double blind, vehicle-controlled clinical studies to support treatment of tinea pedis, tinea cruris, and tinea corporis indications. The November 6, 2007 PIND 77,350 implies that one study in tinea pedis is acceptable to demonstrate safety and efficacy as noted in the following statement: "In order to obtain your desired indication of tinea pedis, tinea cruris, and tinea corporis, you need to conduct at least one study in tinea pedis and one study in tinea cruris." However, the applicant was also advised that "Sufficient numbers of subjects will need to be assessed from tinea pedis studies and separate tinea cruris studies in order to gain an additional indication for tinea corporis." The applicant was referred to the ICH E1a guidance in terms of numbers of patients needed on drug product for long-term safety given the potential for recurrence of tinea infections.

Reviewer comments:

The acceptance of one study conducted in tinea pedis as the basis for providing substantial evidence was not clarified in the PreIND meeting minutes. The applicant was advised at the 2007 PreIND meeting that the proposed study design that includes a study arm of the approved Naftin Cream, 1% product vs. vehicle does not have regulatory utility; nonetheless, the approved 1% product vs. vehicle study arms were included and subsequently the primary efficacy study endpoint was changed based on treatment duration differences between the 2% and 1% formulations. Use of one study to demonstrate efficacy in tinea pedis meets at least one of the recommendations set forth in the "Providing Clinical Evidence of Effectiveness for

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Human Drugs and Biological Products" guidance for demonstrating effectiveness in that a different strength and regimen of the same moiety are being studied.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The indications sought by the applicant are for treatment of tinea pedis, tinea cruris, and tinea corporis.

Reviewer comments:
It should be noted that at the PreIND (pg. 5), the applicant was advised that safety and efficacy studies for tinea pedis should separately analyze efficacy for interdigital tinea pedis, and for the moccasin type of tinea pedis. According to James L. Leyden, M. (2008), fungal infections of the foot can be divided into three major varieties with differing pathophysiologic aspects and therapeutic implications. Tinea pedis is classified clinically as interdigital, macerated erosive infections, and plantar surface involvement consisting of widespread infection (moccasin-type). Interdigital tinea pedis is the most common form, moccasin-type is more difficult to treat, and macerated erosive infections are generally treated with oral antifungal medication.

6.1.1 Methods

Study MUS 90200-0736/1
Tilted: "A Phase 3 Double-Blind, Randomized, Placebo-Controlled, Multicenter, Parallel Group Evaluation of the Efficacy and Safety of NAFT-500 in Subjects with Tinea Pedis"

Study Design:
This is a 6-week, double-blind, randomized, placebo-controlled, multicenter, parallel group Phase 3 study of NAFT-500 compared to vehicle (placebo) and commercially available Naftin® I% (positive control) in the treatment of tinea pedis. Because the treatment duration is different for the two active agents, two separate placebo groups were enrolled, with one group treated for 2 weeks and the other group treated for 4 weeks. Although the study was not powered for a non-inferiority analysis of NAFT-500 vs. Naftin® I%, descriptive comparisons were made between the two active treatment groups. Subjects were assessed for clinical response to treatment by KOH and dermatophyte culture as well as negative signs and symptoms.

Objective:
The stated study objective is to evaluate the efficacy and safety of NAFT-500, applied once daily for 2 weeks, compared to placebo for 2 weeks and a positive control (Naftin® 1%) for 4 weeks in the treatment of subjects with potassium hydroxide (KOH) and culture positive symptomatic tinea pedis.

Second Primary Objective
The second primary objective is to demonstrate superiority of Naftin® 1% over placebo in a 4-week treatment period.

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Key Inclusion Criteria:
I. Males or non-pregnant females ≥12 years of age, of any race or sex. Females of childbearing potential must have a negative urine pregnancy test.
2. Presence of tinea pedis on one or both feet characterized by clinical evidence of a tinea infection (at least moderate erythema, moderate scaling, and mild pruritus) based on signs and symptoms.
3. KOH positive and culture positive baseline skin scrapings obtained from the site most severely affected or a representative site of the overall severity.
6. Subjects must be in good health and free from any clinically significant disease that might interfere with the study evaluations.

Reviewer comment:
The study protocol should have been amended to include and/or exclude various clinical presentations of tinea pedis dependent upon the preferred indication as advised at the Pre-IND.

Exclusion criteria:
Subjects who presented with any of the following were excluded from study enrollment:
1. Subjects who had a life-threatening condition (e.g., autoimmune deficiency syndrome, cancer, unstable angina, or myocardial infarction) within the last 6 months;
2. Subjects with abnormal findings (physical or laboratory) that were considered by the Investigator to be clinically significant and indicative of conditions that complicated interpretation of study results;
3. Subjects with a known hypersensitivity to study drugs or their components;
4. Subjects who had a recent history or who were currently known to abuse alcohol or drugs;
5. Subjects who had uncontrolled diabetes mellitus;
6. Subjects who had hemodialysis or chronic ambulatory peritoneal dialysis therapy;
7. Subjects who had a current diagnosis of immunocompromising conditions;
8. Subjects who had foot psoriasis, corns and/or callus that involved any web spaces, atopic or contact dermatitis;
9. Subjects who had severe dermatophytoses, onychomycosis (on the evaluated foot), mucocutaneous candidiasis, or bacterial skin infection;
10. Subjects who had extremely severe tinea pedis (incapacitating);
11. Female subjects who were pregnant or lactating, who were not using or did not agree to use an acceptable form of contraception during the study, or who intended to become pregnant during the study (females who were surgically sterilized or post menopausal for at least 2 years were not considered to be of childbearing potential). For the purposes of this study, acceptable forms of birth control included: oral contraceptives, contraceptive patches/implants, double barrier methods (e.g., use of condom and spermicide), intrauterine device, and abstinence with second acceptable method if the subject was sexually active; and
12. Subjects who were using the following medications:
    - Topical anti-fungal therapy, foot/shoe powders, or topical corticosteroids applied to the feet within 14 days prior to randomization;
    - Topical terbinafine, butenafine, and naftifine within 30 days prior to randomization;
    - Oral anti-fungal therapies started 3 months (8 months for oral terbinafine) prior to randomization;
    - Systemic antibiotic or corticosteroid treatment taken within 30 days of randomization;
    - Any other significant treatments, except hormonal contraception and multivitamin, at the discretion of the Investigator that interfered with study treatment; and

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- Investigational drug taken within 30 days of randomization.

Reviewer comment:
Exclusion criteria are acceptable.

Randomization
Approximately 624 subjects were planned to be enrolled in a 2:2:1:1 ratio to NAFT-500 Cream, 2%; Naftin 1% Cream; 2-week placebo; or 4-week placebo in order to obtain 438 (146:146:73:73) evaluable subjects with positive baseline cultures. Qualifying subjects with clinical evidence of a tinea pedis infection confirmed by KOH and dermatophyte culture were randomized to NAFT-500 Cream, 2%; Naftin 1% Cream; or placebo; however, randomization occurred prior to availability of culture results.

Identity of the Investigational Medicinal Products
For this study, the term "study drug" applies to NAFT-500 Cream, 2%; Naftin 1% Cream; or matching placebo described as white to off-white shiny, homogeneous cream (Certificate of Analysis: May 2, 2008).

Table 5 (Applicant's Table 2) Identity of Study Drugs

Treatment Code	Study Drug	Lot Number and Expiration Date
Treatment A	NAFT-500 Cream, 2%	AAX-C and AAX-4C (expiration 11/09)
Treatment B and D	Placebo	AAW-4C, AAW-C, and AAW-2C (expiration 11/09); AGB-C (expiration 5/10)
Treatment C	Naftin 1% Cream	ZLBI-1 (expiration 11/09)

Blinding
This was a double-blind study with the Investigator, clinical site staff, and subjects blinded to the assignment.

Procedures
Subjects were evaluated at Day 1 (baseline), Week 2, Week 4, and Week 6. Adverse events, concomitant medications, and study medication compliance were reviewed at each visit. Efficacy assessments included KOH and culture evaluations, clinical signs/symptoms (erythema, scaling, pruritus), and Physicians Global Evaluations.

The areas noted as having clinical evidence (at least moderate erythema, moderate scaling, and mild pruritus) of tinea pedis infection was marked on the electronic CRF. All areas were to be treated, however, only the areas noted as being the most clinically affected at the time of the visit was used for tracking the signs and symptoms. Study product was to be applied topically once daily to all affected areas including a half-inch margin of healthy skin adjacent to the affected area(s) for two or four weeks depending on the treatment schedule. The same evaluator was to be used within a subject for performing the clinical signs and symptoms of disease severity.

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Baseline Signs and Symptoms

Clinical evaluations of signs and symptoms of tinea pedis, i.e., erythema, scaling, pruritus, fissures, macerations and burning, were assessed during Screening using the following 4-point severity scale with a "not done" option.

The severity grades were as follows:

- 0 = absent
- 1 = mild
- 2 = moderate
- 3 = marked
- 4 = not done

Erythema, scaling, pruritus, fissures, macerations and burning were assessed at visit I (day 1). At all subsequent visits erythema, scaling and pruritus of the most clinically affected areas at that visit were to be assessed. The affected areas may vary from visit to visit. The following 4 point scale was used:

Table 6

0	Absent (normal appearing skin
1	Mild (barely abnormal)
2	Moderate (distinctly present abnormality)
3	Marked (intense involvement or marked abnormality)

Table 7. The Physicians Global Evaluation (based on clinical observations and subject report) consisted of the following 5 categories:

1	Clinical cure (normal appearance of skin with signs and symptoms of tinea pedis completely resolved)
2	Effective clinical treatment (marked improvement over Day 1 in signs and symptoms)
3	Moderate clinical improvement (most Day 1 signs and symptoms showed a definite decrease)
4	Mild clinical improvement (some Day 1 signs and symptoms have decreased, significant evidence of disease remained)
5	Worsening of clinical status (some Day 1 signs and symptoms were more severe and/or new signs and symptoms were present)

Reviewer comment:

- *Categories 2-4 of this Physicians Global Evaluation scale are not static. The following comments were provided in the January 7, 2009 Agency advice letter: "Complete cure as defined by a score of 1 on the Physicians Global Evaluation is inadequate as a primary endpoint in these Phase 3 trials. An acceptable scale, a Physicians Global Assessment of disease severity, should be a 5-grade, static scale with morphologic descriptors that incorporate signs of tinea infection (scaling, erythema, and pruritus) such that the severity levels are clearly distinguishable and inter-observer*

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variability is minimized. Overlapping of severity levels is strongly discouraged. The scale should be dichotomized to success vs. failure a priori in the protocol.

- *Inclusion criteria should require that subjects have an appropriate range of scores on the Physician Global Assessment at baseline to ensure that subjects who achieve success have demonstrated adequate improvement from baseline."*

Primary Efficacy Variable

- The first primary efficacy objective was to compare the proportion of complete cure at Week 6 (4 weeks following 2 weeks of treatment) between NAFT-500 Cream, 2% and 2-week placebo and absence of Erythema, Scaling, and Pruritus (grade 0 for each) evaluated using the severity grade scale: 0 = absent, 1 = mild, 2 = moderate, 3 = marked, and 4 = not done.

- The second primary efficacy objective was to compare the proportion of complete cure at Week 6 (2 weeks following 4 weeks of treatment) between Naftin 1% Cream and 4-week placebo and and absence of Erythema, Scaling, and Pruritus (grade 0 for each) evaluated using the severity grade scale: 0 = absent, 1 = mild, 2 = moderate, 3 = marked, and 4 = not done.

Complete cure is defined as negative mycology results from the central laboratory (dermatophyte culture and KOH) and absence of erythema, scaling, and pruritus that were evaluated using a 4-point severity scale.

Reviewer comment:
1) At the PreIND meeting the applicant was advised as follows:
The Agency recommended primary endpoint is the percent of subjects with complete cure at a prespecified time point. Complete cure is defined as subjects with both: Clinical clearance—absence of any signs or symptoms of dermatophyte infections (i.e., a score representing 'clear' on a static global investigator assessment scale). However, the study protocol was not amended to reflect the recommendation.
2) In the original protocol, the primary efficacy comparisons of NAFT-500 cream to placebo and Naftin® 1% cream to placebo based on the percentage of subjects at the 2 week time point post treatment (Week 4) with complete cure, defined as negative mycology results from the central laboratory (dermatophyte culture and KOH) and negative signs and symptoms. However, the December 23, 2009 statistical analysis plan #3 changed the primary efficacy point for the 2 week NAFT500 from week 4 to week 6.

Secondary Endpoints

• Mycological Cure: negative KOH examination and negative dermatophyte culture at Week 4 (NAFT-500 Cream, 2% versus (vs) 2-week placebo); and
• Treatment Effectiveness: negative KOH, negative culture, and Scaling, Erythema, and Pruritus grades of 0 or 1 at Week 4 (NAFT-500 Cream, 2% vs. 2-week placebo).

Other secondary efficacy variables included the following, evaluated at Week 2 and Week 4:

• Clinical Cure: Scaling, Erythema, and Pruritus scores of 0;
• Clinical Success: Scaling, Erythema, and Pruritus scores of 0 or 1;
• Physicians Global Evaluation; and • Subject Satisfaction Assessment.

In addition, mycological cure and treatment effectiveness were evaluated at Week 2 and Week 4.

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The following populations were used in the analysis of the data:

- Safety-evaluation set (SES): The SES population included all subjects who received study drug at least once.
- Full-analysis set (FAS): The FAS population was the subset of all subjects in the SES population with a positive culture at baseline for whom the primary efficacy endpoint was available (which was the case for all subjects, because dropouts and cases with missing information were considered as not completed cures by definition, see below). This was a modified intent-to-treat (MITT) principle because culture results were not available before the start of treatment.
- Per-protocol set (PPS): The PPS population was the subset of subjects in the FAS population without major protocol deviations. Some major protocol deviations were defined as follows:
  - Subjects with insufficient baseline signs and symptoms;
  -Treatment with exclusionary previous and/or concomitant medications;
  -Enrollment prior to study determined wash-out of concomitant medications;
  -Subject visits that occurred > 3 days outside of the expected visit date; or
  -Missing or unknown Week 4 KOH and dermatophyte culture result for NAFT-500 Cream, 2% or Week 6 KOH and dermatophyte culture result for Naftin 1% Cream.

Additional and specific determinations on which subjects were considered major protocol violators were discussed during the BDRM and were finalized prior to database lock and unblinding.

Changes In The Conduct Of The Study Or Planned Analyses

There were 2 protocol amendments and three changes to the statistical analysis plan.

Protocol Amendment 1 was effective July 29, 2008. This amendment covered changes to vendors and clarifications on discrepancies discovered after finalization of the original document.

Protocol Amendment 2 was effective October 21, 2008. This amendment covered changes to vendors and clarifications on discrepancies discovered after finalization of the original document.

Changes to the Statistical Analysis Plan

Based on comments received from the FDA on 07 January 2009, the following changes were made to the planned analyses specified in the protocol:

• The primary efficacy and most important secondary efficacy analyses were now carried out at Week 6;
• The most important secondary variables were changed to mycological cure and treatment effectiveness in place of mycological cure and clinical cure;
• The efficacy analyses now used CMH tests after stratification by pooled clinical site as a replacement for unadjusted chi-square tests; and.
• Since the planned efficacy analyses now incorporated pooled clinical site as stratification variable in all CMH analyses to adjust for its potential confounding or effect modification, the previously planned logistic regression analysis that was proposed to assess this was removed.

Reviewer comments:

According to the FDA Statistical Reviewer (email dated 07/22/11), the statistical plan changing the primary efficacy and most important secondary efficacy analyses from week 4 for the 2% formulation to be carried out at Week 6 was not submitted to the Agency for review and comment.

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Study MUS 90200-0736/1 Results

Study dates: September 12, 2008 (start of clinical phase) to August 29, 2009 (end of clinical phase)

A total of 921 subjects were screened and 709 subjects were randomized for this study. There were 237 subjects randomized to the Naftin® 1% Cream treatment group and 119 subjects randomized to the 4-week placebo treatment group. Overall, 235 subjects were randomized to the NAFT-500 Cream, 2% treatment group and 118 subjects randomized to the 2-week placebo treatment group at the following 15 clinical study sites for NAFT-500 (Source: Table 14.1.2):

Table 8. Clinical Study Sites

Study Site	Name and Location of Investigator	No. Subjects Enrolled
#001	Raza Aly, PhD University of California San Francisco Dept. of Dermatology 1701 Divisadero St., Room 230 San Francisco, CA 94115	14
#002	Jeffrey Adelglass, MD Research Across America 6020 West Parker Rd., Ste. 400 Plano, TX 75093	50
#004	Erin Boh, MD. Ph.D Tulane University Health Services Ctr. 1440 Canal St.,Ste. 1504 New Orleans, LA 70112	8
#006	Zoe Draelos, MD 2444 N. Main Street High Point, NC 27262	12
#008	Robert Haber, M.D. Haber Dermatology 14077 Cedar Rd., Ste. 200 South Euclid, OH 44118	16
#009	JoLynne Herzog Radiant Research 516 Brookwood Blvd., 1st Floor Birmingham, AL 35209	10
#010	Terry Jones, MD J & S Studies 1710 Crescent Point Parkway College Station, TX 77845	27
#011	Lawrence Parish, MD Paddington Testing Company 1760 Market St., Ste. 301 Philadelphia, PA 19103	38
#012	Phoebe Rich, MD Oregon Dermatology & Research Center 2565 NW Lovejoy St. Suite 200 Portland, OR 97210	14
#013	Cynthia Strout	16

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	1156 Bowman Rd, Suite 102 Mt. Pleasant, SC 29464	
#014	Tracey Vlahovic Temple University School of Podiatric Medicine Eighth at Race Street Philadelphia, PA 19107	32
#015	Hector Wiltz , M.D. FXM Research 11760 Bird Rd., Ste. 451 Miami, FL 33175 Phone: (305)220-5222	43
#016	Kimball Silverton, D.O. Silverton Skin Institute 8245 N Holly Rd., Ste. 101 Grand Blanc, MI 48439	2
#19	Francisco Flores, M.D. Francisco Flores, MD FXM Research Miramar 3000 SW 148th Avenue, Suite 216 Miramar, FL 33027	54
#21	Felix Sigal Foot and Ankle Clinic 3875 Wilshire Blvd, Ste 307 Los Angeles, CA 90010-3209	17

Study Subjects

Demographics and Other Baseline Characteristics (Safety Evaluation Set)

Demographics

The majority of subjects were male (502 [71.0%]), of non-Hispanic or Latino ethnicity (455 [64.4%]), and from ≥ 18 to < 65 years of age (658 [93.1%]). Overall, a greater number of subjects had interdigital tinea pedis or both interdigital and moccasin tinea pedis (303 [42.9%] subjects and 287 [40.6%] subjects, respectively) based on post hoc classification of tinea pedis. Study Subjects Demographics and Other Baseline Characteristics Baseline Characteristics for the safety evaluation set were similar.

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Table 9 (Applicant's Table 7) Demographics (SES)

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Table 7: Demographics (SES)

	NAFT-500 (N = 234)	2-Week Placebo (N = 118)	Naftin 1% (N = 236)	4-Week Placebo (N = 119)	Total (N = 707)
Gender [n (%)]					
Male	171 (73.1)	80 (67.8)	165 (69.9)	86 (72.3)	502 (71.0)
Female	63 (26.9)	38 (32.2)	71 (30.1)	33 (27.7)	205 (29.0)
Age (years)					
N	234	118	236	119	707
Mean (SD)	42.7 (13.03)	41.0 (12.91)	41.4 (14.08)	41.4 (14.00)	41.7 (13.52)
Min, Max	17,83	12, 72	12,79	13, 83	12, 83
Q1, Median, Q3	33.0, 42.0, 51.0	30.0, 42.0, 51.0	31.0, 43.0, 51.0	32.0, 41.0, 51.0	32.0, 42.0, 51.0
Age (years) [n (%)]					
< 18 years	2 (0.9)	1 (0.8)	14 (5.9)	6 (5.0)	23 (3.3)
≥ 18 to < 65 years	220 (94.0)	115 (97.5)	212 (89.8)	111 (93.3)	658 (93.1)
≥ 65 years	12 (5.1)	2 (1.7)	10 (4.2)	2 (1.7)	26 (3.7)
Ethnicity [n (%)]					
Hispanic or Latino	76 (32.5)	35 (29.7)	97 (41.1)	44 (37.0)	252 (35.6)
Not Hispanic or Latino	158 (67.5)	83 (70.3)	139 (58.9)	75 (63.0)	455 (64.4)

Data Source: End-of-Text Table 14.1.5.
Abbreviations: SD = standard deviation, Min = Minimum, Max = Maximum, Q1 = 1st quartile, Q3 = 3rd quartile.
Note: %=(n/N)x100.

Reviewer comment:
Although enrollment included patients ≥ 12 years of age, only 1 patient between age 12 and 17 years 11 months and 8 patients ≥ 65 years of age were exposed to the 2% formulation. The applicant's racial demographics classification as to either Hispanic or Latino or non-Hispanic or Latino ethnicity is somewhat unusual; however, the study sites are geographically dispersed.

6.1.3 Subject Disposition

Overall, 235 subjects were randomized to the NAFT-500 Cream, 2% treatment group and 118 subjects were randomized to the 2-week placebo treatment group; 237 subjects were randomized to the Naftin 1% Cream treatment group and 119 subjects were randomized to the 4-week placebo treatment group (See Table 10 that follows.) Baseline characteristics were similar across all treatment groups

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Table 10: (Applicant's Table 14.1.8) Baseline Severity Table (FAS)

Table 14.1.8 Study Subjects
Demographics and Other Baseline Characteristics
Signs and Symptoms at Baseline
(Safety Evaluation Set)

Signs and Symptoms	NAFT-500 (N=234)	Placebo 2-Week (N=118)	Naftin 1% (N=236)	Placebo 4-Week (N=119)	Total (N=707)
Erythema					
Absent	1 (0.4)	0	0	0	1 (0.1)
Mild	0	0	0	0	0
Moderate	162 (69.2)	86 (72.9)	172 (72.9)	80 (67.2)	500 (70.7)
Marked	71 (30.3)	32 (27.1)	64 (27.1)	39 (32.8)	206 (29.1)
Not Done/Missing	0	0	0	0	0
Scaling					
Absent	0	0	0	0	0
Mild	0	0	0	0	0
Moderate	107 (45.7)	60 (50.8)	112 (47.5)	57 (47.9)	336 (47.5)
Marked	127 (54.3)	58 (49.2)	124 (52.5)	62 (52.1)	371 (52.5)
Not Done/Missing	0	0	0	0	0
Pruritus					
Absent	1 (0.4)	0	0	0	1 (0.1)
Mild	24 (10.3)	15 (12.7)	19 (8.1)	14 (11.8)	72 (10.2)
Moderate	84 (35.9)	43 (36.4)	86 (36.4)	35 (29.4)	248 (35.1)
Marked	125 (53.4)	60 (50.8)	131 (55.5)	70 (58.8)	386 (54.6)
Not Done/Missing	0	0	0	0	0

Note: %=(n/N)x100.
Data Source: Listing 9.
Source: (b) (4) Directory: /sasdata2/bsd/merz/mus0736/07MRZ002/programs/rtbsigns.sas (JE)

Baseline severity was similar across treatment study arms.

Table 11 (Table Applicant's Table 4) Disposition of Subjects – Number of Subjects Enrolled (All Screened Subjects)

Table 4: Disposition of Subjects – Number of Subjects Enrolled (All Screened Subjects)

	NAFT-500 n (%)	2-Week Placebo n (%)	Naftin 1% n (%)	4-Week Placebo n (%)	Total n (%)
Subjects Screened					921
Subjects Randomized, N	235	118	237	119	709
Subjects in Safety-Evaluation Set[a]	234 (99.6)	118 (100.0)	236 (99.6)	119 (100.0)	707 (99.7)
Subjects with Positive Baseline Culture	147 (62.6)	70 (59.3)	143 (60.3)	65 (54.6)	425 (59.9)
Subjects in Full-Analysis Set[b]	147 (62.6)	70 (59.3)	143 (60.3)	65 (54.6)	425 (59.9)
Subjects Completing Visit 1 (Day 1)	235 (100.0)	118 (100.0)	237 (100.0)	119 (100.0)	709 (100.0)
Subjects Completing Visit 2 (Week 2)	207 (88.1)	101 (85.6)	220 (92.8)	103 (86.6)	631 (89.0)
Subjects Completing Visit 3 (Week 4)	145 (61.7)	70 (59.3)	142 (59.9)	75 (63.0)	432 (60.9)
Subjects Completing Visit 4 (Week 6)	145 (61.7)	59 (50.0)	135 (57.0)	73 (61.3)	412 (58.1)
Subjects in Per-Protocol Set[c]	105 (44.7)	54 (45.8)	111 (46.8)	48 (40.3)	318 (44.9)

Data Source: End-of-Text Table 14.1.1.
Note: %=(n/Number of subjects randomized)x100.
[a] The safety-evaluation set (SES) included all subjects who received study medication at least once.
[b] Full-analyses set (FAS) was the subset of all subjects in the SES with positive culture at baseline for whom the primary efficacy endpoint was available.
[c] Per-protocol set was the subset of subjects in the FAS without major protocol deviations.

Of these subjects, 412 (58.3%) completed the study and 295 (41.7%) subjects prematurely discontinued the study. Of these 295 subjects who discontinued the study, there was a higher proportion of subjects who discontinued for 'other' reasons (216 [30.6%]) or were lost to follow-up (50 [7.1%]) (Table 5). Of the 216 subjects who discontinued for 'other' reasons, 200 subjects were screen failures.

Table 12 (Applicant's Table 5) Disposition of Subjects- Study Discontinuation (SES)

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Table 5: Disposition of Subjects – Study Discontinuation (SES)

	NAFT-500 (N = 234) n (%)	2-Week Placebo (N = 118) n (%)	Naftin 1% (N = 236) n (%)	4-Week Placebo (N = 119) n (%)	Total (N = 707) n (%)
Completed study	145 (62.0)	59 (50.0)	135 (57.2)	73 (61.3)	412 (58.3)
Prematurely discontinued	89 (38.0)	59 (50.0)	101 (42.8)	46 (38.7)	295 (41.7)
Reason for premature discontinuation					
Progression of study disease	0	0	0	0	0
Adverse event(s)	1 (0.4)	2 (1.7)	0	1 (0.8)	4 (0.6)
Lost to follow-up	17 (7.3)	12 (10.2)	15 (6.4)	6 (5.0)	50 (7.1)
Noncompliance	1 (0.4)	0	1 (0.4)	3 (2.5)	5 (0.7)
Positive pregnancy test	0	0	0	0	0
Voluntary withdrawal	3 (1.3)	2 (1.7)	6 (2.5)	2 (1.7)	13 (1.8)
Termination by sponsor	4 (1.7)	0	0	1 (0.8)	5 (0.7)
Investigator decision	1 (0.4)	1 (0.8)	0	0	2 (0.3)
Other	62 (26.5)	42 (35.6)	79 (33.5)	33 (27.7)	216 (30.6)

Data Source: End-of-Text Table 14.1.3.
Note: %=(n/N)x100.

Type of Tinea Pedis

- According to the applicant (ISE pg. 45 of 58), subjects randomized to treatment with NAFT-500 Cream, 2% or placebo in the Phase 3 tinea pedis study presented at Screening (Visit 1) with different types of infection. The tinea pedis study was not designed to treat a specific type of tinea pedis; rather, subjects were instructed to treat the affected area recorded at Baseline and Investigators were instructed to evaluate the worst site at each visit. Thus as an example, some subjects may have treated interdigital spaces based on the baseline diagnosis, but subsequent Investigator assessments were performed on the moccasin area, and vice versa.

Type of tinea pedis as classified by the applicant is summarized Table 13 that follows.
Table 13 (modified Table 4 Baseline Characteristics of Subjects (Safety Evaluation Set))

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	MUS 90200-0736/1				
Parameter	NAFT-500 Cream, 2% N = 234	Placebo 2-Week N = 118	Naftin 1% Cream N = 236	Placebo 4-Week N = 119	Total N = 707
Type of tinea pedis, n (%)					
Interdigital	103 (44.0)	48 (40.7)	99 (41.9)	53 (44.5)	303 (42.9)
Moccasin	18 (7.7)	7 (5.9)	20 (8.5)	16 (13.4)	61 (8.6)
Both Interdigital and Moccasin	96 (41.0)	54 (45.8)	95 (40.3)	42 (35.3)	287 (40.6)
Other	17 (7.3)	9 (7.6)	22 (9.3)	8 (6.7)	56 (7.9)
Dermatophyte species, n (%)					
Trichophyton rubrum	129 (55.1)	60 (50.8)	123 (52.1)	59 (49.6)	371 (52.5)
Other	19 (8.1)	11 (9.3)	20 (8.5)	7 (5.9)	57 (8.1)

Notes:
1. The Safety-Evaluation Set (SES) includes all subjects who received study medication at least once.
2. Percentages are based on randomized treatment for baseline culture results and on treatment received for analysis populations.
3. (b) (6) in Study MRZ 90200/FI/3001 was randomized to NAFT-500 Cream, 2%, but received Placebo 2-Week.
Abbreviations: NA = not applicable; Q1 = the median of the first half; Q3 = the median of the second half; SD = standard deviation.
Source: ISE Post-text Table 4.

The post hoc assessment schemata provided by the applicant (ISE, Section 8.3) follows:

- Subjects diagnosed with interdigital tinea pedis at Screening (Visit 1) and assessed for treatment of the same type at the Terminal Visit were classified as having interdigital tinea pedis.
- Subjects diagnosed with moccasin-type tinea pedis at Screening and assessed for treatment of the same type at the Terminal Visit were classified as having moccasin-type tinea pedis.
- Subjects diagnosed with interdigital tinea pedis at Screening and assessed for treatment of moccasin-type tinea pedis at the Terminal Visit, or vice versa, were classified as having both interdigital- and moccasin-type tinea pedis.
- Subjects who were not diagnosed or assessed for a specific type of tinea pedis at the Screening and/or Terminal Visit were classified as having either interdigital- or moccasin type tinea pedis on a subject-by-subject basis using the recorded "site of assessment."

Reviewer comment:

- *The manner of assessment of the type of tinea pedis described above based on targeted areas is arbitrary and unacceptable to this reviewer since tinea pedis is clinically diagnosed by global inspection of the feet. Additionally, subjects who were complete cures at the terminal visit should not have clinical signs and symptoms of tinea pedis present.*
- *According to the applicant, the most frequently encountered sites of assessment for the affected subjects included "left foot between 1st and 2nd toe" (classified as interdigital) and "right heel" (classified as moccasin). However according to M. Robbins (2009) and based on clinical*

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experience, interdigital tinea pedis is most often seen between the fourth and fifth toes. Analysis of Primary Endpoint(s)

Primary Efficacy Variables

The first primary efficacy variable was the percentage of subjects in the NAFT-500 Cream, 2% or 2-week placebo treatment groups with a complete cure at Week 6 with the second primary efficacy variable being the percentage of subjects in the Naftin 1% Cream or 4-week placebo treatment groups with a complete cure at the same time interval (Week 6).

Table 14 (Applicant's Table 8) Complete Cure Rate (LOCF)- primary Analysis (FAS)

Table 8: Complete Cure Rate (LOCF) – Primary Analysis (FAS)

	Complete Cure[a]	NAFT-500 (N = 147) n (%)	2-Week Placebo (N = 70) n (%)	Naftin 1% (N = 143) n (%)	4-Week Placebo (N = 65) n (%)
Visit 2 (Week 2)	Yes	4 (2.7)	0	3 (2.1)	0
	No	143 (97.3)	70 (100.0)	140 (97.9)	65 (100.0)
	Difference(97.5% CI)[b]	2.7 (0.1,+ ∞)		2.1 (-0.3, + ∞)	
	P-value[c]	0.100		0.097	
Visit 3 (Week 4)	Yes	6 (4.1)	1 (1.4)	5 (3.5)	1 (1.5)
	No	141 (95.9)	69 (98.6)	138 (96.5)	64 (98.5)
	Difference(97.5% CI)[b]	2.7 (-1.6, + ∞)		2.0 (-2.3, + ∞)	
	P-value[c]	0.234		0.143	
Visit 4 (Week 6)	Yes	26 (17.7)	5 (7.1)	23 (16.1)	2 (3.1)
	No	121 (82.3)	65 (92.9)	120 (83.9)	63 (96.9)
	Difference(97.5% CI)[b]	10.5 (1.9, + ∞)		13.0 (5.7, + ∞)	
	P-value[c]	0.010		0.001	
	P-value[d]	0.010		0.001	
	P-value[e]	0.581		0.640	

Data Source: End-of-Text Table 14.2.1.
Abbreviations: CI = confidence interval; KOH = potassium hydroxide.

Note 1: %=(n/Total number of subjects with non-missing data at each visit)x100.
Note 2: For the most important secondary efficacy variables (NAFT-500 vs placebo at 4 weeks), statistical significance will be assessed using the Hochberg procedure.
[a] Mycological Cure: Negative KOH and negative culture.
[b] Treatment Effectiveness: Negative KOH, negative culture, and Erythema, Scaling and Pruritus grades of 0 or 1.
[c] One-sided 97.5% CI calculated using normal approximation to the binomial for the difference in proportion of 'yes' responses between NAFT-500 and placebo.
[d] *P*-value is from a one-sided Cochran-Mantel-Haenszel (CMH) test comparing NAFT-500 group vs placebo group, with pooled clinical site as the stratification variable.
[e] Adjusted *P*-value from Hochberg's step-up procedure.

Reviewer comment:

The title of Table 8 above is incorrect although the numbers for the NAFT-500 study population is consistent with the Agency Statistical review. *As noted, column a is actually mycological cure (negative*

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KOH and negative culture whereas Complete Cure is defined as mycological cure (negative KOH and negative culture) plus and absence of erythema, scaling, and pruritus.

According to the Agency Statistical reviewer, For the FAS population, the NAFT-500 was statistically superior to vehicle (17.7% vs. 7.1%, p=0.01) using the one-sided CMH test stratified by pooled sites with missing data imputed with LOCF. Using the same statistical test, a sensitivity analysis with data that imputed the missing as failures was carried out whose results are also presented below.

Table 15 (Stat Table 9.) Complete Cure Rate at Week 6

	NAFT-500	Vehicle	p-value
Sponsor's analysis(1)	26/147 (17.7%)	5/70 (7.1%)	0.01
Sensitivity analysis (2)	23/147 (15.7%)	5/70 (7.1%)	0.02
Sponsor's sensitivity analysis(3)	23/128 (18.0%)	5/63 (7.9%)	0.01
Sponsor's sensitivity analysis(4)	18/87 (20.7%)	3/48 (6.3%)	0.01

Complete Cure is defined as having negative mycology results (dermatophyte culture and KOH) and absence of erythema, scaling and pruritus at Week 4. P-value is calculated from a one-sided CMH test stratified by pooled sites.
(1) Sponsor's protocol-specified primary analysis –one-sided CMH test stratified by pooled sites, FAS, LOCF.
(2) Reviewer's sensitivity analysis –one-sided CMH test stratified by pooled sites, missing imputed as failure. FAS.
(3) Sponsor's sensitivity analysis. Observed data only without imputing missing data.
(4) Sponsor's sensitivity analysis. Per Protocol Set. (PPS)

Analysis of Secondary Endpoints(s)

Mycological Cure and Treatment Effectiveness

Applicant's Table 9 shows the proportion of subjects achieving mycological cure (LOCF) at Week 2, 4, and 6 for the FAS population. The *p*-values obtained from the hypotheses tests were from a one-sided CMH test comparing NAFT-500 Cream, 2% or Naftin 1% Cream treatment group vs the corresponding placebo group, with pooled clinical site as the stratification variable. Statistical significance was assessed using the Hochberg step-up procedure (adjusted *p*-values). The Hochberg procedure was used to adjust *p*-values for both treatment effectiveness and mycological cure endpoints in order to account for the simultaneous testing of their corresponding hypotheses.

At Visit 4, Week 6, mycological cure was achieved in 99 (67.3%) of subjects in the NAFT-500 Cream, 2% treatment group and in 15 (21.4%) of subjects for the corresponding 2-week placebo ($p<0.001$; adjusted $p<0.001$); 102 (71.3%) of subjects in the Naftin 1% Cream treatment group and 14 (21.5%) of subjects in the corresponding 4-week placebo ($p<0.001$). Therefore, the null hypotheses were rejected and superiority of the active treatments over placebo was demonstrated.

At Visit 4, Week 6, treatment effectiveness was achieved in 83 (56.5%) of subjects in the NAFT-500 Cream, 2% treatment group and in 14 (20.0%) of subjects for the corresponding 2-week placebo ($p<0.001$; adjusted $p<0.001$); 84 (58.7%) of subjects in the Naftin 1% Cream treatment group and 9 (13.8%) of subjects in the corresponding 4-week placebo ($p<0.001$). Therefore, the null hypotheses were rejected and superiority of the active treatments over placebo was demonstrated.

Table 16 Mycological Cure and Treatment Effectiveness (LOCF)- Secondary

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Table 9: Mycological Cure and Treatment Effectiveness (LOCF) – Secondary Analysis (FAS)

		NAFT-500 (N = 147) n (%)	2-Week Placebo (N = 70) n (%)	Naftin 1% (N = 143) n (%)	4-Week Placebo (N = 65) n (%)
Mycological Cure[a]					
Visit 2 (Week 2)	Yes	41 (27.9)	13 (18.6)	45 (31.5)	12 (18.5)
	No	106 (72.1)	57 (81.4)	98 (68.5)	53 (81.5)
	Difference(97.5% CI)[c]	9.3 (-2.3, +)		13.0 (0.9, +)	
	P-value[d]	0.049		0.028	
Visit 3 (Week 4)	Yes	79 (53.7)	14 (20.0)	76 (53.1)	6 (9.2)
	No	68 (46.3)	56 (80.0)	67 (46.9)	59 (90.8)
	Difference(97.5% CI)[c]	33.7 (21.4, +)		43.9 (33.1, +)	
	P-value[d]	<0.001		<0.001	
Visit 4 (Week 6)	Yes	99 (67.3)	15 (21.4)	102 (71.3)	14 (21.5)
	No	48 (32.7)	55 (78.6)	41 (28.7)	51 (78.5)
	Difference(97.5% CI)[c]	45.9 (33.7, +)		49.8 (37.3, +)	
	P-value[d]	<0.001		<0.001	
	P-value[e]	<0.001			
Treatment Effectiveness[b]					
Visit 2 (Week 2)	Yes	21 (14.3)	9 (12.9)	25 (17.5)	4 (6.2)
	No	126 (85.7)	61 (87.1)	118 (82.5)	61 (93.8)
	Difference(97.5% CI)[c]	1.4 (-8.2, +)		11.3 (2.8, +)	
	P-value[d]	0.460		0.011	
Visit 3 (Week 4)	Yes	52 (35.4)	7 (10.0)	51 (35.7)	4 (6.2)
	No	95 (64.6)	63 (90.0)	92 (64.3)	61 (93.8)
	Difference(97.5% CI)[c]	25.4 (14.9, +)		29.5 (19.7, +)	
	P-value[d]	<0.001		<0.001	
Visit 4 (Week 6)	Yes	83 (56.5)	14 (20.0)	84 (58.7)	9 (13.8)
	No	64 (43.5)	56 (80.0)	59 (41.3)	56 (86.2)
	Difference(97.5% CI)[c]	36.5 (24.1, +)		44.9 (33.2, +)	
	P-value[d]	<0.001		<0.001	
	P-value[e]	<0.001			

Data Source: End-of-Text Table 14.2.6.
Abbreviation: CI = confidence interval; NE = nonestimable.
Note: %=(n/Total number of subjects with non-missing data at each visit-subgroup combination)x100.
[a] Complete cure = Negative mycology results from the central laboratory (dermatophyte culture and KOH) and absence of erythema, scaling and pruritus.
[b] One-sided 97.5% Confidence Interval calculated using normal approximation to the binomial for the difference in proportion of 'yes' responses between NAFT-500 Cream, 2% and 2-week or Naftin 1% Cream and 4-week placebo.
[c] *P*-value was from a one-sided Cochran-Mantel-Haenszel (CMH) test comparing NAFT-500 group or Naftin 1% group vs the corresponding placebo group, with pooled clinical site as the stratification variable.

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Analysis results of secondary efficacy endpoints, mycological cure and treatment effectiveness, performed by Agency's Statistical Reviewer are presented below. According to the Stat review, both secondary endpoints are statistically significant after adjusting for multiplicity using Hochberg's procedure and the secondary endpoint efficacy results are consistent with primary efficacy endpoint results.

Table 17 (Statistical Table 10.) Secondary efficacy analysis results at Week 6

	NAFT-500	Vehicle	p-value
Mycological Cure[(1)]	99/147 (67.3%)	15/70 (21.4%)	<0.001
Treatment Effectiveness [(2)]	83/147 (56.5%)	14/70 (20.0%)	<0.001

One-sided CMH test by center, FAS, LOCF.
Adjusted p-value from Hochberg's step-up procedure.
(1) Mycological cure: negative KOH and negative culture
(2) Treatment effectiveness: negative KOH, negative culture, erythema, scaling and pruritus grades of 0 or 1.

According to the applicant's re-classification, the applicant stated that the majority of subjects had the interdigital type as shown in the table below.

Table 18 (Applicant's Table 8–2) Number (%) of Subjects Assessed for Efficacy of Treatment for Tinea Pedis at the Terminal Visit by Type (SES)

	MUS 90200-0736/1				
	NAFT-500 Cream, 2% N = 234	Placebo 2-Week N = 118	Naftin 1% Cream N = 236	Placebo 4-Week N = 119	Total N = 707
Site	n (%)	n (%)	n (%)	n (%)	
Interdigital	161 (68.8)	88 (74.6)	170 (72.0)	83 (69.7)	502 (71.0)
Moccasin	50 (21.4)	21 (17.8)	44 (18.6)	23 (19.3)	138 (19.5)
Both Interdigital and Moccasin	23 (9.8)	9 (7.6)	22 (9.3)	13 (10.9)	67 (9.5)

Notes:
1. The Safety-Evaluation Set (SES) includes all subjects who received study medication at least once.
2. The Phase 3 tinea pedis study was not designed to treat a specific type of tinea pedis; rather, subjects were instructed to treat the affected area recorded at Baseline and Investigators were instructed to evaluate the worst site at each visit.

Source: ISE Post-text Table 4.

Table 19 (Statistical Table 17.) Complete Cure Rates based on the 're-classified type' of Tinea Pedis

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	NAFT-500 N=147	Vehicle N=70
Sponsor's analysis		
Both interdigital and moccasin	7/15 (46.7%)	0/4 (0%)
Interdigital only	16/98 (16.3%)	4/55 (7.3%)
Moccasin only	3/34 (8.8%)	1/11 (9.1%)

Source: Complete cure rates for each type of Tinea Pedis at baseline based on sponsor's re-classification, FAS, LOCF.

Reviewer comment:
This reviewer concurs with the Statistical reviewer's use of the original baseline diagnosis rather than reclassifying subjects based on multiple assessments based on targeted areas as proposed by the applicant. Overall, the majority of subjects were diagnosed as having interdigital type tinea pedis if the both interdigital/moccasin group are included. A small number of patients were diagnosed with moccasin and others types of tinea pedis. Those diagnosed as others (i.e., vesicular, ulcerative, etc.) should have been excluded from study participation. According to Statistical Reviewer, approximately 40%, 6% and 45% of FAS subjects across the treatment arms were classified as having interdigital, moccasin and both types of tinea pedis at baseline, respectively.

Table 20 (Statistical Table 18) Complete Cure Rates based on the 'original baseline type' of Tinea Pedis

	NAFT-500 N=147	Vehicle N=70
Reviewer's analysis		
Both interdigital and moccasin	13/65 (20.0%)	2/32 (6.3%)
Interdigital	12/57(21.1%)	3/29 (10.3%)
Moccasin	0/12 (0 %)	0/3 (0 %)
Others	1/13 (7.7%)	0/6 (0 %)

Source: Complete cure rates for each type of Tinea Pedis at baseline based on sponsor's original classification of tinea pedis, FAS, LOCF.

As noted, the number within each type of tinea is small. According to the statistical review, due to the small number of patients for each type of tinea pedis, only rough estimates of the complete cure rates for each type of tinea pedis could be obtained and that it is difficult to draw conclusions regarding the complete cure rates for each type of tinea pedis based on the applicant's study. Of note, no patients with moccasin-type tinea pedis at baseline achieved complete cure.

According to the applicant Study Report, pg. 77 of 81), exploratory analyses for descriptive purposes only were performed to compare treatment with NAFT-500 Cream, 2% and Naftin 1% Cream LOCF (FAS). No significant difference was observed between the 2 active groups at Week 6.

Reviewer Conclusion:
Based on data submitted, statistical significance (p=0.01) of NAFT-500 over vehicle was demonstrated with response rates of 17.7% and 7.1%, respectively; however, the proposed indication for treatment of tinea pedis [redacted] (b) (4) is not supported by the data and demonstration of efficacy for each

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type of tinea pedis can only be inferred. Only rough estimates of the complete cure rates for each type of tinea pedis could be obtained to support (b) (4) tinea pedis (b) (4) due to small numbers of patients in each type, due to the applicant's study design, and arbitrary post hoc reclassification. Treatment of interdigital tinea pedis is being recommended for approval because numerically higher numbers of patients appeared to have had interdigital type tinea pedis and no patients with moccasin-type tinea pedis at baseline achieved complete cure. It is also noted that only 1 patient between age 12 and 17 years 11 months was exposed to the 2% formulation; therefore, this seems insufficient to this reviewer to allow inclusion of adolescent patients in labeling.

Study MRZ 90200/FI/3001

Study Title: "A Phase 3, Double-Blind, Randomized, Placebo-Controlled, Multicenter, Parallel Group Evaluation of the Efficacy and Safety of NAFT-500 in Subjects with Tinea Cruris"

Study Period: September 12, 2008 to: August 29, 2009

Overall Study Design
This was a 4-week, double-blind, randomized, placebo-controlled, multicenter, parallel group Phase 3 study of NAFT-500 Cream, 2% compared to 2-week placebo in the treatment of tinea cruris.

Key inclusion criteria included the following:

- Subjects who were males or nonpregnant females ≥ 12 years of age, of any race.
- Females of child-bearing potential must have had a negative urine pregnancy test.
- Subjects who had tinea cruris characterized by clinical evidence of a tinea infection (i.e., presence of at least moderate erythema, moderate scaling, and mild pruritus)

Exclusion Criteria
Exclusion criteria are similar to the t. pedis exclusions except that subjects who had foot psoriasis, corns and/or callus that involved any web spaces was not an exclusion criterion for this study.

Reviewer comments:
The exclusion criteria are acceptable.

Primary Efficacy Variable
The primary efficacy variable was the percentage of subjects at the 4-week time point with complete cure defined as negative mycology results from the central laboratory (dermatophyte culture and KOH) and absence of Erythema, Scaling, and Pruritus (grade 0 for each) evaluated using the severity grade scale: 0 = absent, 1 = mild, 2 = moderate, 3 = marked, and 4 = not done.

Secondary endpoints:
• Mycological Cure: negative KOH examination and negative dermatophyte culture at Week 4 (NAFT-500 Cream, 2% versus (vs) 2-week placebo); and • Treatment Effectiveness: negative KOH, negative culture, and Scaling, Erythema, and Pruritus grades of 0 or 1 at Week 4 (NAFT-500 Cream, 2% vs 2-week placebo).

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Other secondary efficacy variables included the following, evaluated at Week 2 and Week 4:
• Clinical Cure: Scaling, Erythema, and Pruritus scores of 0;
• Clinical Success: Scaling, Erythema, and Pruritus scores of 0 or 1;
• Physicians Global Evaluation; and
• Subject Satisfaction Assessment.
In addition, mycological cure and treatment effectiveness were evaluated at Week 2 and Week 4.

Analysis Sets
Statistical hypotheses tests, as carried out on the primary efficacy variable and most important secondary efficacy variables for inferential purposes, were one-sided at a 0.025 alpha (α) level. All other tests carried out used test statistics that were two-sided at a 0.05 alpha level (α), unless otherwise specified.

The following populations were used in the analyses of the data:
Safety-Evaluation Set (SES): The SES population was the subset of all subjects who received study drug at least once.

Full-Analysis Set (FAS): The FAS population was the subset of all subjects in the SES population with a positive culture at baseline for whom the primary efficacy endpoint was available (because dropouts and cases with missing information were considered as not complete cures by definition, this was true for all subjects). This was a modified intent-to-treat principle because the culture results were not available before the start of treatment.

Per-Protocol Set (PPS): The PPS population was the subset of subjects in the FAS population without major protocol deviations. Major protocol deviations were defined as follows:
• Subjects with insufficient baseline signs and symptoms;
• Treatment with restricted previous and/or concomitant medications;
• Enrollment prior to study-determined wash-out of concomitant medications;
• Subject visits occurring > 3 days outside of the expected visit date;
• Missing or unknown Week 4 KOH and dermatophyte culture results; or
• Missing or unknown Week 4 Scaling, Erythema, and Pruritus scores.
Specific determinations whether subjects were considered major protocol violators were made during the BDRM prior to database lock and unblinding.

Study Results
A total of 617 subjects were screened and 334 subjects were randomized for this study. Overall, 166 subjects were randomized to the NAFT-500 Cream, 2% treatment group and 168 subjects were randomized to the 2-week placebo treatment group at the following clinical study sites (Source: Table 14.1.2)

Table 21 Clinical Study Sites

Study Site	Name and Location of Investigator	No. Subjects Enrolled
#001	Raza Aly, PhD University of California San Francisco Dept. of Dermatology 1701 Divisadero St., Room	10

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#002	Jeffrey Adelglass, M.D. 6020 West Parker Rd., Ste. 400 Plano, TX 75093	46
#004	Erin Boh, M/D., PhD. Tulane University Health Services Ctr. 1440 Canal St.,Ste. 1504 New Orleans, LA 70112	16
#006	Zoe Draelos, M.D. 2444 N. Main Street High Point, NC 27262	10
#008	Robert Haber Haber Dermatology 14077 Cedar Rd., Ste. 200 South Euclid, OH 44118	5
#009	JoLynne Herzog M.D. Radiant Research 516 Brookwood Blvd., 1st Floor Birmingham, AL 35209	18
#010	Terry Jones, M.D. J & S Studies 1710 Crescent Point Parkway College Station, TX 77845	20
#011	Lawrence Parish, M.D. Paddington Testing Company 1760 Market St., Ste. 301 Philadelphia, PA 19103	30
#015	Hector Wiltz FXM Research 11760 Bird Rd., Ste. 451 Miami, FL 33175	22
#016	Kimball Silverton, D.O. Silverton Skin Institute 8245 N Holly Rd., Ste. 101 Grand Blanc, MI 48439	No data listed for this study site.
#19	Francisco Flores, M.D. Francisco Flores, MD FXM Research Miramar 3000 SW 148th Avenue, Suite 216	20
#22	David Sandercock, DO David Sandercock, DO Oakwell Clinical Research 3338 Oakwell Court Su	11
#23	Walter K. Nahm, M.D University Clinical Trials 7695 Cardinal Court Suite 210 San Diego, CA 92123	12
#24	Michael Gold, M.D Tennesse Clinical Research Ctr. 2000 Richard Jones Rd. Suite 223 Nashville, TN 37215	5
#25	Amaury. A Roman,M.D Advanced Medical Concepts, PSC 4 Baladority Street	58

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	Cidra, PR 00739	
#26	Edwin Camilio Vazquez, MD Calle Munoz Rivera #41 Aguas Buenas, PR 00703	9
#27	Isabel Quijano M.D CEMSI, Inc Ave. Jesus T. Pinero #1574 Caparra Terrace Rio Piedras, PR 00921	11
#28	Manuel A. Guzman,M.D Medicina General y Acupuntura Calle Ramon Gomez #2 Sur. Urb. Pereyo Humacao, PR 00791	10
#29	Julio D. Cordero Sepulveda, M.D Medicina General y Cirugia Menor Avenida Miguel Melendez Munoz #9 Cayey, PR 00736	21

Qualifying subjects with clinical evidence of a tinea cruris infection confirmed by KOH and dermatophyte culture were randomized to NAFT-500 Cream, 2% or 2-week placebo. Subjects applied the assigned study drug QD to the affected areas for 2 weeks and returned to the clinical site or a follow-up visit at Week 4. Subjects were evaluated at Day 1 (baseline), Week 2, and Week 4. Assigned study drug was applied topically once daily to all affected areas including a half-inch margin of healthy skin adjacent to the affected area(s) for 2 weeks. The first dose of the study drug was applied at clinical site after the study staff provided application instruction.

Disposition of Subjects

Overall, 166 subjects were randomized to the NAFT-500 Cream, 2% treatment group and 168 subjects were randomized to the 2-week placebo treatment group.

Table 22 (Applicant's Table 4): Disposition of Subjects – Number of Subjects Enrolled (All Screened Subjects)

Reference ID: 3030807

	NAFT-500 n (%)	Placebo n (%)	Total n (%)
Subjects Screened			617
Subjects Randomized, N	166	168	334
Subjects in Safety-Evaluation Set[a]	166 (99.4)	168 (100.6)	334 (100.0)
Subjects with Positive Baseline Culture	74 (44.3)	72 (43.1)	146 (43.7)
Subjects in Full-Analysis Set[b]	75 (44.9)	71 (42.5)	146 (43.7)
Subjects Completing Visit 1 (Day 1)	166 (99.4)	168 (100.6)	334 (100.0)
Subjects Completing Visit 2 (Week 2)	151 (90.4)	145 (86.8)	296 (88.6)
Subjects Completing Visit 3 (Week 4)	144 (86.2)	141 (84.4)	285 (85.3)
Subjects in Per-Protocol Set[c]	56 (33.5)	53 (31.7)	109 (32.6)

Data Source: End-of-Text Table 14.1.1.
Note: %=(n/Number of subjects randomized)x100.
Subject 28/53116 was randomized to NAFT-500, but was given placebo. This subject is included in the placebo group in the Safety-Evaluation Set and in the NAFT-500 group in the Full-Analysis Set.
[a] The Safety-Evaluation Set (SES) includes all subjects who received study medication at least once.
[b] Full-Analyses Set (FAS) is the subset of all subjects in the Safety-Evaluation Set (SES) with positive culture at baseline for whom the primary efficacy endpoint is available.
[c] Per-Protocol Set is the subset of subjects in the FAS without major protocol deviations.

Of these subjects, 285 (85.3%) completed the study and 49 (14.7%) subjects prematurely discontinued from the study. Of these 49 subjects who discontinued the study, there was a higher proportion of subjects who were lost to follow up (21 [6.3%]) or discontinued for 'other' reasons (15 [4.5%]) (Table 5). Of the 15 subjects who discontinued for 'other' reasons, 10 discontinued due to negative cultures at the baseline or Screening visit, 2 subjects were lost to follow-up (1 of whom also had a negative culture), 1 subject arrived early for the Week 3 visit, 1 subject was unable to have procedures done on the last day, 1 subject completed study Visit 3 < 25 days from Screening visit, and 1 subject met exclusion criteria #5 (i.e., uncontrolled diabetes mellitus).

Table 23 (Applicant's Table 5): Disposition of Subjects – Study Discontinuation (SES)

	NAFT-500 (N=166) n (%)	Placebo (N=168) n (%)	Total (N=334) n (%)
Completed Study	144 (86.7)	141 (83.9)	285 (85.3)
Prematurely Discontinued	22 (13.3)	27 (16.1)	49 (14.7)
Reason for Premature Discontinuation			
Progression of Study Disease	0	0	0
Adverse Event(s)	2 (1.2)	1 (0.6)	3 (0.9)
Lost to Follow-up	8 (4.8)	13 (7.7)	21 (6.3)
Non-compliance	0	1 (0.6)	1 (0.3)
Positive Pregnancy Test	0	0	0
Voluntary Withdrawal	3 (1.8)	3 (1.8)	6 (1.8)
Termination by Sponsor	1 (0.6)	0	1 (0.3)
Investigator Decision	1 (0.6)	1 (0.6)	2 (0.6)
Other	7 (4.2)	8 (4.8)	15 (4.5)

Data Source: End-of-Text Table 14.1.3.
Note: %=(n/N)x100.

Protocol Violations/Deviations

There were a total of 11 (3.3%) subjects with protocol violations and 206 (61.7%) subjects with protocol deviations during the study. Inclusion criteria violations accounted for 4 (1.2%) and exclusion criteria violations accounted for 7 (2.1%) of the protocol violations. Of the 206 protocol deviations, 115 (34.4%) were for a study procedure deviation and 68 (20.4%) were for a visit schedule deviation. Of the 115 subjects who had a study procedure deviation, 88 (52%) subjects did not have a KOH analysis done, 29 (17%) did not have a procedure done or had a procedure added, 26 (15%) had a procedure performed by a coordinator, and 25 (15%) subjects had an assessor change. Of the 3 subjects that had protocol deviations for 'other' reasons, 1 subject did not initial and date the ICF; the ICF was missing for 1 subject, and source documents were misplaced for 1 subject.

Demographic and Other Baseline Characteristics

Overall, most subjects were male (282 [84.4%]), White (143 [42.8%]), of Hispanic or Latino ethnicity (171 [51.2%]), and from ≥ 18 to < 65 years of age (288 [86.2%]). In addition, there were 113 (33.8%) subjects in the "other" category for race; these subjects were Hispanic or Hispanic/Latino. Overall, a greater number of subjects had baseline pathogen of *T. rubrum* (141 [42.2%]). Baseline characteristics were similar across treatment groups.

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Table 24 (Applicant's Table 7): Demographics (SES)

	NAFT-500 (N=166)	Placebo (N=168)	Total (N=334)
Gender [n (%)]			
Male	144 (86.7)	138 (82.1)	282 (84.4)
Female	22 (13.3)	30 (17.9)	52 (15.6)
Age (years)			
N	166	168	334
Mean (SD)	47.2 (15.54)	46.2 (14.53)	46.7 (15.03)
Min, Max	12, 88	18, 82	12, 88
Q1, Median, Q3	38.0, 47.5, 58.0	36.0, 46.5, 55.0	38.0, 47.0, 56.0
Age (years) [n (%)]			
< 18 years	4 (2.4)	0	4 (1.2)
≥ 18 to < 65 years	139 (83.7)	149 (88.7)	288 (86.2)
≥ 65 years	23 (13.9)	19 (11.3)	42 (12.6)
Ethnicity [n (%)]			
Hispanic or Latino	81 (48.8)	90 (53.6)	171 (51.2)
Not Hispanic or Latino	85 (51.2)	78 (46.4)	163 (48.8)
Race [n (%)]			
American Indian or Alaskan	0	0	0
Asian	0	1 (0.6)	1 (0.3)
White	68 (41.0)	75 (44.6)	143 (42.8)
Black or African American	42 (25.3)	35 (20.8)	77 (23.1)
Native Hawaiian or other Pacific Islander	0	0	0
Other	56 (33.7)	57 (33.9)	113 (33.8)

Data Source: End-of-Text Table 14.1.5.
Note: %=(n/N)x100.
Abbreviations: SD = standard deviation, Min = Minimum, Max = Maximum, Q1 = 1st quartile, Q3 = 3rd quartile.

Reviewer comment:
Enrollment was open to patients ≥ 12 years of age, although Table 7 above lists 4 subjects <18 years of age in the NAFT-500 study group, according to the FDA Statistical Reviewer, only two patients completed

the NAFT-500 study arms between age ≥ 12 years to 17 years and 11 months. This seems insufficient to this reviewer to allow inclusion of adolescent patients for labeling.

Measurement Of Treatment Compliance

The weight of each tube at the time it was dispensed to the subject, and when it was returned to the clinical site was recorded. Patients record all doses (date(s) and time(s) of application) applied in a diary and diary entries were used as a measurement of compliance. Overall compliance was summarized using the following compliance categories: ≤ 80%, > 80% to ≤ 120%, and > 120%. The majority of subjects were reported as having > 80% to ≤ 120% compliance (285 [91.3%]) with compliance (> 80% to ≤ 120%) similar across treatment groups (NAFT-500 Cream, 2% 145 [91.2%] subjects and 2-week placebo 140 [91.5%].

Efficacy Evaluation

Data Sets Analyzed

All of the 334 randomized subjects completed at least Visit 1 (Day 1) and were included in the SES population. A total of 146 (43.7%) subjects were included in the FAS population and 109 (32.6%) subjects were included in the PPS population.

Efficacy Results And Tabulations Of Individual Subject Data

At Visit 3, Week 4, complete cure (LOCF) was achieved for 19 (25.3%) subjects in the NAFT-500 Cream, 2% treatment group and for 2 (2.8%) subjects for the 2-week placebo treatment group. The results indicated that the proportion of subjects with complete cure in NAFT-500 treatment group was significantly greater than those in the 2-week placebo treatment group (one-sided CMH $p<0.001$) (Table 8). According to the applicant, the null hypothesis for the primary endpoint was therefore rejected and superiority of the active treatment (NAFT-500) over placebo was demonstrated. Homogeneity of treatment effects among clinical sites after pooling was proven with the Breslow-Day test ($p=0.853$) (Table 8).

The primary efficacy variable was the percentage of subjects at the 4-week time point with complete cure. The applicant's Table 8 below shows the proportion of subjects achieving a complete cure (LOCF) at Week 2 and 4 for the FAS population. This analysis used a one-sided CMH test comparing NAFT-500 Cream, 2% treatment group vs. the 2-week placebo treatment group, with pooled clinical site as the stratification variable and nonpooled clinical site as the stratification variable for sensitivity analysis.

Table 25 (Applicant's Table 8): Complete Cure Rate (LOCF) – Primary Analysis (FAS)

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Visit	Complete Cure[a]	NAFT-500 (N=75) n (%)	Placebo (N=71) n (%)
Visit 2 (Week 2)	Yes	4 (5.3)	0
	No	71 (94.7)	71 (100.0)
	Difference (97.5% CI)[b]	5.3 (0.2, + ∞)	
	P-value[c]	0.025	
Visit 3 (Week 4)	Yes	19 (25.3)	2 (2.8)
	No	56 (74.7)	69 (97.2)
	Difference (97.5% CI)[b]	22.5 (11.9, + ∞)	
	P-value[c]	<0.001	
	P-value[d]	<0.001	
	P-value[e]	0.853	

Data Source: End-of-Text Table 14.2.1.
Note 1: %=(n/Total number of subjects with non-missing data at each visit)x100.
Note 2: For the primary endpoint (NAFT-500 vs. placebo at 4 weeks), statistical significance will be declared if one-sided *p*-value ≤ 0.025.
Abbreviation: CI = confidence interval.
[a] Complete cure = Negative mycology results from the central laboratory (dermatophyte culture and KOH) and absence of erythema, scaling and pruritus.
[b] One-sided 97.5% CI calculated using normal approximation to the binomial for the difference in proportion of 'yes' responses between NAFT-500 and placebo.
[c] *P*-value is from a one-sided Cochran-Mantel-Haenszel (CMH) test comparing NAFT-500 group vs placebo group, with pooled clinical site as the stratification variable.
[d] *P*-value is from a one-sided CMH test comparing NAFT-500 group vs placebo group, with nonpooled clinical site as the stratification variable (sensitivity analysis).
[e] *P*-value is from Breslow-Day test to test for homogeneity of treatment effects among clinical sites after pooling.

Table 26 (Statistical Table 5.) Complete Cure Rate at Week 4

	NAFT-500	Vehicle	p-value
Sponsor's analysis(1)	19/75 (25.3%)	2/71 (2.8%)	<0.001
Sensitivity analysis (2)	16/75 (21.3%)	2/71 (2.8%)	0.001
Sponsor's sensitivity analysis(3)	16/57 (28.1%)	2/59 (3.4%)	<0.001
Sponsor's sensitivity analysis(4)	15/52 (28.8%)	2/45 (4.4%)	0.003

Complete Cure is defined as having negative mycology results (dermatophyte culture and KOH) and absence of erythema, scaling and pruritus at Week 4. P-value is calculated from a one-sided CMH test stratified by pooled sites.
(1) Sponsor's protocol-specified primary analysis –one-sided CMH test stratified by pooled sites, FAS, LOCF.
(2) Reviewer's sensitivity analysis –one-sided CMH test stratified by pooled sites, missing imputed as failure. FAS.
(3) Sponsor's sensitivity analysis. Observed data only without imputing missing data.
(4) Sponsor's sensitivity analysis. Per Protocol Set. (PPS)

The analysis results of secondary efficacy endpoints, mycological cure and treatment effectiveness are presented below. According to the applicant's summary, both secondary endpoints are statistically significant after adjusting for multiplicity using Hochberg's procedure. The secondary endpoint efficacy results are consistent with the primary efficacy endpoint results.

Table 27 (Statistical Table 6). Secondary efficacy analysis results at Week 4

	NAFT-500	Vehicle	p-value
Mycological Cure[(1)]	54/75 (72.0%)	11/71 (15.5%)	<0.001 [(1)]
Treatment Effectiveness [(2)]	45/75 (60.0%)	7/71 (9.9%)	0.001 [(2)]

One-sided CMH test by center, FAS, LOCF.
Adjusted p-value from Hochberg's step-up procedure.
(1) Mycological cure: negative KOH and negative culture
(1) Treatment effectiveness: negative KOH, negative culture, erythema, scaling and pruritus greades of 0 or 1.

Reviewer Conclusion:
Statistical significance (p<0.001) was demonstrated with use of NAFT-500 over vehicle at the primary efficacy endpoint, complete cure rate at Week 4, in Study MRZ 90200/FI/3001 for treatment of tinea cruris. Although enrollment was open to patients ≥ 12 years of age, only two patients completed NAFT-500 study arm between age ≥ 12 years to 17 years and 11 months; therefore, it is the recommendation of this reviewer that NAFT-500 not be labeled for use in patients ≤ 18 years of age.

6.1.6 Other Endpoints

Mycological cure defined as negative KOH and negative dermatophyte culture at Week 4 and Treatment effectiveness defined as negative KOH, negative culture, and erythema, scaling and pruritus scores of 0 or 1 at Week 4 are secondary endpoints and results are addressed in body of the study results for both the tinea pedis and tinea cruris studies.

6.1.7 Subpopulations

Gender
Male subjects had higher complete cure rates than females in the tinea cruris study; however, female subjects had higher complete cure rates than males in tinea pedis study. It should be noted in both studies that the majority of the FAS subjects (approximately 70-80%) were men.

Race
The NAFT-500 study arms had higher response rates compared to those of the vehicle arm among those subjects who were classified as 'white' or 'other'; however, the complete cure rates were similar across the treatment arms among the 'black' subjects.

Age
Enrollment was open to subjects ≥12 years of age in both clinical trails and 14 pediatric subjects and 37 subjects ≥ 65 years of age were enrolled in both clinical trails. Of these, only 3 pediatric subjects and 16 subjects ≥ 65 years of age were exposed to NAFT 500 Cream, the 2% formulation. The remainder of pediatric subjects was exposed to either vehicle or the 1% formulation.

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Baseline Pathogen
The percentages of subjects with complete cure at Week 6 in the NAFT-500 Cream, 2% treatment group were numerically higher compared with the 2-week placebo treatment group in patients with *Trichophyton rubrum*.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations
Dose ranging studies were not performed.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects
The applicant alludes to persistence of effect in the ISE, Protection Against Reinfection and Recurrence (Section 5.3). According to the applicant, once-daily topical application of NAFT-500 Cream, 2% for 2 weeks achieved and maintained a statistically significant mycological cure for 4 and 6 weeks after onset of treatment for tinea pedis and for 2 and 4 weeks after onset of treatment for tinea cruris. According to the applicant, these data suggest that NAFT-500 Cream, 2% protects against reinfection and recurrence, at least for short periods of time; however, this is *a post hoc* conclusion.

6.1.10 Additional Efficacy Issues/Analyses
No additional efficacy issues/analyses were performed.

7 Review of Safety

Safety Summary

7.1 Methods

The clinical development program for NAFT-500 Cream, 2% includes six clinical studies supporting the indication for the treatment of tinea pedis and tinea cruris. Four Phase 1 and two Phase 3 pivotal studies were conducted in the clinical development program for NAFT-500 Cream, 2%.

Safety and tolerability of NAFT-500 Cream, 2% were evaluated during the clinical development program with the following safety assessments: adverse event (AE) monitoring (all studies), clinical laboratory tests, urine pregnancy test, vital signs, and physical examinations.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical development safety database includes two pivotal Phase 3, double-blind, randomized, vehicle controlled studies, three Phase 1 studies, bioavailability study of NAFT-500 Cream, 2% under maximal use conditions evaluated in Study MRZ 90200/FI/1002, and QT Study MS 90200/1018/1, titled: “Randomized, Double-Blind, Placebo and Moxifloxacin-Controlled, Single Dose, 3-Arm, Parallel Study in Healthy Subjects to Evaluate the Effects of Naftifine Hydrochloride on Cardiac Repolarization (QT/QTc Interval Duration. Dermal safety studies included the following: irritancy and sensitization (MRZ 90200/FI/1003),

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photoallergenicity (MUS 90200/1014/1), and phototoxicity (MUS 90200/1013/1). A 120-day safety update was provided (SDN 199).

7.1.2 Categorization of Adverse Events

Nonserious and serious AEs were monitored throughout the studies, and incidence, severity, timing, and relationship to administration of the study medication were collected for each AE or serious AE (SAE).

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

Safety data from the tinea pedis and tinea cruris studies were combined to generate the safety database.

7.2 Adequacy of Safety Assessments

Table 28 Table 3–2 Number of Subjects Enrolled and Treated in the NAFT-500 Cream, 2% Clinical Development Program

		Number Treated			
NAFT-500 Cream, 2% Study	Number Enrolled or Randomized	NAFT-500 Cream, 2%	Placebo 2-Week	Naftin 1%	Placebo 4-Week
Tinea pedis	709	234	118	236	119
Tinea cruris	334	166	168	NA	NA
Maximal Use	21	21	NA	NA	NA
Phototoxicity	34	33	NA	NA	NA
Photoallergenicity	57	56	NA	NA	NA
Sensitization/Irritation	250	250	NA	NA	NA
Total	1405	760	286	236	119

Note: Four randomized or enrolled subjects were not treated: 2 subjects due to protocol violations in the tinea pedis study, 1 subject was lost to follow-up in the phototoxicity study, and 1 subject was disqualified in the photoallergenicity study due to the use of an unauthorized concomitant medication.

Abbreviation: NA = not applicable.

Source: MUS 90200-0736/1, MRZ 90200/FI/3001, MRZ 90200/FI/1002, MUS 90200/1013/1, MUS 90200/1014/1, and MRZ 90200/FI/1003 CSRs.

Reviewer comment:
Although 760 subjects were exposed to NAFT-500 during clinical development, inadequate numbers of patients have been exposed to the 2% formulation at the proposed labeled dose and duration. Dermal safety studies subjects are exposed to active study drug but are not included in the systemic safety database because exposure to study drug is limited in amount applied and there is no vehicle control group for comparison.. The total of patients exposed to at least one dose at the proposed labeled amount for NAFT-500 is 421 patients for up to 2 weeks.

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

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As noted in Table 28 above, a total of 400 patients were exposed to active study drug for a total of two weeks in controlled clinical trials. At the 2007 PreIND meeting, the applicant was advised that the proposed indication for your NAFT-500 drug product is considered chronic by the Division, due to the recurrence rate of tinea infections and was advised to follow the ICH E1a guidance document (The Extent of Population Exposure to Assess Clinical Safety: for Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions) on sample size for patients on active drug in trials to demonstrate safety). Nonetheless, the applicant states in the Clinical Overview (Section 5.12, Long-term Safety) that long-term safety of NAFT-500 Cream, 2% has not been studied as the drug is intended for use in treatment periods up to 2 weeks.

7.2.2 Explorations for Dose Response

Dose response studies were not performed.

7.2.3 Special Animal and/or In Vitro Testing

Carcinogenicity studies have not been performed to date in the development program. As noted in the pre-NDA meeting of 12 March 2010, the Division will permit submission of fully acceptable data that concern the carcinogenicity of NAFT-500 Cream, 2% as a postmarketing commitment.

7.2.4 Routine Clinical Testing

Clinical laboratory tests included serum chemistry, hematology, and urinalysis. Blood and urine samples (urine only for Study MRZ 90200/FI/1003/Irritancy and Sensitization Study) were collected at the Screening (Day 1) and termination visits in all studies except MUS 90200/1013/1 (phototoxicity study) and MUS 90200/1014/1 (photoallergenicity study), and at Day 14 in Study MRZ 90200/FI/1002 and Week 4 in Study MUS 90200-0736/1 for the following laboratory parameters:

- Serum chemistry profile: total protein, albumin, blood urea nitrogen (BUN), creatinine, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, sodium, potassium, chloride, calcium, magnesium, glucose, creatine kinase (CK), triglycerides, total cholesterol, and prealbumin.
- Complete blood count (CBC): hemoglobin, hematocrit, red blood cells (RBCs), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), total white blood cells (WBCs), neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count.
- Urinalysis (including dipstick): glucose, bilirubin, ketones, blood, pH, protein, urobilinogen, nitrite, and leukocytes.

Urine Pregnancy Test

An on-site urine pregnancy kit was used to test female subjects of child bearing potential at the Screening visit and/or prior to each treatment phase in all studies and also study exit in some studies.

In the Maximal Use PK Study 90200/076/1, mean and median values for clinical chemistry and hematology parameters show no trends suggesting an effect of study medication in subjects exposed to the maximal use conditions of this study. Eighteen subjects (85.7%) recorded one or more treatment-emergent abnormal values treatment-emergent adverse events (TEAVs) for clinical chemistry parameters. Parameters with more than 2 subjects developing TEAVs include chloride (7 subjects, 33.3%), triglycerides

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(5 subjects, 23.8%), and cholesterol, sodium, and CK (4 subjects each, 19.0%). There is no vehicle study arm for comparison.

All 21 subjects recorded one or more TEAVs for hematology parameters. Parameters with more than 2 subjects developing TEAVs include lymphocytes and monocytes (7 subjects each, 33.3%), basophils (6 subjects, 28.6%), segmented neutrophils (5 subjects, 23.8%), and hematocrit (3 subjects, 14.3%; red cell indices and count and mean platelet volume [MPV] excluded).

In controlled phase 3 studies, mean and median laboratory values for clinical chemistry and hematology parameters showed no trends suggesting an effect of study medication. Mean values, median values, and changes from Baseline in the treatment groups showed no clinically important differences.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not performed.

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

Certain classes of adverse events (AEs) were identified for other currently marketed antifungal products. To monitor safety in relation to these classes of AEs, listings for AEs that occurred on-study were reviewed by the applicant's clinical review team to identify those that were related to liver function abnormalities, kidney function abnormalities, and cardiac abnormalities that were considered AEs of special interest (AESIs) for this program

7.3 Major Safety Results

The Agency's Interdisciplinary Review Team for QT Studies reviewed data from Study Protocol MUS 90200/1018/1 conducted by the applicant titled "Randomized, Double-Blind, Placebo and Moxifloxacin-Controlled, Single Dose, 3-Arm, Parallel Study in Healthy Subjects to Evaluate the Effects of Naftifine Hydrochloride on Cardiac Repolarization (QT/QTc Interval Duration)". It should be noted that single dose 600 mg naftifine hydrochloride capsule is used in the thorough QT study and the study results are applicable to both NAFT-600 Gel 2% and NAFT-500 Cream, 2%.

According to the overall summary of findings of the consult dated 09/09/2011, no significant QTc prolongation effect of naftifine HCl (600 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between naftifine HCl (600 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines.

7.3.1 Deaths

There were no deaths reported in the NAFT-500 Cream, 2% clinical development program.

7.3.2 Nonfatal Serious Adverse Events

One SAE of influenza was reported in the tinea pedis study in a subject assigned to the Naftin® 1% Cream treatment group in Subject (b) (6) a 42-year-old, non-Hispanic or Latino male. The influenza was not considered serious, mild in intensity, and judged unlikely related to study drug. There were no SAEs

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reported in the Irritancy/Sensitization study, the Maximal Use study, the phototoxicity study, the photoallergenicity study, or the NAFT-500 Cream, 2% studies.

Table 29 (Applicant's Table 10–7 Number) (%) of Subjects with Severe Treatment-Emergent Adverse Events in NAFT-500 Cream, 2% Studies (Safety-Evaluation Set)

MedDRA Preferred Term[1]	NAFT-500 Cream, 2% (N=421) n (%)	2-Week Placebo (N=286) n (%)
Subjects with at least one Severe TEAE[2]	3 (0.7)	6 (2.1)
Pruritus	1 (0.2)	2 (0.7)
Application Site Pruritus	1 (0.2)	0
Skin Exfoliation	1 (0.2)	0
Genital Erythema	1 (0.2)	0
Blood Creatine Increased[3]	0	1 (0.3)
Blood Glucose Increased	0	1 (0.3)
Upper Respiratory Tract Infection	0	1 (0.3)
Erythema	0	1 (0.3)

1. Events were coded using MedDRA Version 11.1.
2. A subject with more than one TEAE within a preferred term was counted once at the maximum intensity.
3. Severe "blood creatine increased" was reported for Subject (b) (6) in Study MUS 90200-0736/1. The adverse event verbatim term was "elevated creatine kinase in blood" (Data Source: MUS 90200-0736/1 CSR, Listing 17). The subject's serum creatine kinase (CK) at Visit 1 was 492 U/L and at Visit 4 was 439 U/L (normal range: 26 to 174 U/L) (Data Source: MUS 90200-0736/1 CSR, Listing 18).

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
Data Source: Post-text Table 9.4.

Reviewer comment:
Skin exfoliation is listed in Table 10-7 above; however, was not assessed as study drug related (Table 14.3.2.5 Safety Data, Study MUS 90200-076/1).

7.3.3 Dropouts and/or Discontinuations

Six of the 9 subjects withdrawing from study participation due to adverse events withdrew because of events unrelated to study medication. In the Irritancy/Sensitization study, 1 subject (b) (6) withdrew because of an application site rash of moderate intensity judged definitely related to study medication. In Study MRZ 90200/FI/3001, 1 subject (b) (6)) withdrew because of contact dermatitis of moderate intensity judged definitely related to study medication, and 1 subject (b) (6)) withdrew because of severe inguinal pruritus judged definitely related to study medication; however, the patient was in the vehicle study arm.

Table 30 (Applicant's Table 5–2) Overall Summary of Adverse Events in Controlled Phase 3 Studies (SES)

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	NAFT-500 Cream, 2% (N=400) n (%)	Naftin 1% Cream (N=236) n (%)	Combined Placebo (N=405) n (%)
Any Adverse Event	70 (17.5)	43 (18.2)	78 (19.3)
Any TEAE	70 (17.5)	42 (17.8)	78 (19.3)
Any Related TEAE	19 (4.8)	9 (3.8)	22 (5.4)
Any Treatment-Emergent SAE	0	1 (0.4)	0
Any Related SAE	0	0	0
Any TEAE Leading to Drop-out	3 (0.8)	0	4 (1.0)
Any Related TEAE Leading to Drop-out	1 (0.3)	0	1 (0.2)
Any Fatal TEAE	0	0	0

Abbreviations: SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Source: ISS Post-text Table 6.3.

Table 31 (Applicant's Table 5–3): Overall Summary of Adverse Events in the Controlled Phase 3 Studies by Indication (NAFT-500 Cream, 2%)

	NAFT-500 Cream, 2% Tinea Pedis (N=234) n (%)	NAFT-500 Cream, 2% Tinea Cruris (N=166) n (%)	2-Week Placebo Combined Indications (N=286) n (%)
Any Adverse Event	47 (20.1)	23 (13.9)	48 (16.8)
Any TEAE	47 (20.1)	23 (13.9)	48 (16.8)
Any Related TEAE	12 (5.1)	7 (4.2)	12 (4.2)
Any Treatment-Emergent SAE	0	0	0
Any Related SAE	0	0	0
Any TEAE Leading to Drop-out	1 (0.4)	2 (1.2)	3 (1.0)
Any Related TEAE Leading to Drop-out	0	1 (0.6)	1 (0.3)
Any Fatal TEAE	0	0	0

Abbreviations: SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Source: ISS Post-text Table 6.4, MUS 90200/0736/1 CSR, Table 15, MRZ 90200/FI/3001 CSR, Table 14.

7.3.4 Significant Adverse Events

The Applicant assessed three classes of AEs related to liver, kidney, and cardiac function abnormalities selected as the adverse events of special interest (AESIs) for this program. There were no clinically important between-group differences in the pattern of liver-related AESIs, the frequency of liver-related,

kidney function abnormalities, and cardiac abnormalities, or cardiac-related AESIs in the NAFT-500 Cream, 2% studies or Naftin 1% Cream study groupings. The numbers of events are too small to allow meaningful between-group comparisons in pattern, frequency or time to onset of these AESIs.

7.3.5 Submission Specific Primary Safety Concerns

None were noted.

7.4 Supportive Safety Results

No additional supportive safety data were provided.

7.4.1 Common Adverse Events

Common adverse events were tabulated for ≥2%. The most common TEAEs with an incidence of ≥2% in any treatment group in the controlled Phase 3 studies are shown in Table 10–5. Five TEAEs were reported by at least 2% of subjects in any treatment group. According to the Applicant, there were no clinically important differences in the incidence of TEAEs across treatment groups.

Reviewer comment:

The rationale for tabulation of common AEs at ≥2% was not provided. Generally for topical drug products common adverse events are tabulated for ≥1 % for labeling. Section 6 of product labeling will reflect adverse reactions which have some reasonable level of causation to the study product. According to ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, in the pre-approval clinical experience with a new medicinal product or its new usages, all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out. An adverse event (AE) can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. .

Nearly all of the TEAEs reported in the NAFT-500 Cream, 2% studies were mild or moderate in intensity. Severe TEAEs were reported by 9 subjects, including 3 subjects treated with NAFT-500 Cream, 2% (0.7%) and 6 subjects treated with placebo (2.1%). Severe TEAEs are shown in Table 10–10 for the NAFT-500 Cream, 2% studies. Pruritus was the only TEAE reported with severe intensity by more than a single subject (1 NAFT-500 Cream, 2%-treated subject and 2 placebo-treated subjects).

Table 32 (Applicant's Table 10–4): Overall Summary of Adverse Events in the Controlled Phase 3 Studies by Indication (NAFT-500 Cream, 2%)

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	NAFT-500 Cream, 2%, Tinea Pedis (N=234) n (%)	NAFT-500 Cream, 2%, Tinea Cruris (N=166) n (%)	2-Week Placebo, Combined Indications (N=286) n (%)
Any Adverse Event	47 (20.1)	23 (13.9)	48 (16.8)
Any TEAE	47 (20.1)	23 (13.9)	48 (16.8)
Any Related TEAE	12 (5.1)	7 (4.2)	12 (4.2)
Any Treatment Emergent SAE	0	0	0
Any Related SAE	0	0	0
Any TEAE Leading to Drop-out	1 (0.4)	2 (1.2)	3 (1.0)
Any Related TEAE Leading to Drop-out	0	1 (0.6)	1 (0.3)
Any Fatal TEAE	0	0	0

Abbreviations: SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Data Source: Post-text Table 6.4, MUS 90200-0736/1 CSR, Table 15, MRZ 90200/FI/3001 CSR, Table 14).

Most Common Treatment-Emergent Adverse Events

Table 33 (Applicant's Table 10–6): Number (%) of Subjects with Most Common Treatment-Emergent Adverse Events with Incidence of 2% or Greater) in Controlled Phase 3 Studies, by Indication (Safety-Evaluation Set)

MedDRA Preferred Term[1]	NAFT-500 Cream, 2%, Tinea Pedis (N=234) n (%)	NAFT-500 Cream, 2%, Tinea Cruris (N=166) n (%)	2-Week Placebo Combined Indications (N=286) n (%)
Subjects with at least one TEAE[2]	47 (20.1)	23 (13.9)	48 (16.8)
Headache	10 (4.3)	2 (1.2)	8 (2.8)
Application Site Pruritus	7 (3.0)	3 (1.8)	4 (1.4)
Nasopharyngitis	3 (1.3)	2 (1.2)	3 (1.0)
Application Site Irritation	4 (1.7)	0	3 (1.0)
Pruritus	2 (0.9)	0	6 (2.1)

Note: Most common AEs included TEAEs, based on preferred terms, contributing at least 2% of the total AE occurrences in the clinical development program overall.
Abbreviation: TEAE = treatment-emergent adverse event.
Data Source: Post-text Table 13.4, MUS 90200-0736/1 CSR, Section 14, Table 14.3.2.2, MRZ 90200/FI/3001 CSR, Section 14, Table 14.3.2.2).

According to the applicant, for the five TEAEs most commonly observed during the controlled Phase 3 studies, there were no important differences in incidence among patients treated with NAFT-500 Cream, 2% for tinea pedis, or patients treated with NAFT-500 Cream, 2% for tinea cruris, and patients treated with placebo for 2 weeks (indications combined).

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Reviewer comment:
As noted in Tables 5-6 and 10-8 that follows, the 2% formulation has higher incidence of adverse reactions than Naftin 1% Cream.

Table 34 (Applicant's Table 5–6): Number (%) of Subjects with Most Common Treatment-Emergent Adverse Events That Were Study Drug-Related in the Phase 3 Studies (SES)

MedDRA Preferred Term [a]	NAFT-500 Cream, 2% (N=400) n (%)	Naftin 1% Cream (N=236) n (%)	Combined Placebo (N=405) n (%)
Subjects with at least one Study Drug-Related TEAE [b,c,d]	16 (4.0)	7 (3.0)	16 (4.0)
Application Site Pruritus	7 (1.8)	1 (0.4)	7 (1.7)
Application Site Irritation	2 (0.5)	4 (1.7)	7 (1.7)
Pruritus	1 (0.3)	0	3 (0.7)

a Events were coded using MedDRA Version 11.1.
b Most common AEs included TEAEs, based on preferred terms, contributing at least 2% of the total AE occurrences in the clinical development program overall.
c Treatment-emergent AEs were defined as on-study AEs, pre-existing AEs that worsened in severity after start of treatment, and adverse events that were reported with onset during the 30 days after end of treatment. Treatment-emergent AEs were summarized like all other AEs by preferred terms (PTs) within system organ classes (SOCs) according to the defined study groupings. A subject with more than one TEAE within a PT was counted once in the PT.
d A subject with related and not related TEAEs within a preferred term was counted once as related.
Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
Source: ISS Post-text Table 10.3.

Table 35 (Applicant's Table 10–8): Number (%) of Subjects with Study Drug-Related Treatment-Emergent Adverse Events in Controlled Phase 3 Studies (Safety-Evaluation Set)

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MedDRA Preferred Term[1]	NAFT-500 Cream, 2% (N=400) n (%)	Naftin 1% Cream (N=236) n (%)	Combined Placebo (N=405) n (%)
Subjects with at least one Study Drug-Related TEAE[2]	16 (4.0)	7 (3.0)	16 (4.0)
Application Site Pruritus	7 (1.8)	1 (0.4)	7 (1.7)
Application Site Dryness	3 (0.8)	1 (0.4)	2 (0.5)
Application Site Irritation	2 (0.5)	4 (1.7)	7 (1.7)
Pain	2 (0.5)	2 (0.8)	3 (0.7)
Dermatitis Contact	2 (0.5)	0	0
Alanine Aminotransferase Increased	1 (0.3)	2 (0.8)	2 (0.5)
Pruritus	1 (0.3)	0	3 (0.7)
Application Site Reaction	1 (0.3)	0	1 (0.2)
Blood Bilirubin Increased	1 (0.3)	0	1 (0.2)
Blood Alkaline Phosphatase Increased	1 (0.3)	0	0
Neutrophil Count Decreased	1 (0.3)	0	0
Tinea Cruris	1 (0.3)	0	0
Skin Hyperpigmentation	1 (0.3)	0	0
Genital Erythema	1 (0.3)	0	0
Application Site Erythema	0	1 (0.4)	2 (0.5)
Blood Creatine Increased[3]	0	1 (0.4)	1 (0.2)
Aspartate Aminotransferase Increased	0	1 (0.4)	1 (0.2)
Neutrophil Percentage Decreased	0	1 (0.4)	0
White Blood Cell Count Decreased	0	1 (0.4)	0
Blood Glucose Increased	0	0	1 (0.2)
Creatine Urine Increased	0	1 (0.4)	1 (0.2)
Haematocrit Decreased	0	0	1 (0.2)
Haemoglobin Decreased	0	0	1 (0.2)
Mean Cell Volume Decreased	0	0	1 (0.2)
Red Blood Cell Count Decreased	0	0	1 (0.2)
Laryngitis	0	0	1 (0.2)
Skin Burning Sensation	0	0	1 (0.2)
Pruritus Genital	0	0	1 (0.2)

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MedDRA Preferred Term[1]	NAFT-500 Cream, 2% (N=400) n (%)	Naftin 1% Cream (N=236) n (%)	Combined Placebo (N=405) n (%)
Throat Irritation	0	0	1 (0.2)
Neutropenia	0	0	1 (0.2)
Proteinuria	0	0	1 (0.2)

1. Events were coded using MedDRA Version 11.1.
2. A subject with related and not related TEAEs within a preferred term was counted once as related.
3. "Blood creatine increased" judged possibly related to study medication was reported for 2 subjects in Study MUS 90200-0736/1. For Subject (b) (6) (treated with Naftin 1%), the AE verbatim term was "elevated CK level in blood" and for Subject (b) (6) (treated with 2-Week placebo), the AE verbatim term was "mildly elevated creatine kinase in blood" (Data Source: MUS 90200-0736/1 CSR, Listing 17). Both AEs should be considered elevations of CK.

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
Data Source: Post-text Table 10.3.

Both contact dermatitis adverse events occurred in the active study drug arm in the tinea pedis study in the following patients:

- Subject (b) (6) (44 y.o. male)
- Subject 88 y.o. male)

Reviewer comments:

The applicant's rationale for inclusion of the already approved Naftin 1% Cream study arm is not clear to this reviewer. Although comparative studies are not required for NDA approvals, the duration of the study endpoint was changed by the applicant because the comparative 1% cream formulation was included. It appears to this reviewer that the shortened duration of use therapy is not more efficacious and the 2% formulation is more irritating than the 1% formulation. The applicant has stated their intent to withdraw the Naftin 1% cream formulation following approval of this 2% cream application.

As noted in this AE section, except for application site irritation 2 (0.5) vs. 4 (1.7) for naftifine 2% and naftifine 1%, respectively, overall application site reactions were twice that for the 2 % formulation (i.e., application site pruritus 7 (1.8) vs. 1 (0.4), application site dryness 3 (0.8) vs. 1 (0.4), and contact dermatitis 2 (0.5) vs. 0 for naftifine 2% and naftifine 1%, respectively).

7.4.2 Laboratory Findings

Clinical Chemistry

Two hundred fifty-three subjects (71.3%) recorded one or more treatment-emergent abnormal values (TEAVs) for clinical chemistry parameters, including 172 subjects (72.9%) in the Naftin 1% Cream group and 81 subjects (68.1%) in the 4-Week placebo group. The two parameters with the largest number of subjects developing TEAVs were chloride (94 subjects, 26.5% overall) and glucose (71 subjects, 20.0% overall). For these and other chemistry parameters, there were no observed clinically relevant differences between the Naftin 1% Cream group and the 4-Week placebo group in the frequencies of TEAVs.

Hematology

Two hundred sixty-nine subjects (75.8%) recorded one or more TEAVs for hematology parameters, including 182 subjects (77.1%) in the Naftin 1% Cream group, and 87 subjects (73.1%) in the 4-Week placebo group. The two parameters with the largest number of subjects developing TEAVs were

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monocytes (73 subjects, 20.6% overall) and segmented neutrophils (67 subjects, 18.9% overall). For these and other hematology parameters, there were no observed clinically relevant differences between the Naftin 1% Cream group and the 4-Week placebo group in the frequencies of TEAVs.

Individual Potentially Clinically Significant Abnormal Laboratory Values

Abnormal laboratory values were designated potentially clinically significant if >2x the upper limit of normal (ULN), if >5x ULN, if <0.5x the lower limit of normal (LLN), or if <0.2x LLN. Nearly all of the abnormal clinical chemistry values designated as potentially clinically significant were elevations of CK, triglycerides, or glucose or laboratory results entered as zero value and were identified because they were <0.2 x LLN. Nearly all of the abnormal hematology values designated as potentially clinically significant were deviations from the normal range for white blood cell (WBC) differentials expressed as percentages (proportion

Vital Signs

Vital signs (i.e., systolic blood pressure [SBP], diastolic blood pressure [DBP], and pulse) were collected at the screening, pretreatment, and termination visits for all studies except MRZ 90200/FI/1003, MUS 90200/1013/1, and MUS 90200/1014/1. Physical examinations and medical history were analyzed for all for all studies except MRZ 90200/FI/1003, MUS 90200/1013/1 and MUS 90200/1014/1. Overall, there were no clinically relevant differences between treatment groups in any of the study groupings for subjects with potentially clinically significant pulse rate or blood pressure changes following treatment.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not performed during the clinical development program.

7.4.5 Special Safety Studies/Clinical Trials

Results of the QT Study Report AA95389, titled: "Randomized, Double-Blind, Placebo and Moxifloxacin-Controlled, Single Dose, 3-Arm, Parallel Study in Healthy Subjects to Evaluate the Effects of Naftifine Hydrochloride on Cardiac Repolarization (QT/QTc Interval Duration)" was submitted to the Agency on July 20, 2011 for review. The study was randomized, double-blinded, double-dummy, three-treatment-arm parallel study, where 132 healthy subjects received oral naftifine HCl 600 mg, placebo, and a single oral dose of moxifloxacin 400 mg. The oral dose of 600 mg produces mean C_{max} values 18-fold higher than that following the therapeutic dose of 2% naftifine cream and is sufficient to cover high exposure clinical scenarios. According to the review, the largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated indicating that assay sensitivity was established.

According to the Interdisciplinary Review Team for QT Studies (QT-IRT) overall summary of findings "No significant QTc prolongation effect of naftifine HCl (600 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between naftifine HCl (600 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines." It was noted that the sponsor did not propose any label language on QT effect and QT-IRT deferred final labeling decisions to the review division.

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Irritancy and Sensitization (MRZ 90200/FI/1003)
Title of Study:
A Study to Evaluate the Sensitization and Irritation Potential of Repeat Applications of NAFT-500 in Healthy Human Volunteers

Studied Period: 05 Jan 2009 – 24 October 2009
Objectives: The objectives of this trial are to evaluate the sensitization potential and degree of skin irritation from NAFT-500 Cream on intact skin of healthy adult volunteers.
Methodology: This was a single-site, single-blind, randomized, assessor-blind, controlled study to evaluate the sensitization potential and degree of skin irritation from NAFT-500 Cream on intact skin of healthy adult subjects. The test articles below were applied to the upper outer arms during the induction phase and on the mid to upper back during the challenge phase.

The design was based on the Jordan-King modification of the Draize procedure which involved continuous contact time of the test articles during the irritation phase, followed by a rest phase in which no drug was applied, and a challenge phase.

The Irritation Phase consisted of 21 occluded applications (approximately 23 hours per patch application) of all test articles to each volunteer over an approximate three week period with scoring for irritation approximately 30 minutes after each patch removal.

Following the Irritation Phase, subjects underwent a 14 day Rest Phase in which no test articles were applied to the skin. After the Rest Phase the subjects underwent a five (5) day Challenge Phase in which each volunteer had a 48 hour occluded application of each test article applied to naïve skin sites on the para-spinal region of the mid to upper back. Scoring for skin reactions occurred approximately 30 minutes, 24, 48 and 72 hours after patch removal.

Re-challenges, if necessary, were to be conducted 2-4 weeks after resolution of the original reactions, in order to avoid the conditioned response (angry-back syndrome). The immune response retained its specificity and sensitivity for an extended period, where as hyperirritability should subside.

Main Criteria for Inclusion: All subjects were asymptomatic, non-smoking, healthy, adult subjects 18 to 65 years of age who met the inclusion/exclusion criteria for this study.

Materials Applied

- NAFT-500 (naftifine hydrochloride 2% cream) by Merz Pharmaceuticals, LLC
  Dose: 0.2 ml by pipette
  Mode of Administration: Topical
  Lot Number: AAX-C
- Positive (high) Irritant Control Sodium Lauryl Sulfate 0.05% (w/v), USP in sterile, distilled Water for Injection, USPS
- Negative (low) Irritant Control: Distilled Water for Injection, USP

Reviewer comment:

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The Applicant did not include NAFT-500 cream vehicle in the test battery

Blinding

According to the protocol, the trial will be conducted in an assessor-blinded fashion. The medical staff conducting the skin evaluations will not know which test articles are applied to each of the three sites. All other persons involved in the project (e.g. biostatistician, data managers, monitors) will not be blinded throughout the trial.

Reviewer comment:

Inclusion of the vehicle would have ensured adequate study blinding and perhaps provide additional information as to the effect of vehicle on irritation and sensitization, if present. Inclusion of the vehicle for blinding purposes in dermal safety studies may not be as important in pivotal phase 3 studies but would be informative for the prescriber and patients as to the source of sensitization (i.e., the active moiety or vehicle formulation).

Assessment during Dosing Period

Inflammatory Responses:

0 no evidence of irritation
1 minimal erythema, barely perceptible
2 definite erythema, readily visible; minimal edema or minimal papular response
3 erythema and papules
4 definite edema
5 erythema, edema and papules
6 vesicular eruption
7 strong reaction spreading beyond application site

Other Effects:

0 no other observations
1 slight glazed appearance
2 marked glazed appearance
3 glazing with peeling and cracking
4 glazing with fissures
5 film of dried serous exudates covering all or part of the patch site
6 small petechial erosions and/or scabs

Safety: All subjects were monitored throughout the study dose and assessment periods of the study. Subjects were queried for adverse events at all study visits, including check in and study exit. Urine pregnancy screens were given to female subjects at screening, Days 1, 8, 15, and 22, the first day of the challenge phase (Day 36) and at study exit.

Statistical Methods:

The primary endpoint for the irritation analysis is the cumulative irritation score defined for each subject and application site as the sum of the irritation scores (inflammatory responses) over the irritation phase.
In case of missing values, the Last Observation Carried Forward (LOCF) method was applied.

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The cumulative irritation score was summarized with the statistical characteristics: n, mean, standard deviation, minimum, 1st quartile, median, 3rd quartile, and maximum per treatment (NAFT-500, positive control, negative control).

The primary endpoint for the sensitization analysis was the assessment whether a subject showed a sensitization reaction or not. The number and percent of subjects showing a sensitization reaction was tabulated per treatment. Secondary endpoints were also analyzed descriptively.

Study Results

Two-hundred and fifty (250) subjects were enrolled in the study, 242 completed the irritation phase of the study, and 237 subjects completed the challenge phase of the study. The study was conducted with 250 subjects and 237 subjects completed the study. Cumulative irritation analysis was conducted on 242 subjects for whom the primary clinical endpoint was available (FAS). All subjects who received at least one dose were included in the safety evaluation set (SES).

Table 36 (Applicant's Table 10.1-2): Disposition of Enrolled Subjects

	N	(%)
Total number of subjects enrolled	250	(100.00%)
Number of premature discontinuations during the Irritation Phase	8	(3.20%)
Number of premature discontinuations during the Challenge Phase	5	(2.00%)
Safety Population Total (SES)	250	(100.00%)
Total number (and percent) of subjects enrolled, randomized, and treated, with at least one treatment.		
Evaluable Population Total (FAS)	242	(96.80%)
Total number (and percent) of subjects enrolled, randomized, and treated, with all treatments during the irritation phase.		

Reviewer comment:
Of note, Subject (b) (6) was discontinued from study participation on day 22 due to skin rash; however, further details were not provided.

Table 37 (Applicant's Table 11.1-1): Summary of Study Enrollment and Analysis Populations

Subject Group	N (%)		
	Treatment A	Treatment B	Treatment C
Enrolled	250 (100%)	250 (100%)	250 (100%)
Induction Phase (FAS)	242 (96.8%)	242 (96.8%)	242 (96.8%)
Challenge Phase	237 (94.8%)	237 (94.8%)	237 (94.8%)
Re-Challenge Phase	1 (0.4%)	1 (0.4%)	1 (0.4%)
Safety Population	250 (100%)	250(100%)	250 (100%)

Source: Appendix 16.1.9
Treatment A: NAFT-500, Merz Pharmaceuticals; Lot #: AAX-C
Treatment B: Sodium Lauryl Sulfate Solution, (b) (4) Lot #: 452729/1
Treatment C: Sterile Water for Inj, USP, (b) (4) Lot #: 65-319-DK

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Table 38 (Applicant's **Table 11.2-1): Summary of Mean Demographic Data (± SD)**

Parameters	All Subjects N = 250	Females N = 163	Males N = 87
Age	31.4 (18 - 63)	30.8 (18 - 63)	32.5 (18 - 60)
Weight (lbs)	176.5 (108.0 - 359.0)	163.7 (108.0 - 313.5)	200.6 (128.5 - 359.0)

Parameters	All Subjects N = 250	Females N = 163	Males N = 87
Height (in.)	66.6 (58.4 - 74.9)	64.8 (58.4 – 70.9)	70.0 (65.4 - 74.9)
BMI	27.9 (18.1 - 52.2)	27.4 (18.3 - 52.2)	28.8 (18.1 - 50.5)
Race			
Asian:	2 (0.8%)	1 (0.6%)	1 (1.1%)
African American:	6 (2.4%)	4 (2.5%)	2 (2.3%)
Native Hawaiian or Other Pacific Islander:	1 (0.4%)	-	1 (1.1%)
American Indian or Alaskan Native:	8 (3.2%)	3 (1.8%)	5 (5.7%)
White:	226 (90.4%)	149 (91.4%)	77 (88.5%)
WA (White and Asian):	2 (0.8%)	2 (1.2%)	-
WAN (White, Asian and American Indian or Alaskan Native):	1 (0.4%)	1 (0.6%)	-
WN (White and American Indian or Alaskan Native):	4 (1.6%)	3 (1.8%)	1 (1.1%)

Table 39 (Applicant's **Table 11.4-1): Summary of Mean Irritation Data (± SD)**

Test Article	Cumulative Irritation Score	Cumulative "Other Effects" Score
A (NAFT-500 Cream)	9.48 ± 6.62	1.25 ± 5.27
B (Positive Control)	20.86 ± 8.38	21.72 ± 9.76
C (Negative Control)	6.67 ± 6.71	0.83 ± 3.99

The Positive and Negative controls demonstrated irritation responses consistent with expectations and historical knowledge. The Test Article "A" (NAFT-500 Cream) demonstrated irritation responses similar to, but slightly greater than the Negative (low) irritation control suggesting it would be categorized as having a low propensity for irritation in clinical use.

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Sensitization Analysis
One subject (Subject Number (b) (6) demonstrated a potential sensitization response in the challenge phase to the primary Test Article. In the re-challenge, no sensitization reaction was observed for this subject. The data indicate that the Test Article would not be considered as a primary sensitizer nor would likely demonstrate a maximal population rate of 1.5% likelihood for observing sensitization in clinical use.

Adverse Events
One hundred and fourteen (114) subjects (45.6%) experienced a total of 288 adverse events over the course of the study. No SAEs were reported over the course of this study. Adverse events were mild to moderate in intensity, with approximately 10 % of the AEs being of moderate intensity. Overall, the most common AE reported was application site pruritus. Sixty eight (68) subjects (27.2%) had at least one AE occurrence of application site pruritus which was considered treatment-related by the investigator.

Conclusion:
The applicant concludes that the Positive and Negative (low) irritation controls demonstrated irritation response consistent with expectations and historical knowledge. The Test Article "A" (NAFT-500 Cream) demonstrated irritation responses similar to, but slightly greater than the Negative control suggesting it would be categorized as having a low propensity for irritation in clinical use. The data indicate that the Test Article would not be considered as a primary sensitizer nor would likely demonstrate a maximal population rate of 1.5% likelihood for observing sensitization in clinical use; however, there were two separate reports of study drug related contact dermatitis in the Phase 3 clinical trials.

This reviewer concurs with the applicant's conclusion and under conditions of this study; NAFT-500 does not appear to be a primary sensitizer. However, contact dermatitis leading to discontinuation in the tinea cruris study was reported as an adverse reaction.

Photoallergenicity (MUS 90200/1014/1)
Study dates: July 20, 2009 to September 25, 2009

Objective:
To evaluate the potential of NAFT-500 to produce photoallergenicity reactions in normal use by the population by applying higher doses of NAFT-500 than normally used and comparing responses of sites with test product alone, test product irradiated with UVR and no treatment.

Study Design
This was an open-label, evaluator-blind, controlled study in 53 healthy volunteer subjects with Fitzpatrick Skin Types I, II and III, consisting of an induction phase, a resting phase and a challenge phase. The induction phase consisted of six duplicate, 24 hour exposures to NAFT-500 in occlusive chambers, one site received UV and one site receiving no UV. Duplicate, untreated control sites were also covered with chambers. Before administration of UV doses, chambers were removed, all sites were evaluated and a thin film of NAFT-500 was re-applied to one site that was treated with NAFT-500. UVR doses of 3 MEDs (Minimal Erythema Doses) of UVA and UVB (full-spectrum simulated solar UVR) were then administered to

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that site and one control site that received an empty chamber. Responses of all sites were graded immediately by a blinded evaluator, using the Irritation Response Grading Scale shown below. The entire procedure was repeated five more times over a 3 week period.

UV Doses

UV Doses were administered to 0.8 cm diameter sites on the mid-back using a calibrated 150 watt xenon arc lamp, filtered to simulate the full solar UV spectrum for MED determination. A (b) (4) UVB/UVC blocking filter in place to deliver 10 J/cm2 of UVA only, followed by 0.5 MED of full spectrum UV (with WG-345 removed) for photoallergenicity evaluations.

Investigational Product: NAFT-500

Six progressive full-spectrum UV doses were administered in 25% steps for determination of the minimal erythema dose (MED), which was the lowest dose that produced erythema with defined borders (Grade 2). The erythema grading scale is shown in Table 2.

Grading Scale for Erythema Responses to UV Doses

0 No erythema response
1 Minimally perceptible erythema
2 Mild erythema with clearly defined borders
3 Moderate erythema with sharp borders
4 Dark red erythema with sharp borders
5 Dark red erythema with sharp borders and possible edema
6 Intense erythema with sharp borders and edema

Typical MEDs for subjects with skin types I, II and III ranged from 8 to 16 seconds (10-20 effective mJ/cm2). Subjects whose MEDs were less than 6 seconds or who had no MED response at 20 seconds were not eligible for study enrollment 7 Subjects

Inclusion Criteria

__ Subjects are capable of understanding and willing to sign a statement of Informed Consent and Health Insurance Portability and Accountability Act of 1996 (HIPAA) authorization
_ Male and Female subjects 18-70 years of age.
_ Subjects with Fitzpatrick skin types I-III.
_ Subjects in good general health.
_ Subjects willing to avoid sun exposure, tanning lamps and use of any topical products on the test areas.
_ Subjects willing and able to complete all study visits.
_ Female subjects must be post-menopausal for at least one year; or have had a hysterectomy; or have had a tubal ligation; or if of childbearing potential, must agree to use an approved method of birth control throughout the study (i.e., oral/systemic contraceptives, intrauterine device (IUD), or spermicide in combination with a barrier method of contraception), or must be abstinent, or in a monogamous relationship with a partner who has had a vasectomy and have a negative urine pregnancy test a Screening.
_ Subjects able to receive MED of 6 to 20 seconds (10-20 effective mJ/cm^2)

Exclusion Criteria

_ Use of topical steroids, skin irritating topical preparations, or pigmenting agents (self-tanning agents) applied in the area for 2 weeks prior to Visit 1 and for the duration of the study. Use of any other systemic or topical drugs that might affect responses to UVR or interfere with responses to test product including thiazides, tetracyclines and NSAIDs.
_ History of photosensitivity disease or sensitivity to cosmetics or topical products
_ Pregnant or breastfeeding
_ Significant systemic disease, infection, cataracts, glaucoma, diabetes or lupus
_ History of psoriasis, atopic dermatitis, cancerous or precancerous lesions, dysplastic nevi, or other skin pathology
_ Sunburn, excessive tan, uneven skin tones or blemishes of the midback or use of tanning lamps or beds within 3 months before enrollment
_ Use of systemic or topical drugs that might affect responses to UVR or interfere with responses to test product including: corticosteroids, thiazides, tetracyclines and NSAIDs
_ Subjects who have participated in a study 30 days prior to enrollment
_ Any other condition that might increase the risk of study participation or compromise study results, or subjects with severe physical, neurological or mental disease.
_ Employees or direct relatives of an employee of the Study Center or Merz Pharmaceuticals.
In addition, subjects were required to report any medications, vitamins or herbal preparations used during the study.

Statistical Methods

Subject demographic data and skin response grades were summarized using descriptive statistics (number of observations [n], mean, median, and standard deviation [SD]) and frequency distributions (count [n], and percentage [%]) as appropriate. No inferential statistical analyses were performed. According to the protocol only descriptive statistics will be evaluated, since an irritation grade of 3 or higher is considered indicative of a potentially phototoxicity response.

Study Results

Fifty-seven (57) male and female adult volunteers were enrolled into the study after satisfying the inclusion and exclusion criteria.

Subject Compliance, Demographics and Concomitant Medications

Sixty (60) prospective subjects were screened, of which three (3) were disqualified at screening. Subject number (b) (6) was disqualified due to acne in the test area, subject number (b) (6) had skin type IV and subject number (b) (6) had pre-existing tan in the test area.

Of the 57 subjects were enrolled, 38 were females (66.7%) and 19 were males (33.3%), Mean=38.9, SD=13.4. Ages for the subjects ranged from 19 to 68 years (Mean=39.4, SD=14.0). Of the 57 subjects enrolled, 56 received at least one application of the test product. Subject (b) (6) was disqualified due to the use of concomitant medication (Azithromycin) after completing enrollment procedures and UV doses for MED determination.

Fifty-three (53) completed the study. Subject numbers (b) (6) and (b) (6) were unable to complete due to transportation issues, subject number (b) (6) was unable to complete for personal reasons. Each of these

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subjects completed the Visit 1 procedures of the Induction Phase (one application of the test product) but did not return for evaluation. Subjects who completed the study included thirty-five (35) females (66.0%) and eighteen (18) males (34.0%).

Evaluations of Subject Irritation Grades
For sites treated with NAFT 500, there was only one irritation grade above 2 (grade 3), that occurred during the induction phase, and was not considered significant. For UV irradiated Control sites, there were three irritation grades above 3 (Grade 4). These were not considered significant. For test product application sites there were no irritation grades above 3, and relatively few instances of grade 3 (a total of six at irradiated test product application sites).

Adverse Events:
No serious adverse events were reported, and no subjects dropped out due to adverse events. A total of 14 nonserious adverse events were reported for 12 subjects, and included tape irritation (6), irritation on right side of back due to possible insect bite or scratch (1), headache (3), eye irritation (1), right side pain and abrasions from fall (1) strep throat (1) upper respiratory infection (1). All were resolved before the conclusion of the study.

Overall Conclusions
Comparison of irritation scores between the unirradiated control sites and unirradiated test product application sites and comparison of irritation scores between the irradiated control sites and the irradiated test product application sites showed no significant difference in patterns or distributions of scores or mean scores. The applicant concluded that no evidence of photoallergenicity was observed.

This study was not vehicle controlled as recommended by the Agency; however, the study was evaluator blinded. This reviewer concurs with the applicant's conclusion and that under conditions of this study, no evidence of photoallergenicity was observed as there were no scores assessed above Grade 3 in the challenge phase.

Phototoxicity (MUS 90200/1013/1)
Study dates: August 18, 2009 to September 18, 2009

Objective
The objective was to evaluate the potential of NAFT-500 to produce phototoxicity reactions in normal use, by administering higher doses of NAFT-500 than normally used and comparing responses of test sites with test product alone, test product irradiated and no treatment.

Study Design and Plan
This was an open-label, controlled study consisting of a single, duplicate, occluded 24 hour application of the test article and duplicate untreated control sites, in Finn Chambers (occlusive), followed by removal of the chambers and irradiation of one of the test article treated site and one of the untreated control sites with UVR. Responses of all sites were scored immediately, and at 24 ± 4 hours and 48 ± 4 hours after UVR doses.
Reviewer comment:

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The Agency recommends conduct of a randomized, double-blinded, placebo- controlled, 3 arm-repeat patch test that compares test patch, vehicle patch (without active drug substance), and a blank patch.

Inclusion Criteria

_ Subjects were capable of understanding and willing to sign a statement of Informed Consent and Health Insurance Portability and Accountability Act of 1996 (HIPAA) authorization
_ Male and Female subjects 18-70 years of age.
_ Subjects with Fitzpatrick skin types I-III. (See Table 2)
_ Subjects in good general health.
_ Subjects willing to avoid sun exposure, tanning lamps and use of any topical products on the test areas.
_ Subjects willing and able to complete all study visits.
_ Female subjects were post-menopausal for at least one year; or had a hysterectomy; or had a tubal ligation; or if of childbearing potential, agreed to use an approved method of birth control throughout the study (i.e., oral/systemic contraceptives, intrauterine device (IUD), or spermicide in combination with a barrier method of contraception), or must be abstinent, or in a monogamous relationship with a partner who has had a vasectomy. All prospective female subjects of childbearing potential had a negative urine pregnancy test at Screening.
_ Subjects with MEDs of >8 to <16 seconds (10-20 effective mJ/cm2)

Exclusion Criteria

_ Use of topical steroids, skin irritating topical preparations, or pigmenting agents (self-tanning agents) applied in the area for 2 weeks prior to Visit 1 and for the duration of the study. Use of any other systemic or topical drugs that might affect responses to UVR or interfere with responses to test product including thiazides, tetracyclines and NSAIDs (a list of these medications was provided to each subject at enrollment)
_ History of photosensitivity disease or sensitivity to cosmetics or topical products
_ Pregnant or breastfeeding
_ Significant systemic disease, infection, cataracts, glaucoma, diabetes or lupus
_ History of psoriasis, atopic dermatitis, cancerous or precancerous lesions, dysplastic nevi, or other skin pathology _ Sunburn, excessive tan, uneven skin tones or blemishes of the midback or use of tanning lamps or beds within 3 months before enrollment

The Investigational Product

The investigational product, NAFT 500, was provided in open label tubes by the sponsor.

Table 40 (Applicant's Table 1). Study Flow Chart

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Day	Procedures
First Screening Visit	Consent; Determination of eligibility; MED Exposures (Within one week before Day 0)
Second Screening Visit	Evaluation of MED exposures (May coincide with Day 0)
Day 0	MED Determination (If not done previously); Application of Test Article and Control in Finn chambers
Day 1	Removal of chambers after 24 ± 4 hours; Grading; Re-application of Test Article; UV Exposures to Test Article and Control
Day 3	24 ± 4 Hour Grading
Day 4	48 ± 4 Hour Grading

Procedures

UV Doses were administered to 0.8 cm diameter sites on the mid-back using a calibrated 150 watt xenon arc lamp, filtered to simulate the full solar UV spectrum for MED determination3. A (b) (4) UVB/UVC blocking filter was used to deliver 10 J/cm2 of UVA only then removed to deliver 0.5 MED of full-spectrum UV for phototoxicity evaluations.

Duplicate applications of approximately 20 mg of the investigational product were placed in Finn Chambers and the chambers were applied to the designated locations on the mid-back and secured with Scanpor® tape or equivalent. Duplicate blank chambers were applied to untreated control sites.

Grading Scale for Erythema Responses to UV Doses
0 No erythema response
1 Minimally perceptible erythema
2 Mild erythema with clearly defined borders
3 Moderate erythema with sharp borders
4 Dark red erythema with sharp borders
5 Dark red erythema with sharp borders and possible edema
6 Intense erythema with sharp borders and edema

Study Results

Thirty-four (34) male and female adult volunteers satisfied the inclusion and exclusion criteria and were enrolled. Subject number (b) (6) was lost to follow-up after enrollment, and did not receive NAFT-500.. Subjects who received NAFT-500 included 18 females (54.5%) and 15 males (45.4%), ranging in age from 18 to 69 years. The mean age was 40.5 (n=33, SD=12.7).

Typical MEDs for subjects with skin types I, II and III ranged from 8 to 16 seconds (10-20 effective mJ/cm2). Subjects whose MEDs were less than 6 seconds or who had no MED response at 20 seconds were not eligible for study enrollment. UV doses for the phototoxicity evaluation consisted of 10 Joules/cm^2 of UVA (320-400 nm) using a solar simulator with a (b) (4) filter in place, then with 0.5 MEDs of full-spectrum UV (290-400 nm) radiation (WG-345 filter removed).

Chambers were left in place for 20 ± 4 hours and removed. Sites were evaluated and approximately 2 µl/cm^2 of the investigational product was re-applied to one of the previously treated sites. That site and one of the untreated control sites were then irradiated with the appropriate doses of UV radiation and all sites were evaluated for immediate responses. After 24 + 4 hours, and again after 48 + 4 hours, the sites were evaluated and graded.

Reviewer comment:
The Agency recommends the following:

a) *Study duration of 6 days.*
b) *Randomized, double-blinded, vehicle- controlled, 3 arm-repeat patch test that compares test patch, vehicle patch (without active drug substance), and a blank patch. A minimal erythema dose (MED) evaluation post UVA/UVB irradiation will be performed for each subject.*
c) *Patch application: each subject is tested with 2 sets of 3 study occlusive patches applied to the back for 24 hours. One set of patches (set A) is removed after 24 hours and those test sites are irradiated with 16J/cm² of ultraviolet A light (UVA) and 0.75 MED with UVA/ultraviolet B light (UVB). The second set of patches should be then removed (set B) and those sites serve as non-irradiated controls.*
d) *Evaluation: scoring of skin reactions should be done one hour after patch removal and during follow up visits at 24(±1 hour), 48 (±2 hours), and 72 (±2 hours) after patch removal.*

Measurements
Responses of all sites treated with the investigational products and control sites were scored by an evaluator who was masked to test site identities, using the irritation grading scale in Table 3.

Table 41 (Applicant's Table 4). Irritation Grading Scale
0 = No reaction
1 = minimal (doubtful) response
2 = Definite, mild Erythema
3 = Moderate Erythema
4 = Erythema with slight Edema
5 = Erythema with marked Edema
6 = Erythema with infiltration, raised, spreading beyond borders, with or without vesiculation.
7 = Large vesiculo-bullous reaction

Statistical Methods
Subject demographic data and skin response grades were summarized using descriptive statistics (number of observations [n], mean, median, and standard deviation [SD]) and frequency distributions (count [n], and percentage [%]) as appropriate. No inferential statistical analyses were performed. Only descriptive

Reference ID: 3030807

statistics were evaluated, since an irritation grade of 3 or higher is considered indicative of a potentially phototoxicity response.

Subject Compliance, Demographics and Concomitant Medications

Thirty-six (36) prospective subjects were screened of which 2 were screening failures due to their medical history. Thirty-four (34) subjects were enrolled. Subject number (b) (6) was lost to follow-up after enrollment, and did not receive NAFT-500. Subjects who received NAFT-500 included 18 females (54.5%) and 15 males (45.4%), ranging in age from 18 to 69 years. The mean age was 40.5 (n=33, SD=12.7).

A total of 3 non-serious adverse events were reported by 3 subjects. Sneezing/sinus ache and two reports of Itching on treated sites. According to the reports of itching were most likely due to tape irritation as the itching was generalized to area where tape was applied and there were no associated Grade 3 or higher responses shown in the test sites. However, relationship to the test product cannot be ruled out without further study.

Conclusion

According to the applicant, no significant irritation scores or patterns in distributions of scores or mean scores were observed, other than slight increases in scores for both irradiated and un-irradiated sites after UV doses. There were no irritation grades above 2, and relatively few instances of grade 2. No significant irritation scores or patterns in distributions of scores or mean scores were observed, other than slight increases in scores for both irradiated and un-irradiated sites after UV doses. The applicant concluded that no evidence of phototoxicity was observed.

Although Phototoxicity Study MUS 90200/1013/1 was not vehicle controlled as recommended by the Agency, evaluators were blinded. An evaluation at 72 ±2 hours after patch removal during challenge phase was not performed; however, an additional observation may not have changed the study conclusion in that an irritation grade of 3 or higher was per protocol considered indicative of potentially phototoxicity and the highest score was only 2 during challenge phase and did not change between the 24 and 48 hour scoring. This reviewer finds the study marginally acceptable and concurs that under conditions of this study, no evidence of phototoxicity was observed.

7.4.6 Immunogenicity

This drug product is not expected to induce systemic immunogenicity.

7.5 Other Safety Explorations

Randomized, Double-Blind, Placebo and Moxifloxacin-Controlled, Single Dose, 3-Arm, Parallel Study in Healthy Subjects to Evaluate the Effects of Naftifine Hydrochloride on Cardiac Repolarization (QT/QTc Interval Duration)" was conducted. As previously indicated in Section 7.4.5, no significant QTc prolongation effect of naftifine HCl (600 mg) was detected in this TQT study.

7.5.1 Dose Dependency for Adverse Events

Although the numbers are small, the 2% formulation appears more irritating than the 1% drug product. Except application site irritation 2 (0.5) vs. 4 (1.7) for naftifine 2% and naftifine 1%, respectively, overall application site reactions were twice that for the 2 % formulation (i.e., application site pruritus 7 (1.8) vs. 1 (0.4), application site dryness 3 (0.8) vs. 1 (0.4), and contact dermatitis 2 (0.5) vs. 0 for naftifine 2% and naftifine 1%, respectively). One severe TEAEs of skin exfoliation was reported in the NAFT-500 study arm in the tinea cruris study. According to the applicant for the tinea pedis study, there were infrequent reports of treatment-related TEAEs (12 [5.1%] subjects in the NAFT-500 Cream, 2% group; 9 [3.8%] subjects in the Naftin 1% Cream group (Study report pg. 77 of 81).

7.5.2 Time Dependency for Adverse Events

The maximum duration of exposure was 28 days and time dependency for AEs were not addressed.

Drug-Demographic Interactions

According to the statistical review, the majority of the FAS subjects (approximately 70-80%) were men in both trials and male subjects had higher complete cure rates than females but female subjects had higher complete cure rates than males in the tinea cruris trial and tinea pedis trial, respectively. Overall, small numbers of female patients were enrolled in both trials. Higher response rates occurred among those in the NAFT-500 vehicle arm among patients classified as 'white' or 'other'; however, complete cure rates were similar across the treatment arms among the 'black' subjects. Numbers are too small to draw conclusion based on pediatric and geriatric patients because only 4 subjects (2 in each study) were enrolled between the ages of 12 and 17, and only a small number of geriatric subjects were enrolled. All subjects were from the United States and geographic distribution was not addressed.

7.5.4 Drug-Disease Interactions

Drug disease interaction was not explored.

Drug-Drug Interactions

No evaluations of drug-drug interactions were conducted.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The applicant was advised at the PreIND Meeting that for a drug product intended to be used chronically in humans, the potential to induce carcinogenicity should be evaluated. To date there is no carcinogenicity data available for naftifine HCl. The carcinogenicity potential of NAFT-500 cream product should be evaluated; therefore, a 2-year dermal rat carcinogenicity study will be conducted as a post-marketing requirement.

7.6.2 Human Reproduction and Pregnancy Data

No evaluations of NAFT-500 Cream, 2% were conducted in pregnant or lactating women. NAFT-500 Cream, 2% should not be used during pregnancy unless the potential benefit justifies the potential risk to

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the fetus. It is not known whether NAFT-500 Cream, 2% is excreted in human milk and caution should be exercised if it is administered to a nursing woman.

7.6.3 Pediatrics and Assessment of Effects on Growth

The applicant submitted two pediatric waiver requests:

- A partial waiver request of the requirement to provide information on pediatric patients under the Pediatric Research Equity Act (PREA) for patients 0 – 11 years of age (<12 years). Merz specifically requests a waiver of the requirement to conduct studies in pediatric subjects younger than 12 years of age on the basis that NAFT-500 does not represent a significant therapeutic alternative for this age group and is unlikely to be used in a substantial number of patients younger than 12 years of age. Tinea pedis and tinea cruris occur less frequently in children than in adults, and less frequently in children less than 12 years of age than in adolescents.
- (b) (4)

  On September 21, 2011 (SND 196) the applicant submitted a pediatric plan to conduct the following study "An Open-Label, Single-Center, Multiple-Application Pharmacokinetic Study of NAFT-500 in Pediatric Subjects with Tinea Cruris and Tinea Pedis" in patients 12 – 17 years of age. This reviewer concurs with the waiver request and rationale provided for patients 0 -11 years old for the tinea pedis and cruris indications.

  In regards to the tinea corporis indication, the applicant requests that success in tinea pedis and tinea cruris indications is thereby assumed for the tinea corporis based on pre-IND meeting guidance provided by the Division. This advice was provided to applicants for treatment of adults prior to Pediatric Research Equity Act which now requires all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain and assessment of the safety and effectiveness of the pediatric patients unless this requirement is waived or deferred. This issue will be addressed by Pediatric Review Committee (PeRC).

No growth assessments have been made.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

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According to the applicant, no episodes of abuse of NAFT-500 Cream, 2% were observed during the clinical development program and based on the absence of neuropsychiatric effects and the absence of abuse potential for the marketed Naftin 1% product(s), there is little or no risk of abuse for NAFT-500 Cream, 2%.

7.7 Additional Submissions / Safety Issues

The 120 day safety update was submitted October 3, 2011 and there are no ongoing clinical studies for NAFT- 500 and no new safety data available to the application.

8 Postmarket Experience

NAFT-500 Cream, 2% is currently not marketed in any country.

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9 Appendices

9.1 Literature Review/References

1. Lesher JL. Tinea corporis. eMedicine from WebMD [Internet]. 2009 Dec [cited 2010 Jun 04];[about 3 p.]. Available at: http://www.emedicine.com/derm/topic421.htm.

2. Nobel S, Forbes RC, and Stamm P. Diagnosis and management of common tinea infections. American Family Physician (electronic version) 1998;58(1).

3. Weinstein A and Berman B. Topical treatment of common superficial tinea infections. *American Family Physician* (electronic version) 2002;65(10).

9.2 Labeling Recommendations

Labeling recommendations are under negotiations with the applicant. Key clinical recommendations that differ from the applicants are as follows:

- For treatment of interdigital tinea pedis, tinea cruris, and tinea corporis
- For use in patients ≥ 18 years of age
- (b) (4) Naftin Tradename is unacceptable for the 2% formulation

9.3 Advisory Committee Meeting

Advisory Committee meeting was deemed not necessary.

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/s/

BRENDA E VAUGHAN
10/18/2011

DAVID L KETTL
10/21/2011
Concur with approval recommendation for adults, pending completion of labeling negotiations with applicant. See CDTL review.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019599Orig1s011

CHEMISTRY REVIEW(S)

CHEMIST REVIEW #2
Efficacy Supplement

1. ORGANIZATION: ONDQA
2. NDA /Supp: 19-599 S-011
3. SUPPLEMENT DATES:
Letter/Stamp Date**: 16-Dec-2010**
Original PDUFA Date: 16-Oct-2011
3-month Extension: 16-Jan-2012
4. **AMENDMENTS:**
Feb 2011; Apr 2011; June 2011; 29-Jul-2011; 16-Aug-2011; 9-Jan-2012; 10-Jan-2012
5. RECEIVED BY CHEMIST: Jan 2011

6. SPONSOR NAME AND ADDRESS
Merz Pharmaceuticals, LLC
Greensboro, NC

7. SUPPLEMENT PROVIDES FOR: a change in drug product strength from 1% to 2% naftifine hydrochloride

8. DRUG PRODUCT NAME: Naftin Cream, 1%
9. NONPROPRIETARY NAME: Naftifine Hydrochloride Cream
10. DRUG SUBSTANCE: Naftifine Hydrochloride
11. DOSAGE FORM/STRENGTH Cream, 1%
12. ROUTE OF ADMINSTRATION: Topical
13. INDICATION: treatment of tinea pedis, tinea cruris, and tinea coporis

14. HOW DISPENSED: Rx
15. RELATED IND/NDA/DMF: N/A

16. COMMENTS:
The supplement provides for a change in the drug product strength from 1% to 2% naftifine hydrochloride, with a change in dosing regimen. Most of the approved chemistry, manufacturing and controls will be used in the manufacture of the proposed 2% cream and are acceptable. See chemistry review #1.

Chemistry review #2 evaluates final container/carton, the final agreement for the Post-Marketing Commitment (PMC) regarding viscosity, acceptance of a 24-month expiry, and the Environmental Assessment Categorical Exclusion request.

17. CONCLUSIONS AND RECOMMENDATIONS
All chemistry, manufacturing and controls evaluated in chemistry review #1 and chemistry review #2 are acceptable. This supplement, therefore, is recommended for Approval.

18.	**REVIEWER NAME**	**DATE COMPLETED**
	J. Salemme, Ph.D., Chemistry reviewer, ONDQA	10-Jan-2012

PM: J. David; Reviewed: Dr. Tom Oliver, Branch Chief ONDQA

Reference ID: 3070208

Clarification of Additional Comments from Chemistry Review #1:
The additional comments from Chemistry Review #1 are the following:

The following issues should be provided in the action letter if an approval is recommended:

1) The Naftin 2% Cream is granted a 24 month expiry.

(2) Your proposed viscosity acceptance criterion, [redacted] (b) (4) cps, is acceptable as an interim specification. Collect viscosity data from all available manufactured batches. Submit within 15 months after the S-011 approval date, your final viscosity report, with complete viscosity information/data and a proposal for the final viscosity specification.

Chemistry Review #2
Chemistry review #2 evaluates final labeling, the final agreement for the Post-Marketing Commitment (PMC) regarding viscosity, acceptance of the 24-month expiry, and the Environmental Assessment Categorical Exclusion request.

Labeling and Container Label/ Carton [11-Jan-2012 Amendment]
Final labeling was submitted 11-JAN-12

LABELING
Section 3, Dosage Forms and Strengths, Section 11, Description, and Section 16, How Supplied have been reviewed during Labeling Reviews with the Clinical Division. These sections are acceptable. See final label.

CONTAINER LABEL/Carton
Mock-ups of the tube and carton for 2-g, 30-g and 60-g tubes were provided in the original submission, and mock-ups for the 45-g tube and carton were provided in an amendment. All draft tube labeling and cartons for the four size tubes have been resubmitted in the 11-Jan-2012 amendment.

11-Jan-2012 Amendment
Mock-ups of the 2-g, 30-g, 45-g, and 60-g tube labels are provided. The 30-g tube label is provided below:

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30-g

(b) (4)

<u>Carton</u>
Carton mock-ups have been provided for 2-g, 30-g, 45-g, and 60-g tubes. Provided below is the 30-g carton.

(b) (4)

Evaluation of Labeling: Acceptable.

<u>Final Agreement for the Post-Marketing Commitment regarding Viscosity</u>
The 22-Dec-2011 amendment provides an agreement for the post-marketing commitment regarding viscosity.

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The sponsor commits to the following:

Postmarketing commitment study to be conducted post-approval:

1. Request for additional viscosity data.
   Final Report Submission: 04/2013

Evaluation: Acceptable.

Acceptance of a 24-month Drug Product Expiry

The NDA holder was notified via t-con held on 9-Jan-2012 that the data provided in the supplement submission support a 24-month expiry. The 10-Jan-2012 amendment provides the acceptance of the 24-month expiry.

Evaluation: Acceptable.

Environmental Assessment Categorical Exclusion

A justification is provided to support a categorical exclusion from conducting an Environmental Assessment.

Evaluation: Acceptable.

Reference ID: 3070208

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/s/

JEAN SALEMME
01/11/2012

THOMAS F OLIVER
01/11/2012

CHEMIST REVIEW #1
Efficacy Supplement

1. ORGANIZATION: ONDQA
2. NDA /Supp: 19-599 S-011
3. SUPPLEMENT DATES:
Letter/Stamp Date**: 16-Dec-2010**
Original PDUFA Date: 16-Oct-2011
3-month Extension: 16-Jan-2012
4. **AMENDMENTS:**
Feb 2011; Apr 2011; June 2011; 29-Jul-2011; 16-Aug-2011
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11. DOSAGE FORM/STRENGTH Cream, 1%
12. ROUTE OF ADMINSTRATION: Topical
13. INDICATION: treatment of tinea pedis, tinea cruris, and tinea coporis

14. HOW DISPENSED: Rx
15. RELATED IND/NDA/DMF: N/A

16. COMMENTS:
The supplement provides for a change in the drug product strength from 1% to 2% naftifine hydrochloride, with a change in dosing regimen. Most of the approved chemistry, manufacturing and controls will be used in the manufacture of the proposed 2% cream and are acceptable.

The supplement provides for a change in the drug product strength from 1% to 2% naftifine hydrochloride, with a change in dosing regimen. Most of the approved chemistry, manufacturing and controls will be used in the manufacture of the proposed 2% cream and are acceptable.

Deficiencies identified with the degradation method have been resolved. The method is validated for the analysis of degradants in the drug product. Additionally, deficiencies with the viscosity method and data have been resolved. The applicant's proposed viscosity acceptance criterion, (b) (4) (b) (4) cps, is acceptable as an interim specification. The applicant will be

asked to collect viscosity data from all available manufactured batches during the first 12 months after the supplement (S-011) approval date. Within 15 months after the S-011 approval date, the applicant will be required to submit the final viscosity report, with complete viscosity information/data and a proposal for their final viscosity specification.

Labeling will be evaluated in Chemistry Review #2 along with the final agreement for the Post-Marketing Commitment (PMC) regarding viscosity.

17. CONCLUSIONS AND RECOMMENDATIONS

The final evaluation of this submission is PENDING the acceptance of the Post-Marketing Commitment for viscosity data and PENDING labeling/label review. See following page for additional comments.

18. REVIEWER NAME	**DATE COMPLETED**
J. Salemme, Ph.D., Chemistry reviewer, ONDQA	16-Aug-2011

PM: A. Cuff; Reviewed: Dr. Tom Oliver, Branch Chief ONDQA

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/s/

JEAN SALEMME
10/04/2011

THOMAS F OLIVER
10/04/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019599Orig1s011

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	19599 Supplement-11
Supporting documents:	93, 100, 101
Applicant's letter date:	12/16/2010, 05/10/2011, 05/27/2011
CDER stamp date:	12/16/2010, 05/10/2011, 05/27/2011
Product:	NAFT-500 (naftifine hydrochloride) Cream, 2%
Indication:	Tinea pedis, tinea cruris, and tinea corporis
Applicant:	Merz pharmaceuticals, Greensboro, NC
Review Division:	Dermatology and Dental Products
Reviewer:	Jianyong Wang
Supervisor/Team Leader:	Barbara Hill
Division Director:	Susan Walker
Project Manager:	Dawn Williams

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 19599 Supplement-11 are owned by Merz pharmaceuticals or are data for which Merz pharmaceuticals has obtained a written right of reference.
Any information or data necessary for approval of NDA 19599 Supplement-11 that Merz pharmaceuticals does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 19599 Supplement-11.

Reference ID: 2981933

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1 Executive Summary

1.1 Introduction

Naftifine hydrochloride is a synthetic allylamine derivative. The antifungal activity of naftifine hydrochloride is likely related to its inhibition of squalene epoxidase in dermatophytes, leading to an accumulation of intracellular lipids that ultimately results in irreversible damage to the fungal cell wall. Naftifine hydrochloride is the active ingredient of Naftin® 1% Cream and Naftin® 1% Gel, which have been approved under NDA 19599 and NDA 19356, respectively, for the treatment of tinea pedis, tinea cruris, and tinea corporis. The Naftin® 1% Cream is applied once daily and the Naftin® 1% Gel is applied twice daily. The sponsor submitted this NDA supplement to develop NAFT-500 (naftifine hydrochloride) 2% cream [redacted] (b) (4) to provide shorter treatment duration over the currently marketed Naftin® 1% Cream product. NAFT-500 incorporates the same excipients that are used in the Naftin® 1% Cream product. The only differences in the compositions between the 2% cream and the Naftin® 1% cream are the increase of active ingredient from 1% to 2% [redacted] (b) (4) The sponsor is also developing NAFT-600 (naftifine hydrochloride) 2% gel for the treatment of tinea pedis under IND 105603.

1.2 Brief Discussion of Nonclinical Findings

Naftifine HCl had an apparent stimulating effect on the central nervous system in mice and rats. Naftifine had a very weak effect on the cardiovascular system of anesthetized cats. During IV infusion, the reduction in mean arterial blood pressure and heart rate, carotid occlusion, and nictitating membrane responses were noted; however, such findings were still within the historical control range. No signs of toxicity or ECG changes were observed up to a cumulative IV dose of 18.7 mg/kg. In anesthetized dogs, no significant effects on the cardiovascular parameters, ECG, or diuresis were noted following an intra-arterial dose of 0.005 mg/kg or intraduodenal doses up to 5 mg/kg. A slight increase in heart rate was noted at the 5 mg/kg intraduodenal dose as compared with control.

General toxicology studies have been conducted extensively with various formulations of naftifine HCl in rats, rabbits, guinea pigs, dogs, monkeys, and minipigs. Findings in oral toxicity studies included reduction in body weight gain and increases in serum bilirubin, creatinine, and urea levels. Findings in dermal toxicity studies included very slight erythema and reduction in body weight gain.

In genetic toxicology studies, naftifine HCl was negative in a bacterial mutagenicity test, an in vitro chromosome aberration test, and an in vivo micronucleus test. There is no concern for the genotoxicity of naftifine HCl.

To date there is no carcinogenicity data available for naftifine HCl. The carcinogenicity potential of NAFT-500 cream product should be evaluated. A 2-year dermal rat

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carcinogenicity study will be conducted as a post-marketing requirement. The proposed timeline for the conduct of the carcinogenicity study is considered acceptable.

Reproductive and developmental toxicology studies have been conducted with naftifine HCl in rats and rabbits. Naftifine HCl did not affect fertility in rats at oral doses up to 100 mg/kg/day. Naftifine HCl did not show a teratogenic effect in rats at oral doses up to 300 mg/kg/day or in rabbits at subcutaneous doses up to 30 mg/kg/day. In another teratological study in rats, at subcutaneous dose of 30 mg/kg/day, two out of 308 fetuses exhibited malformations: one fetus with exencephaly and one fetus with rib and vertebral defects. These two defects were within the historical control range and not considered related to treatment. The NOAEL for embryo-fetal developmental effects was considered to be 30 mg/kg/day in this study. Naftifine HCl had no adverse effects on peri- and postnatal development in rats at oral doses up to 100 mg/kg/day.

Naftifine HCl solutions up to 10% were not irritating to rabbit skin. Naftifine HCl 1% cream was slightly irritating to rabbit skin. Naftifine HCl 1% and 3% creams were slightly irritating to the conjunctiva, but not toxic to the cornea of rabbit eye. Naftifine HCl 5% solution was not a contact sensitizer in guinea pigs. Naftifine HCl and NAFT-500 2% cream exhibited minimal UVB absorbance. The extent of UVB absorbance does not trigger the need for a nonclinical photoirritation study.

Overall the toxicity profile of NAFT-500 drug product has been well characterized. Because TK data were not obtained in most toxicology studies, the multiples of human exposure were calculated based on BSA comparison, assuming 100% absorption after dermal application. It should be noted that such evaluation is very conservative for systemic toxicology studies in which test article was administered via gavage or subcutaneous injection. The proposed daily topical dosage of NAFT-500 (2% cream applied once daily) would be comparable to the approved dosage of Naftin® Gel 1% (applied twice daily). From a pharmacology/toxicology perspective, the proposed clinical doses do not elicit a significant safety concern. This efficacy supplement is approvable from a pharmacology/toxicology perspective.

1.3 Recommendations

1.3.1 Approvability

NDA 19599 Supplement-11 is approvable from a pharmacological/toxicological perspective, provided that the recommended changes in the label described in Section 1.3.3 are incorporated into the NAFT-500 2% cream label.

1.3.2 Additional Nonclinical Recommendations

The sponsor has committed to conduct a dermal rat carcinogenicity study as a post-marketing requirement (see Section 8 for details concerning the proposed timeline for conduct of this nonclinical study).

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1.3.3 Labeling

It is recommended that the underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the NAFT-500 2% cream label reproduced below. The pharmacologic class designation for naftifine hydrochloride (i.e., allyamine antifungal) is correct.

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE

[redacted] (b) (4)

8.1 Pregnancy
Pregnancy Category B:

[redacted] (b) (4) (b) (4) -There are~~,~~ (b) (4) no adequate and well-controlled studies of Tradename in pregnant women. Because animal reproduction studies are not always predictive of human response, (b) (4) Tradename should be used during pregnancy only if (b) (4) the potential benefit justifies the potential risk to the fetus.

The animal multiples of human exposure calculations were based on daily dose body surface area comparison (mg/m^2) for the reproductive toxicology studies described in this section and in Section 13.1. The Maximum Recommended Human Dose (MRHD) was set at 8 g 2% cream per day (2.67 mg/kg/day for a 60 kg individual).

Systemic embryofetal development studies were conducted in rats and rabbits. Oral doses of 30, 100 and 300 mg/kg/day naftifine hydrochloride were administered during the period of organogenesis (gestational days 6 – 15) to pregnant female rats. No treatment-related effects on embryofetal toxicity or teratogenicity were noted at doses up to 300 mg/kg/day (18.2X MRHD). Subcutaneous doses of 10 and 30 mg/kg/day naftifine hydrochloride were administered during the period of organogenesis (gestational days 6 – 15) to pregnant female rats. No treatment-related effects on embryofetal toxicity or teratogenicity were noted at 30 mg/kg/day (1.8X MRHD). Subcutaneous doses of 3, 10 and 30 mg/kg/day naftifine hydrochloride were administered during the period of organogenesis (gestational days 6 – 18) to pregnant female rabbits. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 30 mg/kg/day (3.6X 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 were noted at 300 mg/kg/day (18.2X MRHD). No developmental toxicity was noted at 100 mg/kg/day (6.1X MRHD).

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies to evaluate the carcinogenic potential of (b) (4) Tradename have not been performed. (b) (4)

Naftifine hydrochloride revealed no evidence of mutagenic or clastogenic potential based on the results of two *in vitro* genotoxicity tests (Ames assay and Chinese hamster ovary cell chromosome aberration assay) and one *in vivo* genotoxicity test (mouse bone marrow micronucleus assay).

Oral administration of naftifine hydrochloride to rats, throughout mating, gestation, parturition and lactation, demonstrated no effects on growth, fertility or reproduction, at doses up to 100 mg/kg/day (6.1X MRHD).

2 Drug Information

2.1 Drug

CAS Registry Number (Optional): 65473-14-5

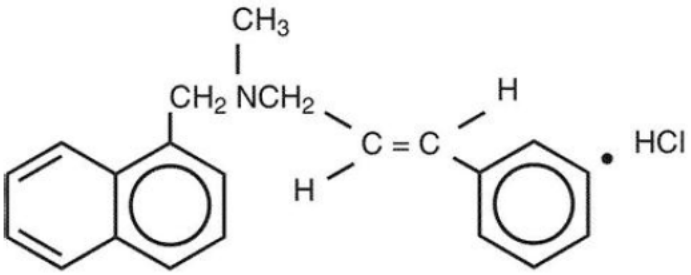
Generic Name: Naftifine hydrochloride 2% Cream

Code Name: NAFT-500, SN 105-843

Chemical Name: (E)-*N*-Cinnamyl-*N*-methyl-*l*-naphthatenemethylamine hydrochloride

Molecular Formula/Molecular Weight: $C_{21}H_{21}N \cdot HCl$ / 323.86

Structure or Biochemical Description:



Pharmacologic Class: Allylamine Antifungal (Note: This is an established pharmacologic class.)

2.2 Relevant INDs, NDAs, BLAs and DMFs

1) IND 77530 [NAFT-500 (naftifine hydrochloride 2% cream), active, DDDP]
2) IND 105603 [NAFT-600 (naftifine hydrochloride 2% gel), active, DDDP]
3) [redacted] (b) (4)
4) IND 22919 [Naftin (naftifine hydrochloride) Cream, 1%, active, DDDP]
5) NDA 19356 [Naftin (naftifine hydrochloride) Gel, 1%, approved, DDDP]
6) NDA 19599 [Naftin (naftifine hydrochloride) Cream, 1%, approved, DDDP]

2.3 Drug Formulation

The composition of NAFT-500 cream, 2%, is listed in the following table. The composition of the 2% cream is the same as that of the approved Naftin® Cream 1%, except the increase of active ingredient (naftifine hydrochloride) from 1% to 2% [redacted] (b) (4)

		NAFT-500	Naftin®	Placebo
Component	Grade	% w/w		
Naftifine hydrochloride	[redacted] (b) (4)	2.00	1.00	0
Purified Water	[redacted] (b) (4)			
Isopropyl Myristate				
Polysorbate 60				
Stearyl Alcohol				
Cetyl Alcohol				
Cetyl Esters Wax				
Sorbitan Monostearate				
Benzyl Alcohol				
Sodium Hydroxide				
[redacted] (b) (4) Hydrochloric Acid				

[redacted] (b) (4)

2.4 Comments on Novel Excipients

N/A.

2.5 Comments on Impurities/Degradants of Concern

N/A.

2.6 Proposed Clinical Population and Dosing Regimen

NAFT-500 cream is indicated for the topical treatment of tinea pedis, tinea cruris, and tinea corporis caused by [redacted] (b) (4) *Trichophyton rubrum*, [redacted] (b) (4) NAFT-500 cream should be applied topically to the affected area including at least ½ inch of healthy skin surrounding the affected area once daily for 2 weeks.

Under the maximum clinical use condition (subjects with both tinea cruris and tinea pedis), the maximum topical dose of NAFT-500 2% cream would be 8 g/day for 2 weeks (2.67 mg/kg/day of naftifine HCl for a 60 kg individual).

2.7 Regulatory Background

Naftin® 1% Cream and 1% Gel were approved under NDA 19599 (on 02/29/1988) and NDA 19356 (on 06/18/1990), respectively, for the treatment of tinea pedis, tinea cruris, and tinea corporis. The sponsor previously opened IND 77530 and now submitted this efficacy supplement to develop NAFT-500 (naftifine hydrochloride) 2% cream [redacted] (b) (4) [redacted] (b) (4) to provide shorter treatment duration over the currently marketed Naftin 1% Cream product. The sponsor is also developing NAFT-600 (naftifine hydrochloride) 2% gel for the treatment of tinea pedis under IND 105603.

3 Studies Submitted

3.1 Studies Reviewed

1. UV/Visible light testing results for the active drug product Naftin 2% gel, reduced alcohol (CIE formula), lot # 856-0217B02, the placebo Naftin 2% gel, reduced alcohol (CIE formula), and each raw material contained in the product (Study# TC.0205.00).

3.2 Studies Not Reviewed

None. All the submitted pivotal toxicology studies were previously reviewed by the Agency.

3.3 Previous Reviews Referenced

1. IND [redacted] (b) (4)
2. IND [redacted]
3. IND 77530 nonclinical review #1 (by this reviewer, 06/30/2008)
4. IND 77530 nonclinical memorandum (by this reviewer, 01/27/2011)

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4 Pharmacology

4.1 Primary Pharmacology

Naftifine hydrochloride is a synthetic allylamine derivative. It is an antifungal agent that acts by inhibiting squalene epoxidase, a key enzyme involved in fungal cell reproduction.

Inhibition of squalene epoxidase results in the accumulation of squalene that is associated with intracellular degenerative processes, such as the deposition of lipid droplets. This accumulation occurs in the cell membrane as well as other membranes (i.e., the endoplasmic reticulum). Alterations in membrane properties will lead to cell wall damage, which explains the fungicidal action.

In vitro studies have demonstrated that naftifine hydrochloride is active against several strains of dermatophytes, including *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Trichophyton tonsurans*, *Trichophyton violaceum spp.*, *Microsporum canis sp.*, and *Epidermophyton floccosum*. Naftifine hydrochloride also showed efficacy in guinea pigs infected with *T. mentagrophytes*.

4.2 Secondary Pharmacology

Naftifine hydrochloride exhibits bactericidal and anti-inflammatory activity, though the exact mechanism of action is unclear.

4.3 Safety Pharmacology

In mice and rats, naftifine had an apparent stimulating effect on the central nervous system following single oral doses (32-320 mg/kg in mice and 10-100 mg/kg in rats), which appeared after a latency period. Naftifine at 50 mg/kg (i.p.) did not have significant effects on apomorphine-induced gnawing behavior or tetrabenazine-induced catalepsy in mice.

Naftifine had a very weak effect on the cardiovascular system of anesthetized cats when administered in increasing IV doses (4-500 mg/kg/min) over a 2-hr period. During drug infusion, there were reduction in mean arterial blood pressure and heart rate, carotid occlusion, and nictitating membrane responses; however, such findings were still within the range obtained for these same variables from a group of control cats. No signs of toxicity or ECG changes were observed up to a cumulative IV dose of 18.7 mg/kg. In anesthetized dogs, no significant changes in the cardiovascular parameters were seen nor were there any effects on diuresis or ECG following an intra-arterial dose of 0.005 mg/kg or intraduodenal doses up to 5 mg/kg. A slight increase in heart rate was noted at the 5 mg/kg intraduodenal dose as compared with the controls.

Reviewer's comment: It would have been preferable if the cardiovascular effects were evaluated in unanesthetized animals.

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5 Pharmacokinetics/ADME/Toxicokinetics

Plasma concentrations of naftifine hydrochloride were obtained from the 1-month and 9-month dermal toxicity studies in minipigs. In the 1-month study (Study# 007-0002), weanling minipigs were treated topically with placebo, 1%, and 3% naftifine cream (0, 6, and 18 mg/kg/day, respectively) twice per day for 30 days. Plasma concentrations were measured on Days 14 and 30 at 3 and 6 hr after the first dose, using a GC-MS method (limit of quantitation: 1 ng/ml).

Plasma concentrations of naftifine hydrochloride measured in the 1-month minipig study (mean ± SD, ng/ml):

Treatment	Dose (mg/kg/day)	Gender	Day14, 3 hr	Day 14, 6 hr	Day 30, 3hr	Day 30, 6 hr
Vehicle	0	Males	BLQ	BLQ	BLQ	BLQ
		Females	BLQ	BLQ	BLQ	BLQ
1% Naftifine Cream	6	Males	6.16 ± 3.11	5.36 ± 1.91	8.67 ± 0.83	8.62 ± 1.79
		Females	6.92 ± 1.49	5.04 ± 2.21	8.16 ± 1.21	8.54 ± 1.72
3% Naftifine Cream	18	Males	23.0 ± 9.21	21.8 ± 6.65	26.4 ± 10.4	27.6 ± 7.84
		Females	19.5 ± 7.04	16.3 ± 7.15	29.0 ± 12.9	21.7 ± 7.78

(b) (4)

Plasma concentrations of naftifine hydrochloride were approximately 2.5 to 4 times higher in the animals treated with 3% cream as compared with the animals treated with 1% cream. Similar plasma levels were measured within each group at 3 and 6 hr on both sampling days. There were no gender differences.

In the 9-month study (Study# OSC00002), minipigs were treated topically with placebo, 3%, 5%, and 10% naftifine solution once per day for 9 months. The sponsor claimed that the initial dose volume of 1 ml/kg was excessive resulting in a thick layer of test article at the application site, so the dose volume was reduced to 0.15 ml/kg on Day 94 and thereafter. Accordingly, the initial doses of 30, 50, and 100 mg/kg/day were reduced to 4.5, 7.5, and 15 mg/kg/day. Plasma concentrations were measured on Days 1 (at predose and 5 min, 15 min, 30 min, 1 hr, 3 hr, 6 hr, 12 hr and 24 hr postdose), 30, 93, 180 (at predose and 6 hr postdose) and 271 (at predose and 6, 24 hr postdose), using a LC-MS/MS method (limit of quantitation: 0.05 ng/ml).

Plasma concentrations of naftifine hydrochloride measured in the 9-month minipig study (mean ± SD, ng/ml):

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Time		Group2 (3% Naftifine HCl, dose: 30 mg/kg/d Day 1-93, 4.5 mg/kg/d Day 94-end)		Group 3 (5% Naftifine HCl, dose: 50 mg/kg/d Day 1-93, 7.5 mg/kg/d Day 94-end)		Group 4 (10% Naftifine HCl, dose: 100 mg/kg/d Day 1-93, 15 mg/kg/d Day 94-end)	
		Male	Female	Male	Female	Male	Female
Day 1	0	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
	5 min	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
	15 min	BLQ	BLQ-0.179	BLQ	BLQ	BLQ	BLQ
	30 min	0.16 ± 0.17	0.14 ± 0.05	0.32 ± 0.06	0.17 ± 0.13	0.11 ± 0.07	0.45 ± 0.50
	1 hr	1.15 ± 0.75	0.78 ± 0.42	0.47 ± 0.08	0.57 ± 0.28	0.55 ± 0.34	0.57 ± 0.22
	3 hr	2.33 ± 1.20	3.21 ± 0.95	3.91 ± 0.51	1.84 ± 0.76	2.87 ± 0.27	2.83 ± 1.58
	6 hr	3.71 ± 1.13	4.41 ± 0.77	2.77 ± 0.64	2.98 ± 0.62	2.95 ± 1.15	2.50 ± 0.61
	12 hr	2.51 ± 0.47	3.73 ± 1.60	3.30 ± 0.85	2.42 ± 0.58	3.50 ± 0.34	2.76 ± 0.68
	24 hr	3.89 ± 0.13	7.34 ± 6.79	2.04 ± 0.52	1.76 ± 0.10	1.81 ± 0.50	1.48 ± 0.47
Day 30	0	6.40 ± 1.24	6.76 ± 3.19	9.15 ± 2.62	6.26 ± 2.77	5.72 ± 1.94	4.89 ± 1.52
	6 hr	11.63 ± 3.32	8.89 ± 3.34	14.56 ± 5.74	8.94 ± 2.30	13.31 ± 10.18	11.30 ± 8.25
Day 93	0	15.52 ± 10.81	8.59 ± 5.25	14.70 ± 9.86	4.14 ± 1.09	4.77 ± 1.17	9.03 ± 2.63
	6 hr	11.42 ± 1.88	9.69 ± 2.58	15.63 ± 3.78	7.40 ± 1.67	13.19 ± 6.78	11.94 ± 7.57
Day 180	0	2.77 ± 0.45	3.23 ± 1.41	2.73 ± 0.26	2.90 ± 0.42	2.26 ± 0.63	3.32 ± 0.59
	6 hr	3.93 ± 0.58	4.33 ± 0.96	4.00 ± 0.57	4.04 ± 1.34	3.51 ± 0.85	3.87 ± 0.68
Day 271	0	2.96 ± 1.13	2.30 ± 0.72	2.34 ± 0.56	2.94 ± 1.62	3.10 ± 1.17	4.16 ± 0.91
	6 hr	3.40 ± 1.17	4.21 ± 3.22	2.69 ± 0.52	4.00 ± 2.06	4.03 ± 1.29	8.47 ± 4.41
	24 hr	3.06 ± 1.20	2.64 ± 0.76	2.28 ± 0.69	3.42 ± 2.30	4.17 ± 2.20	5.80 ± 0.54

BLQ: blow limit quantitation (0.05 ng/ml)

Naftifine hydrochloride was detected in the plasma at 30 min postdose on Day 1. Peak plasma levels were detected 3 to 6 hr after dosing. On Day 30, plasma levels of naftifine HCl greatly increased compared to those on Day 1. There was no clear dose-response relationship with plasma levels being similar in all treated groups. The plasma levels on Day 93 were similar to those on Day 30. When the doses were greatly reduced after Day 93, the plasma levels decreased accordingly on Day 180 and were at similar levels on Day 271.

Reviewer's comment: PK parameters such as AUC were not calculated in the two studies. Data from the one-month study clearly showed dose-dependent increases in plasma levels of naftifine hydrochloride on Days 14 and 30, which is inconsistent with the findings in the 9-month study. The plasma levels on Day 30 at 6 hr postdose appeared higher at 18 mg/kg/day in the 1-month study compared with those at 100 mg/kg/day in the 9-month study. This may be partly due to the formulation difference (cream vs. solution). The TK data obtained in the 1-month minipig study would be more relevant to the evaluation of NAFT-500 2% cream product.

6 General Toxicology

6.1 Single-Dose Toxicity

A number of acute toxicity studies have been conducted by the sponsor and reviewed by the Agency. [redacted] (b) (4). The

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(b) (4)

Study	Species	Dose	Route	Results
1. Acute oral toxicity on naftifine HCl, 1% cream (1984G)	Mice	20 ml/kg	Per os	Minimum lethal dose of naftifine hydrochloride 1% cream was found be greater than 20 ml/kg of body weight.
2. Acute toxicity by intravenous route on SN 105-843 (naftifine HCl), up to 0.415% soln. (1981H)	Mice	20 ml/kg	Intravenous	LD_{50} was found to be 65.2 mg/kg (60.2-70.6) in males and 67.6 mg/kg (61.2-77.0) in females.
3. Acute toxicity by intraperitoneal route on SN 105-843 (naftifine HCl), up to 4% emulsion (1980I)	Mice	20 ml/kg	Intra-peritoneal	LD_{50} was found to be 313 mg/kg (195-368) in males and 420 mg/kg (338-493) in females.
4. Acute oral toxicity on naftifine HCl, 1% cream (1984J)	Rats	20 ml/kg	Per os	Minimum lethal dose of naftifine hydrochloride 1% cream was greater than 20.0 ml/kg of body weight.
5. Acute oral LD50 toxicity on SN 105-843 (naftifine HCl) 3% solution (1981K)	Rats	8, 12, 16, 20, 24, 30 ml/kg	Per os	Predominant dose observations were: loss of righting reflex, ataxia, muscle flaccidity, docility & flattened body position. The calculated LD_{50} was 22.8 ml/kg.
6. Acute toxicity on SN 105-843 (naftifine HCl) 1% gel (1979A)	Mice Rats Rabbits	4000 mg/kg 4000 mg/kg 2000 mg/kg 2000 mg/kg 1200 mg/kg 750 mg/kg	Oral and subcutaneous Oral Subcutaneous Oral Subcutaneous Dermal	Mortality rates were too low to calculate LD_{50}. All surviving mice (37/40) were normal within 4-5 days. All rabbits were normal within 24 hours. Rats exhibited only irritation at injection site.
7. Acute dermal LD50 toxicity study on SN 105-843 (naftifine HCl) 3% solution (1981L)	Rabbits	2.0 ml/kg	Dermal	LD_{50} of SN 105-843 (naftifine HCl) is greater than 2.0 ml/kg. Mortality or signs of toxicity did not occur.

6.2 Repeat-Dose Toxicity

A number of repeat dose toxicity studies have been conducted with different formulations of naftifine hydrochloride in rats, guinea pigs, rabbits, dogs, monkeys and minipigs. The summary information of these studies was cited from the nonclinical review for IND 77530 (06/30/2008):

A 21-day dermal toxicity study with naftifine HCl 1% cream (0.1 ml QD, BID, or TID) was conducted in rats (1984). Slightly irritating to rat intact skin was noted. There was no effect on body weight or general health of animals. Histopathologically, slight epidermal thickening and sporadic dermal inflammation was seen.

A 21-day dermal toxicity study with naftifine HCl 1% cream (0, 0.1 ml QD, BID, or TID) was conducted in guinea pigs (1984). Naftifine cream 1% was found to be mildly irritating to males and mildly to moderately irritating to females. The vehicle was mildly irritating to both sexes. No effects on body weight or general health were noticed. Epidermal thickening and dermal inflammation was seen among treated animals. Complete resolution would be expected with cessation of treatment or passage of time.

A 21-day dermal toxicity study with naftifine HCl 1% shampoo (0.5 ml BID) was conducted in rabbits (1989). Slight irritation in both placebo and naftifine-treated animals was noted. No adverse, treatment-related effects were observed on the general health or behavior of the animals. Epidermal acanthosis and mild dermal chronic inflammation was observed in all groups. Histomorphologically, there were no differences between the vehicle and naftifine-treated animals.

A 28-day subcutaneous toxicity study with naftifine HCl 1% gel (5, 15, and 45 mg/kg/day) was conducted in rabbits (1979). No deaths occurred. Decreased body weight associated with decreased food intake. Significant increase in basophiles at high dose was noted.

A 4-week dermal toxicity study with naftifine HCl 1% gel was conducted in dogs (1979). Only two doses (0, 500 mg/kg/day) were administered. Test article was well tolerated by the skin. No clinical, anatomical or histopathological changes were seen.

A 13-week oral toxicity study with naftifine HCl was conducted in rats (1978). Dose levels were 0, 25, 75, and 225 mg/kg/day. All low dose animals showed no noteworthy findings. In mid dose animals, a slight reduction in feed consumption and body weight gain was noted. A slight rise in serum bilirubin in males and females and liver weight increase in males was also observed. In high dose animals, reduced food consumption and body weight gain was noted. There were also moderate rise in serum bilirubin, increased serum urea in females and increased weight of liver and kidneys in both sexes. The biochemical and histological changes were not significant.

A 13-week oral toxicity study with naftifine HCl was conducted in dogs (1978). Dose levels were 0, 15, 45, and 135 mg/kg/day. A dose-dependent increase in frequency of emesis occurred during the first week. The NOAEL was identified as 135 mg/kg/day.

A 26-week dermal toxicity study with naftifine HCl 1% gel was conducted in rabbits (1980). Dose levels for the 1% gel were 0, 0.5, 1.5, and 2.25 g/kg/day (0, 5, 15, and 22.5 mg/kg/day for naftifine HCl) (Note: This study was not submitted to the efficacy supplement. (b) (4) The recorded doses are assumed to be the doses for 1% gel). The test article was very well tolerated in the study. Hematological, blood biochemical and urinary parameters remained within physiological limits. No anatomical or histopathological lesions were seen. The NOAEL was identified as 22.5 mg/kg/day.

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A 26-week oral toxicity study with naftifine HCl was conducted in monkeys (1981). Dose levels were 0, 50, 100, and 200 mg/kg/day. The test article caused no significant changes. The NOAEL was identified as 200 mg/kg/day.

A one-month dermal toxicity study with naftifine cream was conducted in weanling minipigs (1992, Study# 007-0002). Minipigs (4/sex/group) were treated with placebo cream, 1% naftifine cream (6 mg/kg/day), or 3% naftifine cream (18 mg/kg/day) twice per day for 30 days. Very slight erythema was observed in one placebo female (Days 2 and 3), one low dose female (Day 2), and two high dose females (Days 7 to 9). The erythema resolved within 1 or 2 days. This was not considered to be a significant treatment effect. At necropsy, there were no treatment-related findings. Organ weights were similar in all the groups, and histopathology did not reveal any treatment-related changes. The NOAEL was identified as 18 mg/kg/day.

A six-month dermal toxicity study with 3% naftifine cream was conducted in rats (1984, Study# 1395-0569-1). SD rats (30/sex/group) were treated with vehicle cream (0.3 ml/day) or 3% naftifine cream (0.1 and 0.3 ml/day, 12 and 36 mg/kg/day). 77 rats (32% of all animals) from treated and control groups showed signs of sickness intermittently during the study. 35 rats (15%) died or were euthanized due to moribund conditions. The clinical signs and subsequent deaths were consistent with symptoms of murine respiratory mycoplasmosis and confirmed by blood test. There were no treatment-related effects on body weight, hematology, or clinical chemistry. The NOAEL was identified as 36 mg/kg/day.

A 28-week oral toxicity study was conducted with naftifine HCl in rats (1979, Study# 2018TCR). SD rats (15/sex/group) were treated via gavage at dose levels of 0, 25, 75, and 132/300 mg/kg/day. The high-dose animals were treated with132 mg/kg/day from start to Day 26, 125 mg/kg/day on Days 27 to 32 (due to an error in test article preparation), and 300 mg/kg/day from Day 33 to the end of the study. 25 animals died during the study; most of these deaths were due to dosing errors or anesthetic shock during blood sampling. Signs of hypersalivation were observed in a few animals in the mid and high dose groups. A slight decrease in body weight (5% to 7%) was observed in mid dose and high dose males after 12 weeks of dosing, but no effect was noted in the females. In low dose animals, a rise in serum bilirubin in females at all test times and a rise in serum creatinine at the end of dosing were observed. In mid dose animals, a rise in serum bilirubin, serum creatinine, and blood urea, varying according to sex and sampling time, was noted. In high dose animals, a rise in serum bilirubin in males and a rise in serum creatinine and blood urea, varying according to sex and sampling time were observed. At necropsy, no gross changes were observed. Increased liver weight (both sexes) and kidney weight (males) were reported in the high dose animals after 28 weeks of treatment. By the end of the 4-week recovery period, these organ weights had returned to normal. The histopathological data were not complete; an assessment of potential treatment effects could not be made. The NOAEL was determined to be 25 mg/kg/day by Dr. Jiaqin Yao.

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A 9-month dermal toxicity study with naftifine HCl solutions was conducted in minipigs (2004, Study# OSC00002). Minipigs (6/sex/group) were treated topically with 0, 3%, 5%, or 10% naftifine HCl solutions. Dose levels were initially 0, 30, 50, and 100 mg/kg/day for Days 1-93, and were reduced to 0, 4.5, 7.5, and 15 mg/kg/day for the rest of study. Two animals died during the study due to chronic bronchopneumonia infection, which is not considered to be treatment-related. There were no significant changes in physical appearance or behavior. Dermal findings were mild with no clear indication of dose-related differences between the groups. Body weight growth was sustained in all the groups throughout the study. There were no significant effects on body weight in males. However, there was a clear trend of body weight decrease in the high dose females starting ~Day 99. Mean body weight in the high dose female group was approximately 12% less than that of the control group at the end of the study. There were no significant treatment-related histopathology findings. The NOAEL was identified by the sponsor as 15 mg/kg/d. Due to the significant body weight decrease noted in the high dose females, the NOAEL is identified as the mid dose, 7.5 mg/kg/day (5% solution).

7 Genetic Toxicology

A standard battery of genetic toxicology tests were conducted and the study reports were reviewed by the Agency (b) (4) The results are summarized below:

1. SN 105-843 mutagenicity evaluation using *Salmonella Typhimurium* (1978)

SN 105-843 was tested in five strains, TA1535, TA1537, TA1538, TA98, and TA100, with or without metabolic activation, at doses of 0, 10, 75, 100, 250, 750, and 1000 µg/plate. A slight toxicity was noted at 250 µg/plate and concentrations of 750 and 1000 µg/plate produced significant toxicity. No increase in revertant frequency compared with solvent control levels was noted at any concentration in any of the strains, with or without metabolic activation. The negative and positive control data were within the normal range. SN 105-843 did not show evidence of mutagenic potential under the experimental conditions.

2. In vitro mammalian chromosome aberration test (2004, Study# AA91US.331001.BTL)

Naftifine HCl was tested in Chinese hamster ovary (CHO) cells with or without metabolic activation (S9). A range-finding study was performed first (0.323-3230 µg/ml). Substantial toxicity and visible precipitation was observed at dose levels ≥ 96.9 µg/ml. In the definitive study, for both treatment periods (4 hr and 20 hr), naftifine HCl was tested at concentrations ranging from 2.5 to 100 µg/ml. Dose levels selected for microscopic analysis were 20, 40, and 60 µg/ml for the 4 hr treatment and 2.5, 5, and 10 µg/ml for the 20 hr treatment period, based on cytotoxicity. The study was considered valid because structural aberrations in the negative controls were within normal range and the positive control induced statistically significant increases in structural

aberrations. Naftifine HCl did not increase the percentage of cells with numerical or structural aberrations with or without metabolic activation.

3. SN 105-843: Micronucleus test for mutagenic potential in mice (1978)

SN 105-843 was tested in adult CD-1 mice at oral doses of 0, 130, 420, and 1300 mg/kg/day for two days. None of the treated groups showed a significant increase in the frequency of micronucleated erythrocytes when compared to the negative control. However, no positive control was included. SN 105-843 was negative in the mouse micronucleus test.

8 Carcinogenicity

To date no carcinogenicity study has been conducted with naftifine chloride. During the pre-NDA meeting for IND 77530 (03/12/2010), the Division informed the sponsor that carcinogenicity testing is necessary to support the development of NAFT-500 (tinea infection is considered a chronic indication due to high recurrence rate). However, in consideration of the historical use of naftifine HCl, it is acceptable to conduct the carcinogenicity testing as a postmarketing requirement. The following comments were also relayed to the sponsor during the pre-NDA meeting (meeting minutes dated 05/14/2010):

"*The carcinogenicity potential of NAFT-500 should, in general, be evaluated in two species. At least one of the studies should involve administration of the test materials to the skin for 104 weeks. However, if it is determined that the systemic exposure to the drug substance or its metabolites under maximal use conditions in humans does not occur at a measurable level, then the need for carcinogenicity data may be reduced to a single topical study, involving a single species. Use of the to-be-marketed and enriched (higher active ingredient concentration) formulations are usually recommended. The Division would reserve the right to request data from a second study if, in the opinion of the Division, data from the first study indicated cause for concern (e.g., increased incidence of tumors or preneoplastic lesions).*

The Division also acknowledges that you are developing a NAFT-600 drug product (naftifine HCl 2% gel) under IND 105603 for the treatment of tinea pedis, and you also inquired about the carcinogenicity testing of the NAFT-600 drug product during the pre-Phase 3 meeting for IND 105603 conducted on April 14, 2010. It should be noted that the Division requests only one of the two products (NAFT-500 or NAFT-600) be tested for carcinogenicity to address the concern for carcinogenic potential of naftifine HCl. You should provide a scientific rationale for selecting one of the two drug products for carcinogenicity testing. Generally speaking, the drug product that produces higher systemic exposure should be selected for testing."

The sponsor submitted a dermal rat carcinogenicity protocol to this efficacy supplement (SDN 93). The sponsor also submitted a request for SPA to IND 77530 (SDN 28). Subsequently the sponsor revised the carcinogenicity protocol (SDN 94 under NDA

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19599). The protocol was reviewed under IND 77530 (memorandum, 01/27/2011). The protocol did not receive concurrence from the CDER Executive CAC. The Executive CAC recommendations and conclusions are listed below (meeting minutes 01/26/2011):

"1) The Committee did not have sufficient data on which to base an agreement on doses. The doses proposed by the sponsor have not been evaluated in an adequate dose range-finding study. The MFC should be established and tested in a dose range-finding study.

2) The Committee notes that in a repeat dose dermal toxicity study, the dose volume should be maintained and the dose levels increased by increasing the concentration of the active in the formulation up to the MFC, if tolerated.

3) If the sponsor wishes concurrence, they should conduct an adequate dose range study and submit it with the protocol."

On 05/10/2011 the sponsor submitted a proposed timeline (SDN 100) for the conduct of the 2-year dermal rat carcinogenicity study, which includes the conduct of a dose-range finding study.

Activity	Date of Completion
Begin Dose Range Study	July 2011
Complete Dose Range Study	February 2012
Dose Range Study Report Available	July 2012
2-Year Dermal Rat Carcinogenicity Study Protocol Submitted for Special Protocol Assesment	December 2012
Begin 2-Year Dermal Rat Carcinogenicity Study	July 2013
Complete 2-Year Dermal Rat Carcinogenicity Study	July 2015
2-Year Dermal Rat Carcinogenicity Study Study Report Available	September 2016

The proposed timeline is considered acceptable.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Fertility and general reproductive performance was evaluated in rats (15 males/group and 30 females/group) treated with SN 105-843 at oral doses (via gavage, given to F0 animals) of 0, 10, 30, and 100 mg/kg/day (1980, Study# 99-80694). Males were dosed for 9 weeks prior to mating and through mating up to termination (at lactation Day 19 for the females). Females were dosed for 2 weeks prior to mating and through mating before being allocated to one of the following: (1) 13 or 14 females in each group were dosed to Gestation Day 19 and sacrificed on the next day to investigate possible effects on late in utero development (2) the remaining females were treated till Lactation Day 21 when the animals were terminated. Post-natal development of all young was

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assessed prior to weaning. Selected F1 pups were reared to maturity and their reproductive capacity including F2 embryo-fetal development was assessed. Apart from in utero exposure and from milk, the F1 generation was not treated.

Parameters evaluated for the F0 generation included clinical signs, mortality, body weight, pregnancy rate, mating performance, gestation period, uterine parameters (corpora lutea, number of live young, number of fetal deaths, fetal abnormalities), and gross pathology. For the F1 generation, pre-weaning parameters evaluated included number of live pups delivered, weight, gender, and developmental assessment (righting reflex, pinna unfolding, hair growth, incisor eruption, eye opening, visual placing, hearing ability, pupil response) followed by clinical signs, body weight, behavioral assessment (Irwin screen, hole-board test, tail withdrawal test, rotarod test), vaginal opening, reproductive capacity, and uterine parameters in the F1 post-weaning animals.

At 10 mg/kg one grossly abnormal fetus with exencephalus was seen. At 30 mg/kg, some F0 animals showed increased salivation. At 100 mg/kg, all F0 animals showed increased salivation and post partum body weight gain was slightly lower in dams. Mean fetal weight was minimally lower. Mean litter size at birth was marginally reduced compared to the control but was essentially comparable for all groups from Day 4 post partum. During lactation pup mortality in all treated groups remained lower than that of the concurrent control. During gestation F1 dams derived from parents given 30 or 100 mg/kg/day showed marginally lower body weight gains.

The NOAEL for reproduction and fertility was considered to be 100 mg/kg/day. There was no TK data obtained in this study.

9.2 Embryonic Fetal Development

Study #1

In a teratological study, female rats (30/group) were administered SN 105-843 orally via gavage at doses of 0, 30, 100, and 300 mg/kg/day on Gestation Days 6 to 15 (1980, Study# 1003 77). Animals were sacrificed on Gestation Day 21. Parameters evaluated included survival, clinical signs, body weights, pregnancy rate, uterine examinations (corpora lutea, implantation sites, viable fetuses, resorptions, pre- and post-implantation loss, gross pathology), and fetal examinations (weights, gender, external, visceral and skeletal malformations, and anomalies).

One death occurred in the mid dose group on the first day of dosing; no findings were noted at the necropsy of this animal. There were no test article-related effects on pregnancy rates, body weight, or uterine parameters. Fetal examinations revealed no test article effects on malformations or variations (early or late development phases), weight, or sex ratios. One fetus from the high dose group exhibited a heart defect (classified as a malformation) in which the orifices of the left auricle and aorta were close together and dilated and the valves were rudimentary. The occurrence of this malformation was within the historical control range. Fetal weights were slightly lower in the low dose and mid dose groups as compared with the controls; however, because

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this finding was not observed in the high dose group and the decreases were within historical control values, the finding was not considered to be treatment-related.

The NOAEL for embryo-fetal development and maternal effects was considered to be 300 mg/kg/day in this study. There was no TK data collected in this study.

Study #2

In a teratological study, female rats (30/group) were administered SN 105-843 via subcutaneous injection at doses of 0 (distilled water), 10, and 30 mg/kg/day on Gestation Days 6 to 15 (1978, Study# unknown). Animals were sacrificed on Gestation Day 21. Parameters evaluated included survival, body weights, pregnancy rate, uterine examinations (corpora lutea, implantation sites, viable fetuses, resorptions, pre- and post-implantation loss), and fetal examinations (weights, gender, external, visceral and skeletal malformations, and anomalies).

Moderate skin irritations occurred at both dose levels. There were no deaths or abortions. There were no test article-related effects on pregnancy rates, body weight, or uterine parameters. Fetal examinations revealed no test article effects on fetal variations (early or late development phases) or sex ratios, but a significant decrease in fetal body weight occurred at 30 mg/kg/day; however the fetal body weight was still within historical control range. Two out of 308 fetuses from the high dose group exhibited malformations: one fetus with exencephaly and one fetus with rib and vertebral defects including disturbed rib segmentation, fused ribs, fused thoracic vertebral arches, and scoliosis. These two defects were within the historical control range and not considered related to treatment.

The NOAEL for embryo-fetal developmental effects and for maternal effects was considered to be 30 mg/kg/day. There was no TK data collected in this study.

Study #3

In a teratological study, female rabbits (17/group) were treated with SN 105-843 via subcutaneous injection at doses of 0 (distilled Water), 3, 10, and 30 mg/kg/day on Gestation Days 6 to 18 (1978, Study# unknown). Animals were sacrificed on Gestation Day 29. Parameters evaluated included survival, body weights, pregnancy rate, uterine examinations (corpora lutea, implantation sites, viable fetuses, resorptions, pre- and post-implantation loss), and fetal examinations (weights, gender, external, visceral and skeletal malformations, and anomalies).

Moderate skin irritation at the injection sites were noted in all SN 105-843 treated groups. The incidence increased with dose. One death occurred in the high dose group on Gestation Day 28; this animal exhibited several early resorptions. There were no test article-related effects on pregnancy rates or uterine parameters. In addition, there were no abortions or premature deliveries. Maternal body weight gain was significantly reduced at 10 and 30 mg/kg/day. One fetus each in the control and high

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dose groups exhibited rib and vertebral anomalies: fused ribs, hypoplastic thoracic vertebral arch, thoracic vertebral bodies, and asymmetric ossification centers in the control fetus and thoracic vertebra and corresponding ribs bilaterally doubled in the high dose fetus. These findings were not considered to be test article-related due to their sporadic occurrence in rabbits.

In this study, the NOAEL for embryo-fetal development was 30 mg/kg/day and the NOAEL for maternal effects was 3 mg/kg/day. There was no TK data collected in this study.

9.3 Prenatal and Postnatal Development

Wistar rats (24 females/group) were dosed orally via gavage with SN 105-843 at 0, 30, 100, and 300 mg/kg/day from Gestation Day 15 to Lactation Day 21 (1982, Study# 10381). Parameters evaluated in the F0 dams included mortality, clinical signs, body weight, necropsy (Lactation Day 21), and uterine parameters. On the day of birth, each F1 litter was reduced to 4 males and 4 females. F1 pup evaluations included survival, body weight, and an assessment of physical development (pinna detachment, ear opening, eye opening, descended testes, vaginal opening), functional and behavioral development (auditory function, startle reflex, homing response, air righting, swimming, papillary reflex), and learning and memory. To assess reproductive capabilities, 1 F1 male and female from each litter were selected. These animals were mated at 12 weeks of age. The females were allowed to deliver. The following parameters were evaluated: F1 body weight, precoital interval and pregnancy length, fertility indices, pre- and perinatal loss, postnatal loss, and pup viability, sex ratio, and body weights.

All F0 females survived and there were no test article-related clinical signs or effects at necropsy. Gestation body weight gain was significantly reduced at 300 mg/kg/day; lactation body weight gain was unaffected. There was no effect on pregnancy rate, pregnancy length, number of implantation sites, or live pups at birth.

During the lactation period, F1 pup body weights were decreased in the 300 mg/kg/day group, reaching statistical significance in the females on Lactation Days 7 and 14. Post-natal development including physical, behavioral, functional, learning, and memory indices was unaffected by treatment with naftifine hydrochloride. Gross pathology did not reveal any test article-related effects. One mid dose F1 male died, but all other animals survived. Body weight gain, pregnancy rate, pregnancy length, number of implantation sites, and live pups at birth were similar in all groups. For the F2 pups, body weight, sex ratio, and survival were unaffected.

The NOAEL for peri- and postnatal development effects was considered to be 100 mg/kg/day, based on the decreased weight gain observed in the F0 dams (during gestation) and in the F1 pups (during the lactation period) at 300 mg/kg/day. There were no other effects on developmental parameters. There was no TK data collected in this study.

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10 Special Toxicology Studies

A primary skin irritation study in rabbits and a dermal sensitization study in Guinea pigs were included in this submission. (b) (4) The review was summarized as below. The sponsor also submitted a study of UV/visible light testing of Naftin 2% gel, which was reviewed in this report. The result was similar to that of the UV/visible light testing of NAFT-500 (2% cream) submitted previously to IND 77530 (nonclinical review 06/30/2008), which is more relevant to this efficacy supplement.

Study #1

Naftifine hydrochloride solutions 1%, 3%, 5%, and 10% were tested in a primary skin irritation study in rabbits (2003, Study# 3597.14). Each of 6 New Zealand White rabbits received appropriate test materials as shown in the following table. After a 24 hr exposure period, the binding materials and residual test article were removed.

Group	No. of Males	Amount Applied	Test Article (treatment)			
			Test site 1	Test site 2	Test site 3	Test site 4
1	6	0.5 mL	1% (intact)	1% (abraded)	10% (intact)	10% (abraded)
2	6	0.5 mL	3% (intact)	3% (abraded)	5% (intact)	5% (abraded)
3	6	0.5 mL	Placebo (intact)	Placebo (abraded)	--	--

An increase in the intensity and duration of the dermal response was noted as the concentration increased. In the placebo and 1% groups, very slight erythema was observed on the abraded sites only of not more than 2 animals, which generally cleared within 24 hr. In comparison, in the 3%, 5%, and 10% groups, very slight to well-defined erythema was observed in 1 to 3 animals which required up to 14 days to resolve in some cases. Desquamation was noted on 1/6 abraded test sites treated with 3%, 5%, or 10% solutions. Out of a possible total index of 8.0, none of the primary irritation indices were higher than 1. The respective primary irritation indices for the intact and abraded sites were 0.00 and 0.17 (placebo), 0.00 and 0.08 (1%), 0.33 and 0.50 (3%), 0.17 and 0.75 (5%), and 0.50 and 0.67 (10%), respectively.

Naftifine hydrochloride was not considered a skin irritant in this study.

Study #2

A dermal sensitization study in guinea pigs was conducted with naftifine hydrochloride solution 5%, using a standard Buehler design (2003, Study# 3597.15). Each young adult guinea pig received topical treatment as shown in the following table. The induction procedure was repeated three times a week for three consecutive weeks. Following a 2-week rest period, a challenge was performed on Day 33. After approximately 6 hr exposure, the binding materials and residual test articles were removed. 1-Chloro-2,4-dinitrobenzene (DNCB) was used as a positive control.

Group	No. of Animals	Amount Applied	Phase/Treatment	
			Induction 1 - 9	Challenge
Test	20	0.3 mL	Test article	Test article
Placebo	10	0.3 mL	Placebo	Placebo
Common Challenge Control	10	0.3 mL	--	Test article and Placebo
DNCB Test	10	0.3 mL	DNCB (0.1%)	DNCB (0.1% and 0.5%)
DNCB Control	10	0.3 mL	--	DNCB (0.1% and 0.5%)

Animals were examined for signs of erythema and edema and the responses scored 1, 24, 48, and 72 hours and up to 14 days after patch removal. General health/mortality checks were performed twice daily. Body weights were obtained for each animal on Day -1 and Day 32.

A Dermal Grading System was used to grade for irritation. Following challenge with naftifine hydrochloride solution 5% or placebo, dermal reactions were limited to scores of 0 to ± (± is the score between 0 and 1 in this grading system) in all test animals. Dermal reactions were in the positive control group animals scored 2 to Maximized Grade 3. The animals gained weight during the study and generally appeared in good health. Naftifine hydrochloride solution 5% was not considered to be a contact sensitizer in guinea pigs.

Study #3

Study title: UV/visible light testing results for the active drug product Naftin 2% gel, reduced alcohol (CIE Formula), lot # 856-0217B02, the Placebo Naftin 2% Gel, reduced alcohol (CIE Formula), and each raw material contained in the product (Study# TC.0205.00, protocol# 774.013.008.00)

The drug product Naftin 2% gel, placebo gel, the API naftifine hydrochloride, and each of the following raw materials: propylene glycol, 190 proof USP ethanol, benzyl alcohol, hydroxyethyl cellulose, polysorbate 20, USP edatate disodium (EDTA), and trolamine, were tested for light absorbance with a UV/visible light scan (wavelength 280-700 nm). Both Naftin 2% gel and naftifine hydrochloride exhibited minimal UVB absorbance (290 to 320 nm range) (Figures 1 and 2). There was little or no absorbance for the other ingredients. The extent of UVB absorbance does not trigger the need for a nonclinical photoirritation study. The UV/visible light scan for Naftin 2% cream was similar to the UV/visible light scan for Naftin 2% gel. Therefore, a nonclinical photoirritation study is not needed for Naftin 2% cream.

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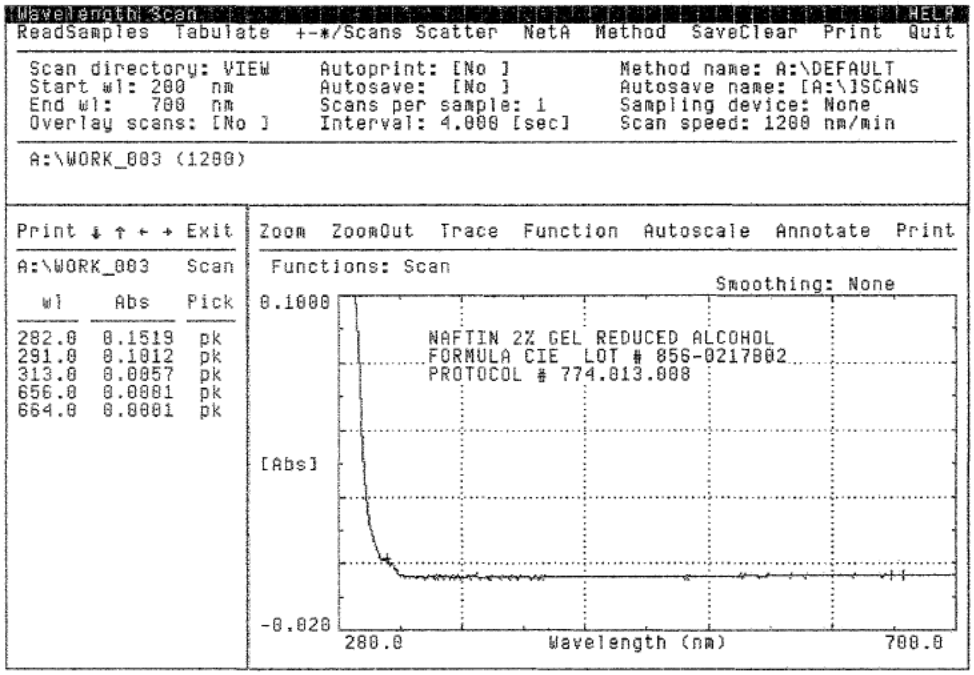

Figure 1. UV/visible light absorbance of Naftin 2% gel (solvent: methanol).

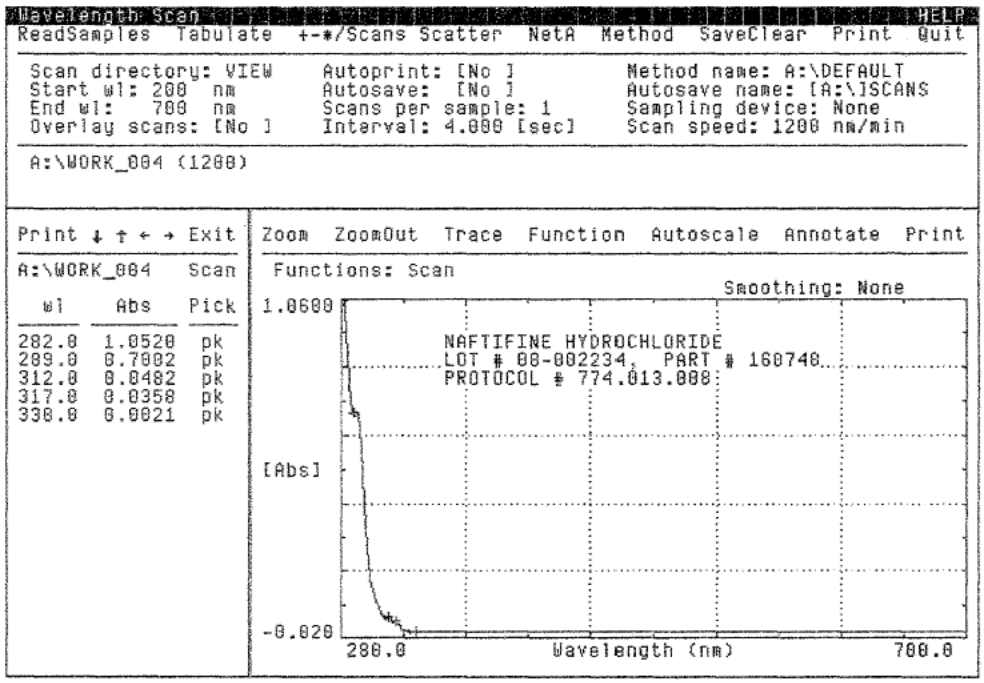

Figure 2. UV/visible light absorbance of naftifine hydrochloride (solvent: methanol).

A number of other special toxicity studies were conducted with naftifine hydrochloride but the study reports were not included in this submission. (b) (4)

Study	Species	Dose	Route	Results
1. Primary skin irritation on SN 105-843 (Naftifine HCl) 3% solution (1980M)	Rabbits		Dermal	Skin irritation was determined by the Draize technique on intact and abraded rabbit skin. After 72 hours there was no skin irritation. SN 105-843 (naftifine HCl) was not considered a primary skin irritant.
2. Acute eye irritation study on naftifine HCl, 1% cream (1984Y)	Rabbits	0.1 ml	Eyes	Naftifine hydrochloride 1% cream was found to be slightly discomforting to the eye, slightly irritating to the conjunctiva, but not toxic to the cornea.
3. Acute eye irritation study on naftifine HCl, 3% cream (1984Z)	Rabbits	0.1 ml	Eyes	Naftifine hydrochloride 3% cream was found to be slightly discomforting to the eye, slightly irritating to the conjunctiva, but not toxic to the cornea.
4. Eye irritation study on SN 105-843 (naftifine HCl) 1% gel (1978AA)	Rabbits	0.1 ml	Eyes	No corneal or iris changes were observed. Conjunctival redness and edema were observed in 2 of the 6 animals. The irritant potential is limited to the conjunctiva. Therefore, instillation into the eye should be avoided
5. Eye irritation study on SN 105-843 (Naftifine HCl) 3% solution (1981BB)	Rabbits	0.1 ml	Eyes	SN 105-843 (naftifine HCl) 3% solution is considered an eye irritant. However, the solution contained 40% ethanol, and the irritation may be attributed to the alcohol.
6. An investigation of local sensitizing effect by intracutaneous administration of SN 105-843 (naftifine HCl), 1% solution (1979OC)	Guinea Pigs	1st 0.05 ml, 2nd-10th 0.1 ml, challenge 0.05 ml	Intracutaneous	No skin reactions occurred during the injection series or with the challenge injection. No evidence of allergic reaction at the challenge injection site was seen upon histopathological examination
7. Cutaneous effects of naftifine cream 1% and vehicle (1979DD)	Rabbits	0.5 g	Cutaneous	Cream vehicle was non-irritating. Naftifine cream 1% was slightly irritating, but the faint lesions resolved in a few days.
8. Cutaneous tolerance of naftifine cream 1% and vehicle (1979EE)	Rabbits	0.5 g	Cutaneous	No mortality or abnormal weight development. No abnormalities seen in postmortem examination. Histological examination revealed thickening of epidermis on treated sites. Mild erythema and a few cases of slight edema reported.

11 Integrated Summary and Safety Evaluation

The treatment duration proposed for the NAFT-500 2% cream product is 2 weeks. The proposed daily dosage of NAFT-500 2% cream is comparable to the approved daily dosage of Naftin 1% gel (once daily for 2% cream vs. twice daily for 1% gel). The topical daily dose of NAFT-500 under maximum clinical use conditions is 8 g/day, which would result in an exposure of 2.67 mg/kg/day to the active ingredient naftifine HCl for a 60 kg individual.

Naftifine HCl had an apparent stimulating effect on the central nervous system following single oral doses of 32-320 mg/kg in mice and 10-100 mg/kg in rats. Naftifine had a very weak effect on the cardiovascular system of anesthetized cats when administered in increasing IV doses (4-500 mg/kg/min) over a 2-hr period. During drug infusion, there were reduction in mean arterial blood pressure and heart rate, carotid occlusion, and nictitating membrane responses; however, such findings were still within the historical control range. No signs of toxicity or ECG changes were observed up to a cumulative IV dose of 18.7 mg/kg. In anesthetized dogs, no significant effects on the cardiovascular parameters, ECG, or diuresis were noted following an intra-arterial dose of 0.005 mg/kg or intraduodenal doses up to 5 mg/kg. A slight increase in heart rate was noted at the 5 mg/kg intraduodenal dose as compared with control.

General toxicology studies have been conducted extensively with various formulations of naftifine HCl.

A 13-week oral toxicity study was conducted in rats, with naftifine HCl doses of 0, 25, 75, and 225 mg/kg/day. All low dose animals showed no noteworthy findings. In mid dose animals, a slight reduction in feed consumption and body weight gain was noted. A slight rise in serum bilirubin in males and females and liver weight increase in males was also observed. In high dose animals, reduced food consumption and body weight gain was noted. There were also moderate rise in serum bilirubin, increased serum urea in females and increased weight of liver and kidneys in both sexes. The biochemical and histological changes were not significant.

A 13-week oral toxicity study was conducted in dogs, with naftifine HCl doses of 0, 15, 45, and 135 mg/kg/day. A dose-dependent increase in frequency of emesis occurred during the first week. The NOAEL was 135 mg/kg/day.

A 26-week oral toxicity study was conducted in monkeys, with naftifine HCl doses of 0, 50, 100, and 200 mg/kg/day. The test article caused no significant changes. The NOAEL was 200 mg/kg/day.

A 28-week oral toxicity study was conducted in rats, with naftifine HCl doses of 0, 25, 75, and 132/300 mg/kg/day. 25 animals died during the study; most of these deaths were due to dosing errors or anesthetic shock during blood sampling. Signs of hypersalivation were observed in a few animals in the mid and high dose groups. In low dose animals, a rise in serum bilirubin in females at all test times and a rise in serum creatinine at the end of dosing were observed. In mid dose animals, a rise in serum bilirubin, serum creatinine, and blood urea was noted. In high dose animals, a rise in serum bilirubin in males and a rise in serum creatinine and blood urea were observed. At necropsy, no gross changes were observed. Increased liver weight (both sexes) and kidney weight (males) were reported in the high dose animals. By the end of the 4-week recovery period, these organ weights had returned to normal. The histopathological data were not complete; an assessment of potential treatment effects could not be made. The NOAEL was determined to be 25 mg/kg/day.

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A one-month dermal toxicity study was conducted in weanling minipigs, with naftifine cream doses of 0, 6, and 18 mg/kg/day (placebo, 1%, and 3% naftifine cream applied BID). Very slight erythema was observed in one placebo female, one low dose female, and two high dose females. The erythema resolved within 1 or 2 days. This was not considered to be a significant treatment effect. At necropsy, there were no treatment-related findings. Organ weights were similar in all the groups, and histopathology did not reveal any treatment-related changes. The NOAEL was 18 mg/kg/day.

A six-month dermal toxicity study with 3% naftifine cream was conducted in rats, with topical doses of 0, 12 and 36 mg/kg/day (vehicle cream and 3% naftifine cream 0.1 and 0.3 ml/day). Approximately 30% of all animals showed symptoms of murine respiratory mycoplasmosis and confirmed by blood test. There were no treatment-related effects on body weight, hematology, or clinical chemistry. The NOAEL was 36 mg/kg/day.

A 26-week dermal toxicity study was conducted with naftifine HCl 1% gel in rabbits, with topical doses of 0, 5, 15, and 22.5 mg/kg/day (0, 0.5, 1.5, and 2.25 g/kg/day for the gel). The test article was very well tolerated in the study. Hematological, blood biochemical and urinary parameters remained within physiological limits. No anatomical or histopathological lesions were seen. The NOAEL was 22.5 mg/kg/day.

A 9-month dermal toxicity study with naftifine HCl solutions (0, 3%, 5%, and 10%) was conducted in minipigs. Dose levels were initially 0, 30, 50, and 100 mg/kg/day for Days 1-93, and were reduced to 0, 4.5, 7.5, and 15 mg/kg/day for the rest of study. Dermal findings were mild with no clear indication of dose-related differences between the groups. There were no significant effects on body weight in males. However, there was a clear trend of body weight decrease in the high dose females starting ~Day 99. There were no significant treatment-related histopathology findings. The NOAEL was identified as the mid dose, 7.5 mg/kg/day (5% solution).

The identified NOAELs and calculated multiples of maximum human exposure are listed in the following table:

Study duration	Species	Route	NOAEL (mg/kg/day)	Human Equivalent Dose (mg/kg/day)	Multiples of human exposure*
13-week	Dog	Oral	135	73	27.3
28-week	Rat	Oral	25	4	1.5
26-week	Monkey	Oral	200	65	24.3
one-month	Minipig	Dermal	18	17	6.4
six-month	Rat	Dermal	36	5.8	2.2
26-week	Rabbit	Dermal	22.5	7.3	2.7
9-month	Minipig	Dermal	7.5	7.1	2.7

*Compared to the human topical dose under maximum clinical use conditions: 2.67 mg/kg/day, assuming 100% absorption.

In genetic toxicology studies, naftifine HCl was negative in a bacterial mutagenicity test, an in vitro chromosome aberration test, and an in vivo micronucleus test. There is no concern for the genotoxicity of naftifine HCl.

Reference ID: 2981933

The carcinogenicity potential of NAFT-500 cream product should be evaluated. A 2-year dermal rat carcinogenicity study will be conducted as a post-marketing requirement.

Reproductive and developmental toxicology studies have been conducted with naftifine HCl in rats and rabbits.

Fertility and general reproductive performance was evaluated in rats treated with naftifine HCl at oral doses (via gavage, given to F0 animals) of 0, 10, 30, and 100 mg/kg/day. Males were dosed for 9 weeks prior to mating and through mating up to termination (at lactation Day 19 for the females). Females were dosed for 2 weeks prior to mating, through mating, and either up to Gestation Day 19 or up to Lactation Day 21. At 30 mg/kg, some F0 animals showed increased salivation. At 100 mg/kg, all F0 animals showed increased salivation and post partum body weight gain was slightly lower in dams. Mean fetal weight was minimally lower. Mean litter size at birth was marginally reduced compared to the control but was essentially comparable for all groups from Day 4 post partum. During gestation F1 dams derived from parents given 30 or 100 mg/kg/day showed marginally lower body weight gains. The NOAEL for reproduction and fertility was considered to be 100 mg/kg/day.

In a teratological study, female rats were treated with naftifine HCl at oral doses of 0, 30, 100, and 300 mg/kg/day during Gestation Days 6-15. There were no test article-related effects on pregnancy rates, body weight, or uterine parameters. Fetal examinations revealed no test article effects on malformations or variations (early or late development phases), weight, or sex ratios. One fetus from the high dose group exhibited a heart defect (classified as a malformation) in which the orifices of the left auricle and aorta were close together and dilated and the valves were rudimentary. The occurrence of this malformation was within the historical control range. Fetal weights were slightly lower in the low dose and mid dose groups as compared with the controls; however, because this finding was not observed in the high dose group and the decreases were within historical control values, the finding was not considered to be treatment-related. The NOAEL for embryo-fetal development and maternal effects was considered to be 300 mg/kg/day in this study.

In a teratological study, female rats were treated with naftifine HCl via subcutaneous injection at doses of 0 (distilled water), 10, and 30 mg/kg/day during Gestation Days 6-15. Moderate skin irritations occurred at both dose levels. There were no deaths, abortions, or article-related effects on pregnancy rates, body weight, or uterine parameters. Fetal examinations revealed no treatment-related effects on fetal variations (early or late development phases) or sex ratios, but a significant decrease in fetal body weight occurred at 30 mg/kg/day; however the fetal body weight was still within historical control range. Two out of 308 fetuses from the high dose group exhibited malformations: one fetus with exencephaly and one fetus with rib and vertebral defects. These two defects were within the historical control range and not

Reference ID: 2981933

considered related to treatment. The NOAEL for embryo-fetal developmental effects and for maternal effects was considered to be 30 mg/kg/day.

In a teratological study, female rabbits were treated with naftifine HCl via subcutaneous injection at doses of 0 (distilled Water), 3, 10, and 30 mg/kg/day during Gestation Days 6-18. Dose-dependent skin irritations at the injection sites were noted in all naftifine HCl-treated groups. One death occurred in the high dose group on Gestation Day 28; this animal exhibited several early resorptions. There were no test article-related effects on pregnancy rates or uterine parameters. In addition, there were no abortions or premature deliveries. Maternal body weight gain was significantly reduced at 10 and 30 mg/kg/day. One fetus each in the control and high dose groups exhibited rib and vertebral anomalies. These findings were not considered to be test article-related due to their sporadic occurrence in rabbits. The NOAEL for embryo-fetal development was 30 mg/kg/day and for maternal effects was 3 mg/kg/day.

In a peri- and postnatal developmental study, female rats were treated with naftifine HCl at oral doses of 0, 30, 100, and 300 mg/kg/day from Gestation Day 15 to Lactation Day 21. All F0 females survived and there were no test article-related clinical signs or effects at necropsy. Gestation body weight gain was significantly reduced at 300 mg/kg/day; lactation body weight gain was unaffected. There was no effect on pregnancy rate, pregnancy length, number of implantation sites, or live pups at birth. During the lactation period, F1 pup body weights were decreased in the 300 mg/kg/day group, reaching statistical significance in the females on Lactation Days 7 and 14. Post-natal development including physical, behavioral, functional, learning, and memory indices was unaffected. Gross pathology did not reveal any test article-related effects. One mid dose F1 male died, but all other animals survived. Body weight gain, pregnancy rate, pregnancy length, number of implantation sites, and live pups at birth were similar in all groups. For the F2 pups, body weight, sex ratio, and survival were unaffected. The NOAEL for peri- and postnatal development effects was considered to be 100 mg/kg/day.

Similarly, the multiples of human exposure are calculated for the reproductive and developmental toxicity studies:

Study type	Species	Route	NOAEL (mg/kg/day)	Human Equivalent Dose (mg/kg/day)	Multiples of human exposure*
Fertility and general reproductive performance	Rats	Oral	100	16.2	6.1
Teratological study	Rats	Oral	300	48.6	18.2
Teratological study	Rats	Subcutaneous	30	4.9	1.8
Teratological study	Rabbits	Subcutaneous	30	9.7	3.6
Peri and postnatal development study	Rats	Oral	100	16.2	6.1

Reference ID: 2981933

*Compared to the human topical dose under maximum clinical use conditions: 2.67 mg/kg/day, assuming 100% absorption.

Naftifine HCl solutions up to 10% were not irritating to rabbit skin. Naftifine HCl 1% cream was slightly irritating to rabbit skin. Naftifine HCl 1% and 3% creams were slightly irritating to the conjunctiva, but not toxic to the cornea of rabbit eye. Naftifine HCl 5% solution was not a contact sensitizer in guinea pigs. Naftifine HCl and NAFT-500 2% cream exhibited minimal UVB absorbance. The extent of UVB absorbance does not trigger the need for a nonclinical photoirritation study.

Overall the toxicity profile of NAFT-500 drug product has been well characterized. Because TK data were not available for most toxicology studies, the multiples of human exposure were calculated based on BSA comparison, assuming 100% absorption after dermal application. It should be noted that such evaluation is very conservative for systemic toxicology studies in which test article was administered via gavage or subcutaneous injection. The proposed daily topical dosage of NAFT-500 (2% cream applied once daily) would be comparable to the approved dosage of Naftin® Gel 1% (applied twice daily). From a pharmacology/toxicology perspective, the proposed clinical doses do not elicit a significant safety concern. This efficacy supplement is approvable from a pharmacology/toxicology perspective.

12 Appendix/Attachments

None.

Reference ID: 2981933

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

/s/

JIANYONG WANG
08/01/2011

BARBARA A HILL
08/01/2011
I concur

Memorandum

To: IND 77530/NDA 19599
From: Jianyong Wang, Ph.D., Pharmacology/Toxicology Reviewer
Through: Barbara Hill, Ph.D., Pharmacology/Toxicology Supervisor
Re:

Submission date: 01/10/2011 / 01/12/2011
Serial No: SDN 28 in IND 77530 / SDN 94 in NDA 19599
Submission type: Special Protocol/Carcinogenicity Assessment Request
Drug: NAFT-500 (naftifine HCl 2% cream)
Drug class: antifungal
Indication: tinea pedis, tinea cruris, and tinea corporis
Route: Topical
Sponsor: Merz Pharmaceuticals, LLC
Greensboro, NC 27410

Clinical formulation:

Table 3.2.P.1–1 Composition of NAFT-500 Cream, 2%

Component	Reference	Concentration (% w/w)	Function
Naftifine hydrochloride	(b) (4)	2.00	Active Ingredient
Purified Water			(b) (4)
Isopropyl Myristate			
Polysorbate 60			
Stearyl Alcohol			
Cetyl Alcohol			
Cetyl Esters Wax			
Sorbitan Monostearate			
Benzyl Alcohol			
Sodium Hydroxide			
(b) (4) Hydrochloric Acid			

(b) (4)

Reviewer's comments: The only differences in the composition between NAFT-500 cream, 2% and Naftin® cream, 1% (approved under NDA 19599) are the increase of active ingredient from 1% to 2% and the corresponding (b) (4).

Introduction:

Naftifine hydrochloride (HCl), a synthetic allylamine derivative, has been developed for the treatment of superficial fungal infection. The antifungal activity of naftifine HCl is likely related to its inhibition of squalene epoxidase in dermatophytes, leading to an accumulation of intracellular lipids that ultimately results in irreversible damage to the fungal cell wall. Naftifine HCl is the active ingredient of Naftin® 1% cream (NDA 19599) and Naftin® 1% gel (NDA 19356), which have been approved for the treatment of tinea pedis, tinea cruris, and tinea corporis. Under IND 77530, the sponsor is developing NAFT-500 (naftifine HCl) 2% cream [redacted] (b) (4) to provide shorter treatment duration over the currently marketed Naftin 1% cream product. The sponsor is also developing NAFT-600 (naftifine HCl) 2% gel for the treatment of tinea pedis under IND 105603.

During the preNDA meeting for IND 77530 (03/12/2010), the Division informed the sponsor that carcinogenicity testing is necessary to support the development of NAFT-500 (tinea infection is considered a chronic indication due to high recurrence rate). However, in consideration of the historical use of naftifine HCl, it is acceptable to conduct the carcinogenicity testing as a postmarketing commitment. The following comments were also relayed to the sponsor during the pre-NDA meeting (meeting minutes dated 05/14/2010):

"*The carcinogenicity potential of NAFT-500 should, in general, be evaluated in two species. At least one of the studies should involve administration of the test materials to the skin for 104 weeks. However, if it is determined that the systemic exposure to the drug substance or its metabolites under maximal use conditions in humans does not occur at a measurable level, then the need for carcinogenicity data may be reduced to a single topical study, involving a single species. Use of the to-be-marketed and enriched (higher active ingredient concentration) formulations are usually recommended. The Division would reserve the right to request data from a second study if, in the opinion of the Division, data from the first study indicated cause for concern (e.g., increased incidence of tumors or preneoplastic lesions).*

The Division also acknowledges that you are developing a NAFT-600 drug product (naftifine HCl 2% gel) under IND 105603 for the treatment of tinea pedis, and you also inquired about the carcinogenicity testing of the NAFT-600 drug product during the pre-Phase 3 meeting for IND 105603 conducted on April 14, 2010. It should be noted that the Division requests only one of the two products (NAFT-500 or NAFT-600) be tested for carcinogenicity to address the concern for carcinogenic potential of naftifine HCl. You should provide a scientific rationale for selecting one of the two drug products for carcinogenicity testing. Generally speaking, the drug product that produces higher systemic exposure should be selected for testing."

The sponsor submitted a dermal rat carcinogenicity protocol to NDA 19599, contained in an efficacy supplement (Supplement-11, SDN 93). The sponsor also submitted a

request for SPA to IND 77530 (SDN 28). Subsequently the sponsor revised the carcinogenicity protocol (SDN 94 under NDA 19599, 1/12/2011).

In their SPA request, the sponsor provided a rationale for the selection of cream formulation over gel formulation for carcinogenicity testing. The sponsor also provided a rational for dose selection, based on a 6-month dermal rat study that was conducted to support approval of Naftin® 1% cream. A dose range-finding study for the carcinogenicity testing was not conducted. In this memo, the 6-month dermal rat study is reviewed and the sponsor's rationales are discussed.

Review of nonclinical toxicology study reports:

Study #1

Study title: Six month chronic skin and systemic toxicity study on 3.0% naftifine cream in male and female rats

Study no.:	1395-0569-1
Study report location:	NDA 19599 SDN 93 (Supplement 11)
Conducting laboratory and location:	(b) (4)
Date of study initiation:	03/13/1984
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	3.0% Naftifine cream, lot# 7172X-6545

Key Study Findings

This was a non-GLP study. Murine respiratory mycoplasmosis (confirmed by serological analysis of blood samples) were found in quite a number of test animals. The infection was not considered treatment-related because it was also seen in untreated control animals; however, the study was compromised in some degree due to the severe infection. In total, 25 males (10, 8, 3, and 4 in untreated, vehicle, low and high dose groups) and 10 females (1, 1, 3, and 5 in untreated, vehicle, low and high dose groups) died early or were euthanized due to moribund condition. All these deaths were preceded by clinical signs of illness consistent with symptoms of murine respiratory mycoplasmosis. Histopathological examination revealed severe suppurative bronchitis and brachiectasis, atelectasis, pneumonia, and tracheitis, which were consistent with respiratory mycoplasmosis and secondary bacterial infection.

About one third of all animals showed signs of sickness intermittently during the study. The most commonly observed clinical signs were respiratory difficulties, bloody lachrymal discharge, weight loss, and general weakness. These clinical signs and subsequent deaths in some of the sick animals were consistent with symptoms of murine respiratory mycoplasmosis and secondary bacterial bronchitis. There were no significant treatment-related effects on body weight or clinical pathology. During the first two weeks of the study, very slight erythema was seen in 13 males and 23 females in

the high dose group, 10 males and 14 females in the low dose group and 2 vehicle control males.

Histopathologically, for animals that were sacrificed on schedule, minimal to slight epidermal hyperplasia was seen in 2 high dose males, 2 low dose males, and 1 low dose female on Day 184. Such finding was also seen in 1 high dose male and 4 vehicle control males on Day 196. These findings were not considered test article-related. Lung lesions that were consistent with murine respiratory mycoplasmosis were noted in some animals, in both untreated and treated groups. These lesions included multifocal suppurative bronchopneumonia, bronchiectasis, and tracheitis. Findings in kidneys (multifocal nonsuppurative nephritis, suppurative pyelitis), spleen (extramedullary hematopoiesis), and liver (mononuclear cell infiltration, multifocal nonsuppurative hepatitis, pericholangitis) were either incidental, seen in both control and dose groups, or related to lung lesions. These findings are not considered treatment-related. Incidental tumors were seen in a few animals, in both untreated and treated groups, and were not considered treatment-related.

The high dose, ~30 mg/kg/day naftifine HCl (0.3 ml 3% naftifine cream per animal), is considered to be the NOAEL, under the study conditions.

Methods

Doses:	0 (untreated), 0 (vehicle), 0.1 ml, and 0.3 ml 3% naftifine cream (~10 and 30 mg/kg naftifine HCl, for a 300 g rat)
Frequency of dosing:	Once daily for 6 months
Route of administration:	Dermal
Dose volume:	0 (untreated), 0.3 ml (vehicle), 0.1 ml, and 0.3 ml per rat
Formulation/Vehicle:	Unknown (provided by the sponsor)
Species/Strain:	Sprague-Dawley albino rats
Number/Sex/Group:	20/sex/group
Age:	Unknown (young mature rats)
Weight:	~360 g for males, ~260 g for females
Satellite groups:	Recovery animals: 10/sex/group
Unique study design:	At the end of treatment, 20/sex/group rats were sacrificed on Day 184 and 10/sex/group rats were observed daily for an additional 14-day treatment-free period for gross skin reactions, general health conditions and behavior before necropsy on Day 196.
Deviation from study protocol:	None remarkable

Observations and Results

Mortality

In total, 25 males and 10 females did not complete the study (died or euthanized due to moribund condition). In the 25 males, 3 were from the high dose group, 4 from the low dose group, 8 from vehicle control and 10 from untreated control group. The largest number of deaths occurred in the second month of the study. In the 10 females, 5 were from the high dose group, 3 from low dose, 1 from vehicle control and 1 from untreated control group. The incidence of death in the females was approximately evenly distributed throughout the study. All these deaths were preceded by clinical signs of illness consistent with symptoms of murine respiratory mycoplasmosis, which was confirmed by serological analysis of blood samples. Necropsy showed lung lesions of extensive consolidation, multiple abscesses, nodules containing caseous material, suppurative exudate, and lymph node enlargement. Histopathological examination revealed severe suppurative bronchitis and brachiectasis, marked atelectasis, mild multi focal granulomatous pneumonia, moderate plasmacytic fibrinosuppurative tracheitis, and marked reactive plasmacytosis of the mediastinal nodes. These lesions were consistent with respiratory mycoplasmosis and secondary bacterial bronchitis. These deaths are not considered treatment-related.

Clinical Signs

About one third of all animals (77 rats) showed signs of sickness intermittently during the study. The incidence of sickness in males (especially in the untreated and vehicle

control groups) was higher than in females (41% vs. 23%). The most commonly observed clinical signs were respiratory difficulties, bloody lachrymal discharge, weight loss, general weakness, and in a few cases torticollis and otitis media. These clinical signs and subsequent deaths in some of the sick animals were consistent with symptoms of murine respiratory mycoplasmosis and secondary bacterial bronchitis and are not considered treatment-related.

One untreated male and one untreated female, one vehicle control female and one low dose female developed masses during the study. Due to the low incidence and lack of a dose-response relationship, these masses were not considered treatment-related.

Gross Skin Reactions

There were no skin reactions in the untreated control animals of either sex. Very slight erythema (Grade 1, barely perceptible) was seen in 13 males and 23 females in the high dose group, 10 males and 14 females in the low dose group and 2 vehicle control males during the first two weeks of the study. Additionally, flaking was seen in 5 males and 10 females from the high dose group, 17 males and 14 females from the low dose group and 12 males and 7 females from the vehicle control group during the same time period. No skin reactions were observed for the remainder of the treatment period and during the treatment-free period.

Body Weights

There were no statistically significant differences in body weight or body weight gain in males among the 4 groups. In females, the mean body weight in the low dose and/or vehicle control groups was slightly higher than that of the untreated control group on several occasions (up to 4%). These differences are not considered adverse effects.

Figure 1
Body Weight Profile from Albino Rats (Females)

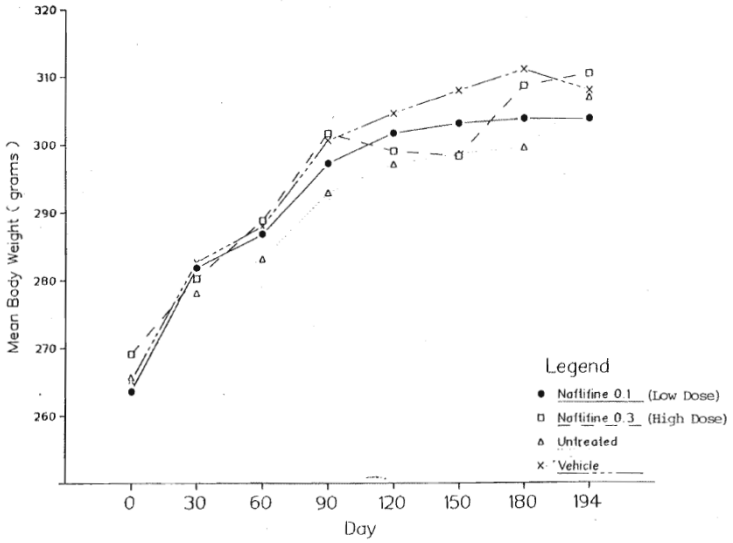
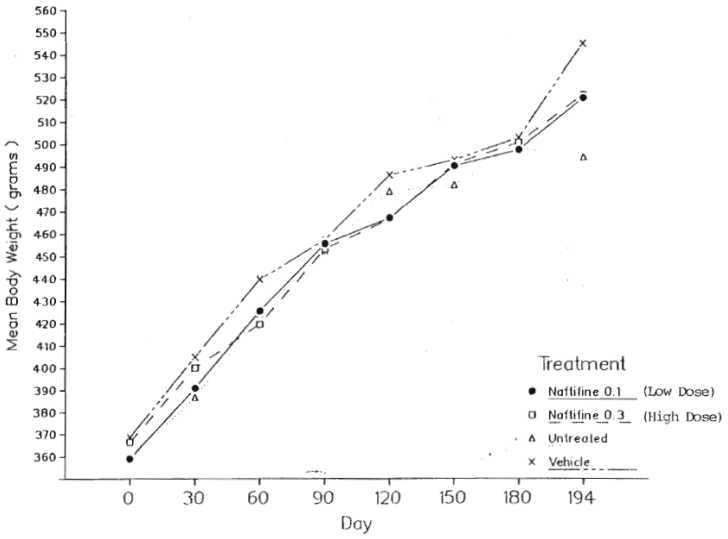


Figure 2
Body Weight Profile from Albino Rats (Males)



Hematology

No significant treatment-related findings.

Clinical Chemistry

No significant treatment-related findings.

Gross Pathology

For animals that died early or were euthanized during the study, see description under mortality section. For animals that were sacrificed on schedule, no significant treatment-related findings were noted.

Organ Weights

The following organs were weighed: adrenal gland, brain, heart, kidneys, liver, lungs, ovaries, pituitary gland, spleen, testicles, thyroid gland, and uterus.

There were no significant treatment-related findings.

Histopathology

Adequate Battery: Yes.

The tissues listed below were examined for animals in untreated control and high dose group (including recovery animals).

Treated skin, spinal chord, optic nerve, sciatic nerve, trachea, thymus gland, aorta, esophagus, tongue, stomach, duodenum, ileum, jejunum, cecum, brain, pituitary gland, thyroid gland, heart, lungs, liver, kidneys, adrenal gland, spleen, uterus, ovaries, testicles, colon, pancreas, urinary bladder, sternum, diaphragm, thigh muscle, mammary gland, bone marrow, femur, salivary gland, lymph gland, eyes with adjacent tissues, and any tissues with gross lesions.

Peer Review: No

Histological Findings:

For animals that died early or were euthanized during the study, see description under mortality section.

For animals that were sacrificed on schedule: minimal to slight epidermal hyperplasia was seen in 2 high dose males, 2 low dose males, and 1 low dose female on Day 184. Such finding was also seen in 1 high dose male and 4 vehicle control males on Day 196. There findings were not considered test article-related. Lung lesions that were consistent with murine respiratory mycoplasmosis were noted in some animals, in both untreated and treated groups. These lesions included multifocal suppurative bronchopneumonia, bronchiectasis, and tracheitis. Findings in kidneys (multifocal nonsuppurative nephritis, suppurative pyelitis), spleen (extramedullary hematopoiesis), and liver (mononuclear cell infiltration, multifocal nonsuppurative hepatitis or pericholangitis) were either incidental, seen in both control and test groups, or related to lung infection. These findings are not considered treatment-related. Incidental tumors were seen in a few animals, in both untreated and treated groups, including adenoma, fibroadenoma, and adenocarcinoma of mammary gland and metastatic liver carcinoma (in an untreated female). The incidence of these tumors was not considered treatment-related.

Toxicokinetics

Not measured.

Dosing Solution Analysis

Not analyzed.

Study #2: the proposed 2-year dermal rat carcinogenicity protocol

Study title: A 104 week carcinogenicity study of naftifine HCl by the dermal route in rats

Study no.:	Unknown
Study report location:	Protocol in SDN 93, amendment in SDN 94, NDA 19599
Conducting laboratory and location:	(b) (4)
Date of study initiation:	In July 2011
GLP compliance:	Will be
QA statement:	Will be
Drug, lot #, and % purity:	Naftifine cream

Methods

Doses:	0 (untreated), 0 (vehicle), 12, 36, and TBD mg/kg/day [0.4 and 1.2 ml/kg 3% naftifine cream for low dose and mid dose, respectively, 1.2 ml/kg naftifine cream at maximum feasible concentration (to be determined) for high dose]
Frequency of dosing:	Once daily for 104 weeks
Route of administration:	Dermal (unoccluded), applied to a skin area of ~5 cm x 6 cm
Dose volume:	See dosing table below
Formulation/Vehicle:	provided by the sponsor
Species/Strain:	Sprague-Dawley rats
Number/Sex/Group:	65/sex/group
Age:	6-8 weeks
Weight:	200-250 g
Satellite groups:	TK animals: 5/sex/group for control groups, 10/sex/group for dose groups
Unique study design:	None
Deviation from study protocol:	N/A

Table 1: Experimental Design

Group	No of main study animals		No of toxicokinetic animals		Test Item	Dose level [mg/kg/day]	Dosage volume [mL/kg]
	Male	Female	Male	Female			
Control 1	65	65	5	5	Untreated	-	-
Control 2	65	65	5	5	Placebo cream	0	1.2
1	65	65	10	10	Naftifine HCl cream 3%	12	0.4
2	65	65	10	10	Naftifine HCl cream 3%	36	1.2
3	65	65	10	10	Naftifine HCl cream, maximum feasible concentration	tbd	1.2

Observations

Mortality/Moribundity:	Twice daily
Detailed clinical observations:	Weekly
Postdose observations:	Daily
Body weight:	Weekly
Food consumption:	Weekly for the first 13 weeks, once every 4 weeks thereafter
Ophthalmology:	Pretrial, Weeks 52 and 104
Clinical Pathology:	Weeks 52 and 104
TK:	Day1, Weeks 26, 52, and 78
Gross pathology:	At necropsy
Organ weights:	At necropsy
Histopathology:	The following list of tissues will be examined for all main study animals. A pathology peer review will be conducted.

Tissues to be collected include: adrenal gland, aorta, bone (femur, sternum), bone marrow (femur, sternum), brain, cervix, epididymis, esophagus, eye, gut-associated lymphoid tissue, harderian gland, heart, intestine (cecum, colon, rectum, duodenum, ileum, jejunum), kidney, lacrimal gland, liver, lung, lymph node (mandibular, mesenteric, other), mammary gland, nerve (optic and sciatic), ovaries, oviduct, pancreas, pituitary gland, prostate gland, salivary gland, seminal vesicles, skeletal muscle (from thigh), skin (treated and untreated), spinal cord, spleen, stomach, testes, thymus, thyroid (with parathyroid) gland, tongue, trachea, ureter, urinary bladder, uterus, vagina, and gross lesions/masses.

Discussion and conclusions:

The sponsor provided a rationale for the selection of cream formulation over gel formulation for the carcinogenicity testing based on human PK data. Two maximum use clinical studies have been conducted with NAFT-500 (2% naftifine HCl cream) and NAFT-600 (2% naftifine HCl gel), respectively. In Study MRZ 90200/FI/1002, 8 g NAFT-500 was applied daily for 2 weeks to the affected areas of patients with tinea pedis and tinea cruris (2 g to each foot, 4 g to the groin area). On Day 14, the mean AUC_{0-t} was 204.3 ng.h/ml and the mean C_{max} was 11.3 ng/ml. In Study MRZ 90200/1010/1, 4 g NAFT-600 was applied daily for 2 weeks to the affected skin of patients with tinea pedis (2 g to each foot). On Day 14, the mean AUC_{0-t} was 70.1 ng.h/ml and the mean C_{max} was 3.7 ng/ml. The sponsor stated that double amount was applied in the NAFT-500 study compared to the NAFT-600 study, if assuming linear kinetics, the systemic exposure in terms of AUC and C_{max} is slightly higher after application of NAFT-500.

This PK comparison is not optimal because the applied skin area was partially different. The skin in the groin area is thinner and the absorption might be higher, compared with foot skin. Therefore, the result may not necessarily indicate that application of NAFT-500 will produce higher systemic exposure than NAFT-600. However, considering that the proposed indication of NAFT-500 (tinea pedis, tinea cruris, tinea corporis) is broader than NAFT-600 (tinea pedis), and it appears that there is no big difference between the systemic exposure to NAFT-500 and NAFT-600, it is considered acceptable for the sponsor to conduct the carcinogenicity testing with the naftifine HCl cream formulation.

The sponsor did not conduct a dose range-finding study to support the dose selection in the 2-year dermal carcinogenicity study protocol. Instead they submitted a previously conducted 6-month dermal study to support the dose selection. In the 6-month study, quite a number of animals died early or became ill due to respiratory mycoplasmosis and secondary bacterial infection, although the infection was not considered treatment-related. Very slight erythema was seen only during the first 2 weeks of the study, in high dose, low dose, and vehicle control groups. There were no significant treatment-related effects on body weight, clinical chemistry, or histopathology. The high dose, ~30 mg/kg naftifine HCl (0.3 ml 3% naftifine HCl cream), is considered to be the NOAEL, under the study conditions. The sponsor stated that in a PK study using the same doses, the high dose (0.3 ml 3% naftifine HCl cream) resulted in a mean AUC_{0-t} of 205.3 ng.h/ml and C_{max} of 15.8 ng/ml (mixed gender). These values are 1.0 and 1.4 times the clinical exposure under maximal use conditions in patients with both tinea pedis and tinea cruris, respectively.

Apparently the high dose, 0.3 ml 3% cream, was below the MTD. In the initial carcinogenicity study protocol (submitted to SDN 93, NDA 19599), the sponsor proposed topical doses of naftifine HCl at 0 (untreated control), 0 (vehicle control), 12, 24, and 36 mg/kg/day (0.4, 0.8, and 1.2 ml/kg 3% cream, which are 0.1, 0.2, and 0.3 ml 3% cream for a 250 g rat). Since the proposed high dose was below the MTD, an

information request was sent to the sponsor for the clarification of the maximum feasible concentration of naftifine HCl in the cream formulation. The sponsor replied that the maximum feasible concentration has not yet been determined. The sponsor stated that a formulation study to determine this concentration has been initiated and once complete, a cream formulation with the maximum feasible concentration of naftifine HCl will be used as the high dose in the carcinogenicity study. The previously proposed high dose, 36 mg/kg/day, will become the mid dose and the previously proposed mid dose, 24 mg/kg/day, will not be tested.

Because there was no informative dose range-finding study, the high dose tested in the compromised 6-month study was below the MTD, and the maximum feasible concentration of naftifine HCl in the cream formulation is unknown, the available information is considered inadequate for the dose selection for the 2-year dermal rat carcinogenicity study. The sponsor revised the protocol by proposing a maximum feasible dose as the high dose; however, it is uncertain if the design is appropriate. The maximum feasible dose may exceed the MTD, and the dose space between the high dose and mid dose may be too big.

In conclusion, it is recommended that an appropriate dose range-finding study be conducted to support the dose selection for the 2-year dermal rat carcinogenicity study. It is also recommended that the maximum feasible dose of naftifine HCl cream be tested in the dose range-finding study. In addition, the dose volume should be constant and the concentration of the naftifine in the cream formulation modified to obtain the three dose levels for evaluation in the 2-year dermal rat carcinogenicity study.

Appendix: Executive CAC meeting minutes

Executive CAC
Date of Meeting: January 25, 2011

Committee: David Jacobson-Kram, Ph.D., D.A.B.T, OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND, IO, Member
Linda Fossom, Ph.D., DPP, Alternate Member
Barbara Hill, Ph.D., DDDP, Supervisor
Jianyong Wang, Ph.D., DDDP, Presenting Reviewer

Author of Draft: Jianyong Wang, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

The committee did not address the statistical evaluation for the 2-year carcinogen bioassay, as this does not affect the sponsor's ability to initiate the bioassay. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following the

CDER/CBER Guidance for Industry, Providing Regulatory Submission in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008) and the associated Study Data Specifications Document.

IND #: 77,530
Drug Name: NAFT-500 (naftifine hydrochloride) 2% cream
Sponsor: Merz Pharmaceuticals, Greensboro, NC 27410

Background:

Naftifine HCl is the active ingredient of Naftin® 1% cream (NDA 19599) and Naftin® 1% gel (NDA 19356), which have been approved by the FDA for the treatment of tinea pedis, tinea cruris, and tinea corporis. Under IND 77530, the sponsor is developing NAFT-500 (naftifine HCl) 2% cream for the same indication to provide shorter treatment duration over the currently marketed Naftin 1% cream product. The sponsor is also developing NAFT-600 (naftifine HCl) 2% gel for the treatment of tinea pedis under IND 105603.

During the preNDA meeting for IND 77530 (03/12/2010), the Division informed the sponsor that carcinogenicity testing is necessary to support the development of NAFT-500. However, in consideration of the historical use of naftifine HCl, it is acceptable to conduct the carcinogenicity testing as a post-marketing commitment. The sponsor was also informed that the Division requests only one of the two products (NAFT-500 or NAFT-600) be tested for carcinogenicity to address the concern for carcinogenic potential of naftifine HCl. A scientific rationale for selecting one of the two drug products for carcinogenicity testing was requested.

The sponsor submitted a 2-year dermal rat carcinogenicity protocol to NDA 19599, contained in an efficacy supplement (Supplement-11, SDN 93). The sponsor also submitted a request for evaluation of this protocol under a SPA to IND 77530 (SDN 28). In their SPA request, the sponsor provided a rationale for the selection of cream formulation over gel formulation for carcinogenicity testing. The sponsor also provided a rational for dose selection, based on a 6-month dermal rat study that was conducted to support approval of Naftin® 1% cream. An information request was sent to the sponsor for clarification of the maximum feasible concentration (MFC) of naftifine HCl in the cream formulation. The sponsor replied that the MFC has not yet been determined. The sponsor stated that a formulation study to determine MFC has been initiated and once complete, a cream formulation with the MFC of naftifine HCl will be used as the high dose in the carcinogenicity study. The sponsor revised the carcinogenicity protocol accordingly (SDN 94 under NDA 19599, 01/12/2011).

Two-year dermal rat carcinogenicity study protocol:

Species/strain: Sprague-Dawley rat
Number/sex/dose: 65/sex/dose for the main study

Duration:	104 weeks
Route:	Topical
Dose volume:	0.4 ml/kg/dose for low dose, 1.2 ml/kg/dose for mid and high doses
Body surface area (BSA) treated:	5 cm x 6 cm
Doses proposed:	0 (untreated control), 0 (placebo cream), 3% cream at 0.4 ml/kg/day, 3% cream at 1.2 ml/kg/day, and MFC cream at 1.2 ml/kg/day
Vehicle:	Clinical vehicle
Dosing procedure:	Test article will be administered topically (unoccluded), once daily for 104 weeks.

Justification for Dose Selection:

Initially the sponsor proposed doses of 0 (untreated control), 0 (placebo cream), 3% cream at 0.4, 0.8, and 1.2 ml/kg/day for the carcinogenicity study. The proposed high dose was a similar dose as the high dose tested in the 6-month dermal rat toxicity study (0.3 ml 3% naftifine HCl cream applied once daily). Murine respiratory mycoplasmosis was noted in about one third of all animals in the 6-month study; however, it was considered unrelated to treatment. No significant treatment-related systemic toxicity was observed. Only very slight erythema was noted during the first two weeks of the study. The high dose is the NOAEL in the 6-month study. A MTD was not established in this study. The 6-month dermal rat toxicity study is not an adequate dose range-finding study to support dose selection for the 2-year dermal rat carcinogenicity study. After receiving an information request from the Division for clarification of the MFC of naftifine HCl in the cream formulation, the sponsor proposed to use a cream formulation with the MFC of naftifine HCl as the high dose and use the 3% cream at 1.2 ml/kg/day and 0.4 ml/kg/day as the mid dose and low dose, respectively.

Executive CAC Recommendations and Conclusions:

1) The Committee did not have sufficient data on which to base an agreement on doses. The doses proposed by the sponsor have not been evaluated in an adequate dose range-finding study. The MFC should be established and tested in a dose range-finding study.

2) The Committee notes that in a repeat dose dermal toxicity study, the dose volume should be maintained and the dose levels increased by increasing the concentration of the active in the formulation up to the MFC, if tolerated.

3) If the sponsor wishes concurrence, they should conduct an adequate dose range study and submit it with the protocol.

David Jacobson-Kram, Ph.D., D.A.B.T
Chair, Executive CAC

cc:\
/Division File, DDDP
/D. Jacobson-Kram, OND IO
/A. Jacobs, OND IO
/P. Brown, OND IO
/B. Hill, Supervisor, DDDP
/J. Wang, P/T reviewer, DDDP
/D. Williams, Project Manager, DDDP
/ASeifried, OND IO

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

/s/

JIANYONG WANG
01/26/2011

BARBARA A HILL
01/27/2011
I concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019599Orig1s011

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	sNDA 019599 / SDN 93
Drug Name:	Naftin 2% (naftifine hydrochloride)
Indication(s):	Tinea Cruris, Tinea Pedis, Tinea Corporis
Applicant:	Merz
Date(s):	Letter date: 12/16/2010
	PDUFA date: 10/16/2011
Review Priority:	Standard
Biometrics Division:	DBIII
Statistical Reviewer:	Carin Kim, Ph.D.
Concurring Reviewers:	Mohamed Alosh, Ph.D.
Medical Division:	Division of Dermatology and Dental Products
Clinical Team:	Brenda Vaughan, M.D.
Project Manager:	Dawn Williams

Keywords: Clinical studies, Superiority trials

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Reference ID: 2983464

1. EXECUTIVE SUMMARY

The Tinea Cruris study demonstrated statistical significance (p<0.001) with response rates of 25.3% and 2.8% for NAFT-500 and vehicle, respectively; and the Tinea Pedis study demonstrated statistical significance (p=0.01) with response rates of 17.7% and 7.1% for NAFT-500 and vehicle, respectively (see Table 1). It should be noted that while the sponsor is seeking approval for subjects 12 years and older; however, only 2 subjects (<2%) in each study at baseline were between the ages of 12 and 17 years.

Table 1. Complete Cure Rate for Tinea Cruris and Tinea Pedis trials

	NAFT-500 N=75	Vehicle N=71	p-value
Tinea Cruris [(1)]	19 (25.3%)	2 (2.8%)	<0.001
Tinea Pedis [(2)]	26 (17.7%)	5 (7.1%)	0.01

Complete Cure is defined as having negative mycology results (dermatophyte culture and KOH) and absence of erythema, scaling and pruritus at Week 4 (1) and Week 6 (2).
P-value is calculated from a one-sided CMH test stratified by pooled sites (FAS, LOCF)

The Agency commented that for the tinea pedis indication, efficacy and safety analyses should be done separately by each type of tinea pedis (Pre-IND meeting: 11/6/2007), and that indication(s) which might be supported by the clinical studies will depend on what has been demonstrated in the clinical studies (including the tinea pedis type(s)) (Pre-NDA meeting: 5/12/2010). In the sponsor's ISE report, the sponsor stated that "the tinea pedis study was not designed to treat a specific type of tinea pedis, rather, subjects were instructed to treat the affected area recorded at baseline, and investigators were instructed to evaluate the worst site at each visit (i.e., Week 2, 4, and 6)." As such, the sponsor conducted a post-hoc analysis that attempted to classify subjects as either having interdigital, moccasin or both types of tinea pedis. However, it should be noted that the lack of specification of the type of tinea pedis in the study led to inconsistent and subjective classification by the sponsor in the analysis. Due to the small number of subjects for each type of tinea pedis, only rough estimates of the complete cure rates for each type of tinea pedis could be obtained, therefore, it would be difficult to draw conclusions regarding the complete cure rates for each type of tinea pedis based on the sponsor's study.

Reference ID: 2983464

2. INTRODUCTION

2.1 Overview

The sponsor currently markets Naftin (naftifine) 1% cream used once daily for 4 weeks for the treatment of tinea infections. In the current development program, the sponsor is developing NAFT-500 (naftifine) 2% cream used once daily for 2 weeks for the treatment of tinea pedis, tinea corporis, and tinea cruris. The sponsor conducted Studies MRZ 90200/FI/3001 (from hereon referred to as "Tinea Cruris study") and MUS 90200-0736/1 (from hereon referred to as "Tinea Pedis study") evaluating the safety and efficacy of NAFT-500 in the treatment of tinea cruris and tinea pedis, respectively.

The Tinea Cruris study had 2 arms: NAFT-500 and vehicle. The objective of this trial was to demonstrate the superiority of NAFT-500 to vehicle. The Tinea Pedis study had 4 arms: NAFT-500 and its vehicle, and Naftin 1% and its vehicle. The objective of this study was to demonstrate that NAFT-500 is superior to its vehicle. According to the sponsor, the Naftin 1% arm was included as 'exploratory analyses for descriptive purposes only' in comparing the NAFT-500 to Naftin 1%. In the cover letter of this sNDA application, the sponsor stated that they intend to withdraw Naftin 1% with the approval of NAFT-500.

There were two meetings held between the Agency and the sponsor and an Advice Letter regarding the proposed Phase 3 studies was sent to the sponsor with Agency comments: Pre-IND (11/6/2007), Advice Letter (1/7/2009) and Pre-NDA (5/12/2009).

At the Pre-IND meeting (11/6/2007) the sponsor was advised that at least one study in tinea pedis and one study in tinea cruris would be needed to obtain the indication of tinea pedis, corporis and cruris. The Agency also stated that safety and efficacy studies should separately analyze efficacy for interdigital and moccasin type tinea pedis.

On 5/30/2008, the sponsor submitted two Phase 3 protocols (Tinea Cruris study and Tinea Pedis study) for Agency comments. Statistical review on the original protocols was completed and signed off in DARRTS on 6/26/2008. Based on the records in DARRTS, the sponsor submitted two amended Phase 3 protocols to the Agency (date of amendment 1: 7/29/2008, stamp date: 8/7/2008; date of amendment 2: 10/21/2008, stamp date: 10/30/2008).
Comments on the original protocol (dated 5/20/2008) were sent to the sponsor as an Advice Letter on 1/7/2009. It should be noted that when the Advice Letter was sent to the sponsor, subject enrollment for the Tinea Cruris and Tinea Pedis studies have already begun in August and September of 2008, respectively.

The Statistical Analysis Plan (SAP) was amended three times (effective dates: 8/10/2009, 10/7/2009, and 12/23/2009), however, the amended SAPs were not submitted to the Agency for comments. According to the sponsor's study report, the changes in the SAP included plans to conduct sensitivity analyses for the primary efficacy endpoint in addition to using LOCF, and also included obtaining one-sided confidence intervals for the primary efficacy endpoint. The sponsor also included conducting Breslow-Day test for testing the homogeneity of treatment effect among pooled clinical sites.

Reference ID: 2983464

Pre-NDA meeting (5/12/2010)

The sponsor inquired whether one Phase 3 study in tinea pedis and one Phase 3 study in tinea cruris would be sufficient to demonstrate that NAFT-500 is effective for tinea cruris, tinea pedis, and tinea corporis. In response, the Agency stated that the adequacy of the completed studies to support an indication would be a review issue. Further, the Agency reiterated its previous comments that "safety and efficacy studies for tinea pedis should separately analyze efficacy for interdigital tinea pedis and for moccasin type tinea pedis." Additionally, the Agency stated that the sponsor should "include analyses for Study MUS 90200-0736/1 (Tinea Pedis study) broken down by interdigital and moccasin tinea pedis in the NDA submission. The indication(s) which might be supported by your clinical studies will depend on what has been demonstrated in the clinical studies (including the tinea pedis type(s))". The Agency reiterated its Pre-IND comment that a successful program would need to include at least one study in tinea pedis and one study in tinea cruris.

On 12/16/2010, the sponsor submitted an sNDA application. According to the cover letter in this submission, the sponsor intends to market the NAFT-500 (naftifine hydrochloride cream, 2% strength), and stated their intention on the cover letter of withdrawing Naftin 1% from the market with the approval of NAFT-500.

2.2 Clinical Studies Program

For enrollment in the two Phase 3 trials, eligible subjects were to be ≥12 years of age with clinical signs and symptoms of tinea cruris of at least moderate erythema, moderate scaling, mild pruritus, and a positive KOH. Subjects were enrolled at 18 centers in the Tinea Cruris study, and 16 centers in the Tinea Pedis study, and all study centers were located in the United States. Features of these studies are presented in Table 4.

Table 2. Phase 3 studies conducted by the sponsor

Study	Treatment Arms	Randomized Subjects	No. of FAS Subjects	Enrollment Period
Tinea Cruris	NAFT-500 Vehicle (2 weeks)	166 168	75 71	August, 2008 to August, 2009
Tinea Pedis	NAFT-500 Vehicle (2 weeks) Naftin 1% Vehicle (4 weeks)	235 118 237 119	147 70 143 65	September 12, 2008 to August 29, 2009

Source: Reviewer's Table. The number of subjects is the Full Analysis Set (FAS) population used for efficacy evaluation.

Reference ID: 2983464

2.2 Data Sources

This reviewer evaluated the sponsor's clinical study reports and clinical summaries, as well as the proposed labeling. This submission was submitted in eCTD format and was entirely electronic. The datasets in this review are archived at the following locations: //cdsesub1/EVSPROD/NDA019599/0004/m5/datasets/ise/analysis/datasets/.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The sponsor submitted two analysis datasets: adecures.xpt and adedm.xpt for both studies. While most primary and secondary analyses could be conducted using these two datasets, the efficacy by center plots based on the original sites required some data extraction from an SDTM dataset (e.g. dm.xpt) because the original site variable was not included in the analysis datasets. For the types of tinea pedis, the sponsor did not include this information in the analysis datasets, therefore, this reviewer extracted the information from an SDTM dataset called fa.xpt. The baseline severity of signs and symptoms of tineas (i.e., erythema, scaling and pruritus) was also obtained from an SDTM dataset, fa.xpt.

3.2 Efficacy Evaluations

3.2.1 Tinea Cruris Trial

Study Design and Endpoints

The primary objective was to evaluate the efficacy and safety of NAFT-500, applied once daily (QD) for 2 weeks, compared to placebo in the treatment of subjects with KOH and culture positive symptomatic tinea cruris.

For enrollment, eligible subjects were to be ≥12 years of age with clinical signs and symptoms of tinea cruris of at least moderate erythema, moderate scaling, mild pruritus, and a positive KOH.

For randomization, the protocol stated "a blocked, unstratified schedule" was generated using SAS version 9.1.3 by an unblinded statistician and programmer who were not otherwise involved in the study. The protocol stated that the (b) (4) IWRS system was used to randomize subjects at Day 1 in a 1:1 ratio to either NAFT-500 or vehicle arms at baseline.

The protocol-specified endpoint was the proportion of subjects with complete cure at Week 4 where complete cure is defined as negative mycology results (dermatophyte culture and KOH), and absence of erythema, scaling and pruritus (grade 0 of each) using a 4-point scale (0=absent, 1=mild, 2=moderate, 3=marked).

The protocol-specified secondary endpoints were:

- Mycological cure: negative KOH and negative dermatophyte culture at Week 4

- Treatment effectiveness: negative KOH, negative culture, and erythema, scaling and pruritus scores of 0 or 1 at Week 4.

The sponsor used the following populations in the analyses of the data:

- Safety-Evaluation Set (SES): The SES population was the subset of all subjects who received study drug at least once.
- Full-Analysis Set (FAS): The FAS population was the subset of the SES population with a positive culture at baseline for whom the primary efficacy endpoint was available. According to the sponsor, all subjects had the primary efficacy endpoint "because dropouts and cases with missing information were considered as not complete cures by definition". This was a modified intent-to-treat principle because the culture results were not available before the start of treatment.
- Per-Protocol Set (PPS): The PPS population was the subset of FAS population without major protocol deviations. Major protocol deviations were defined as:
  - Subjects with insufficient baseline signs and symptoms;
  - Treatment with restricted previous and/or concomitant medications;
  - Enrollment prior to study-determined wash-out of concomitant medications;
  - Subject visits occurring >3 days outside of the expected visit date;
  - Missing or unknown Week 4 KOH and dermatophyte culture results;
  - Or Missing or unknown Week 4 scaling, erythema, and pruritus scores.

Patient Disposition and Baseline Characteristics

The study enrolled 334 subjects of which146 subjects (75 to NAFT-500 and 71 to vehicle) had positive cultures (FAS population). The vehicle arm had a slightly higher rate of discontinuation rate (15%) compared to the NAFT-500 (11%). The most common reason for discontinuation was lost to follow-up.

Reference ID: 2983464

Table 3. Number (proportion) of subjects who discontinued the study: classified by reason for discontinuation

	Tinea Cruris	
	NAFT-500	**Vehicle**
Randomized Subjects (SES) (1)	**166**	**168**
FAS (2) Subjects	**75**	**71**
Completed	67 (89 %)	60 (85%)
Discontinued	8 (11 %)	11 (15%)
Adverse Event	1	0
Lost to follow-up	4	6
Withdrawal by subject	1	3
Other	2	1
Investigator Decision	0	1
Non-compliance	0	0

Source: reviewer's analysis

(1) Safety-Evaluation Set (SES): The SES population was the subset of all subjects who received study drug at least once.

(2) Full-Analysis Set (FAS): The FAS population was the subset of the SES population with a positive culture at baseline. This was a modified intent-to-treat principle because the culture results were not available before the start of treatment.

The baseline severity data were evenly balanced across treatment arms.

Table 4. Baseline Severity Table (FAS)

		NAFT-500 N=75	**2-week Vehicle N=71**
Baseline culture (KOH and dermatophyte)			
	Positive	75 (100%)	71 (100%)
	Negative	--	--
Erythema			
	Absent	--	--
	Mild	1 (1%)	--
	Moderate	36 (48 %)	37 (52%)
	Marked	38 (51 %)	34 (48%)
Scaling			
	Absent	--	--
	Mild	--	--
	Moderate	55 (73 %)	41 (58%)
	Marked	20 (27 %)	30 (42%)
Pruritus			
	Absent	--	1 (1%)
	Mild	2 (3%)	3 (4%)
	Moderate	29 (39%)	29 (41%)
	Marked	44 (59%)	38 (54%)

Source: reviewer's table (erythema, scaling, pruritus data from fa.xpt)

Statistical Methodologies

The sponsor used a one-sided hypothesis test at the level of significance of 0.025, on the FAS (full-analysis set) defined by "all subjects with a positive culture at baseline" (mITT population as defined by the sponsor). The protocol-specified primary analysis for the primary efficacy endpoint is the CMH test stratified by site.

For the analyses of the secondary endpoints, the sponsor used the CMH test stratified by sites. To control the overall Type I error rate for the two secondary endpoints, the Hochberg procedure was used. If the larger p-value from the two tests is ≤0.025, then both comparisons will be considered statistically significant. However, if the larger p-value is >0.025, then this comparison will be considered not statistically significant, and the other comparison must have p≤0.0125 to be considered statistically significant.

For missing data, the sponsor used the LOCF as the primary imputation method as specified in the protocol. The sponsor stated that as a sensitivity analysis to evaluate the impact of the missing data and dropouts on the results, the primary efficacy endpoint will also be analyzed using only observed values with no imputation. In addition, the sponsor considered analyzing the Per Protocol set (PPS) population of the primary efficacy endpoint as a sensitivity analysis as well. As an additional sensitivity analysis, this reviewer imputed missing as failures.

Results and Conclusions

The following table shows the primary efficacy analysis results. For the Tinea Cruris trial, the protocol-specified primary endpoint is the complete cure rate at Week 4, and the p-value met the significance level of 0.025.

Table 5. Complete Cure Rate at Week 4

	NAFT-500	Vehicle	p-value
Sponsor's analysis(1)	19/75 (25.3%)	2/71 (2.8%)	<0.001
Sensitivity analysis (2)	16/75 (21.3%)	2/71 (2.8%)	0.001
Sponsor's sensitivity analysis(3)	16/57 (28.1%)	2/59 (3.4%)	<0.001
Sponsor's sensitivity analysis(4)	15/52 (28.8%)	2/45 (4.4%)	0.003

Complete Cure is defined as having negative mycology results (dermatophyte culture and KOH) and absence of erythema, scaling and pruritus at Week 4. P-value is calculated from a one-sided CMH test stratified by pooled sites.

(1) Sponsor's protocol-specified primary analysis –one-sided CMH test stratified by pooled sites, FAS, LOCF.
(2) Reviewer's sensitivity analysis –one-sided CMH test stratified by pooled sites, missing imputed as failure. FAS.
(3) Sponsor's sensitivity analysis. Observed data only without imputing missing data.
(4) Sponsor's sensitivity analysis. Per Protocol Set. (PPS)

The analysis results of secondary efficacy endpoints, mycological cure and treatment effectiveness, are presented below. Both secondary endpoints are statistically significant after adjusting for multiplicity using Hochberg's procedure. The secondary endpoint efficacy results are consistent with the primary efficacy endpoint results.

Reference ID: 2983464

Table 6. Secondary efficacy analysis results at Week 4

	NAFT-500	Vehicle	p-value
Mycological Cure[(1)]	54/75 (72.0%)	11/71 (15.5%)	<0.001 [(1)]
Treatment Effectiveness [(2)]	45/75 (60.0%)	7/71 (9.9%)	0.001 [(2)]

One-sided CMH test by center, FAS, LOCF.
Adjusted p-value from Hochberg's step-up procedure.
(1) Mycological cure: negative KOH and negative culture
(1) Treatment effectiveness: negative KOH, negative culture, erythema, scaling and pruritus greades of 0 or 1.

3.2.2 Tinea Pedis Trial

Study Design and Endpoints

The tinea pedis trial was a 4-arm study of NAFT-500, 2% (2-week treatment), 2-week placebo, naftifine 1% (4-week treatment), and 4-week placebo. The primary objective was to evaluate the efficacy and safety of NAFT-500, 2% vs. 2-week placebo.

In the submission, the sponsor stated that 'exploratory analyses for descriptive purposes only' were used in comparing the NAFT-500 to Naftin 1%.

For enrollment, eligible subjects were to be ≥12 years of age with clinical signs and symptoms of tinea pedis of at least moderate erythema, moderate scaling, mild pruritus, and a positive KOH.

The protocol-specified endpoint was the proportion of subjects with complete cure at Week 6 where complete cure is defined as negative mycology results (dermatophyte culture and KOH), and absence of erythema, scaling and pruritus (grade 0 for each) on the 4-point scale (0=absent, 1=mild, 2=moderate, 3=marked, 4=not done)

The protocol-specified secondary endpoints were:

- Mycological cure: negative KOH and negative dermatophyte culture at Week 6
- Treatment effectiveness: negative KOH, negative culture, and scaling, erythema, and pruritus scores of 0 or 1 at Week 6

The sponsor used the following populations in the analyses of the data:

- Safety-Evaluation Set (SES): The SES population was the subset of all subjects who received study drug at least once.
- Full-Analysis Set (FAS): The FAS population was the subset of the SES population with a positive culture at baseline for whom the primary efficacy endpoint was available. According to the sponsor, all subjects had the primary efficacy endpoint "because dropouts and cases with missing information were considered as not complete cures by definition". This was a modified intent-to-treat principle because the culture results were not available before the start of treatment.
- Per-Protocol Set (PPS): The PPS population was the subset of FAS population without major protocol deviations. Major protocol deviations were defined as:
  - Subjects with insufficient baseline signs and symptoms;
  - Treatment with restricted previous and/or concomitant medications;

- Enrollment prior to study-determined wash-out of concomitant medications;
- Subject visits occurring >3 days outside of the expected visit date;
- Missing or unknown Week 4 KOH and dermatophyte culture results;
- Or Missing or unknown Week 4 scaling, erythema, and pruritus scores.

Patient Disposition and Baseline Characteristics

The Tinea Pedis trial enrolled a total of 709 subjects at 16 centers, of which 425 subjects (147 NAFT-500 and 70 2-week vehicle, 143 naftifine 1%, and 65 4-week vehicle) had positive cultures (FAS population). The study was conducted from September, 2008 to August, 2009. The discontinuation rate was higher for the vehicle arm (20%) compared to that of the NAFT-500 arm (12%). The most common reason for discontinuation was lost to follow-up.

Table 7. Number (proportion) of subjects who discontinued the study: classified by reason for discontinuation

	Tinea Pedis	
	NAFT-500	**Vehicle**
Randomized Subjects (SES) (1)	**235**	**118**
FAS (2) Subjects	**147**	**70**
Completed	129 (88 %)	56 (80.0 %)
Discontinued	18 (12%)	14 (20 %)
Adverse Event	0	1
Lost to follow-up	9	7
Withdrawal by subject	3	2
Other	4	3
Investigator Decision	1	1
Non-compliance	1	0

Source: reviewer's analysis

(1) Safety-Evaluation Set (SES): The SES population was the subset of all subjects who received study drug at least once.

(2) Full-Analysis Set (FAS): The FAS population was the subset of the SES population with a positive culture at baseline. This was a modified intent-to-treat principle because the culture results were not available before the start of treatment.

Reference ID: 2983464

The baseline severity data were evenly balanced across treatment arms.

Table 8. Baseline Severity Table (FAS)

		NAFT-500 N=147	2-week Vehicle N=70
Baseline culture (KOH and dermatophyte)			
	Positive	147 (100%)	70 (100%)
	Negative	--	--
Erythema			
	Absent	--	--
	Mild	--	--
	Moderate	102 (69%)	48 (69%)
	Marked	45 (31%)	22 (31%)
Scaling			
	Absent	--	--
	Mild	--	--
	Moderate	65 (44%)	33 (47%)
	Marked	82 (56%)	37 (53%)
Pruritus			
	Absent	--	--
	Mild	14 (10%)	8 (11%)
	Moderate	52 (35%)	22 (32%)
	Marked	81 (55%)	40 (57%)

Source: reviewer's analysis

Statistical Methodologies

The sponsor used a one-sided hypothesis test, on the FAS (full-analysis set) which was defined as all subjects with a positive baseline culture. The protocol-specified primary analysis of efficacy is the CMH test by sites. According to the protocol, sites with fewer than 7 FAS subjects was pooled for analysis, and according to the study report, there were three sites with less than 7 FAS subjects. One site did not have any FAS subjects; therefore, the sponsor pooled two small sites.

The sponsor also included several 'sensitivity and supportive statistical analyses' for the primary efficacy endpoints which included CMH test by sites using the per-protocol set (PPS) population, analysis using only the observed data for the FAS population and the PPS population, analyses conducted for Week 2, Week 4, and Week 6 assessments.

For the analyses of the secondary endpoints, the sponsor used the CMH test stratified by sites. To control the overall Type I error rate for the two secondary endpoints, the Hochberg procedure was used. If the larger p-value from the two tests is ≤0.025, then both comparisons will be considered statistically significant. However, if the larger p-value is >0.025, then this

comparison will be considered not statistically significant, and the other comparison must have $p \leq 0.0125$ to be considered statistically significant.

For missing data, the pre-specified imputation method was to impute the missing data using LOCF. The sponsor stated that as a sensitivity analysis to evaluate the impact of the missing data and dropouts on the results, the primary efficacy endpoint will also be analyzed using only observed values with no imputation. In addition, the primary efficacy endpoint will be analyzed using the Per Protocol set (PPS) population as a sensitivity analysis as well.

Results and Conclusions

The following table shows the primary efficacy analysis results with sensitivity analysis results. The primary efficacy analysis was the proportion of subjects achieving complete cure where complete cure is defined as having negative culture (KOH and dermatophyte) along with absence of erythema, scaling and pruritus at Week 6.

For the FAS population, the NAFT-500 was statistically superior to vehicle (17.7% vs. 7.1%, p=0.01) using the one-sided CMH test stratified by pooled sites with missing data imputed with LOCF. Using the same statistical test, a sensitivity analysis with data that imputed the missing as failures was carried out whose results are also presented below.

Table 9. Complete Cure Rate at Week 6

	NAFT-500	Vehicle	p-value
Sponsor's analysis(1)	26/147 (17.7%)	5/70 (7.1%)	0.01
Sensitivity analysis (2)	23/147 (15.7%)	5/70 (7.1%)	0.02
Sponsor's sensitivity analysis(3)	23/128 (18.0%)	5/63 (7.9%)	0.01
Sponsor's sensitivity analysis(4)	18/87 (20.7%)	3/48 (6.3%)	0.01

Complete Cure is defined as having negative mycology results (dermatophyte culture and KOH) and absence of erythema, scaling and pruritus at Week 4. P-value is calculated from a one-sided CMH test stratified by pooled sites.

(1) Sponsor's protocol-specified primary analysis –one-sided CMH test stratified by pooled sites, FAS, LOCF.
(2) Reviewer's sensitivity analysis –one-sided CMH test stratified by pooled sites, missing imputed as failure. FAS.
(3) Sponsor's sensitivity analysis. Observed data only without imputing missing data.
(4) Sponsor's sensitivity analysis. Per Protocol Set. (PPS)

The analysis results of secondary efficacy endpoints, mycological cure and treatment effectiveness, are presented below. Both secondary endpoints are statistically significant after adjusting for multiplicity using Hochberg's procedure. The secondary endpoint efficacy results are consistent with the primary efficacy endpoint results.

Table 10. Secondary efficacy analysis results at Week 6

	NAFT-500	Vehicle	p-value
Mycological Cure(1)	99/147 (67.3%)	15/70 (21.4%)	<0.001
Treatment Effectiveness (2)	83/147 (56.5%)	14/70 (20.0%)	<0.001

One-sided CMH test by center, FAS, LOCF.
Adjusted p-value from Hochberg's step-up procedure.

(1) Mycological cure: negative KOH and negative culture
(2) Treatment effectiveness: negative KOH, negative culture, erythema, scaling and pruritus grades of 0 or 1.

Reference ID: 2983464

Benefit:Risk Assessment

To evaluate the benefit-risk, the complete cure rates of the approved Naftin 1% vs. 4-week vehicle, and the NAFT-500 vs. 2-week vehicle are compared. The complete cure rate is slightly higher for the NAFT-500 arm when compared to that of Naftin 1% arm, however, it should be noted that the complete cure rate for the NAFT-500 vehicle (treatment duration of 2 weeks) arm is twice as high compared to that of the Naftin 1% vehicle (treatment duration of 4 weeks) arm.

Table 11. Complete Cure Rate at Week 6

	Tinea Pedis			
	NAFT-500 N=147	**Vehicle(1) N=70**	**Naftin 1% N=143**	**Vehicle(2) N=65**
Complete Cure Rate(3)	26 (17.7%)	5 (7.1%)	23 (16.1%)	2 (3.1%)
Complete Cure Rate(4)	23 (15.7%)	5 (7.1%)	22 (15.4%)	2 (3.3%)

One-sided CMH test stratified by pooled sites.
(1) Treatment duration of 2 weeks to match that of NAFT-500
(2) Treatment duration of 4 weeks to match that of Naftin 1%
(3) Sponsor's analysis: FAS, LOCF. P-value=0.001 for Naftin vs. 4-week vehicle; p-value =0.01 for NAFT-500 vs. 2-week vehicle.
(4) Reviewer's analysis: FAS, missing imputed as failure. P-value =0.0015 for Naftin 1% vs. 4-week vehicle; p-value= 0.02 for NAFT-500 vs. 2-week vehicle.

3.3 Evaluation of Safety

Tinea Cruris Trial

For safety evaluation, the sponsor used the Safety-evaluation set (SES) defined as all subjects who received study drug at least once. The following table is the summary of adverse events in the Tinea Cruris trial. The adverse events were comparable for both the NAFT-500 and its vehicle arms as well as for the Naftin 1% and its vehicle arms. About 15% of the subjects experienced adverse events (13.9% in NAFT-500: 15.5% in its vehicle). The two most common adverse events were application site pruritus and headache.

Reference ID: 2983464

Table 12. Summary of Adverse Events (SES)

	NAFT-500 N=166	Vehicle N=168
All Adverse Events	23 (13.9%)	26 (15.5%)
Any treatment-emergent adverse events (TEAE)	23 (13.9%)	26 (15.5%)
Application site pruritus	3 (1.8%)	0 (0%)
Headache	2 (1.2%)	4 (2.4%)
Skin and subcutaneous disorders	2 (1.2%)	2 (1.2%)
Application Site Reaction	1 (0.6%)	1 (0.6%)
Application Site Erythema	0 (0%)	1 (0.6%)

Source: Sponsor's study report, page 69.

Tinea Pedis Trial

The adverse events were comparable for both the NAFT-500 and its vehicle arms as well as for the Naftin 1% and its vehicle arms. About 20% of the subjects experienced adverse events (20.1% in NAFT-500: 18.6% in its vehicle). The two most common adverse events were headache and application site pruritus.

Table 13. Summary of Adverse Events (SES)

	NAFT-500 N=234	Vehicle (2wk) N=118	Naftin 1% N=236	Vehicle (4wk) N=119
All Adverse Events	47 (20.1%)	22 (18.6%)	43 (18.2%)	30 (25.2%)
Any treatment-emergent adverse events (TEAE)	47 (20.1%)	22 (18.6%)	43 (18.2%)	30 (25.2%)
Application site pruritus	7 (3.0%)	4 (3.4%)	1 (0.4%)	3 (2.5%)
Headache	10 (4.3%)	4 (3.4%)	9 (3.8%)	3 (2.5%)
Application site irritation	4 (1.7%)	3 (2.5%)	4 (1.7%)	5 (4.2%)
Pain	4 (1.7%)	3 (2.5%)	2 (0.8%)	0 (0%)

Source: Sponsor's study report, page 69-70.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The majority of the FAS subjects (approximately 70-80%) were men in both trials.

- For the Tinea Cruris trial, male subjects had higher complete cure rates than females.
- For the Tinea Pedis trial, female subjects had higher complete cure rates than males.

However, it should be noted that the number of female subjects is small in both trials.

While the NAFT-500 had higher response rates compared to those of the vehicle arm among those subjects who were classified as 'white' or 'other', the complete cure rates were similar across the treatment arms among the 'black' subjects.

While the study was designed to enroll subjects 12 years of age and older, only 4 subjects (2 in each study) were enrolled between the ages of 12 and 17, and only a small number of geriatric subjects were enrolled.

All subjects were from the United States.

Table 14. Complete cure rates (1) by gender, race and age (Tinea Cruris)

	NAFT-500 N=75	Vehicle N=71
Gender		
Male	17/63 (27.0 %)	2/55 (3.6%)
Female	2/12 (16.7 %)	0/16 (7.3%)
Race		
White	8/34 (23.5%)	2/33 (6.1%)
Black	3/14 (21.4%)	0/12 (0 %)
Other	8/27 (29.6%)	0/26 (0 %)
Age		
12-17	0/2 (0%)	-
18-65	18/65 (27.7%)	1/62 (1.6%)
≥ 65	1/8 (12.5%)	1/9 (11.1%)

(1) Complete Cure is defined as having negative mycology results (dermatophyte culture and KOH) and absence of erythema, scaling and pruritus at Week 4. FAS, LOCF.
Source: Sponsor's study report, page 134-142.

Table 15. Complete cure rates (1) by gender, race and age (Tinea Pedis)

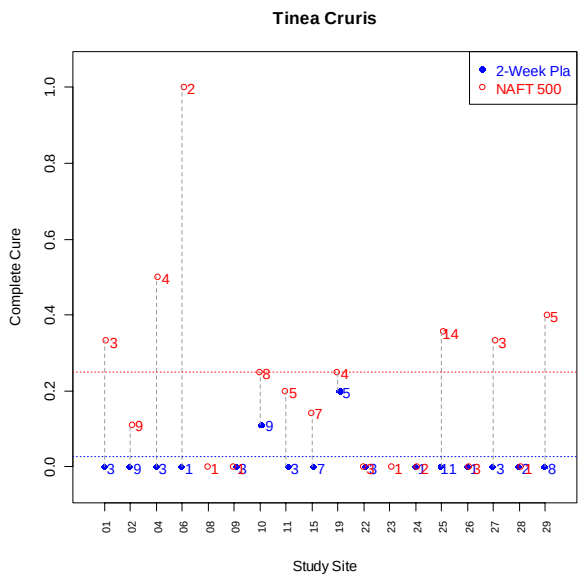
	NAFT-500 N=147	Vehicle N=70
Gender		
Male	16/106 (15.1%)	5/50 (10.0%)
Female	10/31 (24.4%)	0/20 (0 %)
Race		
White	18/78 (23.1%)	2/42 (4.9%)
Black	7/65 (10.8%)	3/27 (11.1%)
Other	1/4 (25.0%)	0/2 (0 %)
Age		
12-17	0/1 (0%)	1/1 (100%)
18-65	24/138 (17.4%)	4/68 (5.9%)
≥ 65	2/8 (25.0%)	0/1 (0 %)

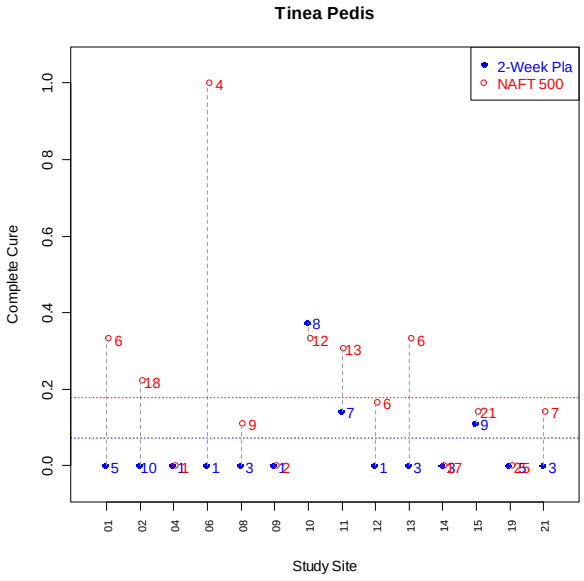
(1) Complete Cure is defined as having negative mycology results (dermatophyte culture and KOH) and absence of erythema, scaling and pruritus at Week 6. FAS, LOCF.
Source: Sponsor's study report, page 149-158.

Reference ID: 2983464

Efficacy by Center

The efficacy results were robust across the pooled study sites. In Tinea Cruris trial, even with Site 25 excluded, which has the most number of subjects with a relatively high treatment effect, the treatment effect was still statistically significant (p-value = 0.0025).





4.2 Other Special/Subgroup Populations

The Agency noted at the Pre-IND, Pre-NDA meetings as well as in the Advice Letter (see Section 2.1 for details) that safety and efficacy studies for tinea pedis should separately analyze efficacy for interdigital tinea pedis and for moccasin type tinea pedis.

Per the Agency's previous comments, the sponsor attempted to provide analyses by tinea pedis type. However, according to the sponsor's ISE report, "the tinea pedis study was not designed to treat a specific type of tinea pedis, rather, subjects were instructed to treat the affected area recorded at baseline, and investigators were instructed to evaluate the worst site at each visit (i.e., Week 2, 4, and 6). The protocol did not pre-specify a method for analyzing the separate types. Therefore, the sponsor proposed a post-hoc method where the clinical sites assessed for efficacy were treated and evaluated for either interdigital- or moccasin-type tinea pedis, or both, in the following manner".

Reference ID: 2983464

Table 16. Sponsor's Classification of Tinea Pedis Type

Type of tinea pedis diagnosed at baseline	Type of tinea pedis assessed at Week 6	Category of tinea pedis for assessment
Interdigital	Interdigital	Interdigital
Moccasin	Moccasin	Moccasin
Interdigital	Moccasin	Both interdigital and Moccasin
Moccasin	Interdigital	Both interdigital and Moccasin

Source: sponsor's table (page 97, ISE report)

According to the sponsor, "subjects who were not diagnosed or assessed for a specific type of tinea pedis at the screening and/or terminal visit were classified as having either interdigital or moccasin-type tinea pedis on a subject-by-subject basis using the recorded site of assessment". According to the sponsor, the most frequent sites of assessment included "left foot between 1st and 2nd toe" (classified as interdigital) and "right heel" (classified as moccasin). That is, for example, subjects noted at baseline to have both interdigital and moccasin tinea pedis could end up in either the interdigital, moccasin or "both" group depending on the recorded assessment site (see Appendix).

Using the sponsor's re-classification, the sponsor stated that the majority of subjects had the interdigital type as shown in the table below.

Table 17. Complete Cure Rates based on the 're-classified type' of Tinea Pedis

	NAFT-500 N=147	Vehicle N=70
Sponsor's analysis		
Both interdigital and moccasin	7/15 (46.7%)	0/4 (0%)
Interdigital only	16/98 (16.3%)	4/55 (7.3%)
Moccasin only	3/34 (8.8%)	1/11 (9.1%)

Source: Complete cure rates for each type of Tinea Pedis at baseline based on sponsor's re-classification, FAS, LOCF.

Because the study inclusion criteria did not specify the specific types of tinea pedis, the study not only included subjects who had interdigital and moccasin types, but also included "other" types of tinea pedis infections at baseline (acute vesicular and acute ulcerative tinea) which require systemic treatment according to the sponsor's ISE report (page 12).

Based on this reviewer's assessment of the dataset (fa.xpt), the sponsor's classification to the types of tinea pedis (i.e., interdigital, moccasin, or both) was subjective. The expanded table based on evaluating each subject in the fa.xpt dataset is presented in the Appendix. Because the report stated that the worst site at each visit (i.e., Week 2, 4, and 6) was evaluated, the sponsor's re-classification method would be difficult to justify. As such, as a sensitivity analysis, this reviewer analyzed the complete cure rates based on the '**original** baseline type of tinea pedis'.

Rather than reclassifying subjects based on multiple assessments, if the original baseline type is used, the following table still shows that the majority of subjects had the interdigital type with a

small number of subjects in moccasin and in the others types of tinea pedis. There is no complete cure among the subjects who had moccasin-type tinea pedis at baseline.

Table 18. Complete Cure Rates based on the 'original baseline type' of Tinea Pedis

	NAFT-500 N=147	Vehicle N=70
Reviewer's analysis		
Both interdigital and moccasin	13/65 (20.0%)	2/32 (6.3%)
Interdigital	12/57(21.1%)	3/29 (10.3%)
Moccasin	0/12 (0 %)	0/3 (0 %)
Others	1/13 (7.7%)	0/6 (0 %)

Source: Complete cure rates for each type of Tinea Pedis at baseline based on sponsor's original classification of tinea pedis, FAS, LOCF.

While the Agency previously commented that the sponsor separately analyze efficacy and safety for each type of tinea pedis, the sponsor stated that for their Phase 3 trial, "the tinea pedis study was not designed to treat a specific type of tinea pedis, rather, subjects were instructed to treat the affected area recorded at baseline, and investigators were instructed to evaluate the worst site at each visit (i.e., Week 2, 4, and 6)." As noted by the sponsor, the study was not designed to include a pre-specified type of tinea pedis nor a target area for each subject to be followed. As a result, the tinea pedis type at baseline was not required to be followed throughout Week 6 assessment.

As other sensitivity analyses, this reviewer:

- matched the tinea pedis type at baseline and that at Week 6
- matched subjects with either the 'same' classification or a 'better' classification (e.g., interdigital at baseline vs. interdigital + none at Week 6 or both at baseline vs. both + interdigital + moccasin + none at Week 6)

Reviewer's analysis by matching the types at baseline and at Week 6 showed that;

- approximately 30% of the subjects had interdigital for both NAFT-500 and vehicle arms (see Table 20) at both timepoints.
- less than 6% of the subjects had moccasin type of tinea pedis at both timepoints.
- approximately 19% and 33% of subjects had both interdigital and moccasin for NAFT-500 and vehicle, respectively at both timepoints.

Reference ID: 2983464

Table 19. Matching of the Types of Tinea Pedis at baseline and at Week 6 (FAS)

	NAFT-500 (N=147)						
	Week 6						
Baseline	**Both**	**Interdigital**	**Moccasin**	**None**	**Other**	**Missing**	**Total**
Both	28	16	12	4	2	3	65
Interdigital	2	44	2	3	0	6	57
Moccasin	1	0	9	0	0	2	12
Other	2	4	0	1	5	1	13
Total	33	64	23	8	7	12	147

	Vehicle (N=70)						
	Week 6						
Baseline	**Both**	**Interdigital**	**Moccasin**	**None**	**Other**	**Missing**	**Total**
Both	23	6	0	1	0	2	32
Interdigital	0	21	0	2	1	5	29
Moccasin	1	0	2	0	0	0	3
Other	2	3	0	0	1	0	6
Total	26	30	2	3	2	7	70

Source: Reviewer's table

Table 20 shows the response rates of NAFT-500 and vehicle for those subjects whose types of tinea pedis match at baseline and at Week 6 (i.e., "Same"), and for those subjects who may have improved (i.e., "Better") at Week 6.

Table 20. Complete Cure Rates based on the subjects whose types of tinea pedis match (or improve) at baseline and at Week 6 (FAS)

	Baseline	Week 6 classification	NAFT-500 (N=147)	Vehicle (N=70)
Same	**Interdigital**	**Interdigital**	9/44 (20.5%)	1/21 (0.1%)
	Moccasin	**Moccasin**	0/9 (0 %)	0/2 (0%)
	Both	**Both**	1/28 (3.6%)	0/23 (0%)
Better	**Interdigital**	**Interdigital + None**	12/47 (25.5%)	3/23 (13.0%)
	Moccasin	**Moccasin + None**	0/9 (0%)	0/2 (0%)
	Both	**Both + Interdigital + None**	10/48 (20.8%)	2/30 (6.7%)
	Both	**Both + Moccasin + None**	7/44 (15.9%)	1/24 (4.2%)
	Both	**Both + Interdigital + Moccasin + None**	12/60 (20%)	2/30 (6.7%)

Source: Reviewer's analysis based on matching FAS subjects with either the 'same' classification or a 'better' classification. Types of tinea pedis matched are those at baseline and those at Week 6. LOCF.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The sponsor conducted two studies with NAFT-500, one in tinea cruris, and one in tinea pedis. Both studies demonstrated significance for the primary efficacy endpoint of complete cure. However, for the tinea pedis study, while the Agency previously commented that the sponsor separately analyze efficacy and safety for each type of tinea pedis, the study's inclusion criteria did not specify the specific types of tinea pedis, and included subjects with all types of tinea pedis (i.e., interdigital, moccasin, and others). Further, the protocol did not pre-specify a way of analyzing the separate types of tinea pedis. Therefore, to address the Agency's comments concerning separate analysis based on tinea pedis types, the sponsor re-classified each subject to interdigital, moccasin or both. However, the sponsor's method of reclassification was found to be inconsistent and somewhat subjective. An analysis using the baseline classification of subjects (interdigital, moccasin, both, or other) showed that most subjects in the study had either interdigital only or interdigital and moccasin tinea pedis at baseline. The complete clearance rates by baseline classification are given below.

Table 21. Complete Cure Rates based on the 'original baseline type' of Tinea Pedis

	NAFT-500 N=147	**Vehicle N=70**
Reviewer's analysis		
Both interdigital and moccasin	13/65 (20.0%)	2/32 (6.3%)
Interdigital	12/57(21.1%)	3/29 (10.3%)
Moccasin	0/12 (0 %)	0/3 (0 %)
Others	1/13 (7.7%)	0/6 (0 %)

Source: Complete cure rates for each type of Tinea Pedis at baseline based on sponsor's original classification of tinea pedis, FAS, LOCF.

5.2 Conclusions and Recommendations

The Tinea Cruris study demonstrated statistical significance ($p<0.001$) with response rates of 25.3% and 2.8% for NAFT-500 and vehicle, respectively; and the Tinea Pedis study demonstrated statistical significance ($p=0.01$) with response rates of 17.7% and 7.1% for NAFT-500 and vehicle, respectively (see Table 1). It should be noted that while the sponsor is seeking approval for subjects 12 years and older; however, only 2 subjects (<0.01%) in each study at baseline were between the ages of 12 and 17 years.

For the Tinea Pedis study, approximately 40%, 6% and 45% of FAS subjects across the treatment arms were classified as having interdigital, moccasin and both types of tinea pedis at baseline, respectively. However, because the study was not designed to evaluate the complete cure rates of individual type of tinea pedis (i.e., interdigital, moccasin), and because the number of sample size is small within each type of tinea pedis, it would be difficult to draw conclusions regarding the complete cure rates of each type of tinea pedis based on the sponsor's study.

APPENDIX

Classification of Tinea Pedis by Matching the Baseline Type and the Week 6 Type of Tinea Pedis

2-Week Placebo (N=70)

Baseline classification	Week 6 INTERDIGITAL[1]						Week 6 MOCCASIN[1]						Week 6 BOTH[1]					
	Missing[2]	B[2]	I[2]	M[2]	N[2]	O[2]	missing[2]	B[2]	I[2]	M[2]	N[2]	O[2]	missing[2]	B[2]	I[2]	M[2]	N[2]	O[2]
Both Interdigital and Moccasin	1 (1.4%)	13 (18.6%)	6 (8.6%)	0	0	0	0	7 (10%)	0	0	1 (1.4%)	0	1 (1.4%)	3 (4.3%)	0	0	0	0
Interdigital	5 (7.2%)	0	21 (30%)	0	2 (2.9%)	1 (1.4%)	0	0	0	0	0	0	0	0	0	0	0	0
Moccasin	0	0	0	0	0	0	0	1 (1.4%)	0	2 (2.9%)	0	0	0	0	0	0	0	0
Other	0	2 (2.9%)	3 (4.3%)	0	0	1 (1.4%)	0	0	0	0	0	0	0	0	0	0	0	0

NAFT-500 (N=147)

Baseline classification	Week 6 INTERDIGITAL[1]						Week 6 MOCCASIN[1]						Week 6 BOTH[1]					
	Missing[2]	B[2]	I[2]	M[2]	N[2]	O[2]	missing[2]	B[2]	I[2]	M[2]	N[2]	O[2]	missing[2]	B[2]	I[2]	M[2]	N[2]	O[2]
Both Interdigital and Moccasin	2 (1.4%)	15 (10.2%)	15 (10.2%)	0	1 (0.7%)	0	1 (0.7%)	9 (6.1%)	0	10 (6.8%)	1 (0.7%)	1 (0.7%)	0	4 (2.7%)	1 (0.7%)	2 (1.4%)	2 (1.4%)	1 (0.7%)
Interdigital	6 (4.1%)	2 (1.4%)	44 (29.9%)	0	1 (0.7%)	0	0	0	0	0	0	0	0	0	0	2 (1.4%)	2 (1.4%)	0
Moccasin	0	0	0	0	0	0	2 (1.4%)	1 (0.7%)	0	9 (6.1%)	0	0	0	0	0	0	0	0
Other	1 (0.7%)	2 (1.4%)	3 (2.1%)	0	1 (0.7%)	5 (3.4%)	0	0	0	0	0	0	0	0	1 (0.7%)	0	0	0

Source: Sponsor's dataset (fa.xpt)

(1) Final classification of tinea pedis by the sponsor

(2) Classification of tinea pedis at Week 6

color codes: Baseline type and Week 6 type match

Baseline type and Week 6 type do not match

B: both interdigital and moccasin

I: interdigital ; M: moccasin; N: none; O: other

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Carin Kim, Ph.D.
Date: August 3, 2011

Concurring Reviewer(s):

Statistical Team Leader: Mohamed Alosh, Ph.D.

Biometrics Division Director: Stephen Wilson, Dr.PH

cc:
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Mohamed Alosh, Ph.D.
Stephen Wilson, Dr.P.H.
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/s/

CARIN J KIM
08/03/2011

KATHLEEN S FRITSCH
08/03/2011
signing for Mohamed Alosh; concur with review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019599Orig1s011

MICROBIOLOGY/VIROLOGY REVIEW(S)

Date Received by CDER: 16 December 2010
Date Assigned: 7 July 2011
Date Review Completed: 22 July 2011
Reviewer: Kerry Snow

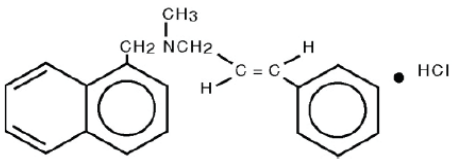
APPLICANT

Merz Pharmaceuticals, LLC
4215 Tudor Lane
Greensboro, NC 27410

Contact: Dr. Bhushan Hardas, MD, MBA, VP and Head of US R&D
336-217-2322

DRUG PRODUCT NAME

Code name: NAFT-500 Cream, 2%
Established name: Naftifine HCl cream, 2%
Proprietary name: Naftin (b) (4)
Chemical name: (E)-N-Cinnamyl-N-methyl-1-naphthalenemethylamine hydrochloride
Molecular formula: $C_{21}H_{21}N \bullet HCl$
Molecular weight: 328.86
Chemical structure:



PROPOSED INDICATION

Treatment of tinea pedis, tinea cruris, and tinea corporis

PROPOSED DOSAGE FORM, STRENGTH, ROUTE OF ADMINISTRATION AND DURATION OF TREATMENT

Dosage form: cream
Route of administration: topical
Strength: 2%
Dosage: to be applied onto affected area plus a ½ inch margin of healthy surrounding skin once-daily for two weeks

DISPENSED

Rx

RELATED DOCUMENTS

NDA 19599 (Naftin 1% cream) 1988 approval, NDA 19356 (Naftin 1% gel) 1990 approval
IND 77530; IND 105603; NDA 19359
DMF [redacted] (b) (4)
DMF [redacted] (b) (4)

REMARKS

The Applicant has submitted an NDA Efficacy Supplement (NDA 19599 SN 0004) for approval to market naftifine hydrochloride cream, 2% (Naftin® [redacted] (b) (4) The currently marketed product, under NDA 19599, is Naftin® Cream 1%. Naftin [redacted] (b) (4) was developed "to provide shorter treatment duration and better dosing schedule for tinea pedis, tinea cruris, and tinea corporis", compared to the 1% naftifine formulation (2 weeks of treatment vs. 4 weeks of treatment). The 2% formulation differs from the 1% formulation only in the concentration of naftifine hydrochloride and the [redacted] (b) (4) [redacted] The 1% naftifine gel and cream formulations were approved for the treatment of *Trichophyton rubrum*, *T. mentagrophytes*, and *Epidermophyton floccosum*. In addition, the 1% gel formulation was approved for the treatment of *Trichophyton tonsurans*.

CONCLUSIONS

The Applicant has provided data from recent in vitro studies that demonstrate the antifungal activity of naftifine against fungal isolates commonly associated with tinea pedis and tinea cruris, including *Trichophyton rubrum*, *T. mentagrophytes*, and *Epidermophyton floccosum*. MIC_{90} values, as determined in three in vitro studies, against all of the above pathogens, were ≤ 1 mcg/mL. Fungicidal activity, defined by the investigators as "a ≥ 99.9% reduction in the number of CFU/mL from the starting inoculum count" was demonstrated against 100% of *T. rubrum* isolates tested (n = 50). Fungicidal activity against isolates of *T. mentagrophytes* (n = 50), as determined in this investigation, was less robust, with only 78% of isolates identified as inhibited at the stated criteria.

Data from the two pivotal clinical trials supports the Applicant's claim of mycological cure associated with NAFT-500 Cream, 2% treatment in cases of tinea pedis and tinea cruris caused by isolates of *Trichophyton rubrum*, compared to treatment with placebo, and of NAFT-500 Cream, 2% (2 week treatment) in cases of tinea pedis caused by isolates of *T. rubrum*, compared to the currently marketed product (4 week treatment). [redacted] (b) (4)

The Applicant did not attempt an analysis of antifungal resistance observed during the clinical trials. Susceptibility results obtained for selected isolates indicated that NAFT-500 was active, in vitro, against all isolates of *T. rubrum* tested. (b) (4)

The following changes to the proposed label are recommended:

- Section 1 (Indications and Usage): delete "… (b) (4) (b) (4) ".
  Rationale: (b) (4) in the proposed label.
- Section 12.4 (Mechanism of Action): add "The inhibition of ergosterol synthesis and the accumulation of toxic concentrations of squalene in the cell may result in death of the fungal cell."
  Rationale: Information provides a proposed cause of cell death.
- Section 12.4 (Mechanism of Resistance): add section heading with the following sentence, "To date, a mechanism of resistance to naftifine has not been described."
  Rationale: Labels for anti-infective products should address the issue of microbial resistance.
- Section 12.4: delete the second paragraph and add
  "Naftifine has been shown to be active against most isolates of the follow fungi, both in vitro and in clinical infections, as described in the INDICATIONS AND USAGE section:
  Trichophyton rubrum"
  Rationale: Paragraph two contains information that is irrelevant (b) (4) , confusing (b) (4) and potentially misleading (b) (4) The suggested wording for the description of antifungal activity is in keeping with current thinking, regarding the labeling of anti-infective products.

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

INTRODUCTION

Tinea pedis is most commonly caused by *Trichophyton rubrum* or *Trichophyton mentagrophytes* (*Trichophyton interdigitale*). *Epidermophyton floccosum* may be a rare cause [Murray 2007]. Chronic varieties of the infection (including "moccasin foot") are more frequently associated with *T. rubrum*, where the more inflammatory varieties (including those that produce vesicles or blisters) are associated with *T. mentagrophytes*.

Diagnosis of tinea pedis is usually by physical examination, in combination with laboratory findings. Direct microscopic examination (KOH/calcofluor prep) and fungal culture increase the sensitivity and specificity of the diagnosis, and are particularly important if oral treatment is considered [Gorbach 2004].

Interdigital tinea pedis, including inflammatory varieties, are typically treated with topical creams and ointments including terbinafine, imidazoles, undecenoic acid, and tolnaftate. Topical therapy is generally continued for 2-4 weeks. "Dry type" infections, including "moccasin foot" are usually difficult to treat with topical antimicrobials and frequently require oral medications including oral terbinafine (250 mg/day for 2-4 weeks), itraconazole (400 mg/day for 1 week per month), and fluconazole (200 mg weekly for 4-8 weeks) [Mandell 2005].

Trichophyton rubrum and *Epidermophyton floccosum* are the fungal pathogens most commonly associated with tinea cruris. Adult men are more commonly affected than women, and the infection is rare in children [Nadalo 2006]. Tinea cruris is commonly treated with a topical fungicidal allylamines or a topical azole antifungal.

Tinea corporis is rarely diagnosed in temperate climates [Mandell 2010]. Infections caused by zoophilic dermatophytes (e.g. *Microsporum canis* and *Trichophyton verrucosum*) are typically associated with more inflammatory lesions than those caused by anthropophilic fungi (e.g. *T. rubrum*). First line treatment for tinea corporis includes topical antifungals, typically a terbinafine or imidazole cream or ointment. In cases of inflammatory infections, oral treatment can include terbinafine, itraconazole, or fluconazole in cases involving small, well-defined lesions, and griseofulvin in cases of larger lesions [Mandell 2010].

Naftifine hydrochloride is a synthetic allylamine derivative. The allylamine antifungals (including terbinafine, butenafine, and naftifine) are fungicidal agents that act by inhibiting squalene epoxidase, a critical enzyme in the biosynthesis of ergosterol (a component of the fungal cell membrane). The allylamines are lipophilic, have broad spectrum activity against dermatophytes, and may have inherent anti-inflammatory activity [Kyle 2004, Gupta 2008, Marks 2010].

MECHANISM OF ACTION

The exact mechanism of antifungal action of naftifine is unknown, but investigations suggest that the drug inhibits squalene epoxidase, a key enzyme in biosynthetic pathway responsible for the formation of cell membrane precursors. Interruption of this step (conversion of squalene to squalene-2,3 oxide) results in the buildup of squalene in cell membranes, cell wall damage, and cell death.

The Applicant has performed no new studies of the mechanism of action of naftifine.

ANTIMICROBIAL SPECTRUM OF ACTIVITY

The Applicant has included several study reports from investigations designed to describe the in vitro antifungal activity of naftifine.

A study titled "Evaluation of the Antifungal Activity of Naftifine Against Agents of Tinea Corporis, Tinea Pedis, and Tinea Cruris, As Measured by Minimum Inhibitory and Fungicidal Concentration", was conducted in 2007 by the Center for Medical Mycology (Cleveland, OH). Testing was performed according to methods approved by CLSI (M27A2 for testing of *Candida albicans* and M38A for testing of dermatophytes), with appropriate quality control performed on each day of testing. Twenty-five isolates of each species (*C. albicans*, *Trichophyton rubrum*, *T. mentagrophytes*, *T. tonsurans*, *Microsporum canis*, and *Epidermophyton floccosum*) were tested against naftifine hydrochloride. In this investigation, minimum inhibitory concentration (MIC) was defined as the lowest concentration of the antifungal exhibiting 80% reduction in tested dermatophytes, compared to the growth control. Minimum fungicidal concentration (MFC) was defined as the minimum antifungal concentration that resulted in >99.9% reduction in the number of CFU/mL from the starting inoculum count. The results are summarized in Tables 1 and 2. The MIC_{range} for all dermatophytes tested was 0.03 – 1.0 mcg/mL, with an MIC_{90} of 0.25 mcg/mL. The MFC_{range} for dermatophytes was 0.06 - >32 mcg/mL, with an MFC_{90} of >32 mcg/mL. The fungicidal activity of naftifine was more pronounced for *Trichophyton* species, and less so for isolates of *E. floccosum* and *M. canis*. Naftifine was less active, generally, against isolates of *C. albicans*.

Table 1: Naftifine MIC values

Naftifine MIC Values (in µg/mL) against Dermatophytes and *Candida albicans*						
	E. floccosum	*M. canis*	*T. mentagrophytes*	*T. rubrum*	*T. tonsurans*	*C. albicans*
Range (n=25)	0.12	0.12 - 0.25	0.03 - 1	0.015 - 0.06	0.03 - 0.12	8 - >64
MIC_{50}	0.12	0.12	0.06	0.03	0.06	16
MIC_{90}	0.12	0.25	1	0.06	0.12	>64

Source: Report CMM#07-01

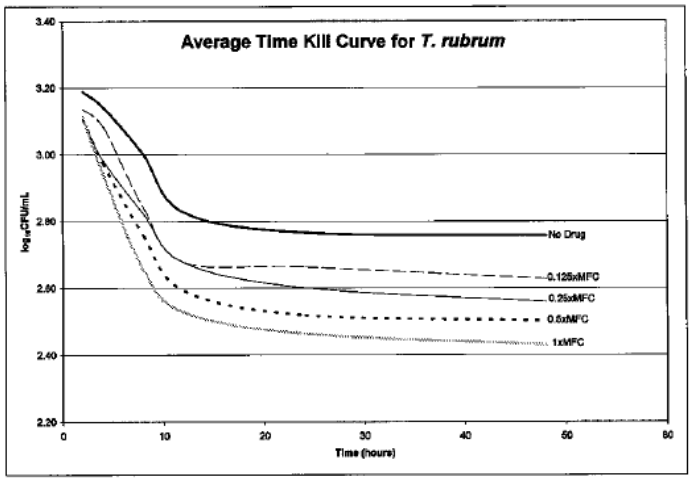
Table 2: Naftifine MFC values

Naftifine MFC Values (in µg/mL) against Dermatophytes and *Candida albicans*						
	E. floccosum	*M. canis*	*T. mentagrophytes*	*T. rubrum*	*T. tonsurans*	*C. albicans*
Range (n=25)	0.5 ->32	0.5 - >32	0.12 - >32	0.06 - 0.25	0.06 - >0.5	>64
MFC_{50}	8	>32	0.25	0.12	0.12	>64
MFC_{90}	>32	>32	8	0.12	0.5	>64

Source: Report CMM#07-01

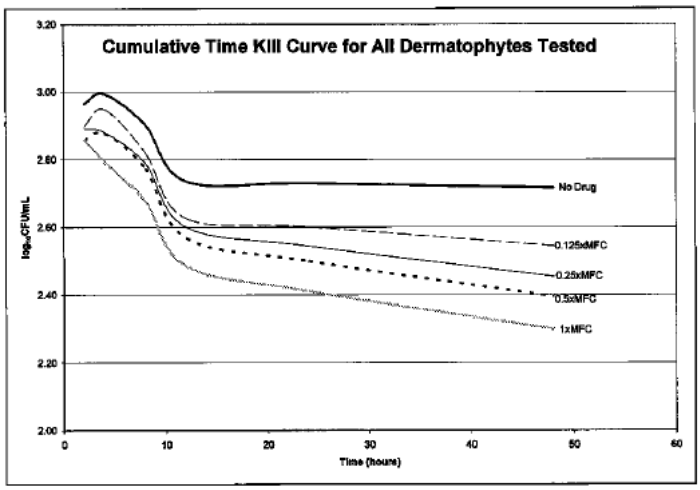
In the second referenced study, also performed at the Center for Medical Mycology in 2007, investigators employed a time-kill assay to determine the antifungal activity of naftifine hydrochloride. In the experiment, suspensions of fungi were added to concentrations of naftifine hydrochloride at 0.125, 0.25, 0.5, and 1 times the MFC for each isolate. Aliquots were removed at timed intervals, diluted with saline, and plated in duplicate on solid media. Colony counts were determined after 4 days, following incubation at 30°C. The results are summarized in Figures 1 and 2. The investigators noted dose-dependent inhibition of growth, against all species tested. At the highest tested concentration (1 x MFC), however, inhibition by the test drug (against all tested species) was apparently < 0.5 $\log_{10}$ CFU/mL greater than that of control (no drug).

Figure 1: Time-kill curve for *Trichophyton rubrum* (n = 4)



Source: Report CMM#07-02

Figure 2: Time-kill curve for all dermatophytes tested (n = 12)



Source: Report CMM#07-02

In a third in vitro study, referenced by the Applicant, investigators at the Center for Medical Mycology repeated Study CMM-07-01 (described above), using 25 additional clinical isolates of *T. rubrum*, *T. mentagrophytes*, *T. tonsurans*, *M. canis*, and *E. floccosum* (125 total isolates). The results are summarized in Table 3. All MIC_{90} values were < 1 mcg/mL. Naftifine had marked fungicidal activity against isolates of *T. rubrum* (the most common etiologic agent associated with dermatologic infections). Fungicidal activity was demonstrated against 100% of the *T. rubrum* isolates tested, and 78% of the *T. mentagrophytes* isolates tested.

Table 3: MIC/MFC values of naftifine against dermatophytes (mcg/mL)

Species	MIC			MFC		
	Range	MIC50	MIC90	Range	MFC50	MFC90
E. floccosum	0.12-0.25	0.12	0.12	0.5->64	8.0	64
M. canis	0.03-0.5	0.12	0.25	0.5->64	>32	>64
T. mentagrophytes	0.03-1.0	0.06	0.5	0.12->32	0.5	4.0
T. rubrum	0.015-0.25	0.06	0.06	0.06-0.25	0.12	0.25
T. tonsurans	0.03-0.12	0.06	0.06	0.06->0.5	0.25	>0.5

Source: Report CMM#07-01d

RESISTANCE STUDIES

The Applicant has referenced a study performed by the Center for Medical Mycology in 2008, designed to investigate the development of antifungal resistance to naftifine hydrochloride in species of dermatophytes. In this study, 3 clinical isolates of *T. mentagrophytes* and 3 clinical isolates of *T. tonsurans* were exposed to naftifine hydrochloride at 0.5 x MIC, 1 x MIC, 2 x MIC, and 4 x MIC in RPMI-1640 for four days. Tubes were centrifuged and the sediment plated for growth. Recovered isolates were re-tested to determine their naftifine MIC. The procedure was performed in duplicate, for a total of 15 passages. Resistance to naftifine was defined as in increase in MIC > 3 dilutions. The investigators determined that "the MICs of all isolates remained constant

throughout the serial passages. No isolate had an increase in MIC of more than three dilutions, demonstrating that no development of resistance took place during the study."

ANIMAL AND HUMAN STUDIES

ANIMAL MODELS OF INFECTION

The Applicant has referenced several studies performed to investigate the efficacy of naftifine in a guinea pig model. In an early study of naftifine efficacy [Petranyi 1984], animals were infected with *Trichophyton mentagrophytes* by skin abrasion. Lesions were allowed to develop for 11-15 days, then treated on 7 consecutive days with topical preparations of naftifine 0.015 %, 0.03%, and 0.06% (with controls). In this investigation, 100% of animals (n=8) treated with 0.06% naftifine demonstrated mycological cure (hair culture negative 1-3 days following last treatment).

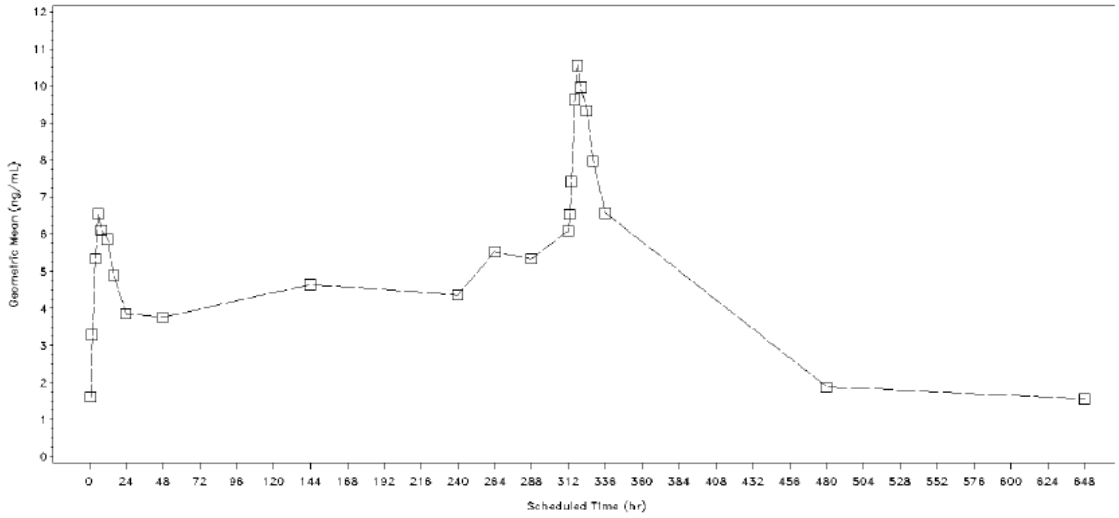
In a review of topical therapy for superficial fungal infections [Brennan 1997], the authors summarized a study of naftifine efficacy in guinea pig models. In this experiment, Hare and Loebenberg [Hare 1998] demonstrated greater efficacy of tested allylamines (including naftifine) (74% to 100% inhibition), compared to imidazoles (54% to 73% inhibition), against infections of *T. mentagrophytes*.

The Applicant has performed no new studies designed to investigate the antifungal efficacy of naftifine in animal models.

HUMAN PHARMACOLOGIC STUDIES

The Applicant has summarized pharmacokinetic findings from a maximal use study (Study MRZ 90200/FI/1002 CSR). In this investigation, 21 subjects were treated topically with 8 g of NAFT-500 Cream, 2% once daily for 14 days (Figure 1). Detectable plasma levels were demonstrated in all subjects in less than 1 hour, with increasing levels from Day 1 (geometric mean 7 ng/mL; CV% 55.6) to Day 14 (geometric mean 11 ng/mL; CV% 29.3). The AUC_{0-24} (geometric mean) on Day 1 was 117 ng*hr/mL (CV% 41.2), and the AUC_{0-t} (geometric mean) on Day 14 was 204 ng*hr/ml (CV% 28.5).

Figure 1: Geometric mean plasma concentrations of NAFT-500 Cream, 2% by time (maximal-use study)



Source: This submission; module 2.5 page 14

CLINICAL TRIALS

The Applicant has presented data from two pivotal, Phase 3 studies, designed to investigate the safety and efficacy of NAFT-500 Cream, 2% in the treatment of tinea pedis and tinea cruris in adolescents and adults.

Study MUS 90200-0736/1

Study MUS 90200-0736/1, entitled "A Phase 3 Double-Blind, Randomized, Placebo-Controlled, Multicenter, Parallel Group Evaluation of the Efficacy and Safety of NAFT-500 in Subjects with Tinea Pedis", occurred between August 2008 (first enrollment) and August 2009 (last subject completed). The study was a 6-week trial, evaluating the safety and efficacy of NAFT-500 Cream, 2% compared to vehicle (placebo) and to commercially available Naftin 1% Cream in the treatment of tinea pedis in male and nonpregnant females ≥ 12 years of age. The study had two primary objectives:

- To compare the proportion of complete cure (clinical cure + mycological cure) at Week 6 (4 weeks following 2 weeks of treatment) between NAFT-500 Cream, 2% and 2-week placebo
- To compare the proportion of complete cure (clinical cure + mycological cure) at Week 6 (2 weeks following 4 weeks of treatment) between Naftin 1% Cream and 4-week placebo.

A total of 709 patients were enrolled in the study and randomized 2:2:1:1 to NAFT-500 Cream 2% (2 week treatment, n = 235), Naftin 1% Cream (4 week treatment, n = 237), 2-week placebo (n = 118), or 4-week placebo (n = 119). Qualifying subjects were those screened subjects with clinical evidences of tinea pedis, confirmed by KOH and dermatophyte culture. The assigned study drug was applied by the subjects to the affected areas. Primary and secondary analyses were based on results recorded in the Per-protocol set (PPS), defined as the subset of subjects in the Full-analysis set (FAS) without major protocol deviations, or the FAS population, defined as the subset of subjects with a positive culture at baseline for whom the primary efficacy endpoint was available.

Mycological procedures (KOH and dermatophyte culture) were performed at each of four study visits (Day 1, Week 2 ± 3 days, Week 4 ± 3 days, Week 6 ± 3 days). KOH interpretation was performed both by the local investigator and the central laboratory. A complete study report from the central laboratory was not included in this submission.

Complete cure was defined as "negative mycology results from the central laboratory (dermatophyte culture and KOH) and absence of erythema, scaling, and pruritis (grade 0 for each).

Results for the complete cure rate in all study arms are summarized in Table 4. Rates were statistically equivalent between the two active arms vs. corresponding placebo arms, and active treatment was superior to placebo in both parallel groups.

Table 4: Complete Cure Rate (LOCF) – Primary Analysis (FAS)

	Complete Cure[a]	NAFT-500 (N = 147) n (%)	2-Week Placebo (N = 70) n (%)	Naftin 1% (N = 143) n (%)	4-Week Placebo (N = 65) n (%)
Visit 2 (Week 2)	Yes	4 (2.7)	0	3 (2.1)	0
	No	143 (97.3)	70 (100.0)	140 (97.9)	65 (100.0)
	Difference(97.5% CI)[b]	2.7 (0.1,+ ∞)		2.1 (-0.3, + ∞)	
	P-value[c]	0.100		0.097	
Visit 3 (Week 4)	Yes	6 (4.1)	1 (1.4)	5 (3.5)	1 (1.5)
	No	141 (95.9)	69 (98.6)	138 (96.5)	64 (98.5)
	Difference(97.5% CI)[b]	2.7 (-1.6, + ∞)		2.0 (-2.3, + ∞)	
	P-value[c]	0.234		0.143	
Visit 4 (Week 6)	Yes	26 (17.7)	5 (7.1)	23 (16.1)	2 (3.1)
	No	121 (82.3)	65 (92.9)	120 (83.9)	63 (96.9)
	Difference(97.5% CI)[b]	10.5 (1.9, + ∞)		13.0 (5.7, + ∞)	
	P-value[c]	0.010		0.001	
	P-value[d]	0.010		0.001	
	P-value[e]	0.581		0.640	

Data Source: End-of-Text Table 14.2.1.
Abbreviations: CI = confidence interval; KOH = potassium hydroxide.
Note 1: %=(n/Total number of subjects with non-missing data at each visit)x100.
Note 2: For the most important secondary efficacy variables (NAFT-500 vs placebo at 4 weeks), statistical significance will be assessed using the Hochberg procedure.
[a] Mycological Cure: Negative KOH and negative culture.
[b] Treatment Effectiveness: Negative KOH, negative culture, and Erythema, Scaling and Pruritus grades of 0 or 1.
[c] One-sided 97.5% CI calculated using normal approximation to the binomial for the difference in proportion of 'yes' responses between NAFT-500 and placebo.
[d] *P*-value is from a one-sided Cochran-Mantel-Haenszel (CMH) test comparing NAFT-500 group vs placebo group, with pooled clinical site as the stratification variable.
[e] Adjusted *P*-value from Hochberg's step-up procedure.
Source: This submission, Module 5.3.5.1.3, page 52

Mycological cure rates and treatment effectiveness (negative KOH + negative dermatophyte culture + erythema, scaling, and pruritis grades of 0 or 1) are summarized in Table 5. At the Week 6 visit (Visit 4), mycological cure (negative KOH + negative dermatophyte culture) was achieved in 67.3% of subjects in the NAFT-500 Cream, 2% arm (n = 99), compared to 71.3% of subjects in the Naftin 1% Cream arm. Both active treatment arms were superior to their corresponding control (placebo) arms.

Table 5: Mycological Cure and Treatment Effectiveness (LOCF) – Secondary Analysis (FAS)

		NAFT-500 (N = 147) n (%)	2-Week Placebo (N = 70) n (%)	Naftin 1% (N = 143) n (%)	4-Week Placebo (N = 65) n (%)
Mycological Cure[a]					
Visit 2 (Week 2)	Yes	41 (27.9)	13 (18.6)	45 (31.5)	12 (18.5)
	No	106 (72.1)	57 (81.4)	98 (68.5)	53 (81.5)
	Difference(97.5% CI)[c]	9.3 (-2.3, +)		13.0 (0.9, +)	
	P-value[d]	0.049		0.028	
Visit 3 (Week 4)	Yes	79 (53.7)	14 (20.0)	76 (53.1)	6 (9.2)
	No	68 (46.3)	56 (80.0)	67 (46.9)	59 (90.8)
	Difference(97.5% CI)[c]	33.7 (21.4, +)		43.9 (33.1, +)	
	P-value[d]	<0.001		<0.001	
Visit 4 (Week 6)	Yes	99 (67.3)	15 (21.4)	102 (71.3)	14 (21.5)
	No	48 (32.7)	55 (78.6)	41 (28.7)	51 (78.5)
	Difference(97.5% CI)[c]	45.9 (33.7, +)		49.8 (37.3, +)	
	P-value[d]	<0.001		<0.001	
	P-value[e]	<0.001			
Treatment Effectiveness[b]					
Visit 2 (Week 2)	Yes	21 (14.3)	9 (12.9)	25 (17.5)	4 (6.2)
	No	126 (85.7)	61 (87.1)	118 (82.5)	61 (93.8)
	Difference(97.5% CI)[c]	1.4 (-8.2, +)		11.3 (2.8, +)	
	P-value[d]	0.460		0.011	
Visit 3 (Week 4)	Yes	52 (35.4)	7 (10.0)	51 (35.7)	4 (6.2)
	No	95 (64.6)	63 (90.0)	92 (64.3)	61 (93.8)
	Difference(97.5% CI)[c]	25.4 (14.9, +)		29.5 (19.7, +)	
	P-value[d]	<0.001		<0.001	
Visit 4 (Week 6)	Yes	83 (56.5)	14 (20.0)	84 (58.7)	9 (13.8)
	No	64 (43.5)	56 (80.0)	59 (41.3)	56 (86.2)
	Difference(97.5% CI)[c]	36.5 (24.1, +)		44.9 (33.2, +)	
	P-value[d]	<0.001		<0.001	
	P-value[e]	<0.001			

Data Source: End-of-Text Table 14.2.6.
Abbreviation: CI = confidence interval; NE = nonestimable.
Note: %=(n/Total number of subjects with non-missing data at each visit-subgroup combination)x100.
[a] Complete cure = Negative mycology results from the central laboratory (dermatophyte culture and KOH) and absence of erythema, scaling and pruritus.
[b] One-sided 97.5% Confidence Interval calculated using normal approximation to the binomial for the difference in proportion of 'yes' responses between NAFT-500 Cream, 2% and 2-week or Naftin 1% Cream and 4-week placebo.
[c] *P*-value was from a one-sided Cochran-Mantel-Haenszel (CMH) test comparing NAFT-500 group or Naftin 1% group vs the corresponding placebo group, with pooled clinical site as the stratification variable.

Source: This submission, Module 5.3.5.1.3, page 54

Results of mycological analysis, conducted during the trial, are summarized in Table 6. The Applicant concluded that there were "no statistically significant differences in the proportion of negative dermatophyte and KOH cultures between the NAFT-500 Cream, 2% group vs. Naftin 1% Cream treatment group at the Week 6 visit (p=0.986 and p=0.963)."

Table 6: KOH and Dermatophyte Culture – Secondary Analysis (FAS)

Visit	Results	NAFT-500 (N = 147) n (%)	2-Week Placebo (N = 70) n (%)	Naftin 1% (N = 143) n (%)	4-Week Placebo (N = 65) n (%)
Dermatophyte Culture					
Visit 2 (Week 2)	Positive	8 (6.0)	40 (65.6)	13 (9.6)	29 (51.8)
	Negative	126 (94.0)	21 (34.4)	123 (90.4)	27 (48.2)
	P-value[a]	<0.001		<0.001	
	P-value[b]	0.348			
Visit 3 (Week 4)	Positive	13 (10.2)	36 (61.0)	9 (7.0)	36 (64.3)
	Negative	114 (89.8)	23 (39.0)	120 (93.0)	20 (35.7)
	P-value[a]	<0.001		<0.001	
	P-value[b]	0.448			
Visit 4 (Week 6)	Positive	7 (5.2)	38 (60.3)	6 (4.5)	41 (66.1)
	Negative	128 (94.8)	25 (39.7)	126 (95.5)	21 (33.9)
	P-value[a]	<0.001		<0.001	
	P-value[b]	0.986			
	P-value[c]	0.098			
KOH					
Visit 2 (Week 2)	Positive	89 (67.9)	44 (72.1)	90 (66.2)	41 (73.2)
	Negative	42 (32.1)	17 (27.9)	46 (33.8)	15 (26.8)
	P-value[a]	0.477		0.359	
	P-value[b]	0.922			
Visit 3 (Week 4)	Positive	49 (39.2)	37 (63.8)	53 (42.1)	37 (67.3)
	Negative	76 (60.8)	21 (36.2)	73 (57.9)	18 (32.7)
	P-value[a]	<0.001		0.002	
	P-value[b]	0.300			
Visit 4 (Week 6)	Positive	35 (27.3)	42 (66.7)	29 (22.7)	39 (63.9)
	Negative	93 (72.7)	21 (33.3)	99 (77.3)	22 (36.1)
	P-value[a]	<0.001		<0.001	
	P-value[b]	0.963			
	P-value[c]	0.033			

Data Source: End-of-Text Table 14.2.16.
Note: % = (n/N)x100.
[a] *P*-values were from the Cochran-Mantel-Haenszel (CMH) test, with clinical site as the stratification variable, comparing either NAFT-500 Cream, 2% group or Naftin 1% Cream group vs the corresponding placebo group.
[b] *P*-values were from the CMH test, with clinical site as the stratification variable, comparing NAFT-500 Cream, 2% group vs Naftin 1% Cream group at the same visit.
[c] *P*-values were from the CMH test, with clinical site as the stratification variable, comparing NAFT-500 Cream, 2% group at Week 4 vs Naftin 1% Cream group at Week 6.
Source: This submission, Module 5.3.5.1.3, page 62

The Applicant submitted a complete laboratory procedure manual describing all pertinent mycological procedures performed in the course of the clinical studies ([redacted] (b) (4) Laboratory Manual), including specimen collection methods, specimen packaging and shipping, KOH preparation and interpretation, culture techniques, and isolate identification.

No line list of fungal isolates, collected during the clinical trial at specific visits, is apparent in the submission, and no enumeration of "other" pathogens (dermatophytes other than *Trichophyton rubrum*) was provided in the study report. The majority of dermatophytes cultured in the course of the trial were identified as *T. rubrum* (371 isolates vs. 54 isolates identified as "other"). Subgroup (descriptive) analysis was performed to determine

complete cure by baseline pathogen (*T. rubrum* vs. "others"). This data is summarized in Table 7.

Table 7: Efficacy Analyses: Secondary and Sensitivity Analyses of the Primary Efficacy Endpoint Complete Cure Rate Subgroup Analyses (LOCF) – Secondary Analysis (Full Analysis Set)

Subgroup	Visit	Complete Cure[1]	NAFT-500 (N=147) n (%)	Placebo 2-Week (N=70) n (%)	Naftin 1% (N=143) n (%)	Placebo 4-Week (N=65) n (%)
Baseline Pathogen						
T. rubrum	Visit 2 (Week 2)	Yes	4 (3.1)	0	3 (2.4)	0
		No	125 (96.9)	60 (100.0)	120 (97.6)	59 (100.0)
		Difference(97.5% CI)[2]	3.1 (0.1,+∞)		2.4 (-0.3,+∞)	
		P-value[3]	0.093		0.095	
	Visit 3 (Week 4)	Yes	6 (4.7)	1 (1.7)	5 (4.1)	1 (1.7)
		No	123 (95.3)	59 (98.3)	118 (95.9)	58 (98.3)
		Difference(97.5% CI)[2]	3.0 (-1.9,+∞)		2.4 (-2.4,+∞)	
		P-value[3]	0.229		0.127	
	Visit 4 (Week 6)	Yes	24 (18.6)	3 (5.0)	21 (17.1)	2 (3.4)
		No	105 (81.4)	57 (95.0)	102 (82.9)	57 (96.6)
		Difference(97.5% CI)[2]	13.6 (4.9,+∞)		13.7 (5.6,+∞)	
		P-value[3]	0.003		0.002	
Other	Visit 2 (Week 2)	Yes	0	0	0	0
		No	18 (100.0)	10 (100.0)	20 (100.0)	6 (100.0)
		Difference(97.5% CI)[2]	NE (NE,NE)		NE (NE,NE)	
		P-value[3]	NE		NE	
	Visit 3 (Week 4)	Yes	0	0	0	0
		No	18 (100.0)	10 (100.0)	20 (100.0)	6 (100.0)
		Difference(97.5% CI)[2]	NE (NE,NE)		NE (NE,NE)	
		P-value[3]	NE		NE	
	Visit 4 (Week 6)	Yes	2 (11.1)	2 (20.0)	2 (10.0)	0
		No	16 (88.9)	8 (80.0)	18 (90.0)	6 (100.0)
		Difference(97.5% CI)[2]	-8.9 (-37.6,+∞)		10.0 (-3.1,+∞)	
		P-value[3]	0.326		0.207	

Note: %=(n/Total number of subjects with non-missing data at each visit-subgroup combination)x100. NE=nonestimable.
[1] Complete cure = Negative mycology results from the central laboratory (dermatophyte culture and KOH) and absence of Erythema, Scaling and Pruritus.
[2] One-sided 97.5% Confidence Interval calculated using normal approximation to the binomial for the difference in proportion of 'yes' responses between NAFT-500 and Placebo 2-Week or Naftin 1% and Placebo 4-Week.
[3] P-value is from a one-sided Cochran-Mantel-Haenszel (CMH) test comparing NAFT-500 group or Naftin 1% group versus the corresponding placebo group, with pooled clinical site as the stratification variable.
Data Source: Listings 9, 10 and 11.
Source: [redacted] (b) (4)

Susceptibility testing of selected isolates collected during the clinical trial was performed by the [redacted] (b) (4) No information describing the rationale for selection of isolates for susceptibility testing is apparent in the submission. The laboratory employed techniques approved by CLSI for susceptibility testing of filamentous fungi (M38-A2) and performed appropriate quality control on every day of testing. The NAFT-500 testing range was 0.03 – 16 mcg/mL. A 1-3 x 10^3 inoculum size was tested, with incubation of growth media for 4 days at 35°C. The investigator included a complete line list of all susceptibility tests in the submitted laboratory report. The results for Study MUS 90200-07361/1 (tinea pedis study) are summarized in Table 8.

Table 8: NAFT-500 susceptibility in isolates collected in Study MUS 90200-07361/1

	Trichophyton rubrum (59)	*T. mentagrophytes* (1)
MIC50	0.03	NA
MIC90	0.03	NA
Range	0.015-0.06	0.03

Source: This submission; Module 5.3.5.4 – Study us1-123

In this study, fungal isolates submitted to the [redacted] (b) (4) included 87 *Trichophyton rubrum* isolates, 3 *T. mentagrophytes* isolates, and 1 *Epidermophyton floccosum* isolate. Susceptibility testing was performed on 59 of the *T. rubrum* isolates, 1 of the *T. mentagrophytes* isolates, and not on the one isolate of *E. floccosum*. The remainder of the isolates were listed as "contaminated" and not tested for susceptibility to NAFT-500. No comparator drugs were tested and reported. No isolates could be identified in the submitted data that appeared to be from a single subject, collected at different visits, so no analysis of resistance to NAFT-500, observed during the clinical trial, could be proposed.

Study MRZ 902000/F1/3001

Study MRZ 90200/FI/3001, entitled "A Phase 3 Double-Blind, Randomized, Placebo-Controlled, Multicenter, Parallel Group Evaluation of the Efficacy and Safety of NAFT-500 in Subjects with Tinea Cruris", occurred between September 2008 (first enrollment) and August 2009 (last subject completed). The study was a 4-week trial, evaluating the safety and efficacy of NAFT-500 Cream, 2% compared to vehicle (placebo) in the treatment of tinea cruris in male and nonpregnant females ≥ 12 years of age. The primary efficacy variable was the percentage of subjects at the 4-week time point with complete cure (defined as negative dermatophyte culture + negative KOH, and absence of erythema, scaling and pruritis).

A total of 334 patients were enrolled in the study and randomized 1:1 to NAFT-500 Cream 2% (2 week treatment, n = 166) or 2-week placebo (n = 168). Qualifying subjects were those screened subjects with clinical evidences of tinea cruris, confirmed by KOH and dermatophyte culture. The assigned study drug was applied QD by the subjects to the affected areas. Evaluation visits included a Baseline Visit (Day 1), a Week 2 Visit, and a Week 4 Visit. Mycological procedures (KOH and dermatophyte culture) were performed at each study visit. All mycological analyses were performed by the central laboratory (Visit 1 and Visit 2 KOH analyses were also performed by the local investigator). Primary and secondary analyses were based on results recorded in the Per-protocol set (PPS), defined as the subset of subjects in the Full-analysis set (FAS) without major protocol deviations, or the FAS population, defined as the subset of subjects with a positive culture at baseline for whom the primary efficacy endpoint was available.

The proportion of patients achieving a complete cure in Study MRZ 90200/FI/3001 is summarized in Table 9. At the Week Four Visit, complete cure was achieved in 25.3 % of

study subjects treated with NAFT-500 Cream, 2%, compared to 2.8% complete cure in the placebo arm.

Table 9: Complete Cure Rate (LOCF) – Primary Analysis (FAS)

Visit	Complete Cure[a]	NAFT-500 (N=75) n (%)	Placebo (N=71) n (%)
Visit 2 (Week 2)	Yes	4 (5.3)	0
	No	71 (94.7)	71 (100.0)
	Difference (97.5% CI)[b]	5.3 (0.2, + ∞)	
	P-value[c]	0.025	
Visit 3 (Week 4)	Yes	19 (25.3)	2 (2.8)
	No	56 (74.7)	69 (97.2)
	Difference (97.5% CI)[b]	22.5 (11.9, + ∞)	
	P-value[c]	<0.001	
	P-value[d]	<0.001	
	P-value[e]	0.853	

Data Source: End-of-Text Table 14.2.1.
Note 1: %=(n/Total number of subjects with non-missing data at each visit)x100.
Note 2: For the primary endpoint (NAFT-500 vs. placebo at 4 weeks), statistical significance will be declared if one-sided *p*-value ≤ 0.025.
Abbreviation: CI = confidence interval.
[a] Complete cure = Negative mycology results from the central laboratory (dermatophyte culture and KOH) and absence of erythema, scaling and pruritus.
[b] One-sided 97.5% CI calculated using normal approximation to the binomial for the difference in proportion of 'yes' responses between NAFT-500 and placebo.
[c] *P*-value is from a one-sided Cochran-Mantel-Haenszel (CMH) test comparing NAFT-500 group vs placebo group, with pooled clinical site as the stratification variable.
[d] *P*-value is from a one-sided CMH test comparing NAFT-500 group vs placebo group, with nonpooled clinical site as the stratification variable (sensitivity analysis).
[e] *P*-value is from Breslow-Day test to test for homogeneity of treatment effects among clinical sites after pooling.

Source: This submission, Module 5.3.5.1.3, page 48

The proportion of patients achieving mycological cure is summarized in Table 10. Superiority of NAFT-500 Cream, 2%, compared to placebo, was demonstrated in the trial.

Table 10: Mycological Cure and Treatment Effectiveness (LOCF) Secondary Analysis (FAS)

Visit		NAFT-500 (N=75) n (%)	Placebo (N=71) n (%)
Mycological Cure[a]			
Visit 2 (Week 2)	Yes	50 (66.7)	8 (11.3)
	No	25 (33.3)	63 (88.7)
	Difference (97.5% CI)[c]	55.4 (42.4, + ∞)	
	P-value[4]	<0.001	
Visit 3 (Week 4)	Yes	54 (72.0)	11 (15.5)
	No	21 (28.0)	60 (84.5)
	Difference (97.5% CI)[c]	56.5 (43.3, + ∞)	
	P-value[d]	<0.001	
	P-value[e]	<0.001	
Treatment Effectivenes[b]			
Visit 2 (Week 2)	Yes	39 (52.0)	6 (8.5)
	No	36 (48.0)	65 (91.5)
	Difference (97.5% CI)[c]	43.5 (30.5, + ∞)	
	P-value[d]	<0.001	
Visit 3 (Week 4)	Yes	45 (60.0)	7 (9.9)
	No	30 (40.0)	64 (90.1)
	Difference (97.5% CI)[c]	50.1 (37.1, + ∞)	
	P-value[d]	<0.001	
	P-value[e]	<0.001	

Data Source: End-of-Text Table 14.2.6.
Note 1: %=(n/Total number of subjects with non-missing data at each visit)x100.
Note 2: For the most important secondary efficacy variables (NAFT-500 vs placebo at 4 weeks), statistical significance will be assessed using the Hochberg procedure.
Abbreviation: CI = confidence interval.
[a] Mycological Cure: Negative KOH and negative culture.
[b] Treatment Effectiveness: Negative KOH, negative culture, and Erythema, Scaling, and Pruritus grades of 0 or 1.
[c] One-sided 97.5% CI calculated using normal approximation to the binomial for the difference in proportion of 'yes' responses between NAFT-500 and placebo.
[d] *P*-value is from a one-sided Cochran-Mantel-Haenszel (CMH) test comparing NAFT-500 group vs placebo group, with pooled clinical site as the stratification variable.
[e] Adjusted *P*-value from Hochberg's step-up procedure.

Source: This submission, Module 5.3.5.1.3, page 50

KOH and dermatophyte culture results for the FAS population are summarized in Table 11. In the active treatment arm, negative dermatophyte cultures were observed in 89.7% of subjects and negative KOH results were observed in 82.5% of subjects at the Week 4 Visit (Visit 3), compared to 35.5% culture negative and 23.7% KOH negative in the placebo arm.

Table 11: KOH and Dermatophyte Culture Secondary Analysis (FAS)

	Visit	Results	NAFT-500 (N=75) n (%)	Placebo (N=71) n (%)
Dermatophyte Culture				
	Visit 2 (Week 2)	Positive	2 (2.8)	40 (65.6)
		Negative	69 (97.2)	21 (34.4)
		P-value*	<0.001	
	Visit 3 (Week 4)	Positive	7 (10.3)	40 (64.5)
		Negative	61 (89.7)	22 (35.5)
		P-value*	<0.001	
KOH				
	Visit 2 (Week 2)	Positive	11 (18.0)	38 (70.4)
		Negative	50 (82.0)	16 (29.6)
		P-value*2-week	<0.001	
	Visit 3 (Week 4)	Positive	10 (17.5)	45 (76.3)
		Negative	47 (82.5)	14 (23.7)
		P-value*	<0.001	

Data Source: End-of-Text Table 14.2.16.
Note: %=(n/Total number of subjects with non-missing data at each visit)x100.
* *P*-values are from a two-sided Cochran-Mantel-Haenszel (CMH) test comparing NAFT-500 group vs placebo group, with pooled clinical site as the stratification variable.

Source: This submission, Module 5.3.5.1.3, page 55

No line list of fungal isolates, collected during the clinical trial at specific visits, is apparent in the submission, and no enumeration of "other" pathogens (dermatophytes other than *Trichophyton rubrum*) was provided in the study report. The majority of dermatophytes cultured in the course of the trial were identified as *T. rubrum* (141 isolates vs. 5 isolates identified as "other"). Subgroup (descriptive) analysis was performed to determine complete cure by baseline pathogen (*T. rubrum* vs. "others"). This data is summarized in Table 12.

Table 12: Efficacy Analyses; Secondary and Sensitivity Analyses of the Primary Efficacy Endpoint – Complete Cure Rate Subgroup Analyses (LOCF) – Secondary Analysis (Full Analysis Set)

Subgroup	Visit	Complete Cure[1]	NAFT-500 (N=75) n (%)	Placebo (N=71) n (%)
Baseline Pathogen				
T. rubrum	Visit 2 (Week 2)	Yes	4 (5.5)	0
		No	69 (94.5)	68 (100.0)
		Difference(97.5% CI)[2]	5.5 (0.3,+∞)	
		P-value[3]	0.027	
	Visit 3 (Week 4)	Yes	19 (26.0)	2 (2.9)
		No	54 (74.0)	66 (97.1)
		Difference(97.5% CI)[2]	23.1 (12.2,+∞)	
		P-value[3]	<0.001	
Other	Visit 2 (Week 2)	Yes	0	0
		No	2 (100.0)	3 (100.0)
		Difference(97.5% CI)[2]	NE (NE,NE)	
		P-value[3]	NE	
	Visit 3 (Week 4)	Yes	0	0
		No	2 (100.0)	3 (100.0)
		Difference(97.5% CI)[2]	NE (NE,NE)	
		P-value[3]	NE	

Note: %=(n/Total number of subjects with non-missing data at each visit-subgroup combination)x100. NE=nonestimable.
[1] Complete cure = Negative mycology results from the central laboratory (dermatophyte culture and KOH) and absence of Erytheme, Scaling and Pruritus.
[2] One-sided 97.5% Confidence Interval calculated using normal approximation to the binomial for the difference in proportion of 'yes' responses between NAFT-500 and Placebo.
[3] P-value is from a one-sided Cochran-Mantel-Haenszel (CMH) test comparing NAFT-500 group versus Placebo group, with pooled clinical site as the stratification variable.
Data Source: Listings 9, 10 and 11.
Source: (b) (4)

Fungal susceptibility testing was employed as described above on selected isolates collected during the study. A total of 58 isolates were sent to the testing facility (57 isolates of *T. rubrum* and 1 isolate of *E. floccosum*). Susceptibility testing was performed on 35 isolates (all of which were identified as *T. rubrum*), with the other 23 shipped isolates rejected as "contaminated." The susceptibility results for the tested isolates are summarized in Table 13. As in the tinea pedis study, described above, no isolates could be identified in the submitted data that appeared to be from a single subject, collected at different visits, so no analysis of resistance to NAFT-500, observed during the clinical trial, could be proposed.

Table 13: NAFT-500 susceptibility in isolates collected in Study 9020000/F1/3001

	Trichophyton rubrum (34)
MIC50	0.03
MIC90	0.03
Range	0.015-0.125

Source: This submission; Module 5.3.5.4 – Study us1-123

APPLICANT'S PROPOSED LABEL
(SECTIONS RELEVANT FOR CLINICAL MICROBIOLOGY REVIEW)

1 INDICATIONS AND USAGE

(b) (4)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Naftin (b) (4) is a topical antifungal drug (see *12.4 Microbiology*)

12.4 Microbiology

Although the exact mechanism of action against fungi is not known, naftifine hydrochloride appears to interfere with sterol biosynthesis by inhibiting the enzyme squalene 2, 3-epoxidase.This inhibition of enzyme activity results in decreased amounts of sterols, especially ergosterol, and a corresponding accumulation of squalene in the cells.

(b) (4)

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

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07/27/2011

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07/27/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019599Orig1s011

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA	19-599/(S-011)
Stamp Date (s)	December 16th, 2010
Code Name	NAFT-500 Cream, 2 %
Generic Name	Naftifine Hydrochloride Cream, 2 %
Brand Name	NAFTIN Cream, 2%
Reviewer	Abimbola Adebowale, Ph.D.
Team Leader	Doanh Tran, Ph.D.
OCP Division	Division of Clinical Pharmacology (DCP)-3
OND division	Division of Dermatology and Dental Products (DDDP)
Applicant	Merz Pharmaceuticals
Submission Type; Code	Efficacy Supplemental New Drug Application (sNDA) to add a new strength of 2 % to the currently marketed Naftin (naftifine hydrochloride) Cream 1% w/v
Indication	Treatment of tinea pedis, tinea cruris and tinea corporis

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1 Executive Summary

This supplemental NDA is for NAFT-500 Cream, 2 %, a topical antifungal containing the active pharmaceutical ingredient (API) naftifine hydrochloride, a synthetic allylamine derivative. NAFT-500 Cream, 2% is proposed to be applied once-daily for the topical treatment of tinea pedis, tinea cruris and tinea coporis, in patients aged 12 years and older for 2 weeks. The applicant stated that the proposed indication does not include children less than 12 years of age because this product is not likely to be used in a substantial

Reference ID: 3035345

number of patients younger than 12 years and will not represent a significant therapeutic alternative for this age group.

Naftifine hydrochloride is currently marketed as 1 % cream and 1 % gel formulations (NDA 19-599 (Approved February 29th, 1988) and 19-356 (Approved June 18th, 1990), respectively) for the topical treatment of tinea pedis, tinea cruris and tinea corporis. It is noted that the approved label for Naftin1 % cream and gel state that safety and effectiveness in pediatric patients have not been established.

NAFT-500 cream, 2 % is being proposed [redacted] (b) (4) and once daily dosing frequency as approved for the 1% strength but with a reduced treatment duration (from 4 weeks to 2 weeks). The applicant stated that NAFT-500 Cream, 2%, is similar to Naftin Cream, 1% with the exception that the concentration of naftifine hydrochloride has been increased from 1% to 2% and the [redacted] (b) (4).

To support the sNDA for NAFT-500 Cream, 2%, 6 clinical studies were conducted. Two clinical studies (Phase 3) were conducted, one for the treatment of tinea pedis and one for the treatment of tinea cruris. In addition, a Phase 1 maximal-use, pharmacokinetic study in patients, and a battery of three Phase-1 dermal safety studies (irritation/sensitization, phototoxicity, and photoallerginicity) were conducted.

The applicant stated that during drug product development their product was referred to by the code name, NAFT-500 Cream, 2%. Throughout the application, NAFT-500 (naftifine hydrochloride) Cream, 2% was used interchangeably with NAFT-500 Cream, 2% or NAFT-500. In some documents the drug product is also referred to as Naftin Extra Strength Cream, Naftin Cream, 2% or Naftin 2% Cream.

We note that the applicant stated that production of Naftin® Cream, 1% will be discontinued upon approval of this application for the NAFT-500 Cream, 2%. The applicant is also developing a naftifine 2 % gel under IND 105,603.

1.1 Recommendations

From a clinical pharmacology perspective, this application is acceptable pending agreements on the recommended labeling changes (see section 3), the Post Marketing Requirement (PMR) for a pediatric (ages 12-17 years old) Pharmacokinetic (PK) study in patients with tinea pedis and tinea cruris and, a possible recommendation by Pediatric Review Committee (PeRC) for a Post Marketing Commitment (PMC)/PMR clinical study for the treatment of tinea corporis in pediatric patients aged ≥ 2 years of age. If PeRC recommends that a clinical study needs to be conducted for the treatment of tinea corporis in pediatric patients aged ≥ 2 years of age as a PMC/PMR, then collection of PK data from this population would also be recommended.

1.2 Phase IV Requirements and Commitments

- We recommend that the applicant evaluate the PK of NAFT-500 cream in adolescents aged 12-17 years old with tinea pedis and tinea cruris as part of a pediatric plan to

Reference ID: 3035345

meet the Pediatric Research Equity Act (PREA) PMR. The PK information obtained in the adolescent population will be important for evaluating systemic safety. Our recommendations are based on the following:

- [redacted] (b) (4)

  - The clinical reviewer informed this reviewer that there were only 3 pediatric patients (aged 12 to 17 years old) on active drug (NAFT-500 cream, 2 %) in the clinical studies and that this was considered insufficient.

  - In addition, the currently marketed Naftifine 1 % cream and gel are not approved for use in pediatric patients.

- We would recommend the collection of PK data from the proposed study in pediatric patients aged ≥ 2 years of age with tinea corporis, if PeRC recommends that a clinical study needs to be conducted in this population as a (PMC)/PMR. The PeRC recommendations are pending because prior to the Pediatric Research Equity Act (PREA), the Division of Dermatology and Dental Products (DDDP) did not recommend the conduct of separate studies in patients with tinea corporis, in addition to studies already conducted in patients with tinea pedis and tinea cruris.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Bioavailability under maximal use conditions:

The bioavailability of NAFT-500 Cream, 2% under maximal use conditions was evaluated in study MRZ 90200/FI/1002. This study was designed as an open label, single-center, multiple application study to evaluate the PK of NAFT-500 Cream, 2% following once-daily topical application for 2 weeks. The plasma and urine concentrations of naftifine was determined in 21 adult subjects (Age range 18-63 years old) with tinea cruris (all subjects) and tinea pedis (all subjects had tinea pedis on both feet with 18 subjects having both interdigital and moccasin-type infections). Maximal use condition was defined as having both feet and bikini area affected. A total of 8 grams per day were to be applied as follows: 2 grams to each foot and 4 grams to the bikini area. However, the total amount applied during the study was actually less than 8g (ranging from 5.3 -7.5g) per day. During the 2-week treatment period, PK blood samples were collected on Days 1 and 14 at 0 hour (pre-application) and at 1, 2, 4, 6, 8, 12, 16, and 24 hours post-application. Pre-application samples were also collected on Days 3, 7, 11, 13, 14, 21 (1 week post-application), and 28 (2 weeks post-application). Samples collected on Days 11 through 14 were used to assess attainment of steady state. Pharmacokinetic urine

Reference ID: 3035345

samples were collected on Days 1 and 14 for 24 hours as follows: pre-application (complete void and only on Day 1); and from 0 to 6, 6 to 12, and 12 to 24 hours post-application.

Plasma
The results showed that the systemic exposure (i.e. Maximum plasma concentration (Cmax) and Area under the curve (AUC)) to naftifine increased over the 2 week treatment period in all 21 subjects. Geometric Mean (CV%) AUC0-24 was 117 ng*hr/mL (41.2) on Day 1, and 204 ng*hr/mL (28.5) on Day 14. Geometric Mean (CV %) of Cmax was 7 ng/mL (55.6) on Day 1 and 11 ng/mL (29.3) on day 14. Median Tmax was 8.0 hours on Day 1 (range: 4 to 24) and 6.0 hours on Day 14 (range: 0 to 16).

It does not appear that steady state was achieved during the 14 day duration of this study. Trough concentrations (Ctrough) generally increased throughout the 14 day study period; geometric mean Ctrough at 24 hours post-application was 6.6 ng/mL (CV% 31.6; range 2.8 to 12.2 ng/mL) on Day 14 versus 3.9 ng/mL (CV% 40.5; range 1.7 to 7.3 ng/mL) reported on Day 1. Accumulation after 14 days of topical application was less than twofold. Naftifine continued to be detected (Limit of Quantitation (LOQ) =1.01 ng/mL) in plasma in 13 subjects on day 28, the mean (SD) plasma concentration was 1.6 ± 0.5 ng/mL (range Below Limit of Quantitation (BLQ) to 3 ng/mL).

Urine
Urine PK results were variable. There was one outlier (Subject [redacted] (b) (6) in the study) whose urine concentrations were markedly higher than the rest of the population, therefore medians were reported. Median amounts excreted in the urine over 24 hours were 2 µg (range of 0.63 to 96.64 µg) on Day 1 versus 3 µg (range of 0.89 to 58.68 µg) on Day 14. Median fraction of the dose excreted in urine during the treatment period, was 0.0016% on Day 1 versus 0.002% on Day 14. Median renal clearance appeared to decrease during the study period from 17 L/hr (range of 6.53 to1330.65 L/hr) on Day 1 to 11 L/hr (range of 5.99 to 460.96) on Day 14.

<u>Pediatrics</u>
The applicant did not provide any PK data for NAFT-500 Cream, 2 % in pediatric subjects in this supplement. The applicant is seeking a waiver of pediatric studies in subjects less than 12 years of age under the Pediatric Research Equity Act (PREA). The applicant specifically requests a waiver of the requirement to conduct studies in pediatric subjects younger than 12 years of age on the basis that NAFT-500 Cream, 2% does not represent a significant therapeutic alternative for this age group and is unlikely to be used in a substantial number of patients younger than 12 years of age. This is currently being reviewed by the Clinical reviewer.

[redacted] (b) (4)

Reference ID: 3035345

1. (b) (4)

2.

3.

(b) (4)

We recommend that the applicant evaluate the PK of NAFT-500 cream in adolescents aged 12-17 years old as part of a pediatric plan to meet the Pediatric Research Equity Act (PREA) PMR . The PK information obtained in the adolescent population will be important for evaluating systemic safety. Our recommendations are based on the following:

(b) (4)

- The clinical reviewer informed this reviewer that there were only 3 pediatric patients on active drug (NAFT-500 cream, 2 %) in the clinical studies and that this was considered insufficient.

- In addition, the currently marketed Naftifine 1 % cream and gel are not approved for use in pediatric patients.

QT Prolongation

On July 8th, 2011, the applicant submitted their final QT-QTc study report "Merz Protocol No. MUS 90200/1018/1" to support cardiovascular safety with use of topical naftifine hydrochloride (HCl) 2% cream. This study report has been reviewed by the Interdisciplinary Review Team for QT Studies (IRT-QT) (review dated 09/09/2011). According to the IRT-QT team overall summary of findings: "No significant QTc prolongation effect of naftifine HCl (600 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between naftifine HCl (600 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines."

Reference ID: 3035345

It was noted that the applicant did not propose any label language on QT effect, however QT-IRT suggested labeling language but deferred final labeling decisions to the review division.

Clinical trial versus the to-be-marketed formulation

The applicant stated that the to-be-marketed formulation was used in the Phase 3 clinical studies and the maximal use PK study.

Signatories:

_____ Date: _____

Abimbola Adebowale, Ph.D.
Senior Clinical Pharmacology Reviewer
Division of Clinical Pharmacology 3
Office of Clinical Pharmacology

_____ Date: _____

Doanh Tran, Ph.D.
Clinical Pharmacology Team Leader
Division of Clinical Pharmacology 3
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_____ Date: _____

CAPT E. Dennis Bashaw, Pharm.D.
Division Director
Division of Clinical Pharmacology 3
Office of Clinical Pharmacology

Reference ID: 3035345

2 Question-Based Review

2.1 General Attributes

Q What is naftifine hydrochloride (HCl)?

Naftifine hydrochloride (HCl), USP is the active pharmaceutical ingredient in NAFT-500 Cream, 2%. Naftifine hydrochloride has an empirical formula of $C_{21}H_{21}N \bullet HCl$ and a molecular weight of 323.86. The structural formula of naftifine hydrochloride is provided in Figure 1 below:

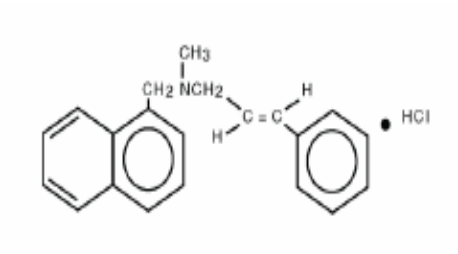

Figure 1

Q What is the proposed indication and dosing regimen for NAFT-500 Cream, 2 %?

The proposed indication for NAFT-500 Cream, 2 % is for the topical treatment of tinea pedis, tinea cruris, and tinea corporis in patients 12 years and older. NAFT-500 Cream 2% is proposed to be applied topically onto affected areas plus a ½ inch margin of healthy surrounding skin once-daily for 2 weeks.

Q What are tinea pedis, tinea cruris and tinea corporis?

Tinea pedis, Tinea cruris and tinea corporis are fungal infections caused by *Trichophyton rubrum, Trichophyton mentagrophytes and Epidermophyton floccosum* respectively.

Q What is the pharmacological rationale for naftifine in the treatment of tinea pedis, cruris and corporis?

NAFT-500, Cream is a topical antifungal. Although the exact mechanism of its action against fungi is not known, naftifine hydrochloride appears to interfere with sterol biosynthesis by inhibiting the enzyme squalene 2, 3-epoxidase, the rate limiting enzyme in the cellular synthesis of ergosterol. This inhibition of enzyme activity results in decreased amounts of sterols, especially ergosterol, and a corresponding accumulation of squalene in the cells.

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2.2 General Clinical Pharmacology

Q What were the design features of the clinical pharmacology and clinical studies used to support NAFT-500 Cream, 2%?

The NAFT-500 Cream, 2 % development program is supported by two Phase 3 clinical trials (MUS90200/076/1 and MRZ 90200/F1/3001), one maximal use PK study (MRZ 90200/F1/1002) and three dermal safety studies to evaluate phototoxicity, photoallergenicity and irritation and sensitization potential, respectively (MUS 90200/1013/1, MUS 90200/1014/1, and MRZ 90200/F1/1003). Table 1 below provides a brief overview of the studies.

Table 1: Tabular Listing of Clinical Studies:

Study Type	Study Protocol/ Identifier	Study Report Location	Study Objectives	Study Design and Type of Control	Test Product(s): Dose, Route, and Regimen;	Subject Number	Subject Description	Treatment Duration	Study Status/ Type of Report
Phase 3	MUS 90200/076/1	5.3.5.1	To evaluate the efficacy and safety of NAFT-500 compared to placebo	Double-blind, randomized, placebo-controlled, multicenter, parallel group	NAFT-500; applied topically once a day to affected areas and a ½ inch margin of adjacent healthy skin	709	Subjects with tinea pedis	14 days	Complete Full
Phase 3	MRZ 90200/FI/3001	5.3.5.1	To evaluate the efficacy and safety of NAFT-500 compared to placebo	Double-blind, randomized, placebo-controlled, multicenter, parallel group	NAFT-500; applied topically once a day to affected areas and a ½ inch margin of adjacent healthy skin	334	Subjects with tinea cruris	14 days	Complete Full
Phase 1	MRZ 90200/FI/1002	5.3.3.2	To quantify the pharmacokinetics under maximal clinical use conditions	Open-label, single-center, multiple-application	NAFT-500; 8g applied topically	21	Subjects with tinea pedis and tinea cruris	14 days	Complete Full

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Study Type	Study Protocol/ Identifier	Study Report Location	Study Objectives	Study Design and Type of Control	Test Product(s): Dose, Route, and Regimen;	Subject Number	Subject Description	Treatment Duration	Study Status/ Type of Report
Phase 1	MUS 90200/1013/1	5.3.3.1	Evaluate the potential to produce phototoxicity reactions	Controlled, open-label, blinded evaluator, single dose	NAFT-500; single, occluded 24 hour application	34	Healthy subjects ages 18 -70 years	Single occluded 24 hour application	Complete Full
Phase 1	MUS 90200/1014/1	5.3.3.1	Evaluate the potential to produce photoallergenicity reactions	Controlled, open-label, blinded evaluator, single dose	NAFT-500; 6 occluded applications during the induction phase and one occluded application during the challenge phase	57	Healthy Subjects ages 18 -70 years	6 days of occluded patches followed by a 14-day rest phase followed by a 24-hour challenge phase	Complete Full
Phase 1	MRZ 90200/FI/1003	5.3.3.1	Evaluate the sensitization potential and degree of skin irritation on intact skin	Single-site, randomized, single-blind, controlled study	NAFT-500; 21 occluded applications during the irritation phase and one occluded application during the challenge phase	250	Healthy subjects ages 18-65 years	21 days of occluded patches followed by a 14-day rest phase followed by a 48-hour challenge phase	Complete Full

NA= Not Applicable

The Phase 3 study (MRZ/90200/F1/1002) evaluating the efficacy and safety of NAFT-500 Cream, 2% in the treatment of tinea pedis included 2 treatment arms. The first treatment arm evaluated patients that were treated once-daily for 2 weeks with NAFT 500 Cream, 2% compared with 2 weeks of treatment with placebo. The second treatment arm evaluated patients that were treated once-daily for 4 weeks with Naftin® 1% Cream compared with 4 weeks treatment with placebo.

Study MRZ 90200/FI/3001 evaluated the efficacy and safety of NAFT-500 Cream, 2% in the treatment of tinea cruris. This study was a 4 week, placebo-controlled, multicenter, double-blind, randomized parallel-group study that evaluated patients that were treated once-daily for 2 weeks with NAFT-500 Cream, 2% compared with two weeks treatment with placebo.

Q What is the bioavailability (or systemic exposure) of Naftin-500 Cream, 2% under maximal use conditions?

The bioavailability of NAFT-500 Cream, 2% under maximal use conditions was evaluated in study MRZ 90200/FI/1002. This study was designed as an open label, single-center, and multiple application study to evaluate the pharmacokinetics (PK) of NAFT-500 Cream, 2% following once-daily topical application for 2 weeks. The plasma

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and urine concentrations of naftifine was determined in 21 adult subjects (Age range 18-63 years old) with tinea cruris (all subjects) and tinea pedis (all subjects had tinea pedis on both feet with 18 subjects having both interdigital and moccasin-type infections). Maximal use condition was defined as having both feet and bikini area affected. A total of 8 grams per day were to be applied as follows: 2 grams to each foot and 4 grams to the bikini area. However, the total amount applied during the study was actually less than 8g (ranging from 5.3 -7.5g) per day. The efficacy, tolerability, and safety of NAFT-500 Cream, 2% were also assessed during the study. Subjects stayed at the study center on Day 1 (first application) and Day 14 (last application). During the 2-week treatment period, PK blood samples were collected on Days 1 and 14 at 0 hour (pre-application) and at 1, 2, 4, 6, 8, 12, 16, and 24 hours post-application. Pre-application samples were also collected on Days 3, 7, 11, 13, 14, 21 (1 week post-application), and 28 (2 weeks post-application). Samples collected on Days 11 through 14 were used to assess steady state. Pharmacokinetic urine samples were collected on Days 1 and 14 for 24 hours as follows: pre-application (complete void and only on Day 1); and from 0 to 6, 6 to 12, and 12 to 24 hours post-application. The PK parameters of naftifine are described below.

Plasma

Mean plasma concentrations of naftifine increased slowly, reaching maximal observed concentrations between 6-8 hours after topical application of NAFT-500 Cream on Day 14 (see figure 2 below).

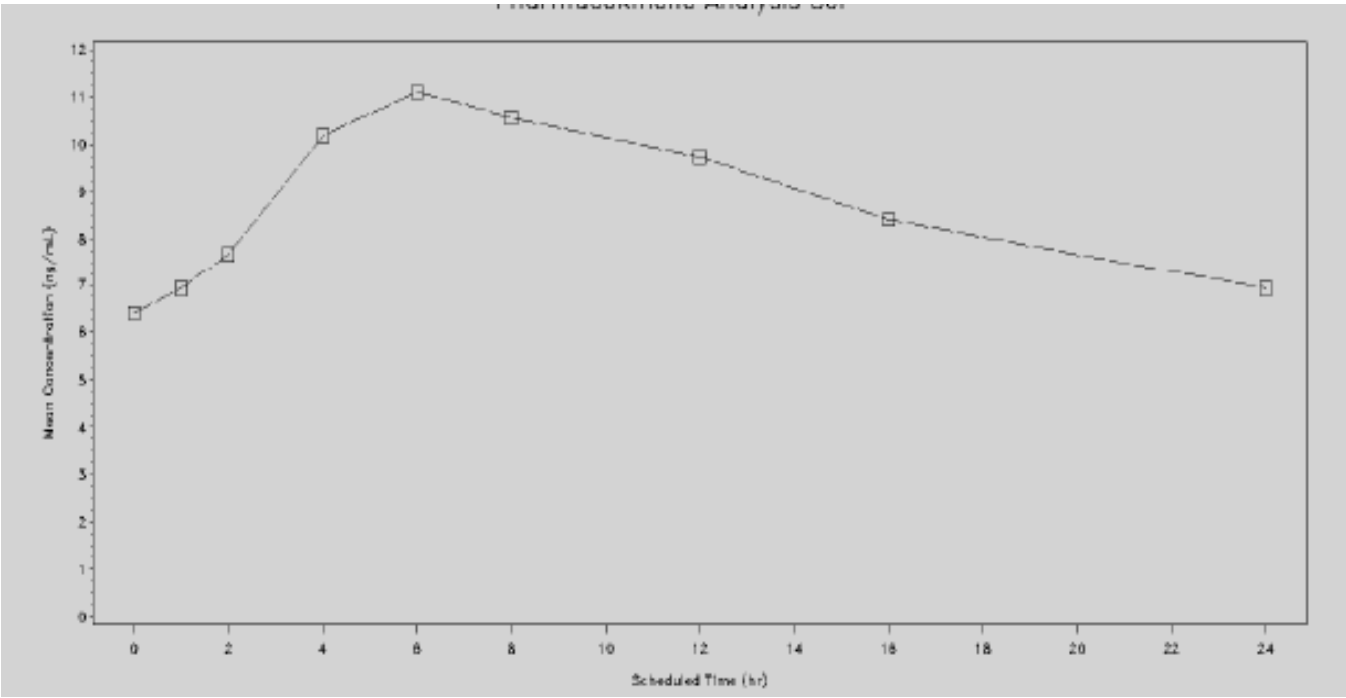

Figure 2: Mean Plasma concentrations of Naftifine by time on Day 14

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The systemic exposure (Cmax and AUC) to naftifine increased over the 2 week treatment period in all the 21 subjects. Geometric Mean (CV%) AUC0-24 was 117 ng*hr/mL (41.2) on Day 1, and 204 ng*hr/mL (28.5) on Day 14. Geometric Mean (CV %) of Cmax was 7 ng/mL (55.6) on Day 1 and 11 ng/mL (29.3) on day 14. Median Tmax was 8.0 hours on Day 1 (range: 4 to 24) and 6.0 hours on Day 14 (range: 0 to 16). Naftifine PK parameters on Day 1 and Day 14 are summarized in Tables 2 and 3 below.

Table 2: Summary of Plasma Naftifine Pharmacokinetics Parameters on Day 1

Statistics	AUC_{0-24} (ng*hr/mL)	$C_{max,SD}$ (ng/mL)	C_{24hr} (ng/mL)	$T_{max,SD}$ (hr)
N	21	21	21	21
Mean	—	—	4.212	8.1
SD	—	—	1.7056	4.36
CV%	41.2487	55.640	40.490	53.8
Geometric Mean	116.7185	7.258	3.859	7.4
Min	66.900	3.79	1.70	4
Median	106.0650	7.150	4.130	8.0
Max	278.560	24.99	7.29	24
90% C.I.(1)	(101.740, 133.902)	(6.202, 8.494)	(3.266, 4.560)	(6.5, 9.7)

Table 3: Summary of Plasma Naftifine Pharmacokinetics Parameters on Day 14

Statistics	AUC_{0-t} (ng*hr/mL)	$C_{max,\ Day\ 14}$ (ng/mL)	C_{24hr} (ng/mL)	$T_{max,\ Day\ 14}$ (hr)
N	21	21	21	21
Mean	—	—	6.929	7.1
SD	—	—	2.1922	3.26
CV%	28.4868	29.291	31.640	45.6
Geometric Mean	204.2620	11.293	6.575	7.1
Min	90.305	4.71	2.76	0
Median	209.1350	11.760	6.890	6.0
Max	331.905	17.30	12.21	16
90% C.I.(1)	(181.6132, 229.7353)	(9.987, 12.769)	(5.775, 7.486)	(5.9, 8.4)

It does not appear that steady state was achieved during the 14 day duration of this study. Trough concentrations (Ctrough) generally increased throughout the 14 day study period; geometric mean Ctrough at 24 hours post-application was 6.6 ng/mL (CV% 31.6; range 2.8 to 12.2 ng/mL) on Day 14 versus 3.9 ng/mL (CV% 40.5; range 1.7 to 7.3 ng/mL) reported on Day 1. Accumulation after 14 days of topical application was less than twofold. Naftifine continued to be detected in plasma in 13 subjects on day 28, the mean (SD) plasma concentrations were 1.6 ± 0.5 ng/mL (range BLQ to 3 ng/mL). Half life was not determined.

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Urine

Urine PK results were variable. There was one outlier ([redacted] (b) (6) in the study) whose urine concentrations were markedly higher than the rest of the population, therefore medians were reported. Median amounts excreted in the urine over 24 hours were 2 µg (range of 0.63 to 96.64 µg) on Day 1 versus 3 µg (range of 0.89 to 58.68 µg) on Day 14. Median fraction of the dose excreted in urine during the treatment period, was 0.0016% on Day 1 versus 0.0020% on Day 14. Median renal clearance appeared to decrease during the study period from 17 L/hr (range of 6.53 to1330.65 L/hr) on Day 1 to 11 L/hr (range of 5.99 to 460.96) on Day 14. Urine PK parameters for Day 1 and Day 14 are summarized in Table 4 below.

Table 4: Summary of Urine Naftifine Pharmacokinetics Parameters on Day1 and Day 14

Subject / Statistics	Ae_{0-24} (µg)	$Fe\%_{0-24}$	CLr (L/h)	CLr (mL/min)
Day 1				
N	21	21	21	21
Mean	7.165	0.006376	83.148	1385.805
SD	20.7062	0.0194344	286.3746	4772.9094
CV%	289.001	304.826594	344.414	344.414
Geometric Mean	2.324	0.001912	19.910	331.830
Min	0.63	0.00038	6.53	108.81
Median	1.920	0.001568	16.803	280.044
Max	96.64	0.09080	1330.65	22177.44
90% C.I.(1)	(-0.628, 14.958)	(-0.000939, 0.013690)	(-24.633, 190.930)	(-410.548, 3182.158)
Day 14				
N	21	21	21	21
Mean	5.954	0.004129	36.055	600.909
SD	12.2670	0.0078262	97.6625	1627.7089
CV%	206.022	189.536832	270.874	270.874
Geometric Mean	3.162	0.002286	15.482	258.040
Min	0.89	0.00047	5.99	99.87
Median	2.831	0.002020	11.131	185.510
Max	58.68	0.03759	460.96	7682.59
90% C.I.(1)	(1.337, 10.571)	(0.001184, 0.007075)	(-0.702, 72.811)	(-11.703, 1213.521)

Q. What new information was provided in this submission on the metabolism, distribution and excretion of naftifine hydrochloride?

The applicant provided additional information on the metabolism and excretion of naftifine from published literature in this submission.

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It is noted that the currently approved label for Naftin 1 % gel and cream has the following information on the metabolism and excretion of natifine:

> "Naftifine and/or its metabolites are excreted via urine and feces with a half-life of approximately two to three days".

The information provided in the published literature below supports the language in the currently approved label for the naftin 1 % cream and gel.

Reference # 1 (Monk et. al., 1991[1]): reported that fifteen different metabolites of naftifine have been identified, nine of which were found in human urine. After oral administration of naftifine, 7 mg/kg; 14.3% of the total oral dose was recovered as metabolites in the urine over 48 hours, with naphthoic acid predominating (7.2% of the administered dose). Similarly, following topical application, 0.8% to 2% of the applied radioactivity was excreted in the urine and 0.8% to 1.6% in the feces. In vitro tests showed that none of the conjugated metabolites exhibited significant antifungal activity. Following topical application of naftifine 0.25 or 0.31 mg/kg as 1 % gel in 2 volunteers, the urinary concentration (1 to 2 mcg/L) and percentage of total radioactivity (2 to 4 %) accounted for by unchanged drug remained relatively constant over 62 hours, suggesting the formation of a depot in the skin or other tissue. The authors reported that in 2 species that received naftifine both orally and topically (humans and guinea-pigs) the major routes of biotransformation appeared to be the same (mainly N-dealkylation and oxidation) with each route of administration.

Q. What is the effect of naftifine on the cytochrome P-450 isozyme system?

The applicant stated that naftifine does not appear to affect the hepatic cytochrome p-450 isozyme system. The applicant provided published literature information that supports the lack of effect of naftifine on cytochrome P-450 from published literature. These are discussed below:

Reference # 2 (Ryder et. al., 1992[2]): reported that naftifine's fungicidal mechanism of action is via inhibition of squalene epoxidase, the rate limiting enzyme in the cellular synthesis of ergosterol. Squalene epoxidase from either fungal or mammalian sources is not an enzyme of the cytochrome P-450 superfamily, so that allylamines have no inherent tendency to inhibit this class of enzymes.

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[1] Monk JP, Brogden RN. 1991. Naftifine. A Review of its Antimicrobial Activity and Therapeutic Use in Superficial Dermatomycoses. *Drugs*. **42**(4);659-72.

[2] Ryder NS, Mieth H. 1992. Allylamine Antifungal Drugs. *Curr Top Med Mycol*. **4**;158-88.

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Reference # 3 (Shuster I., 1985[3]): reported that there are experimental in vitro data demonstrating that in rodents, naftifine bind moderately strongly as Type I substrates to liver and steroidogenic cytochrome P-450 isozymes. However, in human liver it is low; < 5% total naftifine binds to human liver microsomal cytochrome P-450 (i.e. < 0.6 nmol/gram liver). The authors concluded that the allylamines including naftifine are Type-1 substrates for a small portion of cytochrome P-450 of liver microsomes only and there is no spectral evidence for binding to the cytochromes P-450 involved in steroid biosynthesis.

Q. What are the characteristics of exposure-response relationships?

No formal dose-ranging studies were conducted where the optimal plasma concentrations were determined. In the phase 3 study conducted in patients with tinea pedis (MUS 90200/0736/1), it was noted that a comparison of the efficacy of NAFT-500 cream, 2 % versus Naftin 1 % cream indicated that the complete cure rate for the NAFT-500 arm (15.7 %) was slightly higher than that of the Naftin 1 % cream (15.4%), but Naftin 1 % cream had a bigger treatment effect compared to NAFT-500. This was because the complete cure rate for the NAFT-500 vehicle (7.1 %) (treatment duration of 2 weeks) arm was noted to be twice as high compared to that of the Naftin 1% vehicle (3.3 %) (treatment duration of 4 weeks) arm (see biostatics review for further details).

An evaluation of the treatment-emergent adverse events experienced in > 2 % of subjects indicated that a higher number of subjects in the NAFT-500 arm experienced treatment emergent AEs than in the naftin 1 % study arm, 13 (5.6 %) and 5 (2.1%), respectively (see clinical review for further details).

Q. Does NAFT-500 cream, 2% prolong QT intervals?

The clinical reviewer noted in her filing check list that the sponsor plans to conduct the thorough QT (TQT) study under IND 105,603 and submit their study results in July 2011 (IND 77,530 SD 20). On July 8th, 2011, the applicant submitted their final QT-QTc study report "Merz Protocol No. MUS 90200/1018/1" to support cardiovascular safety with use of topical naftifine hydrochloride (HCl) 2% cream. This study report has been reviewed by the Interdisciplinary Review Team for QT Studies (IRT-QT) team (review dated 09/09/2011). According to the IRT-QT overall summary of findings: "No significant QTc prolongation effect of naftifine HCl (600 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between naftifine HCl (600 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines."

[3]Schuster I. 1985. The Interaction of Representative Members from Two Classes of Antimycotics – the Azoles and the Allylamines – with Cytochromes P-450 in Steroidogenic Tissues and Liver. *Xenobiotica*. **15**; 529-546

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It was noted that the applicant did not propose any label language on QT effect, however QT-IRT suggested labeling language but deferred final labeling decisions to the review division.

A brief summary of the TQTstudy design with the applicant's conclusions are described below:

The TQT study utilized a single-dose, randomized, double-dummy, double-blind, 3-treatment, parallel design with a supratherapeutic dose (600 mg naftifine HCl capsule), a placebo control, and a positive control (400 mg moxifloxacin). The results of the TQT study are intended to be applied to NAFT-500 Cream, 2 %. The applicant's rationale for using the 600 mg capsule was that due to the poor systemic absorption from the topical product, an oral formulation was chosen to obtain the supratherapeutic level of exposure. An oral dose of 600 mg administered daily for 4 days was tested in healthy volunteers in a previous study (Study report NAFT-910-SNDZ; NDA 19-599). Following a single 600 mg oral dose, peak plasma levels (Cmax) and the extent of absorption (area under the concentration-versus-time curve [AUC]) were approximately 18 and 2 times higher than that achieved during multiple topical applications of a 2% naftifine HCl cream in patients, respectively, and was, therefore, considered appropriate as the supratherapeutic dose in this study. The applicant's rationale for using 600 mg naftifine capsule in the TQT study was submitted (January 10th, 2011) to the Agency in the protocol and found acceptable by the QT/IRT reviewer (DARRTS entry dated March 16th, 2011) and the clinical reviewer (DARRTS entry dated March 30th, 2011). It is noted that the 600 mg capsule Cmax observed in the TQT study is also about 20 fold higher, however, the AUC is 4 fold higher as compared to 2 fold higher for the data obtained in the original NDA. These data support the applicability of the TQT study conducted with the oral capsule to the topical cream

The applicant concluded that a single supratherapeutic oral dose of 600 mg naftifine HCl capsules (NAFT-600) did not prolong the QTcF interval above the regulatory threshold of concern. The upper bound of the one-sided 95% CI of the difference between the LS means of naftifine HCl capsules (NAFT-600) and placebo dQTcF (ddQTcF) was < 10 msec at all post-dose time points. As a result of this, the applicant concluded that the TQT study was negative. This is consistent with the conclusions of the IRT-QT team.

2.3 Intrinsic Factors

Q. What is the systemic exposure of NAFT-500 in pediatrics?

The applicant did not provide any PK data for NAFT-500 Cream, 2 % in pediatric subjects in this supplement. The applicant is seeking a waiver of pediatric studies in subjects less than 12 years of age under the Pediatric Research Equity Act (PREA). The applicant specifically requests a waiver of the requirement to conduct studies in pediatric subjects younger than 12 years of age on the basis that NAFT-500 Cream, 2% does not represent a significant therapeutic alternative for this age group and is unlikely to be used

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in a substantial number of patients younger than 12 years of age. This is currently being reviewed by the Clinical reviewer.

(b) (4)

1. (b) (4)

2.

3.

We agree with the clinical reviewer that the applicants' Rationale #2 and 3 are reasonable. However, from a clinical pharmacology perspective, the applicant did not provide adequate information (b) (4). Therefore, we cannot make a definitive decision that (b) (4)

A detailed explanation of the reason why the information provided to support Rationale # 1 may not be adequate from a clinical pharmacology perspective is inserted below:

(b) (4)

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(b) (4)

Based on the overall information described above, we recommend that the applicant evaluate the PK of NAFT-500 cream in adolescents aged 12-17 years old with tinea pedis and tinea cruris as part of a pediatric plan to meet the Pediatric Research Equity Act (PREA) PMR. The PK information obtained in the adolescent population will be important for evaluating systemic safety. Our recommendations are based on the following:

- (b) (4)
- The clinical reviewer informed this reviewer that there were only 3 pediatric patients on active drug (NAFT-500 cream, 2 %) in the clinical studies and that it was considered insufficient.
- In addition, the currently marketed Naftifine 1 % cream and gel are not approved for use in pediatric patients.

We would recommend the collection of PK data from the proposed study in pediatric patients aged ≥ 2 years of age with tinea corporis, if PeRC recommends that a clinical study needs to be conducted in this population as a (PMC)/PMR. The PeRC recommendations are pending because prior to the Pediatric Research Equity Act (PREA), the Division of Dermatology and Dental Products (DDDP) did not recommend the conduct of separate studies in patients with tinea corporis, in addition to studies already conducted in patients with tinea pedis and tinea cruris.

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2.4 Extrinsic Factors

Q. What extrinsic factors influence the PK of NAFT-500 Cream, 2 %?

Drug-Drug Interactions: The applicant stated that the in vitro evidence for lack of naftifine drug-drug interactions (i.e. lack of effect on cytochrome P-450) is further supported by clinical data. The applicant conducted a search of the clinical antifungal drug-drug interaction literature from 1985 to the present. No evidence was found for any clinically significant drug interaction effects related to inhibition or induction of cytochrome P-450 enzymes by naftifine. Thus, the applicant concluded that there is convincing experimental and clinical evidence that any naftifine absorbed into the systemic circulation following cutaneous application of NAFT-500 Cream, 2% will not result in clinically significant drug-drug interactions via the hepatic cytochrome P-450 system. This reviewer agrees with the applicant that there is no potential risk of drug-drug interactions following topical application of NAFT-500 Cream, 2%.

2.5 General Biopharmaceutics

Q What is the final product composition of NAFT-500 cream, 2 %?

The final product composition is shown in Table 5 below.

Table 5: Qualitative and Quantitative Composition of the Naftin-500 Cream, 2%

Component	Reference	Concentration (% w/w)
Naftifine hydrochloride	USP	2.00
Purified Water	(b) (4)	
Isopropyl Myristate		
Polysorbate 60		
Stearyl Alcohol		
Cetyl Alcohol		
Cetyl Esters Wax		
Sorbitan Monostearate		
Benzyl Alcohol		
Sodium Hydroxide		
(b) (4) Hydrochloric Acid		

(b) (4)

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Q. Was the to-be-marketed formulation (TBMF) used in the clinical studies?

Yes, the applicant stated that the TBMF was used in the clinical studies (including the PK study). During the clinical development of NAFT500 Cream, 2%, one batch of product (Batch 774011CGT60) was produced and divided into three separate packaging lots (60 g tubes, lots AAX-C, AAX-2C, and AAX-4C) and used in the clinical trials. The applicant stated that batch 774011CGT60 has the same formulation and was produced using the same manufacturing process and at the same manufacturing site as the TBMF.

It was noted that the study report for the maximal use PK trial MRZ 90200/FI/1002 specified a different batch number (23255.1). The Sponsor clarified in a letter dated 2/2/2011, that batch number 23255.1 in the study report for trial MRZ 90200/FI/1002 was assigned by the clinical research laboratory and corresponds to lot number AAX-2C from batch 774011CGT60. Phase 3 trial MRZ 90200/FI/3001 used product lot numbers AAX-C and AAX-2C and Phase 3 trial MUS 90200-0736/1 used product lot numbers AAX-C and AAX-4C.

2.6 Analytical Section

Q What bioanalytical methods were used to assess naftifine drug concentrations?

Plasma

A high performance liquid chromatographic method was used for the determination of naftifine in human EDTA K3 plasma. Basically, naftifine and its internal standard naftifine-N-methyl-d3 were extracted from an aliquot of human EDTA K3 plasma using automated liquid-liquid extraction (Liquid handling system) then the extract is injected into a liquid chromatograph. Detection was made with a tandem mass spectrometry detector.

Urine

A high performance liquid chromatographic method was used for the determination of naftifine in human urine. The analyte naftifine and its internal standard naftifine-N-methyl-d3 were extracted from an aliquot of human urine using an automated liquid-liquid extraction (Liquid handling system). The extracted samples were injected into a liquid chromatograph. Detection was made with a tandem mass spectrometry detector

Q Were the bioanalytical methods adequately validated?

Yes. A summary of the validation parameters for the analytical methods (plasma and urine) are summarized in tables 6 and 7 below.

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Table 6: Analytical Method Validation for Plasma Naftifine:

Standard curve range	1.01 to 1013.60 ng/mL
Linearity	$r^2 \geq 0.9976$
Accuracy (% Bias) ***Inter-Day*** ***Intra-Day***	 99.86 to 101.87% 96.54 to 102.59%
Precision (% CV) ***Inter-Day*** ***Intra-Day***	 1.94 to 5.53% 1.23 to 6.22%
Sensitivity (LOQ)	1.01 ng/mL (% CV=8.12; n=6)
[1]**Mean Recovery Values:**	88.68%, 90.33% and 94.52% for QC1, QC2 and QC3, respectively
Specificity	No significant interference observed
Stability:	Mean % change after 143 days was -13.83 and -8.28% at -20ºC for QC1 and QC 3, respectively Mean % change after 143 days was -11.43 (QC1) and -3.47% (QC3) at -80ºC

[1]Mean Recovery values were obtained from six quality control samples (QC)samples each of low (QC1), medium (QC2) and high (QC3) quality control samples

Table 7: Analytical Method Validation for Urine Naftifine:

Standard curve range	49.80 to 9960.00 pg/mL
Linearity	$r^2 \geq 0.9988$
Accuracy (% Bias) ***Inter-Day*** ***Intra-Day***	 101.17 to 102.27% 101.09 to 105.47%
Precision (% CV) ***Inter-Day*** ***Intra-Day***	 2.18 to 4.24% 0.92 to 3.91%
Sensitivity (LOQ)	49.80 pg/mL (% CV =2.74)
[1]**Mean Recovery Values:**	89.25%, 95.79% and 96.21% for QC1, QC2 and QC3, respectively

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Specificity	No significant interference observed
Stability:	Mean % change after 199 days: -3.50 and 0.32% at -20ºC for QC1 and QC 3, respectively Mean % change after 199 days: 0.73 and 4.70% at -80ºC for QC1 and QC 3, respectively

[1]Mean Recovery values were obtained from six quality control samples (QC)samples each of low (QC1), medium (QC2) and high (QC3) quality control samples

3 Detailed Labeling Recommendations

Please see labeling changes for Section 12 (Clinical Pharmacology) below. This reviewer's changes are shown as ***deletions*** which are ***"strikethroughs"*** and ***additions which*** are ***"underlined".***

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

NAFTIN (b) (4) is a topical antifungal drug [see Microbiology (12.4)]

12.2 Pharmacodynamics

The pharmacodynamics of NAFTIN (b) (4) has not been established.

12.3 Pharmacokinetics

(b) (4)

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(b) (4)

The pharmacokinetics of NAFTIN Cream was evaluated following once-daily topical application for 2 weeks to twenty one adult subjects, both males and females, with both tinea pedis and tinea cruris. The median total amount of cream applied was 6.4 g (range 5.3-7.5 g) per day. The results showed that the systemic exposure (i.e. maximum concentration (Cmax) and area under the curve (AUC)) to naftifine increased over the 2 week treatment period in all the 21 subjects. Geometric Mean (CV%) AUC0-24hr was 117 (41.2) ng*hr/mL on Day 1, and 204 (28.5) ng*hr/mL on Day 14. Geometric Mean (CV %) Cmax was 7 ng/mL (55.6) on Day 1 and 11 ng/mL (29.3) on day 14. Median Tmax was 8.0 hours on Day 1 (range: 4 to 24) and 6.0 hours on Day 14 (range: 0 to 16). Accumulation after 14 days of topical application was less than two fold. Trough concentrations generally increased throughout the 14 day study period. Naftifine continued to be detected in plasma in 13/21 (62%) subjects on day 28, the mean (SD) plasma concentrations were 1.6 ± 0.5 ng/mL (range below limit of quantitation (BLQ) to 3 ng/mL).

In the same pharmacokinetic study conducted in patients with tinea pedis and tinea cruris, median fraction of the dose excreted in urine during the treatment period was 0.0016% on Day 1 versus 0.0020% on Day 14.

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4 Appendices

4.1 Individual Study Reviews:

Synopsis of Study Report MRZ 90200/FI/1002

Title: An Open-Label, Single-Center, Multiple-Application Pharmacokinetic Study of NAFT-500 in Subjects with Tinea Cruris and Tinea Pedis

Study Objectives: The *primary* objective was to quantify the pharmacokinetics (PK) of NAFT-500 Cream, 2% in subjects with tinea pedis and tinea cruris under maximal clinical use conditions of 2 weeks of once-daily application.

The *secondary* objectives were to evaluate efficacy after 2 weeks of treatment and 2 weeks after the last treatment, and to evaluate subject tolerability and safety throughout the

Development Phase: Phase 1

Study Dates: Date of first enrollment: 09 November, 2008
Date when last subject completed the study: 07 February, 2009

Study Design: This study was designed as an open label, single-center, multiple application study to quantify the PK profile of 2 weeks of once-daily application of NAFT-500 Cream, 2%. The plasma and urine concentrations of naftifine in approximately 21 adult subjects (≥18 years old) with tinea cruris and tinea pedis were determined. It was conducted under maximal clinical use conditions with applications of a total of 8 grams of NAFT-500 Cream, 2% to the affected groin area and foot/feet once-daily for 2 weeks. Maximal use condition was defined as having both feet and bikini area affected. The 8 grams were applied as follows: 2 grams to each foot and 4 grams to the bikini area. The efficacy, tolerability, and safety of NAFT-500 Cream, 2% were also assessed during the study. Subjects stayed at the study center on Day 1 (first application) and Day 14 (last application). Efficacy was assessed based on potassium hydroxide (KOH) dermatophyte culture, signs and symptoms, and Physicians Global Evaluation (PGA) results between Baseline and Day 14 (last application) and Day 28 (2 weeks after the last application and 4 weeks after the start of the study). Adverse events (AEs), study medication accountability, and subject compliance were reviewed at each visit. Routine clinical laboratory assessments (serum chemistry, hematology, and urinalysis) were performed at Screening and on Day 14 (end of treatment) and Day 28 (2 weeks after the last application).

Treatments: Treatment consisted of once-daily morning applications of a total of 8 grams of NAFT-500 Cream, 2% applied to tinea pedis and tinea cruris infection sites for 14 days. Two grams of study drug were to be applied to each foot and 4 grams to the bikini area (excluding the buttocks) to affected area and half-inch margin of healthy skin for a total dose of 8 grams. Two grams of study drug was equivalent to 7 centimeters

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(cm); subjects were provided rulers for measurement and were to record date and time of application, as well as the centimeter value, in the study diary. Each diary was reviewed to determine compliance with concomitant medication and for AE reporting for subject safety.

The applications were applied at the clinic during visits on Days 1, 3, 7, 11, 12, 13, and 14. Subjects maintained diary cards documenting all applications at the clinic and at home.

Identity of the Investigational Medicinal Product(s): NAFT-500 Cream, 2%, batch number 23255.1.

Selection of Doses in the Study
The currently marketed cream and gel dosage forms of Naftin® contain 1% naftifine hydrochloride; NAFT-500 Cream, 2% contains 2% naftifine hydrochloride. A clinical study in 11 subjects showed that concentrations of up to 3% naftifine applied to occluded test sites for 21 consecutive days produced no irritation. An 8 g application was specified for all subjects to ensure uniformity in the application dose.

Determination of Sample Size
Approximately 22 eligible subjects were to be assigned to one treatment group to allow for 18 subjects to complete the study. Since this study was not a confirmatory trial, the sample size was not based on a statistical power calculation. It was anticipated that 18 subjects who completed the study would be sufficient for assessment of PK variables.

Pharmacokinetic Sampling: During the 2-week treatment period, PK blood samples were collected on Days 1 and 14 at 0 hour (pre-application) and at 1, 2, 4, 6, 8, 12, 16, and 24 hours post-application. Pre-application samples were also collected on Days 3, 7, 11, 13, 14, 21 (1 week post-application), and 28 (2 weeks post-application). Samples collected on Days 11 through 14 were used to assess steady state. Pharmacokinetic urine samples were collected on Days 1 and 14 for 24 hours as follows: pre-application (complete void and only on Day 1); and from 0 to 6, 6 to 12, and 12 to 24 hours post-application. To collect blood and urine samples for PK analysis, subjects remained in the clinic for 24 hours on Days 1 and 14.

Subjects fasted for 10 hours prior to collection of blood samples for clinical laboratory tests at Screening and on Days 14 and 28. Meals were served at the clinic on Days 1 and 14 following the application of the study medication. No restrictions were placed on activities while in the clinic.

Pharmacokinetic Data Analysis: The concentration of naftifine in plasma and urine over time was used to calculate PK parameter estimates when sufficient data were present. No active and no toxic metabolites were known for naftifine; therefore, no metabolites were included in the PK analyses. Pharmacokinetic variables were calculated from the plasma and urine concentration data using standard, non-compartmental

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methods as implemented in WinNonlin Enterprise version 5.2 (b) (4)
PK variables determined were as follows:
Primary PK variables: AUC0-24, AUC0-t, Cmax;
Secondary PK variables: Ctrough, Tmax, Ae 0-24 (amount excreted in the urine over 24 hours), Fe% 0-24 (fraction of dose excreted in the urine), CLr

Statistical Analysis:
Mean plasma and urine concentration are summarized by descriptive statistics (i.e., n, mean, and SD) by each scheduled time point. PK variables are summarized for Day 1 and Day 14 using appropriate graphs and descriptive statistics (number of subject [n], mean, standard deviation [SD], geometric mean, coefficient of variance [CV%] of geometric mean, minimum, median, and maximum), including two-sided 90% confidence intervals [CI] for the arithmetic or the geometric mean, as appropriate. The maximum plasma concentration (Cmax) and the area under the plasma concentration-time curve (AUC) are summarized using geometric means, also with 90% CIs.

Bioanalytical Method and Validation Summary:

A. Plasma

Analytical Methods: A high performance liquid chromatographic method was used for the determination of naftifine in human EDTA K3 plasma. Basically, naftifine and its internal standard naftifine-N-methyl-d3 were extracted from an aliquot of human EDTA K3 plasma using automated liquid-liquid extraction (Liquid Handling System) then the extract is injected into a liquid chromatograph. Detection was made with a tandem mass spectrometry detector.

Validation of Analytical Methods (SOP (b) (4) 9627.01): A summary of the analytical method validation results is presented below:

Linearity:	$r^2 \geq 0.9976$
Calibration Curve Range:	1.01 to 1013.60 ng/mL
Between-Run Accuracy[1]:	99.86 to 101.87%
Between-Run Precision[2]:	1.94 to 5.53%
Within-Run Accuracy[1]:	96.54 to 102.59%
Within-Run Precision[2]:	1.23 to 6.22%
Recovery of Analyte: QC (1, 2 and 3) means:	88.68, 90.33 and 94.52%
Recovery of Internal Standard: Mean:	106.84%
Matrix Selectivity:	No significant interference observed
Lower Limit of Quantitation (LLOQ):	1.01 ng/mL (% CV=8.12; n=6)
Freeze and Thaw Stability Accuracy at -20°C[1]:	97.03 and 94.43%
Freeze and Thaw Stability Precision at -20°C[2]:	3.03 and 1.87%
Freeze and Thaw Stability Accuracy at -80°C[1]:	99.12 and 95.85%
Freeze and Thaw Stability Precision at -80°C[2]:	3.80 and 1.06%
Long-Term Stability of Analyte in Solution	
Mean % change after 136 days:	3.66% at -80°C:

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Long-Term Stability of Internal Standard Mean % change after 158 days:	3.22% in Solution at -80°C:
Long-Term Stability of Analyte in Matrix Mean % change after 143 days:	-13.83 (QC1) and -8.28% (QC3) at -20ºC:
Long-Term Stability of Analyte in Matrix Mean % change after 143 days:	-11.43 (QC1) and -3.47% (QC3) at -80ºC:

[1] QC % nominal concentrations; [2] QC coefficients of variation

The applicant stated that during the analysis of the samples, the analytical range of SOP (b) (4) 9627.01 (1 to 1000 ng/mL) was too high and thus did not provide appropriate coverage of the study samples concentrations. A new range (1 to 100 ng/mL) was validated with SOP (b) (4) 9711.01 and all study samples were analyzed with that new range. In order to validate this change, the revised method was partially validated. A summary of the partial validation data obtained is presented below:

Within-Run Accuracy: QC % nominal concentrations: -9.67 to 3.36%
Within-Run Precision: QC coefficients of variation: 2.57 to 6.43%

The new range using the same method was also validated during in-study performance. A summary of the in-study validation parameters is presented below:

Linearity:	$r^2 \geq 0.9944$
Calibration Curve Range:	1.00 to 99.60 ng/mL
Between-Run Accuracy[1]:	-1.74 to 1.00
Between-Run Precision[2]:	3.43 to 5.63

The applicant provided the following information on the storage of the Plasma samples:

Sample Storage Temperature: -20ºC
First Date of Analysis to Last Date of Analysis: 2009-02-09 to 2009-02-18
Duration of Sample Storage (first collection date (PK1) to last analysis): 128 days
Demonstrated Stability of Analyte in Matrix: 143 days at -20ºC

The applicant's conclusions were that the performance of the analytical method was successfully demonstrated in the validation report (summary provided above) and also during in-study method performance (between-run accuracy (% bias = -1.74 to 1.00) and precision (% CV = 3.43 to 5.63).

Reviewer's Comments: I agree with the applicant's conclusions. Although the validation method for the reduced calibration range was not ideal, however, since it is within the range of the already validated method I believe it is acceptable.

B. Urine

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Analytical Methods: A high performance liquid chromatographic method was used for the determination of naftifine in human urine. The analyte naftifine and its internal standard naftifine-N-methyl-d3 were extracted from an aliquot of human urine using an automated liquid-liquid extraction (Liquid handling system). The extracted samples were injected into a liquid chromatograph. Detection was made with a tandem mass spectrometry detector

Validation of the Analytical Method (SOP (b) (4) 9725.01): A summary of the validation results is presented below:

Linearity:	$r^2 \geq 0.9988$
Calibration Curve Range:	49.80 to 9960.00 pg/mL
Between-Run Accuracy:	QC % bias: 1.17 to 2.27%
Between-Run Precision:	QC coefficients of variation: 2.18 to 4.24%
Within-Run Accuracy:	QC % bias: 1.09 to 5.47%
Within-Run Precision:	QC coefficients of variation: 0.92 to 3.91%
Recovery of Analyte:	QC means (QC1, 2, 3): 89.25%, 95.79% and 96.21%
Recovery of Internal Standard:	Mean: 88.59%
Dilution Integrity Accuracy:	QC % bias: 1.15 and -7.93%
Dilution Integrity Precision:	QC coefficients of variation: 1.44 and 2.28%
Lower Limit of Quantitation (LLOQ):	49.80 pg/mL (% CV =2.74 and % Bias =4.64)
Matrix Selectivity:	No significant interference observed in 10 of 10 tested matrices for naftifine and internal standard.
Freeze and Thaw Stability at -20°C:	QC % bias: -3.23 and -1.21%
Freeze and Thaw Stability at -80°C:	QC % bias: -3.91 and -1.09%

Long-Term Stability of Analyte in Matrix at -20ºC: Mean % change after 3 days: -4.13 and -2.05%
Long-Term Stability of Analyte in Matrix at -80ºC: Mean % change after 3 days: -2.44 and -1.29%

A partial validation was performed to extend stabilities using the method described in SOP (b) (4) 9725.01: A summary of the validation results is presented below:

Long-Term Stability of Analyte in Matrix at -20ºC: Change after 199 days: -3.50 and 0.32%
Long-Term Stability of Analyte in Matrix at -80ºC: Change after 199 days: 0.73 and 4.70%

The applicant provided the following information on the storage of the Plasma samples:
Storage Temperature: -80ºC
Number of Subjects Analyzed: 21
First Date of Analysis to Last Date of Analysis: 2009-02-10 to 2009-04-20
Duration of Sample Storage (first collection date (PK1) to last analysis): 189 days
Demonstrated Stability of Analyte in Matrix: 199 days at -80ºC

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The applicant's conclusions were that the performance of the analytical method was successfully demonstrated in the validation report (see above) and also during in-study method performance (between-run accuracy (% bias = -7.29 to 1.08) and precision (% CV = 0.5 to 1.79).

Reviewer's Comments: Applicant's conclusions are acceptable

RESULTS

Demographics and Baseline Characteristics: 21 subjects were enrolled and they all completed the study,

Table 8: Demographics and Baseline Characteristics

Category	NAFT-500 Cream, 2% (N=21)
Gender	
Male	20 (95.2%)
Female	1 (4.8%)
Race	
White	19 (90.5%)
Black or African American	2(9.5%)
Asian	0
American Indian or Alaska Native	0
Native Hawaiian or Other Pacific Islander	0
Ethnicity	
Hispanic or Latino	6 (28.6%)
Not Hispanic or Latin	15 (71.4%)
Age (years)	
N	21
Mean	37.0
SD	13.69
Min	18
Median	36.0
Max	63
Height (cm)	
N	21
Mean	179.10
SD	6.529
Min	160.0
Median	180.30
Max	187.9
Weight (kg)	
N	21
Mean	109.33
SD	21.945
Min	65.8
Median	111.40
Max	145.5
Tinea Pedis Classification	
Infected Foot	
Right Foot Only	0
Left Foot Only	0
Both Right Foot and Left Foot	21 (100.0%)
Type	
Interdigital Only	2 (9.5%)
Moccasin Type Only	1 (4.8%)
Both Interdigital and Moccasin Types	18 (85.7%)
Other	0

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The [redacted] (b) (6) subject in the study was [redacted] (b) (6) (Subject [redacted] (b) (6).

Measurement of Treatment Compliance: The mean average daily dose of naftifine in NAFT-500 Cream, 2% was 0.114 g and ranged from 0.09 g to 0.13 g.

Table 9: Summary of Treatment Compliance

	NAFT-500 Cream, 2% Average Amount (g) Dispensed from Tube (1)	NAFT-500 Cream, 2% Average Daily Dose(g) (1)	NAFT-500 Cream, 2% Total Dose(g) Used (2)	Compliance (%) (3)
N	21	21	21	21
Mean	6.435	0.114	1.598	80.434
SD	0.7319	0.0130	0.1818	9.1485
Min	5.28	0.09	1.31	65.98
Median	6.400	0.114	1.590	80.000
Max	7.46	0.13	1.85	93.30

(2) Total Dose Used = (total dispensed) - (total returned).
(3) Compliance = 100*(total used dose)/ (total expected dose). Expected dose = 8 grams once a day for 2 weeks.
Note: Average Daily Dose=average amount of active ingredient. Total Dose=total amount of active ingredient.

Reviewer's Comments: An IR was sent to the sponsor on 07/07/2011 as follows:

In the study report for the maximal use PK study MRZ 90200/FI/1002, you stated that "the mean average daily dose of NAFT-500 Cream, 2% was 0.114 g and ranged from 0.09 g to 0.13 g" however in the protocol you stated that the" Treatment consisted of once-daily morning applications of a total of 8 grams of NAFT-500 Cream, 2% applied to tinea pedis and tinea cruris infection sites for 14 days". Therefore, it appears that the average dose used in the study was much less than what was intended per protocol to represent maximal use application.

The applicant responded on July 11th, 2011 as follows

The protocol correctly states that "Treatment consisted of once-daily morning applications of a total of 8 grams of NAFT-500 Cream, 2% applied to tinea pedis and tinea cruris infection sites for 14 days."

Section 12.1 and Text Table 20 are supported by Table 14.2.4. For Table 14.2.4, the data summarized in Columns 2 and 3 are adjusted based on the actual amount of "free naftifine" within the formula (meaning the weight of naftifine free base, not the hydrochloride salt, administered to the subject not including the weight of the excipients in the cream formulations).

The following calculations were used for each of the 4 columns within Table 4:

- 1st column (Average daily dose from tube) = ((Dose dispensed) - (Dose returned))/14
- 2nd column (Average daily dose) = ((Dose dispensed) - (Dose returned)) *0.02*0.887/14
- 3rd column (Total Dose (g) Used) = ((Dose dispensed) - (Dose returned)) *0.02*0.887
- 4th column (Compliance) = 100*((Total Dose (g) Used)) / (8*14*0.02*0.887)

The above calculations were used in the creation of the table, but are not presented in the listings (that is, Listing 16.2.3 presents the dose dispensed and the dose returned, but not the further calculated information above).

Reviewer's Comments: Despite the applicant's explanation, the average daily dose was still less than the 8g (median = 6.4g, range = 5.28g-7.46g) stated in the protocol and claimed in the label. Label will reflect correct amount. It is noted that the range of the amount used in the study seems closer to the upper limit of the amount used in the

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individual clinical trials for each indication. Inserted below is the gram amount of study medication used in the clinical trial (extracted from the response to the filing communication letter dated March 31st, 2011)

Table 10 Medication use in Grams per Day in Study MRZ 90200/0736/1 (Tinea pedis)

Weight used adjusted per day (g/day)[1]	NAFT-500 (N=221)	2-Week Placebo (N=110)	Naftin 1% (N=209)	4-Week Placebo (N=110)
Mean (Standard Deviation)	1.70 (1.031)	1.63 (0.947)	1.77 (0.929)	1.77 (0.786)
Median	1.53	1.39	1.61	1.66
Minimum, Maximum	0.00, 6.35	0.12, 4.67	0.05, 6.66	0.27, 3.46
Q1, Q3	0.99, 2.22	0.98, 2.28	1.11, 2.40	1.15, 2.30

1 Computed as weight used/days of exposure to study medication.

Data Source: Listings 13, 14, and 15 Study MRZ 90200/0736/1 (Tinea Pedis)

Table 11 Medication use in Grams per Day in Study MRZ 90200/FI/3001 (Tinea cruris)

Weight used adjusted per day (g/day)[1]	NAFT-500 (N=157)	2-Week Placebo (N=151)
Mean (Standard Deviation)	1.66 (1.015)	1.88 (1.371)
Median	1.46	1.55
Minimum, Maximum	0.12, 4.69	0.14, 12.50
Q1, Q3	0.87, 2.21	0.94, 2.61

1 Computed as weight used/days of exposure to study medication.

Data Source: Listings 13, 14, and 15 Study MRZ 90200/FI/3001 (Tinea Cruris)

Analysis of Plasma Concentration Data:

Mean plasma concentrations of naftifine increased slowly, reaching maximal observed concentrations between 6-8 hours after topical application of NAFT-500 Cream on Day 14 (see figure 3 below).

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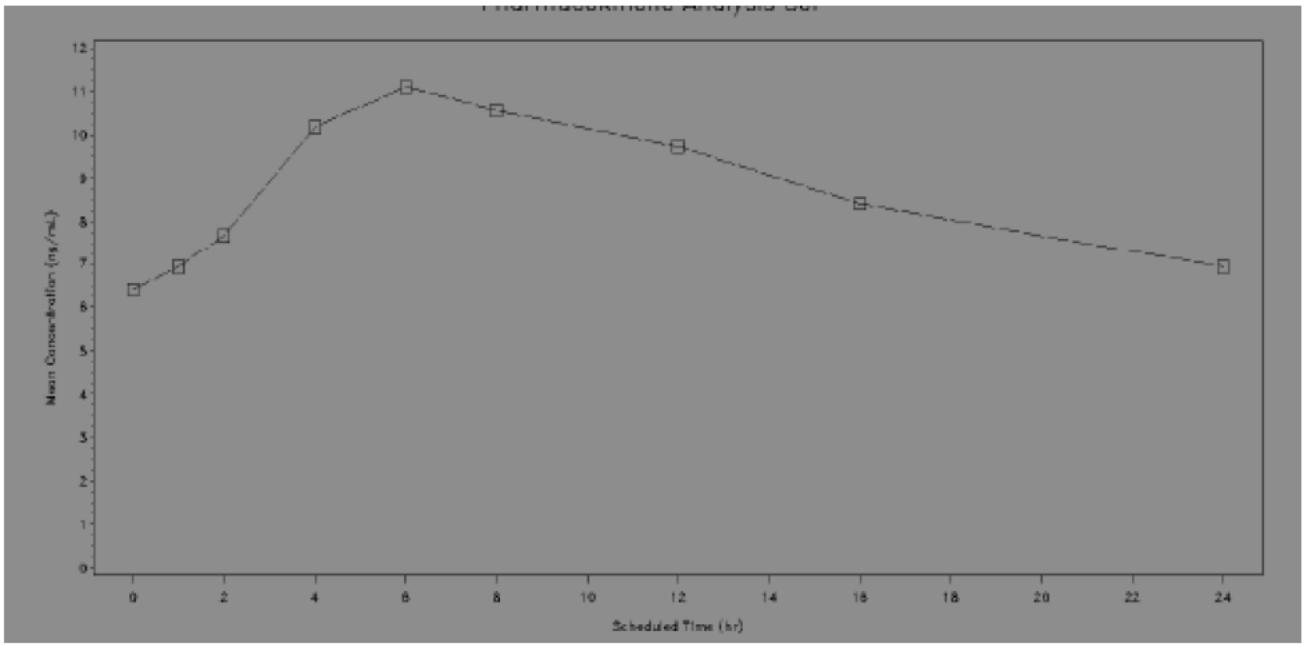

Figure 3: Mean Plasma concentrations of Naftifine by time on Day 14

Measurable concentrations of naftifine appeared in plasma within 1 hour of application and increased through the treatment period. Mean (± SD) plasma concentrations peaked at 6 hours on both Days 1 and 14 (7 ± 4.6 ng/mL and 11 ± 3.3 ng/mL, respectively). Within 24 hours after application on Day 14, mean plasma concentrations of naftifine were near pre-application levels (6.9 ng/mL versus 6.4 ng/mL, respectively).

Table 12 Summary of Plasma Concentrations (ng/mL) of Naftifine over time on Day 1

Statistics	Pre-Dose (N=21)	1 Hour (N=21)	2 Hours (N=21)	4 Hours (N=21)	6 Hours (N=21)	8 Hour (N=21)	12 Hours (N=21)	16 Hours (N=21)	24 Hours (N=21)
N	21	21	21	21	21	21	21	20	21
Mean	0.000	0.866	3.176	5.931	7.414	6.776	6.240	5.165	4.212
SD	0.0000	0.8938	2.2848	2.9556	4.5803	3.7768	2.5406	1.7781	1.7056
CV%		103.241	71.945	49.834	61.777	55.740	40.714	34.426	40.490
Geometric Mean		1.611	3.293	5.346	6.554	6.117	5.860	4.899	3.859
Min	0.00	0.00	0.00	2.31	2.36	3.32	3.59	3.06	1.70
Median	0.000	1.190	2.470	5.150	6.490	5.600	5.580	4.690	4.130
Max	0.00	2.47	8.82	14.36	24.99	20.20	14.39	8.93	7.29
90% C.I.(1)		(1.421, 1.828)	(2.702, 4.013)	(4.495, 6.358)	(5.459, 7.869)	(5.201, 7.195)	(5.143, 6.678)	(4.313, 5.564)	(3.266, 4.560)

(1) 90% CIs were calculated based on the geometric mean

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Table 13 Summary of Plasma Concentrations (ng/mL) of Naftifine over time on Day 14

Statistics	Pre-Dose (N=21)	1 Hour (N=21)	2 Hours (N=21)	4 Hours (N=21)	6 Hours (N=21)	8 Hour (N=21)	12 Hours (N=21)	16 Hours (N=21)	24 Hours (N=21)
N	21	21	21	21	21	21	21	21	21
Mean	6.410	6.931	7.686	10.186	11.114	10.572	9.742	8.429	6.929
SD	2.1247	2.4437	2.0611	3.3273	3.3148	3.5172	2.6600	2.8061	2.1922
CV%	33.144	35.255	26.815	32.667	29.825	33.268	27.305	33.291	31.640
Geometric Mean	6.099	6.535	7.420	9.631	10.571	9.972	9.336	7.982	6.575
Min	3.56	3.07	4.33	4.54	4.20	4.08	3.50	3.76	2.76
Median	6.280	6.830	7.980	9.450	11.410	10.720	9.310	8.250	6.890
Max	11.10	12.94	12.67	17.27	16.70	17.30	14.62	13.95	12.21
90% C.I.(1)	(5.405, 6.882)	(5.718, 7.469)	(6.687, 8.233)	(8.425, 11.010)	(9.293, 12.025)	(8.696, 11.435)	(8.284, 10.522)	(7.014, 9.084)	(5.775, 7.486)

Variability in plasma concentration was considerably greater at the 6-hour time point on Day 1, because Subject (b) (6) had a plasma concentration of 25 ng/mL, nearly 4 times as high as the mean (7 [CV% 61.8]); the Day 14 plasma concentrations were higher and less variable (mean 11 ng/mL [CV% 29.8]). Naftifine continued to be detected in plasma in 13 subjects at Day 28. Plasma levels ranged from BLQ to 3 ng/mL.

<u>Achievement of Steady State:</u>

Table 14 Summary of Ctrough Plasma Concentrations (ng/mL) of Naftifine over time

Statistics	Day 2 (N=21)	Day 3 (N=21)	Day 7 (N=21)	Day 11 (N=20)	Day 12 (N=21)	Day 13 (N=21)	Day 14 (N=21)	Day 15 (N=21)
N	21	21	21	20	21	21	21	21
Mean	4.212	4.107	5.270	5.767	5.944	5.750	6.410	6.929
SD	1.7056	1.6938	2.4862	4.3023	2.3073	2.0779	2.1247	2.1922
CV%	40.490	41.241	47.172	74.608	38.819	36.137	33.144	31.640
Geometric Mean	3.859	3.758	4.640	4.366	5.529	5.336	6.099	6.575
Min	1.70	1.51	1.65	1.33	2.38	1.72	3.56	2.76
Median	4.130	4.340	4.740	4.490	5.260	5.510	6.280	6.890
Max	7.29	7.87	10.20	16.93	11.09	9.08	11.10	12.21
90% C.I.(1)	(3.266,4.560)	(3.175, 4.447)	(3.774, 5.704)	(4.103, 7.430)	(5.075, 6.812)	(4.968, 6.532)	(5.611, 7.210)	(6.104, 7.754)

Trough concentrations generally increased through the study period; mean Ctrough, 24 hr was 7 ng/mL (CV% 31.6; range 2.8, 12.2 ng/mL) on Day 15 versus 4 ng/mL (CV % 40.5; range 1.70, 7.3 ng/mL) on Day 2.

Reviewer's Comments: It does not appear that steady state was achieved during the 14 day duration of this study.

Reference ID: 3035345

Pharmacokinetic Parameter Estimates

A. Plasma

Table 14 Summary of Day 1 Naftifine Pharmacokinetic Parameters

Statistics	AUC_{0-24} (ng*hr/mL)	$C_{max,SD}$ (ng/mL)	C_{24hr} (ng/mL)	$T_{max,SD}$ (hr)
N	21	21	21	21
Mean	—	—	4.212	8.1
SD	—	—	1.7056	4.36
CV%	41.2487	55.640	40.490	53.8
Geometric Mean	116.7185	7.258	3.859	7.4
Min	66.900	3.79	1.70	4
Median	106.0650	7.150	4.130	8.0
Max	278.560	24.99	7.29	24
90% C.I.(1)	(101.740, 133.902)	(6.202, 8.494)	(3.266, 4.560)	(6.5, 9.7)

(1) 90% CIs were calculated based on the arithmetic mean, with the exception of C_{max}, AUC, and C_{trough} which present 90% CIs for the geometric mean.

Table 15 Summary of Day 14 Naftifine Pharmacokinetic Parameters

Statistics	AUC_{0-t} (ng*hr/mL)	$C_{max, Day 14}$ (ng/mL)	C_{24hr} (ng/mL)	$T_{max, Day 14}$ (hr)
N	21	21	21	21
Mean	—	—	6.929	7.1
SD	—	—	2.1922	3.26
CV%	28.4868	29.291	31.640	45.6
Geometric Mean	204.2620	11.293	6.575	7.1
Min	90.305	4.71	2.76	0
Median	209.1350	11.760	6.890	6.0
Max	331.905	17.30	12.21	16
90% C.I.(1)	(181.6132, 229.7353)	(9.987, 12.769)	(5.775, 7.486)	(5.9, 8.4)

(1) 90% CIs were calculated based on the arithmetic mean, with the exception of C_{max}, AUC, and C_{trough} which present 90% CIs for the geometric mean.

Systemic exposure to naftifine increased over the 2-week treatment period; geometric mean AUC0-24 was 117 ng*hr/mL (CV% 41.2) on Day 1, and AUC0-t was 204 ng*hr/mL (CV% 28.5) on Day 14. Maximum concentration increased over the treatment period; Cmax single dose (SD) was 7 ng/mL (CV% 55.6) on Day 1; Cmax on Day 14 was 11 ng/mL (CV% 29.3). Median Tmax was 8.0 hours after the first application of study drug on Day 1 (range: 4, 24) and 6.0 hours on Day 14 (range: 0, 16). Accumulation after 14 days of topical application was less than twofold. Half-life was not determined.

Reviewer's Comments: It is not clear why the arithmetic mean for AUC and Cmax were not calculated. This reviewer calculated the Arithmetic mean for AUC and Cmax and they were close in value to the geometric mean.

B. Urine Pharmacokinetics

Reference ID: 3035345

Table 16 Summary of Urine Naftifine Pharmacokinetic Parameters on Day 1 and Day 14

Subject / Statistics	Ae_{0-24} (µg)	$Fe\%_{0-24}$	CLr (L/h)	CLr (mL/min)
Day 1				
N	21	21	21	21
Mean	7.165	0.006376	83.148	1385.805
SD	20.7062	0.0194344	286.3746	4772.9094
CV%	289.001	304.826594	344.414	344.414
Geometric Mean	2.324	0.001912	19.910	331.830
Min	0.63	0.00038	6.53	108.81
Median	1.920	0.001568	16.803	280.044
Max	96.64	0.09080	1330.65	22177.44
90% C.I.(1)	(-0.628, 14.958)	(-0.000939, 0.013690)	(-24.633, 190.930)	(-410.548, 3182.158)
Day 14				
N	21	21	21	21
Mean	5.954	0.004129	36.055	600.909
SD	12.2670	0.0078262	97.6625	1627.7089
CV%	206.022	189.536832	270.874	270.874
Geometric Mean	3.162	0.002286	15.482	258.040
Min	0.89	0.00047	5.99	99.87
Median	2.831	0.002020	11.131	185.510
Max	58.68	0.03759	460.96	7682.59
90% C.I.(1)	(1.337, 10.571)	(0.001184, 0.007075)	(-0.702, 72.811)	(-11.703, 1213.521)

Urine PK was quite variable. Median Ae_{0-24} increased from 2 µg (range 0.63, 96.64 µg) on Day 1 to 3 µg (range 0.89, 58.68 µg) on Day 14. The median for fraction of the dose eliminated in urine over 24 hours (Fe%) also increased slightly during the treatment period from 0.001568% at Day 1 to 0.002020% on Day 14. Renal clearance (CLr), reported in liters per hour decreased during the study period, median results were 17 L/hr on Day 1 and 11 L/hr on Day 14.

The applicant reported that there was one extreme outlier (Subject [redacted] (b) (6) in the study) that markedly skewed the urine PK results; therefore, medians are reported. This subject's urine concentration results were more than 10-fold higher than the mean, thus they were queried at both the laboratory and the clinical study sites; both sites affirmed that collection procedures and testing were all performed per protocol and no deviations had been noted. Medical review of the subject's results and history showed [redacted] (b) (6) and it is suspected that the urine samples may have been contaminated during collection; other data collected did not suggest abnormalities that may have contributed to the abnormal results. The PK plasma values of the subject were in the lower range on the study population (see table below). Therefore, the systemic exposure of this subject is not higher despite the high values of naftifine found in urine.

Table 17 PK parameters for Subject # [redacted] (b) (6)

Reference ID: 3035345

Subject # (b) (6)	AUC (ng*hr/mL)	Range of all 21 subjects	Cmax (ng/mL)	Range for all 21 subjects
Day 1	72.6	66.9-278.5	3.79	3.79-24.99
Day 14	127.3	90.3-331.9	7.32	4.71-17.30

A summary of the amount of naftifine excreted in urine is presented in Table 18.

Table 18 Summary of Naftifine Amount (ng) Excreted in urine by Scheduled time on Day 1 and Day 14

Subject /Statistics	Pre-Dose (N=19)	0-6 Hours (N=21)	6-12 Hours (N=21)	12-24 Hours (N=21)	Total (N=21)
Day 1					
N	19	21	21	21	21
Mean	17.861	4548.743	868.886	1730.964	7164.754
SD	55.8127	15732.3077	1029.2949	4165.4206	20706.2290
CV%	312.484	345.861	118.461	240.642	289.001
Geometric Mean	27.124	642.438	569.193	722.925	2323.843
Min	0.00	93.17	187.15	95.73	631.51
Median	0.000	427.999	520.464	917.206	1919.889
Max	241.26	72410.85	4471.72	19762.28	96644.84
90% C.I.(1)	(5.892, 124.873)	(358.919, 1149.916)	(410.104, 789.997)	(465.652, 1122.343)	(1515.211, 3564.025)
Day 14					
N	–	20	21	21	21
Mean	–	3678.827	1098.082	1352.509	5954.236
SD	–	11043.1692	1139.8245	931.2077	12267.0318
CV%	–	300.182	103.801	68.850	206.022
Geometric Mean	–	970.940	775.028	1087.710	3162.460
Min	–	132.00	210.27	305.56	890.43
Median	–	950.678	745.174	1085.403	2830.704
Max		50365.83	5360.99	3567.90	58684.22
90% C.I.(1)		(575.617, 1637.765)	(568.706, 1056.200)	(1002.035, 1702.982)	(1337.362, 10571.110)

(1) 90% CIs were calculated based on the geometric mean.

The amount (ng) of naftifine excreted in urine was generally greatest over the last 12 hours of the 24-hour collection period on both Day 1 and Day 14. The geometric mean amount of naftifine excreted for the 12-24 hours collection period on Day 1 was 723 ng (CV% 240.6) compared with the 0-6 hours (geometric mean amount of naftifine was 642 (CV% 346)) and 6-12 hours (geometric mean amount of naftifine was 569 (CV% 119)) collection period although variability in the results overall made interpretation difficult. On Day 14, naftifine amounts excreted in urine were higher than on Day 1 at all time

Reference ID: 3035345

periods and less variable for the 12-24 collection period. The geometric mean amount of naftifine excreted for the 12-24 hours collection period on Day 14 was 1088 ng (CV% 68.9) compared with the 0-6 hours (geometric mean amount of naftifine was 971 (CV% 300)) and 6-12 hours (geometric mean amount of naftifine was 775 (CV% 100))

The applicant stated that in some urine samples pre-dose positives were observed. Naftifine was detected in pre-dose urine samples on Day 1 in 5 subjects identified in Table 19 below. The geometric mean pre-dose urine concentrations were (27.1 ng /mL with a range of 0-241.3 ng/mL). The applicant stated that these results were confirmed by the analytical laboratory. The clinical site confirmed that collection procedures were followed per protocol and that contamination of these subjects within the clinic was not indicated.

Table 19: Subjects with Naftifine in Pre-dose Urine Samples

Subject Number	Pre-dose Naftifine (pg/mL)
(b) (6)	101.36
	101.36
	2412.64
	72.72
	133.52

Reviewer's Comments: Subjec (b) (6) was definitely an outlier. It is unclear why these pre-dose positives were observed.

Applicant's Pharmacokinetic Conclusions

Pharmacokinetic analysis of plasma and urine samples from 21 subjects treated with the maximum dose (8 g) of NAFT-500 Cream, 2% once daily for 14 days showed increased exposure to naftifine over the 2-week treatment period; geometric mean AUC0-24 was 117 ng*hr/mL (CV% 41.2) on Day 1, and AUC0-t was 204 ng*hr/mL (CV% 28.5) on Day 14. Maximum concentration also increased over the treatment period; Cmax was 7 ng/mL (CV% 55.6) on Day 1; Cmax on Day 14 was 11 ng/mL (CV% 29.3). Median Tmax was 8.0 hours after the first application of study drug on Day 1 (range: 4- 24) and 6.0 hours on Day 14 (range: 0-16). Trough concentrations generally increased through the study period; geometric mean Ctrough, 24 hr was 7 ng/mL (CV% 31.6; range 2.76- 12.21 ng/mL) on Day 15. Accumulation after 14 days of topical application was less than twofold.

Urine PK results were skewed by an outlier whose urine concentrations were markedly higher than the rest of the population. Median Ae0-24 increased over the course of the study from 2 µg (range 0.63, 96.64 µg) on Day 1 to 3 µg (range 0.89, 58.68 µg) on Day 14. Median Fe% also increased during the treatment period from 0.0016% at Day 1 to 0.0020% at Day 14. Median CLr decreased during the study period from 17 L/hr on Day 1 to 11 L/hr on Day 14.

Reference ID: 3035345

Comparison of topical PK data with oral PK data

The TQT study utilized a single-dose, randomized, double-dummy, double-blind, 3-treatment, parallel design with a supratherapeutic dose (600 mg naftifine HCl capsule), a placebo control, and a positive control (400 mg moxifloxacin). The results of the TQT study are intended to be applied to NAFT-500 Cream, 2 %.

The applicant's rationale for using the 600 mg capsule was that due to the poor systemic absorption from the topical product, an oral formulation was chosen to obtain the supratherapeutic level of exposure. An oral dose of 600 mg administered daily for 4 days was tested in healthy volunteers in a previous study (Study report NAFT-910-SNDZ; original NDA 19-599 for Naftin 1 % Cream). Following a single 600 mg oral dose, peak plasma levels (Cmax) and the rate of absorption (area under the concentration-versus-time curve [AUC]) were approximately 18 and 2 times higher than that achieved during multiple topical applications of a 2% naftifine HCl cream in patients, respectively, and was, therefore, considered appropriate as the supratherapeutic dose in this study. The applicant's rationale for using 600 mg naftifine capsule in the TQT study was submitted (January 10th, 2011) to the Agency in IND 105,603 in the protocol and found acceptable by the QT/IRT reviewer (DARRTS entry dated March 16th, 2011) and the clinical reviewer (DARRTS entry dated March 30th, 2011). Summarized in the table below is the PK information (extracted from IRT-QT review of March 16th, 2011) provided by the sponsor to justify their rationale for selecting the 600 mg oral capsule.

Table 20: Values (mean or median, (CV) %) for the (AUC0-t), (C_{max}) and t_{max} following oral (single and multiple dose)[1] and topical application of naftifine[2]

	Single oral dose of 600 mg capsule[4] (median values)	Multiple oral doses of 600 mg capsule QD for 4 days[4] (median values)	Multiple topical application of 8 g QD of NAFT-500 cream, 2% for 14 days.[6] (geometric mean)
AUC_{0-t} (ng*h/mL):	460 (8)	376 (41)	204 (29)
C_{max} (ng/mL):	200(12)	212 (46)	11 (29)
t_{max} (hour):	1.5 (33)	1.5 (33)	8.1 (54)

[1]The pharmacokinetic data for the three oral formulations was taken from Study Report NAFT-910-SNDZ included in the original NDA 19-599 submission. The oral PK data were measured using HPLC methods following 4 daily administrations of 600 mg/day using a three-way crossover study design in three volunteers (i.e., all three volunteers received all four daily treatments with each of the three formulations).

[2]The pharmacokinetic data for the topical formulation is taken from NAFT-500 Cream, 2% maximal-use PK Study Report MRZ 90200/FI/1002.

Reference ID: 3035345

Based on the data in the table above, the IRT-QT reviewer stated that ***"The sponsor's rationale for using 600-mg oral capsule in the TQT study appears to be reasonable. The C max following a single dose of 600-mg oral capsule is about 20-fold higher than the steady state Cmax 8 g q.d. of 2% NAFT-500 cream for 14 days."***

Reviewer's Comments: The above comments by the IRT –QT reviewer is further supported by the PK data obtained in 44/133 subjects in the currently conducted TQT study following administration of the 600 mg capsule as shown in the table below:

Table 21: Summary of Naftifine Pharmacokinetic Parameters Following One 600 mg Capsule of NAFT-600 and One Matching Moxifloxacin Placebo Tablet in the TQTstudy (Treatment A)

	AUC_{0-t} (ng*hr/mL)	AUC_{0-Inf} (ng*hr/mL)	$AUC_{extrap\%}$ (%)	C_{max} (ng/mL)	t_{max} (hr)	k_{el} (1/hr)	$t_{1/2}$ (hr)
N	44	42	42	44	44	42	42
Mean ± SD	731.7 ± 515.7	790.7 ± 533.0	5.35 ± 1.92	221 ± 177	2.01 ± 0.617	0.0996 ± 0.0216	7.27 ± 1.54
Median (min, max)	611.9 (165.1, 2599)	669.7 (212.0, 2654)	5.03 (2.08, 11.7)	172 (47.3, 953)	1.89 (1.12, 4.12)	0.0949 (0.0630, 0.151)	7.30 (4.58, 11.0)

Source: Table 14.2.2.2

Note: The single-dose treatment was administered orally in the morning at Hour 0 on Day 1.

Following a single 600 mg oral dose administration of a single NAFT-600 capsule, the mean peak exposure to naftifine was 221 ng/mL and was reached approximately 2 hrs post dose, and the mean extent of exposure (AUC0-inf) was 790.7 ng*hr/mL. The CV of both AUC and Cmax was > 60%. In general, the elimination phase of naftifine in plasma was well characterized, with the mean apparent half-life of 7.27 hrs. The applicant stated that the PK profile of naftifine was well characterized, with concentrations remaining above the lower limit of quantitation (LLOQ) of 1.00 ng/mL up to 24 hrs post-dose.

Reviewer's Comments: The 600 mg capsule Cmax observed in the TQT study is also about 20 fold higher, however, the AUC is 4 fold higher as compared to 2 fold higher for the data obtained in the original NDA. These data support the applicability of the TQT study conducted with the oral capsule to the topical cream.

Reference ID: 3035345

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/s/

ABIMBOLA O ADEBOWALE
11/01/2011

DOANH C TRAN
11/02/2011

EDWARD D BASHAW
11/02/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019599Orig1s011

<u>OTHER REVIEW(S)</u>

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label and Labeling Memorandum

Date:	January 11, 2012
Reviewer:	Loretta Holmes, BSN, PharmD Division of Medication Error Prevention and Analysis (DMEPA)
Team Leader:	Irene Z. Chan, PharmD, BCPS Division of Medication Error Prevention and Analysis (DMEPA)
Drug Name and Strength:	Naftin (Naftifine Hydrochloride) Cream 2%
Application Type/Number:	NDA 019599/S-011
Applicant:	Mertz Pharmaceuticals, LLC
OSE RCM #:	2011-524

***** This document contains proprietary and confidential information that should not be released to the public.*****

1 INTRODUCTION

This memorandum responds to a request from the Division of Dermatology and Dental Products (DDDP) for DMEPA's evaluation of revised container labels and carton labeling for Naftin (Naftifine Hydrochloride) Cream 2% (NDA 019599/S-011). DMEPA previously reviewed the initial proposed labels and labeling under OSE RCM #2011-524, dated September 12, 2011.

2 METHODS AND MATERIALS

DMEPA reviewed the revised label and labeling received on January 11, 2012 (see Appendices A and B). We compared the revised labels against the recommendations contained in OSE review #2011-524, dated September 12, 2011.

3 CONCLUSIONS AND RECOMMENDATIONS

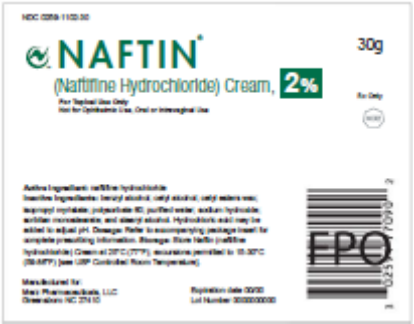
Review of the revised documents show that the Applicant implemented DMEPA's recommendations under OSE review #2011-524. We have no additional recommendations at this time, and we find these revised container labels and carton labeling acceptable.

If you have further questions or need clarifications, please contact Janet Anderson, OSE Project Manager, at 301-796-0675.

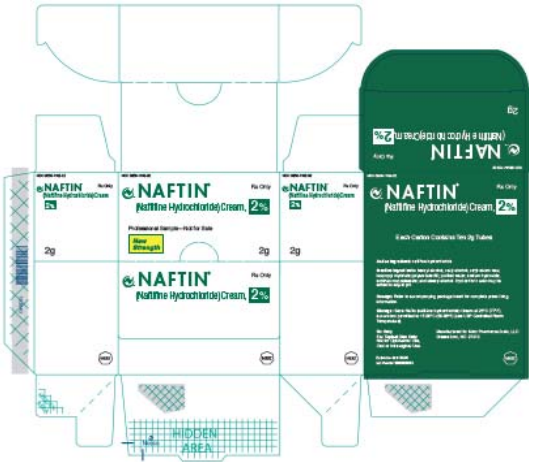
Reference ID: 3070707

APPENDICES

<u>Appendix A:</u> Container Labels: 2 g (professional sample), 30 g, 45 g, and 60 g (not to scale)



Appendix B: Carton Labeling: 2 g (professional sample), 30 g, 45 g, and 60 g (not to scale)



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/s/

LORETTA HOLMES
01/11/2012

IRENE Z CHAN
01/12/2012

SEALD Director Sign-Off Memo and Labeling Review

Product Trade Name (Non-Propriety Name)	**NAFTIN (naftifine hydrochloride) Cream, 2% for topical use**
Application Number/Supplement Number	NDA 19-599/11
Type of Application	Efficacy Supplement
Indication	Treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organism *Trichophyton rubrum* in adult patients ≥18 years of age.
Applicant	Merz Pharmaceuticals LLC
Office/Division	ODE III/DDDP
Division Project Manager	Dawn Williams, BSN
Submission Date	December 16, 2010
PDUFA Goal Date	January 16, 2012
SEALD Review Date	January 10, 2012
SEALD Labeling Reviewer	Jeanne M. Delasko, RN, MS
SEALD Director	Laurie B. Burke, RPh, MPH

This memo confirms that a Study Endpoints and Labeling Development (SEALD) review of final agreed-upon prescribing information (USPI) determined that there are **NO** outstanding labeling issues in the USPI. This determination follows active engagement throughout the review process between the Division and the SEALD Labeling Team concerning labeling regulations (21 CFR 201.56 and 201.57), labeling guidances, and best labeling practices. The 46-item Selected Requirements for Prescribing Information (SRPI) checklist contains a subset of these policies that apply to all approved USPIs. At this time, no SRPI deficiencies were found (see below for the SRPI checklist).

This memo also confirms that because there are no outstanding SRPI issues in the USPI, the SEALD Director has **NO OBJECTION** to the approval of the USPI at this time.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

PRE-DECISIONAL AGENCY MEMO

Date: September 13, 2011

To: Dawn Williams, DDDP

From: Lynn Panholzer, PharmD, DDMAC

Re: NDA# 019599/011
Naftin (naftifine hydrochloride) Cream, 2%

As requested in your consult dated March 1, 2011, DDMAC has reviewed the draft labeling (package insert [PI], carton and container labels) for Naftin (naftifine hydrochloride) Cream, 2%. DDMAC's comments are based on the proposed substantially complete, marked-up version of the PI e-mailed to us on August 23, 2011, and the proposed carton/container labels submitted by the applicant on December 16, 2010.

DDMAC's comments on the PI are provided directly on the attached copy of the labeling.

DDMAC has the following comments on the attached carton and container labels:

1. The proprietary name on the draft carton and container labels includes [redacted] (b) (4)" [redacted] (b) (4), whereas [redacted] (b) (4) has been deleted from the PI. We recommend that the proprietary name be consistent on all labeling.

2. The carton and container labels read, "Dosage: [redacted] (b) (4) [redacted]. Refer to accompanying literature for complete prescribing information." These instructions omit important, specific details about dosing from the PI, which reads, "Apply a thin layer of NAFTIN Cream once-daily to the affected areas plus a ½ inch margin of healthy surrounding skin for 2 weeks." We recommend that the carton and container labels contain accurate, informative dosing information, or that dosing information be omitted in favor of a statement referring to the PI for dosage information.

3. The storage information on the carton and container labels reads, [redacted] (b) (4) at [redacted] (b) (4) 25°C (77°F); excursions permitted between 15 - 30°C (59 - 86°F). This is inconsistent with the draft PI, which reads, [redacted] (b) (4) [redacted] at [redacted] (b) (4) 25°C [redacted] (b) (4) 77° F) [redacted] (b) (4)

excursions permitted to 15-30°C (59-86°F)." We recommend that the storage information be consistent on all labeling.

If you have any questions about DDMAC's comments, please contact Lynn Panholzer at 6-0616 or at Lynn.Panholzer@fda.hhs.gov.

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

LYNN M PANHOLZER
09/13/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label and Labeling Review

Date:	September 12, 2011
Reviewer:	Loretta Holmes, BSN, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Team Leader:	Irene Z. Chan, PharmD, BCPS, Team Leader Division of Medication Error Prevention and Analysis (DMEPA)
Division Director:	Carol A. Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
Drug Name and Strength:	Naftin (Naftifine) Cream 2%
Application Type/Number:	NDA 019599/S-011
Applicant:	Mertz Pharmaceuticals, LLC
OSE RCM #:	2011-524

***** This document contains proprietary and confidential information that should not be released to the public.*****

Reference ID: 3013288

1 INTRODUCTION

This review evaluates the container labels, carton and insert labeling submitted on December 16, 2010 for Naftin (Naftifine HCl) 2% cream in response to a request from the Division of Dermatology and Dental Products.

1.1 BACKGROUND OR REGULATORY HISTORY

Naftin (Naftifine) 1% cream (NDA 019599) and Naftin 1% gel (NDA 019356) are currently marketed in the United States and were approved on February 29, 1988 and June 18, 1990, respectively. This NDA efficacy supplement provides for a 2% strength of Naftin cream.

Naftin Cream 2% is indicated for the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by [redacted] (b) (4) *Trichophyton rubrum,* [redacted] (b) (4) in adult patients 18 years of age and older.

The frequency of administration is the same for both the 1% and 2% strengths; however, the products differ in the tinea pedis indication. Naftin 1% cream and gel are indicated for the treatment of tinea pedis whereas Naftin cream 2% is indicated for the treatment of interdigital tinea pedis. Additionally, the products differ in the recommended duration of therapy. The 1% cream and gel can be administered for up to four weeks whereas the duration of therapy recommended for the 2% cream is two weeks. According to the Applicant, Naftin 1% cream will be discontinued upon approval of the 2% strength.

DMEPA reviewed the proposed proprietary name for this product, [redacted] (b) (4) in OSE Review 2010-2598, dated June 2, 2011 and found the use of the [redacted] (b) (4) unacceptable. The request for proprietary name review of [redacted] (b) (4) was submitted to IND 077530. The Applicant submitted a request for proprietary name reconsideration to the aforementioned IND on July 22, 2011. On September 6, 2011, the Applicant submitted a request for proprietary name review to the NDA.

1.2 PRODUCT INFORMATION

Naftin cream 2% is a topical antifungal indicated for the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by [redacted] (b) (4) *Trichophyton rubrum,* [redacted] (b) (4) in adult patients 18 years of age and older.

Apply a thin layer of Naftin cream 2% once daily to the affected areas plus a ½ inch margin of healthy surrounding skin for 2 weeks. Naftin cream will be supplied in tubes containing 30 g, 45 g or 60 g. The recommended storage is [redacted] (b) (4) 25°C [redacted] (b) (4) 77°F) with excursions permitted to 15°C-30°C (59°F-86°F).

Reference ID: 3013288

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis[1] and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted December 16, 2010 (2 g, 30 g, and 60 g)
- Carton Labeling submitted December 16, 2010 (30 g and 60 g)
- Carton Labeling submitted on August 1, 2011 (2 g)
- Insert Labeling submitted May 27, 2011.

Additionally, we compared the Naftin 2% cream labels and labeling to the currently marketed Naftin 1% cream and gel to identify any look-alike similarities that would present a safety concern (see Appendices C and D).

Additionally, since Naftin 1% cream and gel are currently marketed, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Naftin 1% cream or gel. The AERS search conducted on March 7, 2011 used the following search terms: active ingredient "naft%", trade name "Naftin", and verbatim term "naft%". The reaction terms used were the MedDRA High Level Group Terms (HLGT) "Medication Errors" and "Product Quality Issues". No time limitation was set.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the label or labeling of the product, the case was considered pertinent to this review. Reports excluded from the case series include those that did not describe a medication error or did not describe an error applicable to this review.

3 RESULTS AND DISCUSSION

The following sections describe the findings and assessment of the AERS data and the label and labeling review.

3.1 FDA ADVERSE EVENTS REPORTING SYSTEM (AERS) SELECTION OF CASES

Our AERS search retrieved one case (ISR #1435601) that reported an adverse drug reaction unrelated to a medication error. We determined the case did not inform this review.

3.2 CONTAINER LABELS AND CARTON LABELING

We identified the following deficiencies:

- The labels and labeling are imprinted with the name Naftin [redacted] (b) (4) [redacted] in the name was found unacceptable by DMEPA. The Applicant has submitted a request for reconsideration of proprietary name which is currently

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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under review. Thus, the name (b) (4) may not or may not be found acceptable pending the outcome of DMEPA's reconsideration of the name.

- The layout and presentation of pertinent information such as the established name, strength, route of administration and net quantity is not optimal.
- The route of administration statement (i.e., "For topical use only—Not for Ophthalmic Use") does not match the route of administration statement in the insert labeling.
- The text printed in (b) (4) does not provide adequate contrast against the white background and (b) (4) background colors.
- The graphic located adjacent to the proprietary name is too large.
- The labels are not optimally differentiated from those of Naftin 1% cream.
- The active ingredient statement contains a trailing zero.
- The dosage statement is not complete.
- The storage conditions stated on the container labels do not correspond with the storage conditions stated in the insert labeling.
- The location of the lot number and expiration date is not indicated.
- The net quantity statement is too prominent.
- The NDC number is denoted by a placeholder.

The deficiencies noted in the carton labeling for the 2 g size does not include all of the aforementioned items.

3.3 CONTAINER LABELS

We identified the following deficiencies:

- The proprietary name and established name are too small in size.
- The "S" shaped graphics on the right side of the label limit the optimal use of available space on the label.

3.4 CARTON LABELING (EXCEPT 2 G SIZE)

We identified the following deficiency

- The NDC statement is not in the proper location per regulation.

3.5 INSERT LABELING

- The storage conditions as stated in Section 16 *How Supplied/Storage and Handling* do not correspond with the storage conditions as stated on the container labels and carton labeling.
- The insert labeling is currently a working document requiring frequent revisions. We reserve review of and further recommendations for the insert labeling for the

Reference ID: 3013288

labeling meetings scheduled with the Division of Dermatology and Dental Products.

4 CONCLUSIONS AND RECOMMENDATIONS

We conclude that the proposed labels and labeling are unacceptable and may introduce vulnerability that can lead to medication errors for the reasons stated in Sections 3.2 through 3.5, above. We recommend the following:

A. General Comments

1. The labels and labeling are imprinted with the name (b) (4) in the name was found unacceptable by DMEPA. The Applicant has submitted a request for reconsideration of proprietary name which is currently under review. Thus, the name (b) (4) may or may not be found acceptable pending the outcome of DMEPA's reconsideration of the name.
2. The container labels and carton labeling for the 45 g size were not submitted. We request the following recommendations be applied to the 45 g size as well and that revised labels and labeling submitted to the Agency include the 45 g size.

B. Container Labels (30 g and 60 g) and Carton Labeling (30 g and 60 g)

1. The layout and presentation of pertinent information such as the established name, strength, route of administration and net quantity is not optimal. We have the following recommendations:
   a. Ensure the established name (which includes the active ingredient and dosage form statements) is printed in letters that are at least ½ as large as the letters comprising the proprietary name and that the established name has a prominence commensurate with the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features [21 CFR 201.10(g)(2)].
   b. Delete the (b) (4) shaped lines that separate the proprietary name and established name. These lines are considered intervening matter per 21 CFR 201.10(a).
   c. Use the following format for the presentation of the proprietary name, established name, strength, and route of administration. Please note the route of administration should be revised and relocated to a position below the strength as shown below:

      Naftin
      Naftifine HCl Cream
      2%

      For Topical Use Only
      Not for Ophthalmic, Oral or Intravaginal Use

   d. Increase the size and prominence of the strength.
   e. Decrease the size of the logo that is located adjacent to the proprietary name.

Reference ID: 3013288

2. The text printed in (b) (4) is difficult to read because it does not have sufficient contrast against the white background and (b) (4) background colors. Use a text color that provides sufficient contrast against its background in order to improve the readability of the text.

3. The container labels and carton labeling are not optimally differentiated from Naftin 1% cream. Both the 1% and 2% strengths (b) (4) (b) (4) . Consider the prominent use of a (b) (4) for the labels and labeling of Naftin 2% cream. Additionally, ensure the color used does not overlap with colors used for Naftin 1% gel.

4. The active ingredient statement contains a trailing zero (i.e., naftifine hydrochloride **2.0**%). Trailing zeros are on the "ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations". Therefore, delete the trailing zero so that the statement reads: "naftifine hydrochloride 2%".

5. The dosage statement is not complete because it does not contain all of the dosage information as provided in the insert labeling. Therefore, delete the dosage information (i.e., (b) (4) and leave the statement "Refer to accompanying literature for complete prescribing information."

6. The storage conditions stated on the container labels do not correspond with the storage conditions stated in the insert labeling. Ensure the storage conditions statement is consistent throughout all labels and labeling.

7. The (b) (4) colored net quantity statement is too prominent. Unbold the statement and relocate it to the bottom portion of the respective panels.

8. The NDC number is noted by a placeholder. Print the actual NDC number on the container labels and carton labeling.

C. Container Labels (2 g, 30 g and 60 g)

1. The proprietary name and established name are too small in size. Increase the size of the proprietary name and established name.

2. The location of the lot number and expiration date is not indicated. If the tube will not have the lot number and expiration date imprinted on it directly, then this information should be on the container label. If this is the case, we request you show the location of the lot number and expiration date on the label.

3. Delete the "S" shaped graphics on the container labels in order to provide additional space to increase the size of the product identifying information such as the proprietary name, established name, strength, and route of administration.

D. Carton Labeling (30 g and 60 g)

1. The location of the lot number and expiration date is not indicated. Please show the location of the lot number and expiration date.

2. The NDC statement is located at the bottom right corner of the panels. Relocate the NDC statement to the top 1/3 portion of the panel per 21 CFR 207.35(3)(i).

E. Carton Labeling (2 g)

1. See Recommendations (B.1.a), (B.1.c), (B.1.e), (B.3), (B.4), (B.5), (B.6), and (D.1), above.
2. The established name and strength lack prominence. Increase their prominence with the use of a heavier font weight.
3. It is not clear whether the 2 g size is a professional sample since it is not stated on the label. If it is in fact a professional sample, provide a statement to that effect (e.g., "Professional Sample—Not for Sale", or similar verbiage) and place it on the principal display panel.
4. The net quantity statement states "2 g (b) (4). Delete the dosage form (b) (4) from the net quantity statement.
5. Revise the "(b) (4)..." statement to read: Each carton contains ten 2 g tubes".

F. Insert Labeling

The storage conditions as stated in Section 16 *How Supplied/Storage and Handling* do not correspond with the storage conditions as stated on the container labels and carton labeling. Ensure the storage conditions statement is consistent throughout all labels and labeling.

If you have further questions or need clarifications, please contact Janet Anderson, OSE Project Manager, at 301-796-0675.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 3013288

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

/s/

LORETTA HOLMES
09/11/2011

IRENE Z CHAN
09/12/2011

CAROL A HOLQUIST
09/12/2011

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	19599
Brand Name	NAFT-600 Gel 2%
Generic Name	Naftifine hydrochloride (HCl)
Sponsor	Merz Pharmaceutical
Indication	Treatment of Tinea Cruris, Tinea Pedis and Tinea Corporis
Dosage Form	Capsule
Drug Class	Antifungal
Therapeutic Dosing Regimen	600 mg q.d.
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	600 mg/day (maximum dose tested)
Submission Number and Date	SDN 103, 12 Jul 2011
Review Division	

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of naftifine HCl (600 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between naftifine HCl (600 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 5, indicating that assay sensitivity was established.

In this randomized, double-blinded, double-dummy, three-treatment-arm parallel study, 132 healthy subjects received naftifine HCl 600 mg, placebo, and a single oral dose of moxifloxacin 400 mg. An overall summary of findings is presented in Table 1.

Reference ID: 3012247

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Naftifine HCl (600 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
Naftifine HCl	2	5.5	(2.7, 8.3)
Moxifloxacin 400 mg*	4	13.5	(11.2, 15.9)

** Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 10.4 ms.*

The supratherapeutic dose (600 mg orally administered) produces mean C_{max} values of 18-fold higher than the mean exposure for the therapeutic dose (multiple topical applications of 2% naftifine HCl cream). The rate and extent of exposure following single and multiple oral dose administration are significantly higher compared to multiple topical applications and show that, at these concentrations, there are no detectable prolongations of the QT-interval. It is expected from drug interaction studies that co-administration with CYP450 inhibitors or inducers will not have significant effect on the exposures, as naftifine is not eliminated via this route (primary route of elimination is by renal mechanisms). Exposure data in patients with hepatic or renal impairment is not available. Other intrinsic factors (e.g., age, gender or race) and extrinsic factors (e.g., drug interactions, food effect), have not been explored as potential factors of PK variability.

2 PROPOSED LABEL

2.1 THE SPONSOR PROPOSED LABEL:

The sponsor did not propose any label language on QT effect.

2.2 QT-IRT PROPOSED LABEL:

QT-IRT recommends that following language in the label. Our recommendations are suggestions only. We defer final labeling decisions to the review division.

The effect of orally administered naftifine 600 mg on QTc interval was evaluated in a randomized, double-blinded, double-dummy, placebo-, and active-controlled (moxifloxacin 400 mg), three-treatment-arm parallel study in 132 healthy subjects. In the study with demonstrated ability to detect small QT effects, the upper bound of the one-sided 95% confidence interval for the largest placebo-adjusted, baseline-corrected QTc based on Fridericia correction method (QTcF) was below 10 ms, the threshold for regulatory concern. The oral dose of 600 mg produces mean C_{max} values 18-fold higher than that following the therapeutic dose of 2% naftifine cream and is sufficient to cover high exposure clinical scenarios.

Reference ID: 3012247

3 BACKGROUND

3.1 PRODUCT INFORMATION

Naftifine hydrochloride is a synthetic allylamine derivative, and it was the first topical antifungal agent in its class for the treatment of superficial fungal infections. The antifungal activity of naftifine hydrochloride is likely related to its inhibition of squalene epoxidase, leading to an accumulation of squalene. Naftifine hydrochloride is also fungistatic against Candida. In addition to its fungicidal properties, naftifine hydrochloride also exhibits antibacterial activity against both Gram-positive and Gram-negative bacteria, and has an anti-inflammatory activity.

3.2 MARKET APPROVAL STATUS

NAFT-600 is not approved for marketing in any country.

Naftifine hydrochloride is the active ingredient in two prescription products currently marketed by Merz Pharmaceuticals, LLC in the United States, Naftin® 1% Cream and Naftin® 1% Gel (NDA 19-599 and NDA 19-356, respectively).

3.3 PRECLINICAL INFORMATION

There is no mention of safety pharmacology studies (S7A and S7B guidance).

3.4 PREVIOUS CLINICAL EXPERIENCE

From eCTD 2.7.4 Summary of Clinical Safety

"The clinical development program for NAFT-500 Cream, 2% includes six clinical studies supporting the indication for the treatment of tinea pedis and tinea cruris in adolescents and adults (Table 1–1): two pivotal Phase 3, double-blind, randomized, controlled studies and four Phase 1 studies (one single-blind, blinded-evaluator, randomized, controlled study; two blinded evaluator, open-label studies; and one unblinded open-label study). A total of 1405 healthy subjects (27 adolescents aged 12 to 17 years and 1378 adults aged ≥18 years) were enrolled in these studies, 760 (54.1%) of which were treated with at least one application of NAFT-500 Cream, 2% (Table 1–1). The efficacy and safety of NAFT-500 Cream, 2% were evaluated against placebo in 217 subjects (147 active vs 70 placebo, full analysis set; the safety evaluation set excluded 2 subjects randomized but not exposed to study medication) treated for tinea pedis and 146 subjects (75 active vs 71 placebo) treated for tinea cruris. Efficacy and safety were also evaluated in 21 subjects treated with NAFT-500 Cream, 2% for both tinea pedis and tinea cruris (maximal use).

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Table 2: Number of Subjects Enrolled and Treated in the NAFT 500 Cream, 2% Clinical Development Program

NAFT-500 Cream, 2% Study	Number Enrolled	Number Treated			
		NAFT-500 Cream, 2%	Placebo 2-Week	Naftin 1% Cream	Placebo 4-Week
Efficacy and Safety Studies					
Phase 3 Tinea pedis MUS 90200/0736/1	709	234	118	236	119
Phase 3 Tinea cruris MRZ 90200/FI/3001	334	166	168	NA	NA
Phase 1 Maximal Use/ Pharmacokinetics MRZ 90200/FI/1002	21	21	NA	NA	NA
Other Safety Studies					
Phase 1 Phototoxicity MUS 90200/1013/1	34	33	NA	NA	NA
Phase 1 Photoallergenicity MUS 90200/1014/1	57	56	NA	NA	NA
Phase 1 Sensitization/ Irritation MRZ 90200/FI/1003	250	250	NA	NA	NA
Total	1405	760	286	236	119

Note: Four enrolled or randomized subjects were not treated: 2 subjects due to protocol violations in the tinea pedis study, 1 subject was lost to follow-up in the phototoxicity study, and 1 subject was disqualified in the photoallergenicity study due to the use of an unauthorized concomitant medication.

Abbreviations: NA = not applicable.

Source: MUS 90200/0736/1, MRZ 90200/FI/3001, MRZ 90200/FI/1002, MUS 90200/1013/1, MUS 90200/1014/1, and MRZ 90200/FI/1003 CSRs (Module 5)

Source: Summary of Clinical Safety, Table 1-1

Table 3: Number (%) of Subjects with Most Common Treatment-Emergent Adverse Events that were Study Drug-Related in the Phase 3 Studies (SES)

MedDRA Preferred Term [a]	NAFT-500 Cream, 2% (N=400) n (%)	Naftin 1% Cream (N=236) n (%)	Combined Placebo (N=405) n (%)
Subjects with at least one study drug-related TEAE [b,c,d]	16 (4.0)	7 (3.0)	16 (4.0)
Application Site Pruritus	7 (1.8)	1 (0.4)	7 (1.7)
Application Site Irritation	2 (0.5)	4 (1.7)	7 (1.7)
Pruritus	1 (0.3)	0	3 (0.7)

a Events were coded using MedDRA Version 11.1.

b Most common AEs included TEAEs, based on preferred terms, contributing at least 2% of the total AE occurrences in the clinical development program overall.

c Treatment-emergent AEs were defined as on-study AEs, pre-existing AEs that worsened in severity after start of treatment, and AEs that were reported with onset during the 30 days after end of treatment. Treatment-emergent AEs were summarized like all the other AEs by preferred terms (PTs) within system organ classes (SOCs) according to the defined study groupings. A subject with more than one TEAE within a PT was counted once in the PT.

d A subject with related and not related TEAEs within a preferred term was counted once as related.

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Source: ISS Post-text Table 10.3.

Source: Summary of Clinical Safety, Table 2-6

Reference ID: 3012247

Reviewer's comments: No syncope, seizures, sudden cardiac death or ventricular arrhythmias were reported. No clinically relevant ECG changes were reported.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of naftifine's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 105603. The sponsor submitted the study report AA95389, a thorough QT study, and other related materials for naftifine hydrochloride, including electronic datasets and waveforms, to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

Randomized, Double-Blind, Placebo and Moxifloxacin-Controlled, Single Dose, 3-Arm, Parallel Study in Healthy Subjects to Evaluate the Effects of Naftifine Hydrochloride on Cardiac Repolarization (QT/QTc Interval Duration)

4.2.2 Protocol Number

MUS 90200/1018/1

4.2.3 Study Dates

28 February 2011- 9 March 2011

4.2.4 Objectives

The primary objectives were to evaluate the effects on ventricular repolarization of a single supratherapeutic oral dose of naftifine HCl compared to the effects of the placebo treatment, while also demonstrating assay sensitivity by evaluating moxifloxacin-induced changes on ventricular repolarization when compared to the placebo treatment among healthy volunteers.

The secondary objectives of this study were as follows:

1. To examine the single-dose PK profile of naftifine following the administration of a supratherapeutic oral dose;
2. To assess the concentration and QT interval relationship (i.e., time course of QT/QTc interval prolongation in relation to plasma levels of naftifine), if any;
3. To evaluate the safety and tolerability of naftifine HCl following the administration of a supratherapeutic oral dose; and
4. To evaluate the safety and tolerability of a single dose administration of moxifloxacin.

Reference ID: 3012247

4.2.5 Study Description

4.2.5.1 Design

This is a randomized, single-dose, double-blinded, double-dummy, positive and negative placebo controlled parallel study with three treatment arms. The study consisted of the following treatments:

Table 4: Study Treatment Arms

Naftifine HCl (NAFT-600) (Treatment A):	One 600 mg capsule of naftifine HCl and 1 matching moxifloxacin placebo tablet.
Placebo (Treatment B):	One matching naftifine HCl placebo capsule and 1 matching moxifloxacin placebo tablet.
Moxifloxacin (Treatment C):	One matching naftifine HCl placebo capsule and one 400 mg moxifloxacin tablet.

Source: Sponsor's report, page 18.

4.2.5.2 Controls

The Sponsor used both negative and positive (moxifloxacin) controls.

4.2.5.3 Blinding

All treatment arms were administered blinded using a double dummy approach.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

There were three treatment arms. Subjects were assigned randomly to one treatment arm. The treatment allocation ratio was 1:1:1.

- Treatment A: one 600-mg oral capsule of natfifine HCl and one moxifloxacin placebo tablet.
- Treatment B: One natfifine HCl placebo capsule and one moxifloxacin placebo tablet.
- Treatment C: One naftifine HCl placebo capsule and one 400-mg moxifloxacin tablet.

4.2.6.2 Sponsor's Justification for Doses

"To obtain the supratherapeutic exposure of naftifine, an oral formulation was chosen due to the poor systemic absorption from the topical product. In a previous study, an oral dose of 600 mg administered daily for 4 days was tested in healthy volunteers and was well tolerated (Study NAFT-910-SNDZ). Following a single 600-mg oral dose, peak plasma levels (C_{max}) and the rate of absorption (area under the concentration-versus-time curve [AUC]) were approximately 18 and 2 times higher than that achieved during multiple topical applications of a 2% naftifine HCl cream in patients, respectively, and was, therefore, considered appropriate as the supratherapeutic dose in this study."

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"A single 400-mg dose of moxifloxacin produces a known prolongation of the QT interval on the ECG and is well established as a positive control in TQT studies."

Reviewer's Comments: Based on prior clinical experience of naftifine, the supra-therapeutic dose selected for the TQT study is reasonable. Moreover, the exposure obtained by the supratherapeutic dose selected (600 mg) is higher than what has been observed in the repeated administration of the topical formulation. The doses chosen for the TQT study, for both naftifine and moxifloxacin, are appropriate.

4.2.6.3 Instructions with Regard to Meals

Standardized food was provided during the clinical study and standardized food with the same composition was provided on the evenings before and on the ECG and PK sampling days.

Subjects were required to fast overnight for at least 10 hours prior to Hour 0 on Day -1 and Day 1 and continued to fast for at least 1 hour thereafter. Lunch, dinner, and evening snack were scheduled to be completed at least 1 to 1.5 hours before any scheduled ECG time point Meals were provided to all subjects on Day -1 and Day 1 at approximately Hours 1, 4.25, 8.25, and 12.5.

Water was not permitted from 1 hour before until 1 hour after dosing. Subjects were required to drink 240 mL of water at 2, 3, and 4 hours following dosing. Water was allowed as desired at all other times.

(Source Clinical Study Report No. AA95389, Section 9.4.7.1, Pg 25)

Reviewer's Comments: Since the administration is via topical route, effect of food on naftifine pharmacokinetics is not anticipated. The C_{max} following naftifine 600-mg oral dose is 18-fold that following standard therapeutic dose using topical cream (2%).

4.2.6.4 ECG and PK Assessments

Study Day	**-1**	**1**
Intervention	No treatment (Baseline)	One (1) 600-mg oral capsule of naftifine HCL
12-Lead ECGs	0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 hours relative to the start (clock time) of subsequent day's infusion of study medication on Day 1	0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 hours relative to the start of infusion of study medication.
PK Samples for drug	None collected	Pre-dose (prior to dosing), and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24, hours, relative dosing of study medication on Day 1.

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Reviewer's Comment: The PK and ECG assessments are adequate to capture QT at peak concentrations of naftifine (median T_{max} ~ 5 hours). This T_{max} is within the expected range of 1 to 2 hours upon oral dosing of naftifine.

4.2.6.5 Baseline

The sponsor used a time-matched baseline.

4.2.7 ECG Collection

M12R Holter monitors were used to collect continuous, 12-lead ECG data for approximately 50 hrs starting on Day -1 up to Day 2. For study conduct, ECGs were classified as safety ECGs or cardiodynamic ECGs.

On-study safety ECGs were planned as single, 12–lead ECGs using Bluetooth® transmission from the Holter monitor and interpreted on-site by the PI.

Cardiodynamic ECGs were used as a primary endpoint of the study (cardiodynamic evaluation of QT/QTc interval). Timing and recording technique for ECGs were standardized for all subjects. Subjects were required to lie quietly in a supine position with minimal movement and minimal exposure to noise and other environmental stimuli for at least 10 minutes prior to and 5 minutes during the ECG extraction to allow for quality ECG extraction. All ECG extractions were to occur in a 5-minute time window around the scheduled/nominal time.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 133 subjects entered the study and were randomized to study treatment. A total of 132 subjects completed the study (see Table 5). One subject discontinued early (Subject (b) (6), following treatment with moxifloxacin. This subject withdrew consent for study participation for personal reasons and was not replaced.

Table 5: Subject Demographic Data

Trait	Treatment Group		
	Naftifine HCl (NAFT-600) N = 44	Moxifloxacin N = 44	Placebo N = 45
Males (n, %)	27 (61.4%)	27 (61.4%)	27(60.0%)
Females (n, %)	17 (38.6%)	17 (38.6%)	18 (40.0%)
Age (years, range)	32.9 (18 – 44)	33.8 (18 – 45)	32.7 (19 – 45)
Weight (kg, range)	70.24 (48.8 – 92.0)	72.34 (49.5 – 91.2)	74.00 (52.8 – 97.1)
Height (cm, range)	165.0 (146 – 184)	167.8 (150 – 191)	168.1 (151 – 201)
BMI (kg/m^2, range)	25.75 (18.59 – 29.99)	25.68 (18.95 – 29.63)	26.12 (19.98 – 29.92)

Source: Table 14.1.2

Source: Sponsor's report, page 42, In Text Table 3.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

Reference ID: 3012247

The sponsor used QTcF as the primary measure of change in QT interval. For the primary analysis, change from time-matched baseline in QTcF (ΔQTcF) was modeled using ANCOVA for repeated measures. The covariate was each subject's time-matched baseline value and the repeated variable was the time point (h) at which ΔQTcF was measured. The sponsor's results are shown in Table 6 and Figure 1. The sponsor found that the supratherapeutic dosage of naftifine HCl did not result in elongated QT intervals.

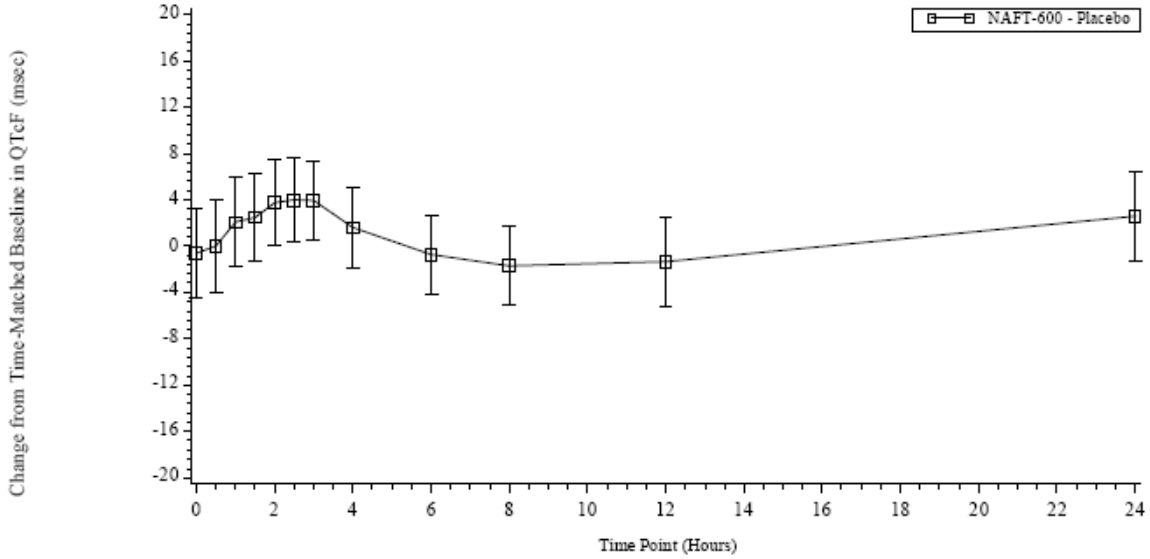
Table 6: Sponsor's Statistical Comparisons of Change from Time-matched Baseline in QTcF between Naftifine HCl 600 mg and Placebo

Time Point (hr)	LS Means of dQTcF (msec)		Difference Between LS Means (ddQTcF) (msec)	p-value	2-sided 90% CI for Difference of LS Means	
	Naftifine HCl (NAFT-600)	Placebo				
0.0	1.400	1.997	-0.597	0.7976	-4.454	3.260
0.5	-1.448	-1.453	0.006	0.9981	-3.987	3.999
1.0	0.157	-1.914	2.071	0.3667	-1.723	5.865
1.5	5.049	2.561	2.488	0.2807	-1.322	6.298
2.0	3.659	-0.074	3.732	0.0981	0.022	7.443
2.5	1.705	-2.259	3.964	0.0733	0.329	7.600
3.0	-0.304	-4.232	3.928	0.0599	0.501	7.354
4.0	-5.858	-7.435	1.577	0.4614	-1.965	5.120
6.0	-5.409	-4.677	-0.732	0.7250	-4.179	2.714
8.0	-5.926	-4.213	-1.714	0.4030	-5.103	1.676
12.0	-2.102	-0.738	-1.364	0.5576	-5.216	2.487
24.0	-2.181	-4.751	2.570	0.2738	-1.308	6.447

Source: Table 14.2.1.3.

Source: Sponsor's report, page 50, In Text Table 4.

Figure 1: Sponsor's Mean and 90% CI ΔΔQTcF for All Treatments



Source: Sponsor's report, page 51, In Text Figure 7.

Reviewer's Comments: Our independent analysis agrees with the sponsor's conclusion. See section 5.2.

Reference ID: 3012247

4.2.8.2.2 Assay Sensitivity

The sponsor's results on assay sensitivity are shown in Table 7. At least one of the lower bounds on the 90% confidence intervals is above 5 ms.

Table 7: Sponsor's Comparisons of Change from Time-matched Baseline in QTcF between Moxifloxacin and Placebo

Time Point (hr)	LS Means of dQTcF (msec)		Difference Between LS Means (ddQTcF) (msec)	p-value	Two-Sided 90% CI for Difference of LS Means	
	Moxifloxacin	Placebo				
0.0	2.451	1.997	0.454	0.8444	-3.378	4.286
0.5	7.386	-1.453	8.840	0.0004	4.877	12.802
1.0	10.374	-1.914	12.288	<0.0001	8.518	16.057
1.5	12.935	2.561	10.374	<0.0001	6.588	14.160
2.0	11.280	-0.074	11.354	<0.0001	7.668	15.040
2.5	9.074	-2.259	11.333	<0.0001	7.718	14.947
3.0	7.416	-4.232	11.648	<0.0001	8.243	15.053
4.0	6.079	-7.435	13.514	<0.0001	9.993	17.035
6.0	5.685	-4.677	10.363	<0.0001	6.942	13.783
8.0	5.310	-4.213	9.523	<0.0001	6.154	12.892
12.0	7.556	-0.738	8.294	0.0005	4.463	12.125
24.0	1.874	-4.751	6.624	0.0054	2.762	10.487

Source: Table 14.2.1.4.

Source: Sponsor's report, page 53, In Text Table 5.

Reviewer's Comments: Our independent analysis agrees with the sponsor's conclusion. See section 5.2.

4.2.8.2.3 Categorical Analysis

Categorical analysis for maximum QT, QTcB, and QTcF intervals were classified by the sponsor using the following thresholds: ≤ 450 ms, > 450 to ≤ 480 ms, > 480 to ≤ 500 ms, and > 500 ms. The sponsor's categorical analysis for QT/QTc intervals and changes from baseline are shown in Table 8.

Reference ID: 3012247

Table 8: Sponsor's Categorical Analysis

Parameter	Interval Category (msec)	Naftifine HCl (NAFT-600) N = 44 n (%)*	Placebo N = 45 n (%)*	Baseline Change Category (msec)	Naftifine HCl (NAFT-600) N = 44 n (%)*	Placebo N = 45 n (%)*
QT	≤ 450	43 (97.7%)	43 (95.6%)	< 0	4 (9.1%)	5 (11.1%)
	> 450 to ≤ 480	1 (2.3%)	2 (4.4%)	≥ 0 to ≤ 30	39 (88.6%)	39 (86.7%)
	> 480 to ≤ 500	0 (0%)	0 (0%)	> 30 to ≤ 60	0 (0%)	1 (2.2%)
	> 500	0 (0%)	0 (0%)	> 60	0 (0%)	0 (0%)
QTcF	≤ 450	44 (100%)	45 (100%)	< 0	1 (2.3%)	2 (4.4%)
	> 450 to ≤ 480	0 (0%)	0 (0%)	≥ 0 to ≤ 30	42 (95.5%)	43 (95.6%)
	> 480 to ≤ 500	0 (0%)	0 (0%)	> 30 to ≤ 60	0 (0%)	0 (0%)
	> 500	0 (0%)	0 (0%)	> 60	0 (0%)	0 (0%)
QTcB	≤ 450	44 (100%)	44 (100%)	< 0	0 (0%)	0 (0%)
	> 450 to ≤ 480	0 (0%)	0 (0%)	≥ 0 to ≤ 30	38 (86.4%)	45 (100%)
	> 480 to ≤ 500	0 (0%)	0 (0%)	> 30 to ≤ 60	5 (11.4%)	0 (0%)
	> 500	0 (0%)	0 (0%)	> 60	0 (0%)	0 (0%)

Source: Tables 14.2.1.5 and 14.2.1.6

Source: Sponsor's study, page 54, In Text Table 6.

4.2.8.3 Safety Analysis

There were no serious adverse events (SAEs) or ECG-related AEs reported during this study. There were no subjects discontinued due to AEs in this study. There were a total of 5 laboratory-related AEs reported during this study. Two of them were in subjects under NAFT-600:

> **Subject** (b) (6) a White, 30-year-old male, had an increased CPK result of 2179 IU/L (reference range: males: 44 – 329 IU/L) at the 24-h laboratory assessment following treatment with naftifine HCl capsules (NAFT-600). The PI considered the result to be clinically significant; the event was considered an AE, mild in intensity, and possibly related to the study treatment. The result on recheck analysis 5 days later was within normal limits at 212 IU/L and the event was considered resolved at this time. Screening and baseline CPK results were within normal limits for this subject, with results of 97 IU/L and 201 IU/L, respectively.
>
> **Subject** (b) (6)**,** a White, 35-year-old male, had a positive microscopic result for urine RBCs of 15 – 20 HPF (reference range: < 0 – 3 HPF) at the 24-h laboratory assessment following treatment with naftifine HCl capsules (NAFT-600); the corresponding occult blood result was 4+ (reference range: males: negative). Screening and baseline results were within normal limits. The PI considered the event to be clinically significant and it was considered an AE. The AE was considered to be mild in intensity and unrelated to the study treatment. The result on recheck analysis approximately 4 days later was 0 HPF for RBCs and negative for occult blood; the AE was considered resolved at this time.

A total of 27 AEs were reported by 18 (13.5%) subjects in this study. The most common AEs reported, overall, were within the system organ class (SOC) of gastrointestinal disorders – these included diarrhea, reported 5 times by 2 (1.5%) subjects overall following naftifine HCl capsules (NAFT-600); nausea, reported 3 times by a total of 3 (2.3%) subjects overall (2 subjects following naftifine HCl capsules [NAFT-600] and 1 subject following placebo); and lower abdominal pain, reported once by 1 (0.8%) subject following naftifine HCl capsules (NAFT-600).

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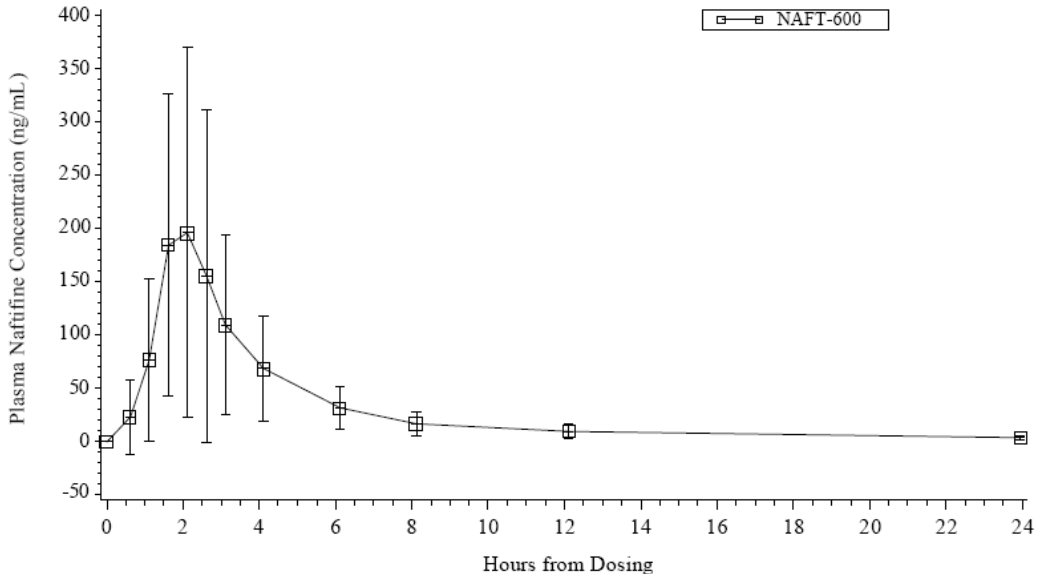
4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results of the supratherapeutic dose of naftifine (600 mg p.o.) are presented in Figure 2 and Table 9. The therapeutic dose of naftifine (8 g of 2% cream QD for 14 days) and moxifloxacin PK was not investigated within this trial. Exposure following administration of 600 mg of oral naftifine in the thorough QT study was 18-fold C_{max} and 2-fold SUC exposure reported with 8g QD of naftifine 2% cream for 14 days (C_{max}: 11±29, AUC: 204±29, geometric mean and standard deviation).

Figure 2: Mean Naftifine Concentration-Time Profiles for 600 mg Oral Formulation



(Source: Sponsor's study, page 308, Figure 14.4.1.1.)

Table 9: Sponsor's Summary of Naftifine Pharmacokinetic Parameters

	AUC_{0-t} (ng*hr/mL)	AUC_{0-inf} (ng*hr/mL)	$AUC_{extrap\%}$ (%)	C_{max} (ng/mL)	t_{max} (hr)	k_{el} (1/hr)	$t_{1/2}$ (hr)
N	44	42	42	44	44	42	42
Mean ± SD	731.7 ± 515.7	790.7 ± 533.0	5.35 ± 1.92	221 ± 177	2.01 ± 0.617	0.0996 ± 0.0216	7.27 ± 1.54
Median (min, max)	611.9 (165.1, 2599)	669.7 (212.0, 2654)	5.03 (2.08, 11.7)	172 (47.3, 953)	1.89 (1.12, 4.12)	0.0949 (0.0630, 0.151)	7.30 (4.58, 11.0)

Source: Table 14.2.2.2
Note: The single-dose treatment was administered orally in the morning at Hour 0 on Day 1.

(Source: Sponsor's study, page 57, In Text Table 7.)

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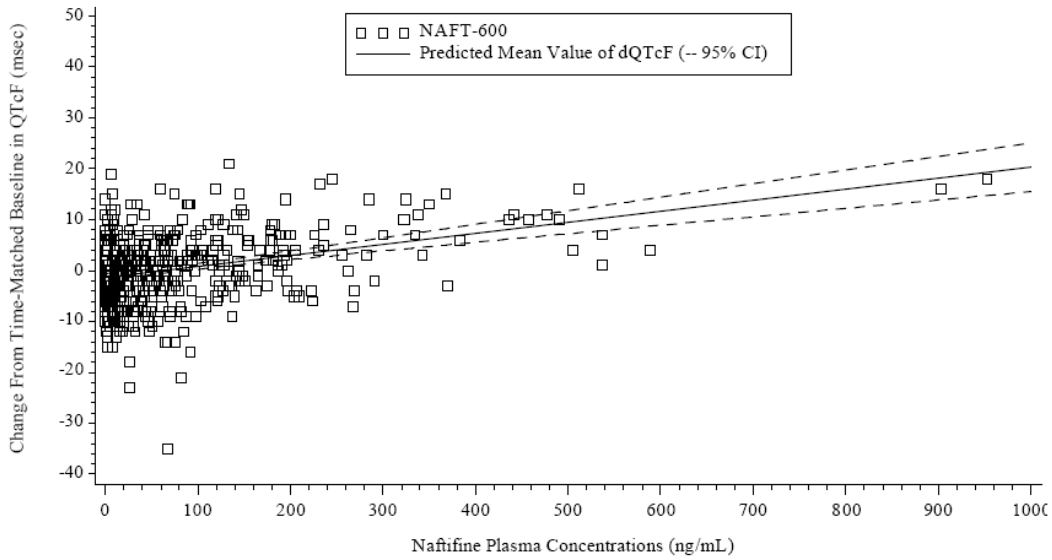
4.2.8.4.2 Exposure-Response Analysis

Figure 3: ΔΔ QTcF vs. Naftifine Concentration – Sponsor's Analysis



(Source: Sponsor's study, page 59, In Text Figure 9.)

Reviewer's Analysis: The relationship between ΔΔQTcF and naftifine concentrations is visualized in Figure 3 and an evident exposure-response relationship is seen. The sponsor reports a slope for linear regression of plasma naftifine concentrations versus ΔQTcF to be 0.022 ms/ng/mL (95%CI: 0.016-0.027), but concludes there was no meaningful association (no p-value provided). Independent review yielded a positive relationship between naftifine plasma concentrations and ΔΔQTcF with a slope of 0.026 ms/ng/mL (95%CI: 0.0158 – 0.035, p-value = 0.0005). The reviewer's analysis is presented in Figure 6.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and QTcB). Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

We used the mixed model of the pooled post-dose data of QTcF and QTcB, distinguished by an indicator of correction method, to evaluate the linear relationships between different correction methods and RR. The model included RR, correction type (QTcF or QTcB), and the interaction term of RR and correction type. The slopes of QTcF and QTcB versus RR are compared in magnitude as well as statistical significance in

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difference. As shown in Table 10, it appears that QTcF had smaller absolute slopes than QTcB. Therefore, QTcF is a better correction method for the study data.

Table 10: Comparison of QTcF and QTcB Using a Mixed Model

Treatment Groups	Slope of QTcB	Slope of QTcF	P-value
Moxifloxacin 400 mg	-0.0757	0.0020	0.0000
Naftifine 600 mg	-0.0701	0.0024	0.0000
Placebo	-0.0511	0.0174	0.0000
All	-0.0661	0.0073	0.0000

We also confirmed this conclusion by using the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 11, it also appears that QTcF is the best correction method. Therefore, this statistical reviewer used QTcF for the primary statistical analysis. This is consistent with the sponsor's choice of QTcF for their primary analysis.

Table 11: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	Correction Method			
	QTcB		QTcF	
	N	MSSS	N	MSSS
Moxifloxacin 400 mg	44	0.0092	44	0.0021
Naftifine 600 mg	44	0.0074	44	0.0022
Placebo	45	0.0040	45	0.0028
All	133	0.0069	133	0.0024

The relationship between different correction methods and RR is presented in Figure 4.

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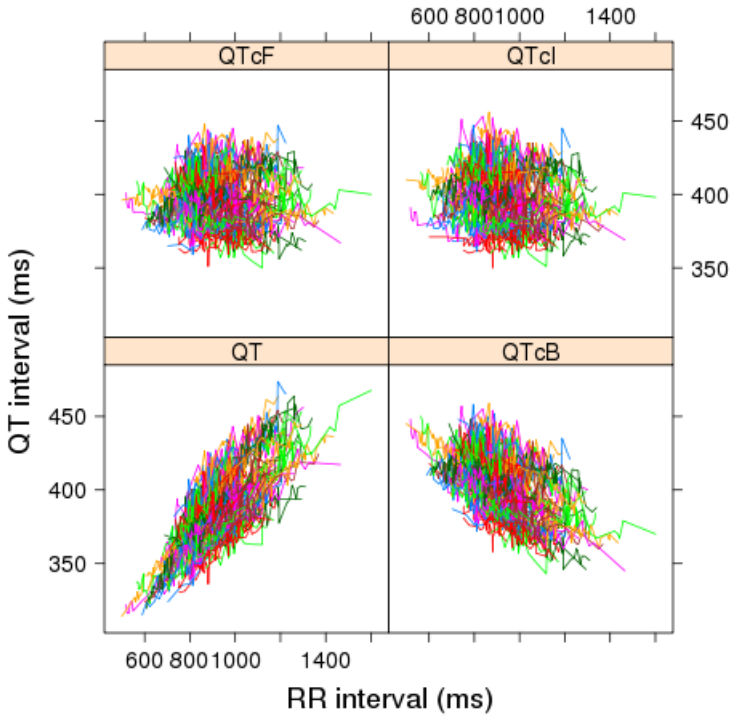
Figure 4: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Naftifine HCl

The statistical reviewer used mixed model to analyze the ΔQTcF effect. The model includes treatment as a fixed effect and subject as a repeated effect. Baseline values are also included in the model as a covariate. The analysis results are listed in the following tables.

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Table 12: Analysis Results of ΔQTcF and ΔΔQTcF for Treatment Group A: Naftifine HCl 600 mg

	ΔQTcF: Naftifine HCl			ΔQTcF: Placebo			ΔΔQTcF		
Time (hr)	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0	44	1.9	0.9	45	0.4	0.8	89	1.5	(-0.8, 3.8)
0.5	43	-2.6	1.2	45	-4.1	1.1	88	1.5	(-1.6, 4.6)
1	44	-1.3	1.0	45	-4.9	1.0	89	3.6	(1.0, 6.2)
1.5	44	2.3	1.1	45	-1.4	1.0	89	3.7	(0.9, 6.6)
2	44	4.7	1.0	45	-0.7	1.0	89	5.5	(2.7, 8.3)
2.5	44	4.0	1.1	45	-0.6	1.0	89	4.6	(1.8, 7.4)
3	44	2.4	1.0	45	-2.6	1.0	89	5.0	(2.2, 7.8)
4	43	-1.3	0.9	44	-4.2	0.9	87	2.9	(0.5, 5.3)
6	42	-3.5	0.9	43	-4.1	0.9	85	0.7	(-1.8, 3.1)
8	43	-3.8	0.9	44	-2.9	0.9	87	-0.9	(-3.2, 1.5)
12	43	1.5	0.9	43	1.8	0.9	86	-0.3	(-2.8, 2.1)
24	44	-1.7	1.1	45	-6.4	1.1	89	4.7	(1.6, 7.8)

The largest upper bound of the 2-sided 90% CI for the mean difference between naftifine HCl 600 mg and placebo was 8.3 ms.

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 13. The largest unadjusted 90% lower confidence interval is 11.2 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 10.4 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

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Table 13: Analysis Results of ΔQTcF and ΔΔQTcF for Moxifloxacin

	ΔQTc: Moxifloxacin			ΔQTc: Placebo			ΔΔQTcF			
Time (hr)	N	Mean	SD	N	Mean	SD	N	Mean	Unadjusted 90% CI	Adjusted* 90% CI
0	44	0.4	0.9	45	0.4	0.8	89	0.0	(-2.3, 2.3)	(-3.0, 3.0)
0.5	44	4.9	1.1	45	-4.1	1.1	89	9.0	(5.9, 12.0)	(5.0, 12.9)
1	44	7.7	1.0	45	-4.9	1.0	89	12.6	(10.0, 15.2)	(9.2, 16.0)
1.5	44	9.2	1.1	45	-1.4	1.0	89	10.6	(7.8, 13.5)	(7.0, 14.3)
2	44	10.7	1.0	45	-0.7	1.0	89	11.4	(8.6, 14.2)	(7.8, 15.0)
2.5	44	10.0	1.1	45	-0.6	1.0	89	10.6	(7.7, 13.4)	(6.9, 14.2)
3	44	8.4	1.0	45	-2.6	1.0	89	11.1	(8.3, 13.9)	(7.4, 14.7)
4	43	9.3	0.9	44	-4.2	0.9	87	13.5	(11.2, 15.9)	(10.4, 16.6)
6	43	6.6	0.9	43	-4.1	0.9	86	10.7	(8.3, 13.2)	(7.6, 13.9)
8	43	6.3	0.9	44	-2.9	0.9	87	9.2	(6.9, 11.5)	(6.2, 12.2)
12	43	8.6	0.9	43	1.8	0.9	86	6.8	(4.4, 9.3)	(3.6, 10.0)
24	42	0.1	1.2	45	-6.4	1.1	87	6.5	(3.4, 9.6)	(2.5, 10.5)

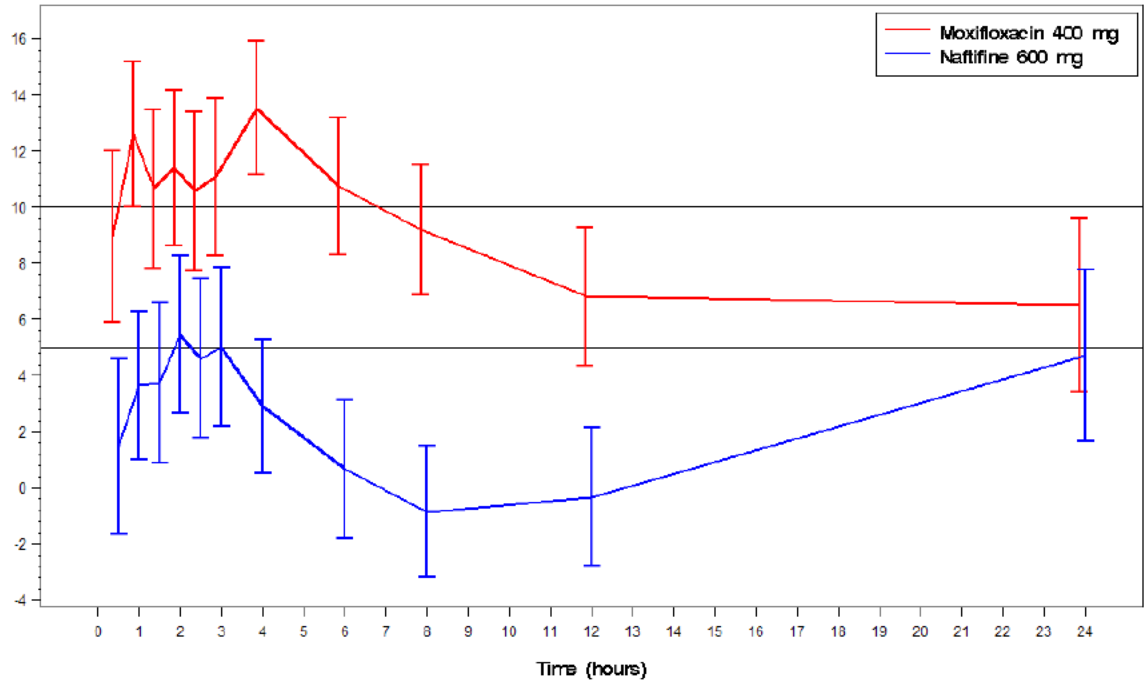
* Bonferroni correction was applied for multiple endpoint adjustment for 4 time points.

5.2.1.3 Graph of ΔΔQTcF Over Time

Figure 5 displays the time profile of ΔΔQTcF for different treatment groups.

Reference ID: 3012247

Figure 5: Mean and 90% CI ΔΔQTcF Time Course



Note: all CIs are unadjusted, including moxifloxacin.

Reviewer's comments: the largest single delta change from the baseline for moxifloxacin was at 2 hours post-dose. The largest double delta for moxifloxacin at hour 1 seems to be driven by the negative placebo effect.

5.2.1.4 Categorical Analysis

Table 14 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms. No subject's QTcF was above 450 ms.

Table 14: Categorical Analysis for QTcF

	Total N	Value<=450 ms	Value>450
Treatment Group			
Moxifloxacin 400 mg	44	44 (100%)	0 (0.0%)
Naftifine 600 mg	44	44 (100%)	0 (0.0%)
Placebo	45	45 (100%)	0 (0.0%)

No subject's change from baseline was above 30 ms.

Reference ID: 3012247

5.2.2 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 15. The largest upper limit of 90% CI for the PR mean difference between naftifine HCl and placebo is 4.5 ms.

The outlier analysis results for PR are presented in Table 16. There are 2 (4.4%) subjects who experienced PR interval greater than 30 ms in the placebo treatment group.

Table 15: Analysis Results of ΔPR and ΔΔPR for Treatment Group A: Naftifine HCl 600 mg

	ΔPR: naftifine HCl			ΔPR:placebo			ΔΔPR		
Time (hr)	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0	43	2.9	0.9	44	0.8	0.9	87	2.0	(-0.1, 4.1)
0.5	42	0.5	1.1	44	-1.5	1.0	86	2.0	(-0.5, 4.5)
1	43	-0.4	0.9	45	-0.8	0.9	88	0.4	(-1.7, 2.5)
1.5	43	-1.2	1.0	45	-1.6	1.0	88	0.3	(-2.0, 2.7)
2	43	-3.4	1.0	45	-0.9	1.0	88	-2.5	(-4.9, -0.2)
2.5	43	-3.5	1.0	45	-2.3	1.0	88	-1.2	(-3.6, 1.2)
3	43	-4.2	1.1	45	-2.8	1.1	88	-1.4	(-3.9, 1.2)
4	42	-3.1	1.1	44	-2.0	1.1	86	-1.1	(-3.6, 1.4)
6	41	-3.0	1.1	43	-1.3	1.1	84	-1.7	(-4.3, 1.0)
8	42	-2.0	1.1	44	-1.0	1.1	86	-1.0	(-3.5, 1.6)
12	42	2.4	0.9	43	1.5	0.9	85	0.9	(-1.3, 3.1)
24	43	0.1	1.2	44	0.7	1.2	87	-0.6	(-3.4, 2.2)

Table 16: Categorical Analysis for PR

	N	PR < 200 ms	PR >=200 ms
Treatment Group			
Naftifine 600 mg	44	43 (97.7%)	1 (2.3%)
Placebo	45	43 (95.6%)	2 (4.4%)

5.2.3 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 17. The largest upper limit of 90% CI for the QRS mean differences between naftifine HCl and placebo is 0.9 ms. No subjects experienced QRS interval greater than 120 ms.

Reference ID: 3012247

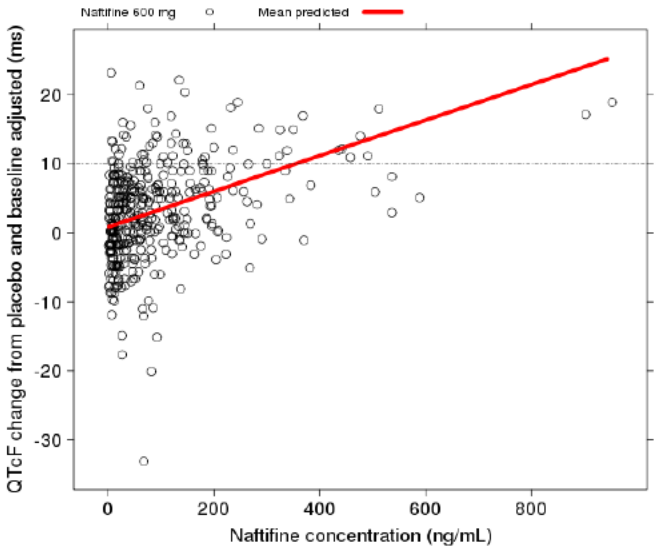
Table 17: Analysis Results of ΔQRS and ΔΔQRS for Treatment Group A: Naftifine HCl 600 mg

	ΔQRS: Naftifine HCl			ΔQRS: Placebo			ΔΔQRS		
Time (hr)	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0	43	0.4	0.1	44	0.1	0.1	89	0.3	(-0.0, 0.6)
0.5	42	0.1	0.2	44	0.2	0.2	88	-0.2	(-0.6, 0.2)
1	43	0.4	0.1	45	0.4	0.1	89	0.0	(-0.3, 0.3)
1.5	43	0.2	0.2	45	0.4	0.2	89	-0.2	(-0.7, 0.3)
2	43	-0.1	0.2	45	0.3	0.2	89	-0.4	(-0.9, 0.1)
2.5	43	0.2	0.2	45	0.3	0.2	89	-0.1	(-0.5, 0.4)
3	43	-0.3	0.2	45	0.2	0.2	89	-0.4	(-0.9, 0.1)
4	42	-0.1	0.1	44	-0.3	0.1	87	0.1	(-0.2, 0.5)
6	41	-0.5	0.2	43	-0.9	0.2	85	0.4	(-0.0, 0.9)
8	42	-0.5	0.2	44	-0.3	0.2	87	-0.2	(-0.6, 0.2)
12	42	0.3	0.2	43	0.3	0.2	86	0.0	(-0.4, 0.4)
24	43	0.3	0.1	44	-0.2	0.1	89	0.5	(0.1, 0.8)

5.3 Clinical Pharmacology Assessments

The mean drug concentration-time profile is illustrated in Figure 2. The relationship between ΔΔQTcF and drug concentrations is visualized in Figure 6. Independent review yielded a positive and significant relationship between naftifine plasma concentrations and ΔΔQTcF with a positive slope of 0.026 ms/ng/mL (95%CI: 0.0158 – 0.035, p-value = 0.0005).

Figure 6: ΔΔ QTcF vs. Naftifine Concentration – Reviewer's Analysis



Reference ID: 3012247

5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. Measurements were performed on the 'global' presentation of superimposed representative (median) PQRST complexes from all leads. According to ECG warehouse statistics less than 0.05 % of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

One subject had a PR slightly >200 ms, this was not clinically meaningful.

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6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	2 g per foot and 4 g in the groin area (8 g total once daily for 14 days)	
Maximum tolerated dose	600 mg/day	
Principal adverse events	AEs are summarized by frequency below. **Preferred Term** — **Naft-600 (N=44)** Overall — 11(18.2%) Abdominal Pain Lower — 1 (2.3%) Diarrhoea — 2 (4.5%) Nausea — 2 (4.5%) Blood creatine phosphokinase increased — 1 (2.3%) Red blood cells urine positive — 1 (2.3%) Dizziness — 1 (2.3%) Headache — 1 (2.3%) Erythema — 1 (2.3%) Rash Macular — 1 (2.3%)	
Maximum dose tested	Single Dose	600 mg
	Multiple Dose	8 g once daily for 2 weeks (Topical)
Exposures Achieved at Maximum Tested Dose	Single Dose	Day 1 Mean C_{max} (%CV) = 221 ng/mL (60%) $AUC_{0\text{-}24hr}$ = 790.7 ng*hr/mL
	Multiple Dose	Day 1 (Topical) Mean C_{max} (%CV) = 4 ng/mL (40.5%) $AUC_{0\text{-}24hr}$ = 117 ng*hr/mL (41.2%) Day 14 Mean C_{max} (%CV) = 7 ng/mL (31.6%) $AUC_{0\text{-}\tau}$ = 204 ng*hr/mL (28.5%)
Range of linear PK	Not determined	
Accumulation at steady state	Not determined; administered as a single 600 mg dose	
Metabolites	There are no known toxic or active metabolites of naftifine hydrochloride	
Absorption	Absolute/Relative Bioavailability	Not determined
	Tmax	• Median (90% CI) for parent Day 1 – 1.89 hr (1.12, 4.12)

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Distribution	Vd/F or Vd	Not determined
	% bound	Not determined
Elimination	Route	• Primary route- urine (9% to 14%) • Other routes – not determined
	Terminal t½	• Mean (%CV) for parent- 7.27 hrs
	CL/F or CL	Not determined
Intrinsic Factors	Age	In the completed study, patients ranged from 18-44 years of age with a median age of 33.1 years. No subgroup analyses were performed based on age.
	Sex	In the completed study, 61.4% of patients were male and 38.6% were female. No subgroup analyses were performed based on sex.
	Race	In the completed study, 95.5% of subjects were white and 4.5% of subjects were black. No subgroup analyses were performed based on race.
	Hepatic & Renal Impairment	Patients with impaired hepatic or renal function were excluded from the completed study.
Extrinsic Factors	Drug interactions	not studied
	Food Effects	not studied
Expected High Clinical Exposure Scenario	The completed study was designed to assess a single supratherapeutic oral dose of 600 mg naftifine HCl capsules (NAFT-600) with the rationale that if no QTc prolongation was observed at supratherapeutic doses, the risk of QTc prolongation at therapeutic doses would be minimal. Following a single 600 mg oral dose, peak plasma levels (Cmax) and the rate of absorption (area under the concentration-versus-time curve [AUC]) were approximately 18 and 2 times higher than that achieved during multiple topical applications of a 2% naftifine HCl cream in patients, respectively, and was, therefore, considered appropriate as the supratherapeutic dose in this study.	

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/s/

JOANNE ZHANG
09/09/2011
Dr. Janice Brodsky was the primary statistical reviewer for this study report.

MONICA L FISZMAN
09/09/2011

HAO ZHU
09/09/2011
Dr. Satjit Brar is the primary clinical pharmacology reviewer.

NORMAN L STOCKBRIDGE
09/09/2011

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: August 4, 2011

TO: Dawn Williams, Regulatory Project Manager
Brenda Vaughan, M.D., Medical Officer
Division of Dermatologic and Dental Drug Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Lauren Iacono-Connors, Ph.D.
Team Leader (Acting)
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Jean Mulinde, M.D.
Branch Chief (Acting)
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 19-599/S-011

APPLICANT: Merz Pharmaceuticals

DRUG: NAFT-500 (naftifine hydrochloride) Cream, 2%

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of tinea pedis, tinea cruris, and tinea corporis

CONSULTATION REQUEST DATE: March 7, 2011

DIVISION ACTION
GOAL DATE: September 30, 2011

PDUFA DATE: October 16, 2011

I. BACKGROUND:

The Applicant submitted this application for the use of NAFT-500 (naftifine hydrochloride) Cream, 2% to support an indication for the treatment of tinea pedis, tinea cruris, and tinea corporis. The pivotal studies, Protocol #s MRZ-90200-F1-3001, entitled "A Phase 3 Double-Blind, Randomized, Placebo-Controlled, Multicenter, Parallel Group Evaluation of the Efficacy and Safety of NAFT-500 in Subjects with Tinea Cruris" and MUS-90200-0736-1**,** entitled "A Phase 3 Double-Blind, Randomized, Placebo-Controlled, Multicenter, Parallel Group Evaluation of the Efficacy and Safety of NAFT-500 in Subjects with Tinea Pedis" were submitted in support of the indication.

The conduct of Protocols MUS-90200-0736-1 and MRZ-90200-F1-3001 were inspected. Protocol MUS-90200-0736-1 was a six-week, double-blind, randomized, placebo-controlled multicenter, parallel group study that compared NAFT-500 to placebo (vehicle) and to a positive control (Naftin® 1%) in the treatment of tinea pedis. Protocol MRZ-90200-F1-3001 was a four week, randomized, double-blind, placebo-controlled, parallel group Phase 3 study of NAFT-500 compared to vehicle (placebo) in the treatment of tinea cruris.

The primary efficacy endpoint for Protocol MUS-90200-0736-1 was the percentage of subjects at two weeks post-treatment who were completely cured as defined by negative mycology results from the central laboratory (dermatophyte culture and KOH) and negative signs and symptoms.

The primary efficacy endpoint for Protocol MRZ-90200-F1-3001was the percentage of subjects at the 4 week time point with complete cure defined as negative mycology results from the central laboratory (dermatophyte culture and KOH) and a Physicians Global Evaluation Score of 1.

Two Clinical Investigator (CI) sites were selected for inspection based on high number of treatment responders and the relatively large numbers of subjects at the sites.

II. RESULTS (by Site):

Name of CI, Location	**Protocol #/ # of Subjects/**	**Inspection Dates**	**Final Classification**
Site No. 25 Amaury Roman, M.D. Advanced Medical Concepts, PSC PSC4 Balldorioty Street Cidra, PR 00739	MRZ-90200-F1-3001 / 25/	23-26 May 2011	NAI. Pending final classification.
Site No. 06 Zoe Draelos, M.D. 2444 N. Main Street High Point, N.C. 27262	MUS-90200-0736-1/ 20/	3-5 May 2011	NAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Site No. 25
   Amaury Roman, M.D.
   Advanced Medical Concepts, PSC
   PSC4 Baldorioty Street
   Cidra, PR 00739

   a. **What was inspected:** At this site, 102 subjects were screened, 58 enrolled, and 49 completed the study. The records of all 58 enrolled subjects were reviewed. The records reviewed included, but were not limited to, informed consent documents, eligibility criteria, laboratory results (including sampling for KOH analysis), primary efficacy endpoint data, adverse event documentation and reporting, concomitant medications, and test article dispensation and accountability. Other documentation reviewed included, but was not limited to, sponsor/monitor/IRB correspondence, test article storage documents, and protocol deviation reports.

   b. **General observations/commentary**: A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations. In general, the study appeared to be conducted adequately.

   c. **Assessment of data integrity**: The study appears to have been conducted adequately, and the data appear acceptable in support of the respective indication.

2. Site 06
   Zoe Draelos, M.D.
   2444 N. Main Street
   High Point, N.C. 27262

   a. **What was inspected**: At this site, 41 subjects were screened for the study, 27 were enrolled, and 12 completed the study. The records of all 41 screened subjects were reviewed. Records reviewed included, but were not limited to, all informed consent documents, a comparison of source documents with line listings, sponsor and IRB correspondence, financial disclosures, test article accountability, training documentation, dosing diaries, concomitant medications, adverse events, protocol deviations, clinical evaluations, and laboratory reports.

   b. **General observations/commentary**: A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations. In general, the study appeared to be conducted adequately.

   c. **Assessment of data integrity**: The study appears to have been conducted adequately, and the data appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigator sites of Drs. Roman and Draelos were inspected in support of this NDA. No regulatory violations were observed during these inspections, and they are classified No Action Indicated (NAI).

The studies conducted at the sites of Drs. Roman and Draelos appear to have been conducted adequately, and the data generated by these clinical sites appear acceptable in support of the respective indication.

Note: The observations notes above for Dr. Roman are based on the preliminary communications provided by the FDA field investigator. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIR.

{See appended electronic signature page}

Roy Blay, Ph.D.
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Division of Good Clinical Practice Compliance
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CONCURRENCE: *{See appended electronic signature page}*

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/s/

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JEAN M MULINDE
08/08/2011