

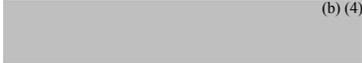
**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204286Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type	NDA
Application Number(s)	204286
Priority or Standard	Standard
Submit Date(s)	August 31, 2012
Received Date(s)	September 6, 2012
PDUFA Goal Date	July 1, 2013
Reviewer Name(s)	Milena M. Lolic, MD
Review Date	May 8, 2013
Review Revision Date	May 31, 2013
Established Name	Naftifine hydrochloride
Trade Name	Naftin Gel 2%
Therapeutic Class	Antifungal
Applicant	Merz Pharmaceuticals, LLC
Formulation(s)	Gel 2%
Dosing Regimen	Daily for 2 weeks
Proposed Indication(s)	Interdigital  (b) (4) tinea pedis
Intended Population(s)	 (b) (4) years of age and older

## Table of Contents

<b>1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT .....</b>	<b>6</b>
1.1 Recommendation on Regulatory Action .....	6
1.2 Risk Benefit Assessment .....	7
1.3 Recommendations for Postmarket Risk Management Activities .....	8
1.4 Recommendations for Postmarket Studies/Clinical Trials .....	8
<b>2 INTRODUCTION AND REGULATORY BACKGROUND .....</b>	<b>8</b>
2.1 Product Information .....	9
2.2 Tables of Currently Available Treatments for Proposed Indications .....	9
2.3 Availability of Proposed Active Ingredient in the United States .....	11
2.4 Important Safety Issues with Consideration to Related Drugs .....	11
2.5 Summary of Presubmission Regulatory Activity Related to Submission .....	12
2.6 Other Relevant Background Information .....	12
<b>3 ETHICS AND GOOD CLINICAL PRACTICES .....</b>	<b>12</b>
3.1 Submission Quality and Integrity .....	12
3.2 Compliance with Good Clinical Practices .....	13
3.3 Financial Disclosures .....	21
<b>4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES .....</b>	<b>21</b>
4.1 Chemistry Manufacturing and Controls .....	21
4.2 Clinical Microbiology .....	22
4.3 Preclinical Pharmacology/Toxicology .....	24
4.4 Clinical Pharmacology .....	25
4.4.1 Mechanism of Action .....	25
4.4.2 Pharmacodynamics .....	25
4.4.3 Pharmacokinetics .....	25
<b>5 SOURCES OF CLINICAL DATA .....</b>	<b>26</b>
5.1 Tables of Studies/Clinical Trials .....	26
5.2 Review Strategy .....	27
5.3 Discussion of Individual Studies/Clinical Trials .....	28
<b>6 REVIEW OF EFFICACY .....</b>	<b>32</b>
Efficacy Summary .....	32
6.1 Indication .....	32
6.1.1 Methods .....	33
6.1.2 Demographics .....	33
6.1.3 Subject Disposition .....	34
6.1.4 Analysis of Primary Endpoint .....	34
6.1.5 Analysis of Secondary Endpoints(s) .....	35
6.1.6 Other Endpoints .....	36
6.1.7 Subpopulations .....	37
6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations .....	38
6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects .....	38
6.1.10 Additional Efficacy Issues/Analyses .....	38
<b>7 REVIEW OF SAFETY .....</b>	<b>40</b>
Safety Summary .....	40
7.1 Methods .....	41

7.1.1 Studies/Clinical Trials Used to Evaluate Safety.....	41
7.1.2 Categorization of Adverse Events.....	41
7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.....	41
7.2 Adequacy of Safety Assessments.....	41
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations.....	41
7.2.2 Explorations for Dose Response.....	43
7.2.3 Special Animal and/or In Vitro Testing.....	43
7.2.4 Routine Clinical Testing.....	43
7.2.5 Metabolic, Clearance, and Interaction Workup.....	43
7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class.....	43
7.3 Major Safety Results.....	44
7.3.1 Deaths.....	44
7.3.2 Nonfatal Serious Adverse Events.....	44
7.3.3 Dropouts and/or Discontinuations.....	44
7.3.4 Significant Adverse Events.....	45
7.3.5 Submission Specific Primary Safety Concerns.....	46
7.4 Supportive Safety Results.....	48
7.4.1 Common Adverse Events.....	48
7.4.2 Laboratory Findings.....	49
7.4.3 Vital Signs.....	49
7.4.4 Electrocardiograms (ECGs).....	49
7.4.5 Special Safety Studies/Clinical Trials.....	50
7.4.6 Immunogenicity.....	56
7.5 Other Safety Explorations.....	56
7.5.1 Dose Dependency for Adverse Events.....	56
7.5.2 Time Dependency for Adverse Events.....	56
7.5.3 Drug-Demographic Interactions.....	56
7.5.4 Drug-Disease Interactions.....	58
7.5.5 Drug-Drug Interactions.....	58
7.6 Additional Safety Evaluations.....	58
7.6.1 Human Carcinogenicity.....	58
7.6.2 Human Reproduction and Pregnancy Data.....	58
7.6.3 Pediatrics and Assessment of Effects on Growth.....	59
7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	60
7.7 Additional Submissions.....	60
<b>8 POSTMARKET EXPERIENCE.....</b>	<b>60</b>
<b>9 APPENDICES.....</b>	<b>61</b>
9.1 Literature Review/References.....	61
9.2 Labeling Recommendations.....	61
9.3 Advisory Committee Meeting.....	64

## Table of Tables

Table 1	Currently Available Treatments for Tinea Pedis .....	10
Table 2	List of Investigators for Trial 3015 .....	13
Table 3	List of Investigators for Trial 3016 .....	17
Table 4	Summary of Trials of NAFT-600 for the Tinea Pedis Clinical Program .....	27
Table 5	Analysis Sets .....	33
Table 6	Baseline Demographics-FAS .....	33
Table 7	Subjects Disposition-FAS .....	34
Table 8	Primary Endpoint Efficacy Analysis-Complete Cure .....	35
Table 9	Secondary Endpoint Efficacy Analysis-Effective Treatment .....	35
Table 10	Secondary Endpoint Efficacy Analysis-Mycological Cure .....	35
Table 11	Sensitivity Analysis <span style="background-color: #cccccc; padding: 0 20px;"> </span> <sup>(b) (4)</sup> .....	36
Table 12	Demographics-SES .....	42
Table 13	Subject Disposition-SES .....	42
Table 14	All Serious Adverse Events .....	44
Table 15	Subjects Discontinuation (safety population) .....	45
Table 16	Severe Adverse Events .....	46
Table 17	Application Site Reactions Trial 3015 .....	47
Table 18	Applications Site Reactions Trial 3016 .....	47
Table 19	Most Common AE in Trial 3015 .....	48
Table 20	Most Common AE in Trial 3016 .....	48
Table 21	Most Common AE in Trial 1010 .....	48
Table 22	Summary of Mean Cumulative Data During the Irritation Phase .....	51
Table 23	Age-related Most Common AEs .....	57
Table 24	Gender-related Most Common AEs .....	57

## Table of Figures

Figure 1 Trial Design .....	28
Figure 2 Efficacy Results by Center .....	38
Figure 3 Naftin-600 Irritancy Graph.....	51
Figure 4 Positive Irritancy Control Graph .....	52
Figure 5 Negative Control Irritancy Graph.....	52

## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

I recommend that NDA 204,286 Naftin Gel 2% be approved for the treatment of interdigital tinea pedis caused by the organisms *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum* in patients 18 years or older.

Two phase 3 trials (MRZ/3015 and MRZ/3016) demonstrated the efficacy and safety of once daily Naftin Gel 2% for adult patients with interdigital tinea pedis.

This reviewer's recommended indication differs from the applicant's proposed indication, "the treatment of interdigital (b) (4) tinea pedis caused by the organisms *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum* in patients (b) (4) years of age and older."

The differences and rationales are as follows:



## 1.2 Risk Benefit Assessment

The risk to benefit assessment for this application is primarily based on the clinical trial results.

The primary efficacy endpoint defined as the proportion of subjects with complete cure of interdigital tinea pedis at Week 6 was achieved by 17% of subjects treated with Naftin Gel 2% in trial 3015 and by 26% in trial 3016. Complete cure for vehicle-treated subjects was 2% and 3% for respective trials ( $p < 0.001$ ). The analysis of secondary endpoints (mycological cure of interdigital tinea pedis and effective treatment of interdigital tinea pedis) supported primary endpoint. Observed treatment effect is comparable to approved topical products for the treatment of tinea pedis.

In two pivotal Phase 3 clinical trials, the most common adverse reactions were local skin reactions (rate occurrence 2% for Naftin Gel 2% v. 1% for vehicle) the vast majority of which were mild to moderate and resolved spontaneously. The new safety information is the potential of Naftin Gel 2% to cause irritancy as demonstrated in dermal safety study.

This new product differs from the currently approved Naftin Gel 1 % in four ways:

- higher concentration (2% v. 1%)
- dosing regimen (once daily v. twice daily application)
- duration of treatment (2 weeks v. 4 weeks)
- irritancy potential

Direct comparison of two Naftin Gel concentrations was not done. While the question of comparative effectiveness remains unanswered, the proposed advantage of Naftin Gel 2 % is that the duration of treatment is reduced from 4 weeks to 2 weeks and dosing interval from twice daily to once daily. The benefit of more convenient dosing of Naftin Gel 2% should be weighed against the irritancy potential for patients with tolerability problems.

In conclusion, benefits outweigh the risks. If approved, Naftin 2% Gel could offer an additional therapeutic option for interdigital type tinea pedis. The adverse events associated with the drug product can be adequately informed by labeling. The label also provides adequate information for instructions for use.

### 1.3 Recommendations for Postmarket Risk Management Activities

There are no recommendations for a specific postmarketing risk management plan beyond labeling. Routine risk minimization measures such as professional labeling, prescription status, and spontaneous adverse event reporting, comprise an adequate risk management plan for this application.

### 1.4 Recommendations for Postmarket Studies/Clinical Trials

The applicant requested a waiver of the requirement to conduct studies in pediatric subjects younger than 12 years of age, and a deferral to conduct studies in pediatric subjects 12-<sup>(b)(4)</sup> years (7.6.3 Pediatrics and Assessment of Effects on Growth).

The request for partial waiver and deferral was presented to Pediatric Review Committee (PeRC) on May 22, 2013.

The Committee agreed with Division's recommendation that a waiver for pediatric subjects less than 12 years of age be granted. The decision was based on section 505B(a)(4)(B)(iii) of the Pediatric Research Equity Act where the Agency may grant the partial waiver if the drug or biological product (1) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group and (2) is not likely to be used by a substantial number of pediatric patients in that age group).

The Committee agreed with review team recommendation that a deferral to conduct studies in pediatric subjects 12-<sup>(b)(4)</sup> years be granted and that the following PMR be attached to this NDA approval:

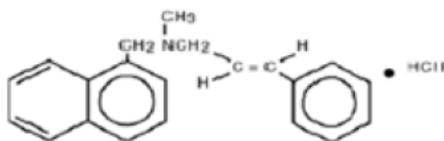
1. Pharmacokinetic/Safety/Tolerability trial under maximal use conditions in adolescent subjects ages 12 years to 17 years 11 months with a minimum of at least 18 evaluable subjects with tinea pedis interdigital type.

## 2 Introduction and Regulatory Background

Tinea pedis (athlete's foot) is dermatophytic infection of the feet characterized by erythema and chronic desquamation between the toes (interdigital type) or with widespread erythema, hyperkeratosis, and scaling on the sole and heel of the foot (moccasin or plantar type). Less common types of tinea pedis infections are vesicular and ulcerative types. [Weinstein and Berman, 2002<sup>1</sup>; Noble et al, 1998<sup>2</sup>]. The most common cause of tinea pedis is *Trichophyton rubrum*.

## 2.1 Product Information

Naftifine HCl is an allylamine antifungal. Chemically, naftifine HCl is (E)-N-Cinnamyl-N-methyl-1-naphthalenemethylamine hydrochloride with an empirical formula C<sub>21</sub>H<sub>21</sub>N•HCl and a molecular weight of 323.86. Its structural formula is:



Naftin Gel 2% is a colorless to yellow gel containing naftifine hydrochloride (naftifine HCl) 2% as the active ingredient and the excipients (b) (4), propylene glycol, polysorbate 20, alcohol (b) (4), hydroxyethyl cellulose, benzyl alcohol, trolamine and edetate disodium. The composition of Naftin Gel 2% is presented below:

Component	Reference	Concentration (% w/w)	Function
Naftifine hydrochloride	USP	2.00	Active Ingredient
(b) (4)	USP	(b) (4)	(b) (4)
Propylene Glycol	USP		
Polysorbate 20	NF		
Alcohol (b) (4)	USP		
Hydroxyethyl Cellulose	NF		
Benzyl Alcohol	NF		
Trolamine	NF		
Edetate Disodium	USP		

NF=National Formulary, USP=United States Pharmacopeia  
 Source: Table 1 from 3.2.P.1 section

Throughout the clinical review, the terms Naftin Gel 2% and NAFT-600 are used interchangeably.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

**Table 1 Currently Available Treatments for Tinea Pedis**

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

Butenafine (Mentax)	NDA 020-524	Once daily for 4 weeks	combined label	October 18, 1996	Mentax® (butenafine HCl cream), 1%, is indicated for the topical treatment of the following dermatologic infections: tinea (pityriasis) versicolor due to <i>M. furfur</i> (formerly <i>P. orbicularis</i> ), interdigital tinea pedis (athlete's foot), tinea corporis (ringworm) and tinea cruris (jock itch) due to <i>E. floccosum</i> , <i>T. mentagrophytes</i> , <i>T. Rubrum</i> , and <i>T tonsurans</i> (2002).
Butenafine (Mentax)	NDA 020-663	combined label	Once daily for two weeks	December 31, 1998	Mentax® (butenafine HCl cream), 1%, is indicated for the topical treatment of the following dermatologic infections: tinea (pityriasis) versicolor due to <i>M. furfur</i> (formerly <i>P. orbicularis</i> ), interdigital tinea pedis (athlete's foot), tinea corporis (ringworm) and tinea cruris (jock itch) due to <i>E. floccosum</i> , <i>T. mentagrophytes</i> , <i>T. Rubrum</i> , and <i>T tonsurans</i> (2002).
(OTC) Butenafine (Lotrimin Ultra)	NDA 021-307	BID 1 week	QD 2 weeks	December 7, 2001	Uses: cures most athlete's foot between the toes, jock itch and ringworm. Relieves itching, burning, cracking, and scaling which accompany these conditions (2001)
Sertaconazole (Ertaczo)	NDA 021-385	BID 4 weeks	No indication for tinea corporis or cruris	December 10, 2003	ERTACZO (sertaconazole nitrate) Cream, 2%, is indicated for the treatment of interdigital tinea pedis in immunocompetent patients 12 years of age or older, caused by: <i>Trichophyton rubrum</i> , <i>Trichophyton mentagrophytes</i> , and <i>Epidermophyton floccosum</i> .
Ketoconazole (Generic)	ANDA 075-561 and 076-294	QD 6 weeks	QD 2 weeks	75-561: April 25, 2000 76-294: April 28, 2004	Ketoconazole Cream 2% is indicated for the topical treatment of tinea corporis, tinea cruris and tinea pedis caused by <i>Trichophyton rubrum</i> , <i>T. mentagrophytes</i> and <i>Epidermophyton floccosum</i> ; in the treatment of tinea (pityriasis) versicolor caused by <i>Malassezia furfur</i> ( <i>Pityrosporum orbicularis</i> ); in the treatment of cutaneous candidiasis caused by <i>Candida</i> spp. and in the treatment of seborrheic dermatitis (2002).
Naftifine (Naftin)	NDA 019-599	QD for 2 weeks	QD for 2 weeks	January 13, 2012	NAFTIN Cream, 2% is an allylamine antifungal Indicated for the treatment of interdigital tinea pedis, tinea, cruris, and tinea corporis caused by the organism <i>Trichophyton rubrum</i> in adults ≥ 18 years of age.

Source: Internal DDDP database

## 2.3 Availability of Proposed Active Ingredient in the United States

Approved products with Naftifine HCl as an active ingredient are:

- Naftin Cream 1% for the topical treatment of tinea pedis, tinea cruris and tinea corporis caused by the organisms *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum* (approved February 29, 1988)
- Naftin Gel 1% for the topical treatment of tinea pedis, tinea cruris and tinea corporis caused by the organisms *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Trichophyton tonsurans* and *Epidermophyton floccosum* (approved June 18, 1990)
- Naftin Cream 2% 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 (approved January 13, 2012).

## 2.4 Important Safety Issues with Consideration to Related Drugs

Naftifine hydrochloride is a synthetic allylamine derivative. Other allylamine antifungals include terbinafine, and butenafine. With oral administration of terbinafine, liver failure, taste and smell disturbance, depressive symptoms, neutropenia and Stevens-Johnson's syndrome have been reported. However, as with topical terbinafine, these types of adverse events have not been

observed with approved naftifine hydrochloride drug products and consequently are not expected with this new formulation.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

Relevant pre-submission regulatory activity for NAFT-600 was notable for the following:

- Guidance Meeting April 14, 2010
  - In consideration of the historical use of naftifine hydrochloride, the Division might consider submission of fully acceptable data which regarding carcinogenicity of NAFT-600 as a postmarketing commitment
  -  (b) (4)
  - The Agency recommended conducting an appropriate dose ranging study. There was no EOP 2 meeting with the applicant and Special Protocol Assessment was not submitted.
- Pre-NDA Meeting May 16, 2012
  - It is acceptable for applicant to cross reference all of Module 4 documents within NDA 019599/S-011 application (NAFT-500)
  - A deferral can be submitted for an assessment under the Pediatric Research Equity Act (PREA) for subjects ages 12 to 17 with tinea pedis

## 2.6 Other Relevant Background Information

 (b) (4)

## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

The overall quality of the clinical information contained in this submission was acceptable.

### 3.2 Compliance with Good Clinical Practices

The applicant affirmed that the studies were conducted in accordance with the ethical principles originating from the Declaration of Helsinki and the International Conference on Harmonization (ICH) harmonized tripartite guidelines for Good Clinical Practice and the compliance with local and FDA regulatory requirements. The protocol and Informed Consent Forms were reviewed by the Investigations Review Board (IRB) associated with the trial sites or by consulting central IRB. Written informed consents were obtained from subjects at the first (baseline) visit.

**Table 2 List of Investigators for Trial 3015**

Principal Investigator, Site Address, Email, and Phone Number	Site Number	Other Important Personnel	Number of Subjects Enrolled
Raza Aly, PhD UCSF Dermatology Research 1701 Divisadero Street, Room 430 San Francisco, California 94115 Email: alyr@derm.ucsf.edu Tel: 415-353-9684	001-001	(b) (4)	42
Suzanne Bruce, MD Suzanne Bruce and Associates The Center for Skin Research 1900 St James Place, Suite 650 Houston, Texas 77056 Email: sbruce@sba-skincare.com Tel: 713-985-0210	001-003		71
Joseph L Jorizzo, MD Wake Forest University Health Sciences Department of Dermatology Medical Center Boulevard Winston-Salem, North Carolina 27157 Email: jjorizzo@wakehealth.edu Tel: 336-716-3775	001-004		37

Clinical Review  
 Milena Lolic, MD  
 NDA 204-286  
 Naftin (naftifine hydrochloride) Gel 2%

Principal Investigator, Site Address, Email, and Phone Number	Site Number	Other Important Personnel	Number of Subjects Enrolled
Linda Murray, DO Radiant Research, Inc 6010 Park Boulevard Pinellas Park, Florida 33781 Email: lindamurray@radiantresearch.com Tel: 727-544-6367	001-020	(b) (4)	77
Richard A Pollak, DPM, MS Endeavor Clinical Trials, PA 8042 Wurzbach, Suite 420 San Antonio, Texas 78229 Email: drpollk@hotmail.com Tel: 210-949-0807	001-021		60
Ronald C Savin, MD The Savin Center, PC 134 Park Street New Haven, Connecticut 06511 Email: study@savincener.com Tel: 203-752-9821	001-022		12
Michael H Gold, MD Tennessee Clinical Research Center 2000 Richard Jones Road, Suite 223 Nashville, Tennessee 37215 Email: research@goldskincare.com Tel: 615-383-9660	001-024		9
Daniel M Stewart, DO Michigan Center for Skin Care Research 43900 Garfield Road, Suite 106 Clinton Township, Michigan 48038 Email: dstewart@skincarereseach.com Tel: 586-286-7325	001-025		29
Tory P Sullivan, MD, PA Tory Sullivan, MD, PA 16100 NE 16 <sup>th</sup> Avenue, Suite A N Miami Beach, Florida 33162 Email: torysullivan@gmail.com Tel: 5305-652-8600	001-026		80

Principal Investigator, Site Address, Email, and Phone Number	Site Number	Other Important Personnel	Number of Subjects Enrolled
Michael J Bernhardt, MD Jacksonville Center for Clinical Research 4085 University Boulevard South, Suite 1 Jacksonville, Florida 32216 Email: mbernhardt@encoredocs.com Tel: 904-730-0101	001-013	(b) (4)	21
Amaury A Roman Miranda, MD Advanced Medical Concepts, PSC 4 Balldorioty Street Cidra, Puerto Rico 00739 Email: research@clinicalzone.com Tel: 787-739-3376	001-015		39
James Mazur, DPM PMG Research of Salisbury 410 Mocksville Avenue Salisbury, North Carolina 28144 Email: sthompson@pmg-research.com Tel: 704-647-9913	001-016		44
Alicia R Barba, MD International Dermatology Research, Inc 8370 West Flagler Street, Suite 200 Miami, Florida 33144 Email: Abarba@intldermatology.com Tel: 305-225-0400	001-017		72
Brock A McConnehey, DO, CPI Northwest Clinical Trials 7373 West Emerald Street Boise, Idaho 83704 Email: drbrock@nwct.com Tel: 208-685-0600	001-018		17
Arthur J Tallis, DPM Associated Foot & Ankle Specialists, LLC 6707 N 19 <sup>th</sup> Avenue, Suite 103 Phoenix, Arizona 85015 Email: atallis@hriaz.com Tel: 602-288-4673	001-019		16

Principal Investigator, Site Address, Email, and Phone Number	Site Number	Other Important Personnel	Number of Subjects Enrolled
Linda Murray, DO Radiant Research, Inc 6010 Park Boulevard Pinellas Park, Florida 33781 Email: lindamurray@radiantresearch.com Tel: 727-544-6367	001-020	(b) (4)	77
Richard A Pollak, DPM, MS Endeavor Clinical Trials, PA 8042 Wurzbach, Suite 420 San Antonio, Texas 78229 Email: drpllk@hotmail.com Tel: 210-949-0807	001-021		60
Ronald C Savin, MD The Savin Center, PC 134 Park Street New Haven, Connecticut 06511 Email: study@savincener.com Tel: 203-752-9821	001-022		12
Michael H Gold, MD Tennessee Clinical Research Center 2000 Richard Jones Road, Suite 223 Nashville, Tennessee 37215 Email: research@goldskincare.com Tel: 615-383-9660	001-024		9
Daniel M Stewart, DO Michigan Center for Skin Care Research 43900 Garfield Road, Suite 106 Clinton Township, Michigan 48038 Email: dstewart@skincarereseach.com Tel: 586-286-7325	001-025		29
Tory P Sullivan, MD, PA Tory Sullivan, MD, PA 16100 NE 16 <sup>th</sup> Avenue, Suite A N Miami Beach, Florida 33162 Email: torysullivan@gmail.com Tel: 5305-652-8600	001-026		80

Clinical Review  
 Milena Lolic, MD  
 NDA 204-286  
 Naftin (naftifine hydrochloride) Gel 2%

Principal Investigator, Site Address, Email, and Phone Number	Site Number	Other Important Personnel	Number of Subjects Enrolled
John H Tu, MD Skin Search of Rochester, Inc 100 White Spruce Boulevard Rochester, New York 14623 Email: Johntu@dermrochester.com Tel: 585-697-1818	001-027	(b) (4)	50
Janet C DuBois, MD DermResearch, Inc 8140 N Mopac, Building 3, Suite 120 Austin, Texas 78759 Email: Jdubois@dermresearch.net Tel: 512-349-9889	001-028	(b) (4)	19

Source: 5.3.5.1.Clinical Study Report MRZ 90200/3105/1

**Table 3 List of Investigators for Trial 3016**

Principal Investigator, Site Address, Email, and Phone Number	Site Number	Other Important Personnel	Number of Subjects Enrolled
Jeffrey M. Adelglass, MD Research Across America 9 Medical Parkway Plaza 4, Suite 202 Dallas, Texas 75234 Email: jadelglass@researchacrossamerica.com Tel: 972-241-1222	001-002	(b) (4)	47
Terry M Jones, MD J&S Studies, Inc 1710 Crescent Pointe Parkway College Station, Texas 77845 Email: tjones@js-studies.com Tel: 979-774-5933	001-010	(b) (4)	43
Phoebe Rich, MD Oregon Dermatology & Research Center 2565 NW Lovejoy, Suite 200 Portland, Oregon 97210 Email: phoeberich@aol.com Tel: 503-226-3376	001-012	(b) (4)	34
Tracey C Vlahovic, DPM Temple University School of Podiatric Medicine 148 North 8 <sup>th</sup> Street Philadelphia, Pennsylvania 19107 Email: traceyv@temple.edu Tel: 215-625-5252	001-014	(b) (4)	26

Principal Investigator, Site Address, Email, and Phone Number	Site Number	Other Important Personnel	Number of Subjects Enrolled
Walter K Nahm, MD, PhD University Clinical Trials, Inc 7695 Cardinal Court, Suite 210 San Diego, California 92123 Email: tire99@yahoo.com Tel: 858-278-8470	001-023	(b) (4)	45
Steven C Bowman, MD Tampa Bay Medical Research 3251 McMullen Booth Road Suite 303 Clearwater, Florida 33761 Email: bowman@tbmr.net Tel: 727-724-3316	001-035		25
Alicia D Bucko, DO, JD Academic Dermatology Associates 1203 Coal SE Albuquerque, New Mexico 87106 Email: flamingolaw@mac.com Tel: 505-247-4220	001-036		53
Norman E Bystol, MD Radiant Research, Inc 7840 East Broadway Tucson, Arizona 85710 Email: normanbystol@radiantresearch.com Tel: 520-885-6793	001-037		8
Scott D Clark, MD Longmont Clinic, PC 1925 W Mountain View Avenue Longmont, Colorado 80501 Email: sclark11@mindspring.com Tel: 303-776-8718	001-038		29
Charles Hudson, MD Hudson Dermatology 3501 Washington Avenue Evansville, Indiana 47714 Email: hudsonderm@aol.net Tel: 812-477-2760	001-039		8
Michael T Jarratt, MD DermResearch, Inc 8140 N Mopac, Bldg 3, Suite 120 Austin, Texas 78759 Email: mjarratt@dermresearch.net Tel: 512-349-9889	001-040		60

Principal Investigator, Site Address, Email, and Phone Number	Site Number	Other Important Personnel	Number of Subjects Enrolled
Mark S Lee, MD Progressive Clinical Research 4499 Medical Drive, Suite 145 San Antonio, Texas 78229 Email: mlee@progclin.com Tel: 210-614-5557	001-041	(b) (4)	25
Joe Blumenau, MD Research Across America 9 Medical Parkway Plaza 4, Suite 202 Dallas, Texas 75234 Email: jblumenau@raasites.com Tel: 972-241-1222	001-042		75
Michael J Noss, MD Radiant Research, Inc 11500 Northlake Drive, Suite 320 Cincinnati, Ohio 45249 Email: michaelnoss@radiantresearch.com Tel: 513-247-5577	001-043		80
T Joseph Raouf, MD T Joseph Raouf, MD, Inc 16133 Ventura Boulevard, Suite 340 Encino, California 91436 Email: joseph@drrooof.com Tel: 818-783-5060	001-044		39
Douglas R Schumacher, MD Radiant Research, Inc 1275 Olentangy River Road, Suite 202 Columbus, Ohio 43212 Email: drschumachermd@sbcglobal.net Tel: 614-294-3854	001-045		51
Harry H Sharata, MD, PhD Madison Skin and Research, Inc 6510 Grand Teton Plaza, Suite 302 Madison, Wisconsin 53719 Email: Hsharata@madskin.com Tel: 608-826-0251	001-046		11
James M Swinehart, MD Colorado Medical Research Center 950 E Harvard #630 Denver, Colorado 80210 Email: cmrc@pcisys.net Tel: 303-744-7000	001-047		8

Principal Investigator, Site Address, Email, and Phone Number	Site Number	Other Important Personnel	Number of Subjects Enrolled
Nathan Segall, MD, CPI Clinical Research Atlanta 175 Country Club Drive Building 100, Suite A Stockbridge, Georgia 30281 Email: nsegall@clinicalresearchatlanta.net Tel: 770-507-6867	001-048	(b) (4)	19
Erin M Warshaw, MD Department of Veterans Affairs One Veterans Drive, Dept. 111K Dermatology Minneapolis, Minnesota 55417 Email: erin.warshaw@va.gov Tel: 612-467-3225	001-049	(b) (4)	32
Patricia P Westmoreland Palmetto Clinical Trial Services, LLC 611 NE Main Street, Suite A Simpsonville, South Carolina 29681 Email: westmoreland@palmettoclinical.com Tel: 864-962-0431	001-050	(b) (4)	2
David C Wilson, MD The Education and Research Foundation, Inc 2095 Langhorne Road Lynchburg, Virginia 24501 Email: davidwilson@educationandresearch.com Tel: 434-847-8400	001-051	(b) (4)	41
Robert P Dunne, DPM Lake Washington Foot and Ankle Center 2717 N Wickham Road, Suite 4 Melbourne, Florida 32935 Email: lvfac@att.net Tel: 321-253-6191	001-052	(b) (4)	60
Stanley Russell, DPM Endeavor Clinical Trials, PA 8042 Wurzbach, Suite 420 San Antonio, Texas 78229 Email: Dr.rstanley@yahoo.com Tel: 210-949-0807	001-053	(b) (4)	39

Source: 5.3.5.1.Clinical Study Report MRZ 90200/3016/1

The Division of Scientific Investigators (DSI) was consulted to review the conduct of both clinical trials, and included the inspection of site 001-027 in Rochester, NY and site 001-052 in Melbourne, FL. Both sites were selected by the Division based on high number of patients enrolled and the high number of treatment responders.

DSI review of the trial sites concluded: “Based upon the review of inspectional findings for these clinical investigator sites, the study data collected appears reliable in support of the requested indication.”

### 3.3 Financial Disclosures

Financial disclosure forms were reviewed, and all investigators reported no financial interests. The applicant certified in Form 3454 that they had not entered into any financial arrangements with any of the clinical investigators. It was also affirmed that none of the clinical investigators disclosed any proprietary interest in the product, or significant equity interest in the sponsor company. Certification was made that no 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

Naftin Gel 2% is clear to yellow gel that contains naftifine hydrochloride (b) (4). The amount of (b) (4) alcohol has been reduced in comparison to Naftin Gel 1% (b) (4) with an intention to reduce irritation. The inactive ingredients are listed as follows: (b) (4), propylene glycol, polysorbate20, alcohol, hydroxyethyl cellulose, benzyl alcohol, trolamine, and edentate disodium. All excipients are below approved levels listed in the FDA's database of inactive ingredients in approved drug products. Per CMC review, the microbial limits testing met the specification criteria and submitted stability data are sufficient to support the proposed expiration dating period of 24 months.

Naftin Gel, 2% will be packaged in the same container closure systems (aluminum tube 2g physician sample and 45g for commercial distribution) that are used to package the marketed Naftin, Cream 2%.

The Office of Compliance found that the compliance to the cGMP involving all facilities pertaining to the drug substance manufacturing and testing operations was acceptable.

In his Executive Summary of NDA 204286, the CMC review Rajiv Agarwal, Ph.D. concluded:

“This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The Office of Compliance has made an “Acceptable” recommendation for the facilities involved in this application. The proposed labels and labeling (Description and How Supplied sections) have required information. Therefore, from the ONDQA perspective, this NDA is recommended for approval with an expiration dating period of 24 months.”

*Comment: There are no outstanding review issues from the CMC perspective.*

## 4.2 Clinical Microbiology

The most common dermatophytes that cause tinea pedis are *Trichophyton rubrum*, *T. mentagrophytes* and *Epidermophyton floccosum*. Diagnosis of tinea pedis is made by physical examination and confirmed by microscopic examination with KOH (potassium hydroxide) and culture.

Included in the application are the results of *in vitro* antifungal susceptibility testing of isolates obtained from Phase 3 clinical trials MRZ 90200-3015 and MRZ 902000/3016. The minimum inhibitory concentration (MIC) was defined as the lowest concentration that resulted in an 80% reduction in growth as compared to the control wells. Minimum inhibitory concentrations (MIC) were determined on day 4. Applicant's results are shown below (from 5.3.5.4. section)

MRZ 90200/3015/1 (N=872)

	<i>Epidermophyton floccosum</i> (30)	<i>Trichophyton rubrum</i> (793)	<i>T. mentagrophytes</i> (49)
MIC50	0.06	0.03	0.03
MIC90	0.06	0.06	0.125
Range	0.008-0.06	0.004-2	0.008-0.125

MRZ 902000/3016/1 (N=966)

	<i>Epidermophyton floccosum</i> (36)	<i>Trichophyton rubrum</i> (895)	<i>T. mentagrophytes</i> (35)
MIC50	0.06	0.06	0.06
MIC90	0.25	0.125	0.125
Range	0.03-0.25	0.015->2	0.03-2

In her review, Microbiology reviewer Simone M. Shurland, Ph.D. noted the following mycological cure by baseline pathogen MIC (combined Phase 3 trials data -Week 6):

NAFT-600 (mcg/mL)	Mycological Cure at week 6 (FAS Population)		
	<i>T. rubrum</i>	<i>T. mentagrophytes</i>	<i>E. floccosum</i>
0.004	1/1 (100.0)	NA	NA
0.008	0/1 (0)	NA	NA
0.015	18/24 (75.0)	0/1 (0)	2/3 (66.7)
0.03	97/157 (61.9)	5/7 (71.4)	5/5 (100.0)
0.06	138/214 (64.5)	4/9 (44.4)	10/10 (100.0)
0.125	13/24 (54.2)	1/3 (33.3)	2/3 (66.7)
0.25	3/4 (75.0)	NA	0/1 (0)
1	1/2 (50.0)	NA	1/2 (50.0)
2	2/3 (67.7)	0/1 (0)	NA

Source: Table 12 from Division of Anti-Infective Products Clinical Microbiology Review

Mycological cure for interdigital type tinea pedis at Week 6 was one of the pre-specified key secondary points in the Phase 3 trials. Applicant's analysis of the data supportive of that endpoint is presented below:

Visit	Mycological Cure <sup>a</sup>	NAFT-600 Gel, 2% (MVTF)			Placebo (MVTF)			NAFT-600 Gel, 2% (Observed)
		90200/3015/1 N=382 n (%)	90200/3016/1 N=400 n (%)	Total N=782 n (%)	90200/3015/1 N=179 n (%)	90200/3016/1 N=213 n (%)	Total N=392 n (%)	90200/1010/1 N=32 n (%)
Week 2	Yes	167 (43.7)	139 (34.8)	306 (39.1)	33 (18.4)	33 (15.5)	66 (16.8)	19 (63.3)
	No	215 (56.3)	261 (65.3)	476 (60.9)	146 (81.6)	180 (84.5)	326 (83.2)	—
	Difference (90% CI) <sup>b</sup>	—	—	—	—	—	—	(46.7, 77.9)
Week 4	Yes	—	—	—	—	—	—	21 (65.6)
	Difference (90% CI) <sup>b</sup>	—	—	—	—	—	—	(49.6, 79.4)
Week 6	Yes	250(65.4)	235(58.8)	485(62.0)	25(14.0)	22(10.3)	47(12.0)	—
	No	132(34.6)	165(41.3)	297(38.0)	154(86.0)	191(89.7)	345(88.0)	—
	Difference (LL 97.5% CI) <sup>c</sup>	51.5(44.5)	48.4(42.1)	50.0(45.3)	—	—	—	—
	p-value <sup>d</sup>	<0.0001	<0.0001	<0.0001	—	—	—	—
	p-value <sup>e</sup>	<0.0001	<0.0001	<0.0001	—	—	—	—

CI=confidence interval, CSR=clinical study report, FAS=full analysis set, ISE=integrated summary of efficacy, KOH=potassium hydroxide, LL=lower limit, MVTF=missing value treated as failure

- For the Phase 3 trials, treatment effectiveness was defined as negative KOH and negative culture, and Erythema, Scaling and Pruritus grades of 0 or 1; for the maximal use trial, treatment effectiveness was defined as negative culture and negative KOH and Investigator Global Assessment of 0 or 1. Mycological cure was defined as negative dermatophyte culture and negative KOH results from the central laboratory in all three trials.
- Two-sided 90% CIs were calculated for the maximal use trial using exact methods.
- Difference between NAFT-600 and placebo with the lower limit of the one-sided 97.5% CI calculated for effective treatment and mycological cure used the normal approximation to the binomial for the Phase 3 trials.
- For the individual Phase 3 trials, p-value is from a one-sided Cochran-Mantel-Haenszel test, stratified by trial site. For the pooled Phase 3 trial results, p-value was from a one-sided Cochran-Mantel-Haenszel test comparing NAFT-600 Gel, 2% versus placebo, with pooled clinical site as the stratification variable.
- Adjusted p-value from Hochberg's step-up procedure.

Source: Table 13 from ISE

From the Summary of the Microbiology Review by Simone M. Shurland, Ph.D.:

“From a clinical microbiology perspective the information provided by the Applicant supports the efficacy of NAFT-600 Gel 2% for the treatment of interdigital type (b) (4) tinea pedis. Naftin Gel 2% was shown to be active against *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum*.”

*Comment: It should be noted, that Naftin 2% Cream was shown to be active only against Trichophyton rubrum. According to Clinical Microbiology Consultation completed July 22, 2011 for the application for Naftin Cream 2%: "Insufficient data has been presented to support the inclusion of any pathogens other than Trichophyton rubrum in the proposed label."*

*Sufficient microbiological evidence of the drug's action against specified fungal isolates have been submitted for Naftin Gel 2%. The labeling recommendations from Clinical Microbiology are acceptable and have been incorporated into draft labeling to be submitted to the applicant. No susceptibility testing interpretive criteria for naftifine are recommended at this time. To date, a mechanism of resistance to naftifine has not been described.*

#### 4.3 Preclinical Pharmacology/Toxicology

The applicant cross-referenced nonclinical studies contained in NDA 19599-S11 for Naftin Cream 2% to support this submission. Consequently, no additional non-clinical toxicology studies were conducted.

The summary of pertinent, previously conducted nonclinical studies includes:

- In oral toxicity studies reduction in body weight gain and increases in serum bilirubin, creatinine, and urea levels were demonstrated.
- In dermal toxicity studies slight erythema and reduction in body weight gain were demonstrated.
- 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.
- In reproductive and developmental toxicology studies no treatment-related effects on embryofetal toxicity or teratogenicity were noted at oral doses up to 300 mg/kg/day and subcutaneous doses of 30 mg/kg/day. No developmental toxicity was noted at oral doses of 100 mg/kg/day. There was no effects on growth, fertility or reproduction, at doses up to 100 mg/kg/day administered to rats throughout mating, gestation, parturition and lactation.
- In special toxicology studies naftifine HCl solutions 1%, 3%, 5%, and 10% were tested in a primary skin irritation in rabbits and based on that study results naftifine HCl was not considered a skin irritant. Naftifine HCl solution 5% was not considered a contact sensitizer in guinea pigs. A nonclinical phototoxicity study was not conducted based on the minimal UVB absorbance (290 to 320 nm range) of naftifine HCl.

There are no carcinogenicity data available for naftifine HCl. The Agency requested a carcinogenicity study as a post-marketing requirement (PMR) attached to approval of NDA 19599/S-11 for Naftin Cream 2% (7.6.1 Human Carcinogenicity).

Pharmacology/Toxicology Review Jianyong Wang, Ph.D. recommended: “Overall the toxicity profile of NAFTIN® Gel, 2% has been well characterized...NDA 204286 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 label for NAFTIN® Gel, 2%.”

*Comment: I agree with Dr. Wang that there are no outstanding pharm/tox issues that preclude approval of Naftin Gel 2%. A 2-year dermal rat carcinogenicity study will be conducted as a PMR attached to the Naftin Cream 2% approval.*

## 4.4 Clinical Pharmacology

### 4.4.1 Mechanism of Action

According to the approved labeling for Naftin Cream 2% “...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.”

### 4.4.2 Pharmacodynamics

No pharmacodynamics trials were included in this submission.

### 4.4.3 Pharmacokinetics

The pharmacokinetics of NAFT-600 was evaluated in 32 adult subjects with tinea pedis on one or both feet treated with the maximum dose of 4 grams of NAFT-600 daily for 2 weeks. Cmax on Day 14 was 3.7 ng/mL. Median Tmax on Day 1 was 20 hours and on Day 14, 8 hours. Steady state is reached after approximately 11 days. Naftifine concentration continued to be detected in plasma in all 32 subjects at Day 28. The fraction excreted in urine is  $\leq 0.01\%$  of applied dose.

In his review, Clinical Pharmacology reviewer Doanh Tran, Ph.D., noted: “Based on a cross study comparison, the systemic naftifine exposure (both AUC and Cmax) following application of naftifine gel, 2% to subjects with tinea pedis were about 3 fold lower than those seen for Naftin Cream, 2% applied to subjects with both tinea pedis and tinea cruris.”

*Comment: Sufficient evaluation of the PK of this drug product is presented by the applicant to support labeling for adults. The applicant proposed an indication for treatment of patients (b) (4) years of age, however, no subjects younger than 18 years of age were studied in PK trial*

*described above. I agree with Clinical pharmacology reviewer Doanh Tran, Ph.D. who recommended that the indication be limited to adults and recommended the following postmarketing requirement:*

*“Pharmacokinetic/Safety/Tolerability trial 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 towards the upper end of disease severity in the patient population.”*

## **5 Sources of Clinical Data**

### **5.1 Tables of Studies/Clinical Trials**

The data reviewed were from trials conducted by the sponsor. There are total of 7 trials: 2 pivotal trials (MRZ 90200/3015/1 and MRZ 90200/3016/1), one pharmacokinetic trial (MRZ 90200/1010/1), three dermal safety trials (MRZ 90200/1019/1, MRZ 90200/1020/1, MRZ 90200/1021/1), and one QT trial (MRZ 90200/1018/1). See Table 2 for a listing and summary of these trials (modified from sponsor’s Table 2.7.6).

**Table 4 Summary of Trials of NAFT-600 for the Tinea Pedis Clinical Program**

Study Type	Study Protocol/ Identifier	Study Title
Phase 1	MRZ 90200/1019/1	A Study to Evaluate the Sensitization and Irritation Potential of Repeat Applications of NAFT-600 in Healthy Human Volunteers
Phase 1	MRZ 90200/1021/1	A Controlled, Open-Label, Blinded Evaluator Single Dose Study of Ultraviolet Radiation to Evaluate the Phototoxicity Potential of NAFT-600
Phase 1	MRZ 90200/1020/1	A Controlled, Open-Label, Blinded Evaluator, Multiple Dose of Ultraviolet Radiation Study to Evaluate the Photosensitization Potential of NAFT-600
Phase 1	MRZ 90200/1010/1	An Open Label, Single Center, Multiple Application Pharmacokinetic Study of NAFT-600 in Subjects with Tinea Pedis
Phase 1	MRZ 90200-1018/1	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)
Phase 3	MRZ 90200/3015/1	A Phase 3 Double-Blind, Randomized, Placebo-Controlled, Multicenter, Parallel Group Evaluation of the Efficacy and Safety of NAFT-600 in Subjects with Tinea Pedis
Phase 3	MRZ 90200/3016/1	A Phase 3 Double-Blind, Randomized, Placebo-Controlled, Multicenter, Parallel Group Evaluation of the Efficacy and Safety of NAFT-600 in Subjects with Tinea Pedis

Source: 5.2. Tabular Listings of All Clinical Studies

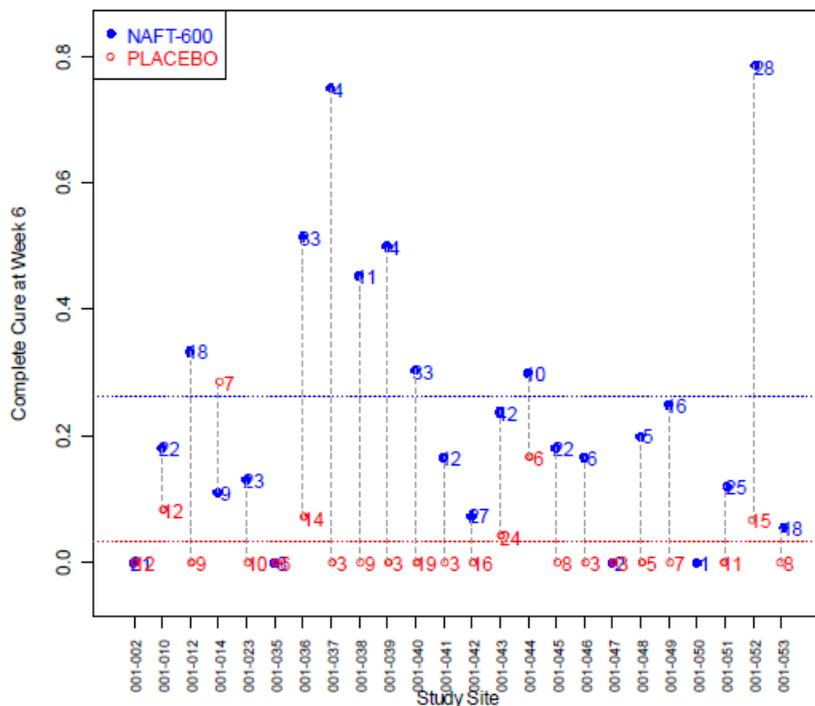
## 5.2 Review Strategy

A brief review of the protocol for pivotal trials will be presented in this section.

Efficacy evaluation regarding this NDA is presented in section 6 Review of Efficacy. Efficacy analysis is based on modified intent-to-treat (ITT) population.

Safety evaluation regarding this NDA is presented in section

MRZ3016 - Complete Cure at Week 6



Source: Agency Statistical review

*Comment: In regard to similar clearance rates among the centers, statistical reviewer Carin Kim Ph.D. noted: "The Breslow-Day test results also supported this conclusion with p-values of 0.206 and 0.133 for Studies MRZ 3015 and MRZ 3016, respectively."*

7 Review of Safety. The review includes all of the safety data from pivotal and pharmacokinetic trials. All of the safety data analysis is based on safety population defined as a subset of all subjects who received study drug at least once.

Review of the pharmacokinetic trial was deferred to Clinical Pharmacology. Only key review points are presented in section 7.2.5 Metabolic, Clearance, and Interaction Workup. However, all of the safety data from this trial are included in integrated safety analysis in section

The review of the three dermal safety trials is provided in section 7.4.5 Special Safety Studies/Clinical Trials.

A brief summary of thorough TQT study is provided in the section 7.4.4 Electrocardiograms (ECGs).

Current labeling for Naftin Cream 2%, published literature, internal FDA data, and Clinical Review of NDA 19-599/ ES 11 were used for reference.

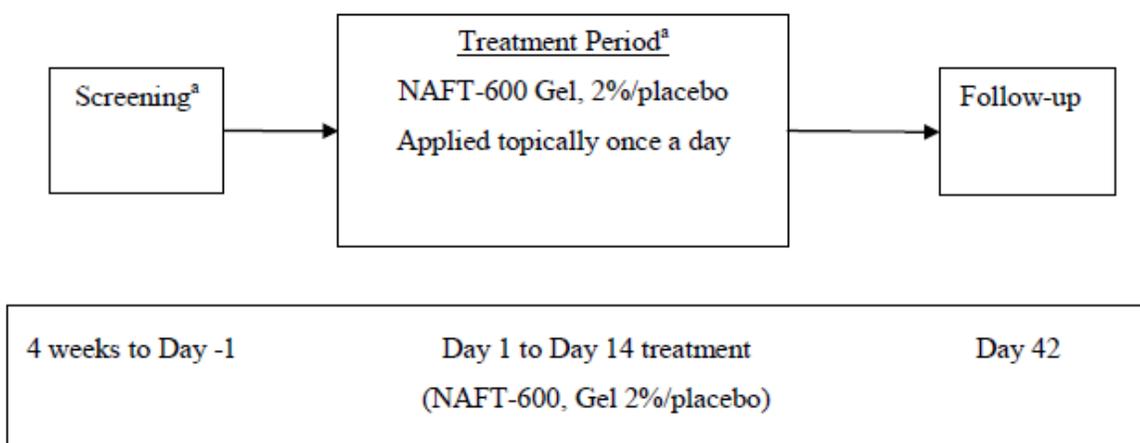
### 5.3 Discussion of Individual Studies/Clinical Trials

Identical protocols MRZ90200/3015 and MRZ90200/3016 were submitted under IND 105603. There were no amendments on the protocols. Trials were conducted from February 2011 to January 2012 at 47 sites, all in USA.

#### Trial design(s)

The design of the trials was identical: randomized, vehicle controlled, double blind, 2 arm parallel trial of approximately 10 weeks duration. Treatment period was for 2 weeks and follow up and primary efficacy assessment was at 6 weeks (4 weeks post treatment) as presented in Figure 1 below:

**Figure 1 Trial Design**



#### Major inclusion criteria:

- Males or non-pregnant females,  $\geq 12$  years of age, of any race or sex.

- Presence of interdigital only or both interdigital and moccasin types 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 in the affected area(s) and using the following scale:

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

- KOH-positive and culture-positive baseline skin scrapings obtained from the site most severely affected or a representative site of the overall severity.
- Subject was in good health and free from any clinically significant disease that might have interfered with the trial evaluations.



Major exclusion criteria:

- Subjects with a known hypersensitivity to study drugs or their components.
- Uncontrolled diabetes mellitus.
- Hemodialysis or chronic ambulatory peritoneal dialysis therapy.
- Current diagnosis of immunocompromising conditions.
- Foot psoriasis, corns, and/or callus involving any web spaces, atopic or contact dermatitis.
- Severe dermatophytoses, onychomycosis (on the evaluated foot), mucocutaneous candidiasis, or bacterial skin infection.
- Extremely severe tinea pedis (incapacitating).

Prohibited medications:

- Topical antifungal 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 antifungal therapies three months (eight months for oral terbinafine) prior to randomization.

- Systemic antibiotic or corticosteroid treatment within 30 days prior to randomization.

### Treatment

Subjects applied the assigned study drug topically once a day for two weeks to all affected area(s) including a half-inch margin of healthy skin adjacent to the affected area(s). For subjects with tinea pedis interdigital-type, assigned study drug was applied to all interdigital areas. For subjects with tinea pedis both moccasin-type and interdigital-type, assigned study drug was applied to the sole of the foot and all interdigital areas.

### Efficacy assessment

Efficacy assessment included clinical and mycological evaluations. IGA scale used for clinical assessment is presented below:

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

*Comment: This 5 –point scale would not ordinarily be acceptable for clinical assessment because it is not a static scale and there is a significant overlap between categories 1-4. However, only grade 0 (Clinical Cure) is part of the primary endpoint evaluation and that grade is clearly defined thus acceptable.*

### Statistical analysis plan

Analysis sets were:

- Safety evaluation set (SES)

The SES was the subset of all subjects who received study drug at least once.

- Full analysis set (FAS)

The FAS was the subset of all subjects in the SES with a positive culture at baseline for whom the primary efficacy variable was available (dropouts and cases with missing information were considered as not complete cures by definition). Culture results were not available at the time of randomization, therefore FAS represent modified intent-to-treat subset of data.

- Per-protocol set (PPS)

The PPS was the subset of subjects in the FAS without major protocol deviations.

The protocol-specified primary efficacy endpoint was the proportion of subjects with complete cure of interdigital tinea pedis at Week 6 where complete cure is defined as clinical cure (absence of erythema, scaling, and pruritus) and mycology cure (negative dermatophyte culture and KOH).

The primary efficacy analysis evaluated the superiority of NAFT-600 Gel, 2% over vehicle using Cochran-Mantel-Haenszel (CMH) test after stratification by (pooled) clinical site. This test was conducted with the FAS (using the missing value treated as failure [MVTF] imputation) at a one-sided level of significance of  $\alpha=0.025$ .

The protocol-specified secondary endpoints were:

- the proportion of subjects with effective treatment of interdigital tinea pedis: negative KOH, negative culture, and erythema, scaling and pruritus scores of 0 or 1 at Week 6.
- the proportion of subjects with mycological cure of interdigital tinea pedis: negative KOH results and negative dermatophyte culture at Week 6

Other secondary endpoints were:

- complete cure of (b) (4) at Week 6
- effective treatment of (b) (4) at Week 6
- mycological cure of (b) (4) at Week 6.

The applicant acknowledged in Statistical methods, that the analyses of other secondary endpoints “will not be inferential in nature.”

*Comment: The Phase 3 clinical trials are appropriately designed to evaluate interdigital tinea pedis. The primary endpoint is appropriate to determine primary efficacy of the drug product and is consistent with prior Agency advice, as well as previous applications. Secondary endpoints are supportive of primary endpoint.*

*However, in regard to the “other secondary endpoints” the protocol did not include methods to adjust the multiplicity to control the Type I error thus, (b) (4)*

### Safety assessment

Safety assessment included general physical examination, routine laboratory testing, and AEs (local and systemic).

## 6 Review of Efficacy

### Efficacy Summary

The applicant submitted two phase 3 trials (3015 and 3016) utilizing NAFT-600 gel against vehicle. Agency Analysis of the two phase 3 trials demonstrated that NAFT-600 gel was effective as topical treatment for interdigital tinea pedis in adult population.

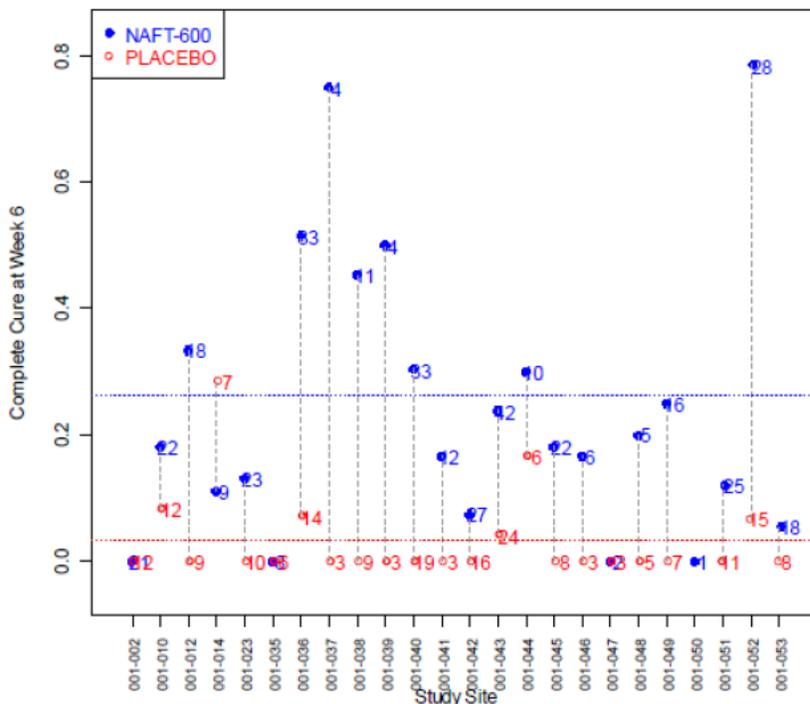
Success at the primary endpoint- the proportion of subjects with complete cure of interdigital tinea pedis -was achieved by 17% of subjects treated with NAFT-600 in trial 3015 and by 26% in trial 3016. Complete cure for vehicle-treated subjects was 2% and 3% for respective trials ( $p < 0.001$ ).

Statistical superiority of the two pre-specified secondary endpoints (proportion of subjects with effective treatment and mycological cure of interdigital tinea pedis) was achieved.

Efficacy assessment for subjects between the ages 12 to 18 was limited to 14 subjects. (b) (4)



MRZ3016 - Complete Cure at Week 6



(  
 Source: Agency Statistical review

*Comment: In regard to similar clearance rates among the centers, statistical reviewer Carin Kim Ph.D. noted: "The Breslow-Day test results also supported this conclusion with p-values of 0.206 and 0.133 for Studies MRZ 3015 and MRZ 3016, respectively."*

7 Review of Safety).



In summary, this reviewer concludes that efficacy of Naftin Gel 2% was demonstrated for interdigital type tinea pedis caused by the organisms *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum* in patients 18 years of age and older when applied daily for two weeks.

## 6.1 Indication

The sponsor proposes that Naftin Gel 2% receive the following indication: for the treatment of interdigital (b) (4) caused by the organisms *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum* in patients (b) (4) years of age and older.

As noted below, the conclusion of this clinical review, as well as the recommendation of the review team, is that only the indication of interdigital tinea pedis in adults is supported by the applicant's clinical development program.

### 6.1.1 Methods

The primary population for the efficacy analysis of pivotal trials 3015 and 3016 is a full analysis set. Due to the open label design of the PK study 1010, review of the efficacy from that trial will not be conducted.

**Table 5 Analysis Sets**

	Naftin Gel 2%		Vehicle	
	3015	3016	3015	3016
	n (%)		n (%)	
Randomized	571	573	284	287
Safety set	571	572	284	287
Full analysis set*	382 (67)	400 (70)	179 (63)	213 (74)
Per-protocol set	296 (52)	329 (57)	140 (49)	180 (63)

\*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.

### 6.1.2 Demographics

There were no notable differences in demographic characteristics between either arms or trials.

**Table 6 Baseline Demographics-FAS**

	Study MRZ 3015		Study MRZ 3016	
	NAFT-600	Vehicle	NAFT-600	Vehicle
<b>FAS Subjects</b>	382	179	400	213
<b>Age</b>				
<18	3 (1%)	1 (1%)	7 (2%)	3 (1%)
18-64	352 (92%)	158 (88%)	357 (89%)	189 (89%)
≥65	27 (7%)	20 (11%)	36 (9%)	21 (10%)
<b>Sex</b>				
Female	103 (27%)	29 (16%)	79 (20%)	54 (25%)
Male	279 (73%)	150 (84%)	321 (80%)	159 (75%)
<b>Race</b>				
White	202 (53%)	105 (59%)	266 (67%)	144 (68%)
Black	157 (41%)	64 (36%)	114 (29%)	62 (29%)
Asian	5 (1%)	2 (1%)	6 (2%)	2 (1%)
Other	18 (5%)	8 (5%)	14 (4%)	5 (2%)

Source: Agency Statistical review

### 6.1.3 Subject Disposition

The most common reason for discontinuation was lost to follow up.

**Table 7 Subjects Disposition-FAS**

	Study MRZ 3015		Study MRZ 3016	
	NAFT-600	Vehicle	NAFT-600	Vehicle
<b>Randomized Subjects (SES)</b>	<b>571</b>	<b>284</b>	<b>573</b>	<b>287</b>
<b>FAS Subjects</b>	<b>382</b>	<b>179</b>	<b>400</b>	<b>213</b>
<b>Completed</b>	340 (89%)	157 (88%)	365 (91%)	200 (94)
<b>Discontinued</b>				
<i>Adverse Event</i>	2	0	1	0
<i>Protocol violation</i>	9	5	5	2
<i>Lost to follow-up</i>	22	10	14	7
<i>Subject decision/withdrawal of consent</i>	9	5	11	4
<i>Other</i>	0	2	4	0

Source: Agency Statistical review

*Comment: Distribution of FAS subjects according to the reason for discontinuation across arms was comparable (see Table 15 Subjects Discontinuation (safety population))*

#### 6.1.4 Analysis of Primary Endpoint

The primary endpoint was proportion of subjects with complete cure of interdigital tinea pedis, defined as both a clinical cure (absence of erythema, scaling, and pruritus) and mycological cure (negative KOH and culture) at six weeks after the start of treatment (4 weeks after the last treatment).

Efficacy of Naftin Gel 2% versus vehicle was demonstrated in both trials ( $p < 0.001$  from a one-sided Cochran-Mantel-Haenszel test, stratified by trial site).

**Table 8 Primary Endpoint Efficacy Analysis-Complete Cure**

trial	Naftin Gel 2%	Vehicle
<b>3015</b>	64/382 (17%)	3/179 (2%)
<b>3016</b>	104/400 (26%)	7/213 (3%)

Source: Adopted from Agency Statistical review

*Comment: Disparity in primary efficacy endpoint is commonly seen with topical product and does not raise concern.*

#### 6.1.5 Analysis of Secondary Endpoints(s)

Most important secondary efficacy endpoints were:

- 1) Proportion of subjects with effective treatment of interdigital tinea pedis, defined as negative KOH result, negative culture, and erythema, scaling, and pruritus scores of 0 or 1 at Week 6
- 2) Proportion of subjects with mycological cure of interdigital tinea pedis, defined as negative KOH examination and negative dermatophyte culture at Week 6

The analysis of secondary endpoints is presented in Tables 9 and 10 (adopted from Agency Statistical review):

**Table 9 Secondary Endpoint Efficacy Analysis-Effective Treatment**

<b>trial</b>	<b>Naftin Gel 2%</b>	<b>Vehicle</b>
<b>3015</b>	207/382 (54%)	11/179 (6%)
<b>3016</b>	203/400 (50%)	15/213 (7%)

**Table 10 Secondary Endpoint Efficacy Analysis-Mycological Cure**

<b>trial</b>	<b>Naftin Gel 2%</b>	<b>Vehicle</b>
<b>3015</b>	250/382 (65%)	25/179 (14%)
<b>3016</b>	235/400 (59%)	22/213 (10%)

*Comment: The analysis of two pre-specified secondary endpoints showed statistically significant superiority of Naftin Gel 2% versus vehicle.*

#### 6.1.6 Other Endpoints

Other endpoints will be presented for descriptive and exploratory purposes given that the protocol did not include plans to adjust for the Type I error.

Included in the other endpoints was the complete cure, effective treatment, and mycological cure in subjects [REDACTED] <sup>(b) (4)</sup> at Week 6.

Statistical reviewer, Carin Kim, Ph.D. provided the following sensitivity analysis for (b) (4)  
(excluding those subjects that did not meet the inclusion criteria):



#### 6.1.7 Subpopulations

The review will consider only the complete cure, as this is regarded the most clinically meaningful treatment outcome necessary for labeling. The trials were not designed and powered to detect treatment differences in subgroups; therefore, the subgroups analyses are descriptive.

### Gender

Naftin Gel 2% was superior to vehicle in both, men and women and cure rates were slightly higher for females (males 125/600; 21% v. 43/182; 24% females).

### Race

The most prevalent races in FAS were white (60%) and African American (36%). The enrollment of other races was not large enough to draw conclusions. In both, white and African American subgroup, Naftin Gel 2% showed higher cure rates vehicle.

### Age

The enrollment was open to subjects  $\geq 12$  years of age, however only 26 subjects who were 12 to 18 years of age were randomized. The FAS has 14 subjects in that subgroup (10 subjects received Naftin Gel 2% and 4 received vehicle gel).

*Comment: Number of subjects in 12-18 years of age group is not large enough to draw meaningful conclusion about efficacy. In general, when the disease characteristics are similar between adult and adolescent populations, the efficacy can be extrapolated from adult population. However, in order to grant the indication for interdigital tinea pedis* (b) (4)

In the category of subjects who were  $\geq 65$  years of age, total of 157 subjects were randomized, and 104 are included in FAS (63 in active and 41 in vehicle arm). Naftin Gel 2% had again higher cure rates than vehicle.

*Comment: Seemingly, subjects  $\geq 65$  years of age showed higher cure rates (23/63; 37% active v. 1/40; 2% for vehicle) then the rest of population, however the limiting factor of this comparison is small sample size.*

### Baseline Pathogen

More than 85% of all subjects in FAS had *Trichophyton rubrum* isolated at the baseline. The percentages of subjects with complete cure at Week 6 in the Naftin Gel 2% treatment group were 21% for *T. rubrum*, 33% for *T. mentagrophytes* and 17% for *E. floccosum* (2%, 7% and 0% in respective vehicle groups).

#### 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

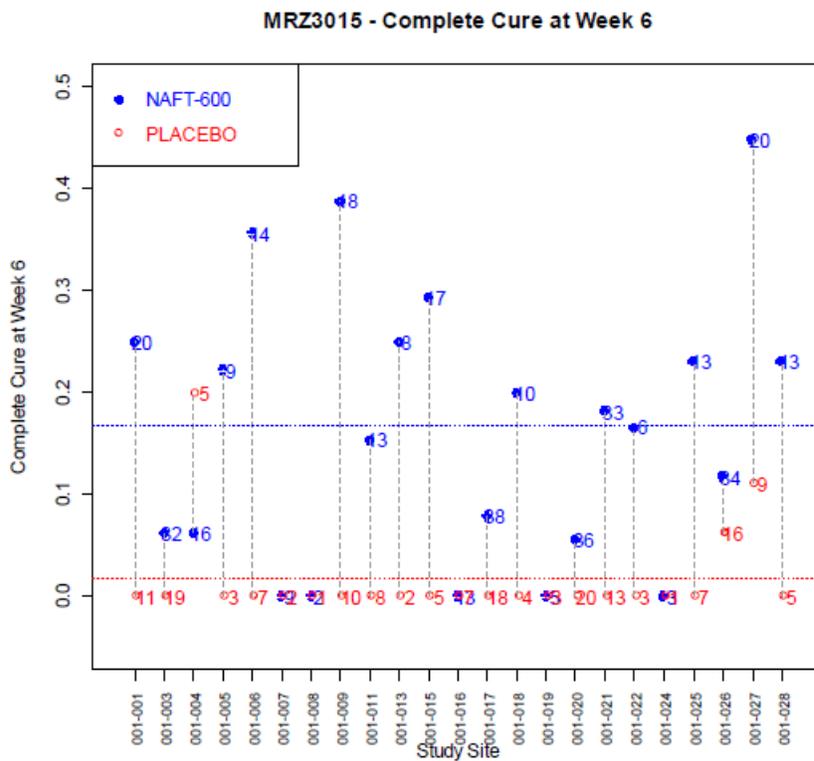
The efficacy of Naftin Gel 2% was demonstrated at Week 6 (4 weeks after completion of treatment). No follow up for successfully treated subjects was provided, therefore the persistence of efficacy and/or tolerance cannot be established.

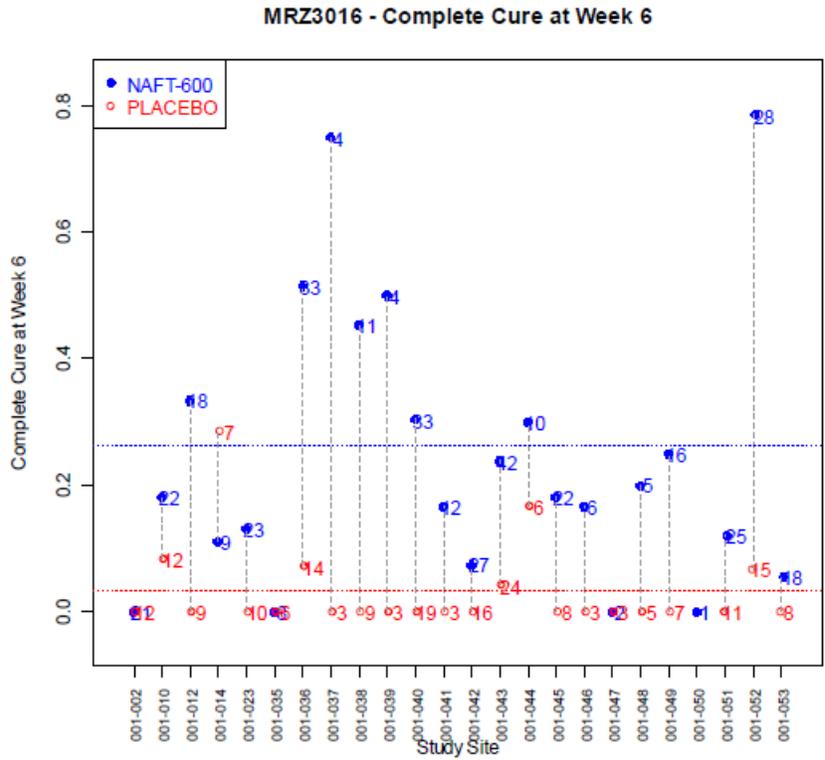
No data related to antimicrobial resistance was included in the application.

### 6.1.10 Additional Efficacy Issues/Analyses

Within each study, the complete clearance rates for each center are fairly similar, with no centers dominating the results.

**Figure 2 Efficacy Results by Center**





Source: Agency Statistical review

*Comment: In regard to similar clearance rates among the centers, statistical reviewer Carin Kim Ph.D. noted: "The Breslow-Day test results also supported this conclusion with p-values of 0.206 and 0.133 for Studies MRZ 3015 and MRZ 3016, respectively."*

## 7 Review of Safety

### Safety Summary

The data base for safety evaluation of Naftin Gel 2% is comprised of 1747 subjects (1144 randomized to NAFT-600 and 571 subjects randomized to vehicle in two phase 3 trials plus 32 subjects from uncontrolled PK trial).

Results from 3 provocative dermal safety studies in healthy volunteers were analyzed separately. The safety evaluation consisted of adverse events, local skin reactions, vital signs, and laboratory test. There was no EKG data in this submission.

The drop-out rate from safety population was about 15%. The exposure to the drug was adequate to assess safety issues and define language appropriate for labeling.

There were no deaths reported.

Serious adverse events (SAEs) were reported by 9 subjects (5 in NAFT-600) and did not appear to be related to the drug.

Approximately 20% of subjects treated with NAFT-600 reported adverse events (AE), most of which had similar rates when compared to vehicle and did not appear to be related to the drug. Application site reactions were reported by 2% of subjects in the Naftin Gel 2% arm and 1% in vehicle arm. These data should be included in labeling as they are supported by dermal safety studies which showed that NAFT-600 has the potential to cause application site irritation. The reactions were mild to moderate and resolved spontaneously.

There were two severe application site reactions (erosion and fissure), both reported in the same subject. The certainty of the adverse reaction severity is compromised by the initial presentation and incomplete final assessment. ([7.3.4 Significant Adverse Events](#)).

The adverse event profile was largely consistent with what is known about topical naftifine hydrochloride from previous clinical trials and from the post-approval use of Naftin Cream 1% and Naftin Gel 1%. The new safety information for this 2% formulation is the potential of Naftin Gel 2% to cause irritancy and that should be captured in the labeling.

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data were reviewed from 7 clinical trials and: two pivotal trials MRZ 90200/3015/1 and MRZ 90200/3016/1 (referred as 3015 and 3016 trials), one pharmacokinetic trial MRZ 90200/1010/1 (referred as 1010 trial), three dermal safety trials MRZ 90200/1019/1, MRZ 90200/1020/1, MRZ 90200/1021/1 (referred as 1019, 1020 and 1021 trials), and one QT trial MRZ 90200/1018/1 (referred as 1018 trial). The two pivotal randomized, double-blind, multicenter, placebo-controlled trials utilized 2 week twice-daily treatment with NAFT-600. The pharmacokinetic trial 1010 was an open label trial in duration of 2 weeks utilizing 4 gm of NAFT-600 daily.

Three dermal safety studies 1019, 1020, and 1021 were conducted in healthy volunteers according to typically used dermal safety protocols.

The thorough QT study was a randomized, double-dummy, double-blind, 3-treatment, parallel design study, with a 600 mg oral single-dose naftifine HCL, placebo control and a positive control (400 mg moxifloxacin). The results of this study were previously submitted to NDA 19-599/ ES 11 to support approval of Naftin Cream 2%.

### 7.1.2 Categorization of Adverse Events

In the opinion of this reviewer, the sponsor adequately categorized the adverse events using MedDRA classification Version 14.0 terminology.

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

Pooling of data across two pivotal trials and the maximal use PK trial was done by reviewer.

## 7.2 Adequacy of Safety Assessments

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

A total of 1176 subjects in three trials were randomized to Naftin Gel 2%. Target population demographics were similar between all trials and reflective of typical population affected with tinea pedis.

**Table 12 Demographics-SES**

Characteristics	Naftin Gel 2% (N= 1176)	Vehicle (N=571)	Total (N=1747)
	n (%)	n (%)	n (%)
Male	893 ( 76)	435 ( 76)	1328 ( 76.0)
Female	283 ( 24)	136 ( 24)	419 ( 24.0)
Age (mean)	45	46	45
≥12 to <18 years	20 (2)	6 (1)	26 (2)
≥18 to <65 years	1057 (90)	507 (89)	1564 (90)
≥65 years	99 (8)	58 (10)	157 (9)
Race			
white	692 (59)	353 (62)	1045 (60)
African American	435 (37)	197 (34)	632 (36)
other	49 (4)	21 (4)	70(4)

**Table 13 Subject Disposition-SES**

	Naftin Gel 2%	Vehicle
	n (%)	n (%)
Number of randomized subjects	1176	571
Completed	953 (84)	488 (85)
Discontinued	193 (16)	83 (15)

*Comment: For details on discontinuation, please see [Table 15](#).*

For 2 week therapy, subjects use on average 30 g of gel (the mean weight applied per day was 2.2g in the NAFT-600 Gel, 2% group and 2.2g in the vehicle group). Weight-based medication compliance (weight of medication used/extent of exposure) averaged 2 g/day for both, active and vehicle.

The proportion of subjects with 80% to 120% compliance (self-reported number of applications) was 88% in the NAFT-600 Gel, 2% group (both trials) and about 85% in the placebo group.

*Comment: Overall, the exposure was adequate to analyze safety. The 16% discontinuation rate is typical of topical product trials for indications such as tinea pedis.*

#### 7.2.2 Explorations for Dose Response

The applicant did not conduct any Phase 2 dose ranging studies, but instead proceeded directly to Phase 3.

#### 7.2.3 Special Animal and/or In Vitro Testing

No special animal or *in vitro* testing was conducted given the sponsor's right to cross reference the nonclinical studies completed during naftifine hydrochloride development.

#### 7.2.4 Routine Clinical Testing

The schedule of clinical safety assessments for each of the studies consisted of vital signs, general physical examination, routine laboratory testing, and monitoring for AE (local and systemic). The methods and tests used as well as the frequency of testing were adequate.

#### 7.2.5 Metabolic, Clearance, and Interaction Workup

For the more detailed review of the pharmacokinetic trial MRZ 90200/1010/1, a reader is referred to the Clinical Pharmacology review. An overview of that trial is presented below.

This was an open-label, single center, pharmacokinetic trial designed to quantify the PK profile of NAFT-600 following 2 weeks of once daily applications of NAFT-600. Population consisted of 32 adult subjects with tinea pedis on one or both feet treated with the maximum dose of 4 grams of NAFT-600 daily, 2 grams on each foot. PK parameters for NAFT-600 were calculated from the plasma and urine samples collected on Days 1 and 14.

The plasma concentrations of naftifine were relatively low. C<sub>max</sub> after day 14 was 3.7 ng/mL. Median T<sub>max</sub> was 20.0 hours after a single application on Day 1 and 8.0 hours on Day 14. The fraction of dose excreted also increased during the treatment period from 8.6% at Day 1 to 14.3% at Day 14. Interaction workup was not conducted based upon the fact that systemic exposure was low.

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

Naftifine hydrochloride is a topical allylamine antifungal. Since initial approval of the 1% formulation in 1988, the most common adverse reactions were local skin reactions.

Terbinafine is systemic allylamine antifungal. With oral administration of terbinafine liver failure, taste and smell disturbance, depressive symptoms, neutropenia and Stevens-Johnson's syndrome have been observed. It should be noted that these adverse events were not observed with topical terbinafine or with naftifine hydrochloride.

*Comment: The applicant's effort to detect specific AEs was adequate.*

### 7.3 Major Safety Results

#### 7.3.1 Deaths

There were no deaths reported in NAFT-600 development program.

#### 7.3.2 Nonfatal Serious Adverse Events

There were 9 subjects who experienced a SAE. All but one event resolved and none of the subjects withdrew from the trials due to the SAEs.

**Table 14 All Serious Adverse Events**

treatment	trial	subject	AE (preferred term)	outcome
Naftin Gel 2%	3015	09/1229	skull fractured base	resolved
	3015	19/1690	muscle spasms	resolved
	3016	52/5913	urethral stenosis	resolved
	1010	54020	gastroenteritis viral	resolved
	1019	004	conjunctival melanoma	ongoing
Vehicle	3015	03/1773	abscess	resolved
	3015	09/1231	respiratory tract infection	resolved
	3016	41/5470	appendicitis	resolved
	3016	49/5786	osteoarthritis	resolved

*Comment: Based on the reviewed narratives it is not likely that any of the SAE was related to the treatment, particularly in light of the pharmacokinetic information described above which details the limited systemic exposure of naftifine when applied topically for tinea pedis.*

### 7.3.3 Dropouts and/or Discontinuations

A total of 1747 subjects were randomized in trials 1010, 3015, and 3016 and that number will be used for safety analysis. However, one subject (12/5166 in MRZ 90200/3016/1) did not use any trial medication thus, to be precise safety population consist of 1746 subjects.

In the Naftin Gel 2% arm 193 subjects discontinued (16%) in comparison to 83 from vehicle group (15%). Reasons for discontinuation are presented in Table 15.

**Table 15 Subjects Discontinuation (safety population)**

Reasons for discontinuation	Naftin Gel 2% (N= 1176)	Vehicle (N=571)
	n (%)	n (%)
Negative baseline culture	68 (6)	28 (5)
Lost to follow up	54 (5)	27 (5)
Withdrawal of consent	36 (3)	13 (2)
Protocol violation	19 (2)	12 (2)
Other	9 (<1)	3 (<1)
Adverse event	6 (<1)	0
Progressive disease	1 (<1)	0

Out of six subjects who discontinued due to AE, 4 subjects had application site reactions: severe application site erosion/fissure, moderate application site rash/vesicles moderate hypersensitivity, and mild application site dermatitis. The other 2 subjects developed moderate bronchitis and moderate vomiting/diarrhea, respectively.

*Comment: While the overall rate of discontinuation appears high, analysis of discontinuation data does not raise safety concerns. Per CRF, a subject 24/1253 with severe site erosion/fissure was assessed as having disease progression and discontinued on the last day of treatment. However, upon discontinuation from the study, the condition improved and reason for discontinuation was changed to AE.*

#### 7.3.4 Significant Adverse Events

Severe adverse events were rare: eight subjects in active arm (<1%) and 9 in vehicle (1.6%) reported severe AEs. There were total of 3 severe application site reactions (2 in active arm and one in vehicle arm). The summary of all severe AEs in all 3 trials from this submission is presented in Table 9 (source: ISS Table 23).

**Table 16 Severe Adverse Events**

Preferred Term	Naftin Gel 2% (N= 1176)	Vehicle (N=571)
	n	n
Toothache	2	0
Back pain	1	2
Application site erosion	1	0
Application site fissure	1	0
Cellulitis	1	0
Hypertriglyceridemia	1	0
Staphylococcal infection	1	0
Urethral stenosis	1	0
Abscess	0	1

Appendicitis	0	1
Application site pruritus	0	1
Influenza	0	1
Injury	0	1
Osteoarthritis	0	1
Skin bacterial infection	0	1

*Comment: Prevalence and distribution of AEs do not raise safety concerns. Application site erosion and application site fissure occurred in the same subject (24/1253). This subject had marked erythema, marked scaling, moderate fissuring, and maceration at the baseline. Subject received treatment from June 2 until June 15 (thus, 13 days of treatment) when he was terminated due to the disease progression. At follow-up visit at Week 6, he had marked erythema and marked scaling (fissuring and maceration were not assessed) which was interpreted as improvement thus reason for discontinuation was changed to possible adverse event. The interpretation of severe application site reaction is compromised by the initial severity of disease and incomplete termination assessment. Due to temporal relationship with the treatment, I agree with the investigator that adverse reaction is possible. However, due to the questionable disease progression, incomplete severity assessment and isolated nature of event (1/1167) as well as lack of severe reactions in the maximal use study, I do not think that this event should impact labeling.*

### 7.3.5 Submission Specific Primary Safety Concerns

Overall, there were no clinically meaningful trends observed for any of the liver function parameters. Following the treatment, abnormal liver tests of interest were detected in 8 subjects treated with NAFT-600 and 9 subjects treated with vehicle gel.

Number of subjects with any application site reaction was 21 (2%) in active arms and 5 (1%) in vehicle arm. The most common was application site pain. The majority of application site reactions resolved spontaneously. There were no application site reactions reported in PK trial 1010.

**Table 17 Application Site Reactions Trial 3015**

PT	NAFT-600 (N = 571)			PLACEBO (N = 284)		
	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)

Application site dermatitis	1	1	0.18	0	0	0
Application site dryness	1	1	0.18	1	1	0.35
Application site erosion	1	1	0.18	0	0	0
Application site fissure	1	1	0.18	0	0	0
Application site pain	4	3	0.53	2	1	0.35
Application site paraesthesia	1	1	0.18	0	0	0
Application site pruritus	0	0	0	1	1	0.35
Application site swelling	1	1	0.18	0	0	0
Application site warmth	1	1	0.18	0	0	0

**Table 18 Applications Site Reactions Trial 3016**

PT	NAFT-600 (N = 573)			PLACEBO (N = 287)		
	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)
Application site dryness	1	1	0.17	0	0	0
Application site erythema	0	0	0	1	1	0.35
Application site exfoliation	1	1	0.17	0	0	0
Application site fissure	1	1	0.17	0	0	0
Application site pain	2	2	0.35	1	1	0.35
Application site paraesthesia	1	1	0.17	0	0	0
Application site pruritus	1	1	0.17	0	0	0
Application site rash	1	1	0.17	0	0	0
Application site reaction	2	2	0.35	0	0	0
Application site vesicles	1	1	0.17	0	0	0

*Comment: As presented in section 7.4.5 Special Safety Studies/Clinical Trials Naft-600 was found to be an irritant. It is somewhat surprising that only 2% of subjects experienced application site reactions in the clinical trials. One explanation may be that it is hard to recognize the signs of irritation on already red, inflamed and occasionally macerated skin as it is the case with tinea pedis. Most of the reactions were mild to moderate. The onset of application site reactions since the start of therapy was very variable (from day 0-26), and due to the small number of subjects in each category it is not possible to generalize the conclusion on the onset of AE.*

*Applicant did not include application site reaction in the proposed labeling. It is my recommendation that application site reaction rate (cumulative) be included in labeling.*

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

The following three tables summarize the most frequent AE in the active arm of each trial irrespective of the placebo arm rates.

**Table 19 Most Common AE in Trial 3015**

PT	NAFT-600 (N = 571)			PLACEBO (N = 284)		
	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)
Headache	16	13	2.28	2	2	0.7
Back pain	7	7	1.23	5	5	1.76
Sinusitis	6	6	1.05	2	2	0.7

**Table 20 Most Common AE in Trial 3016**

PT	NAFT-600 (N = 573)			PLACEBO (N = 287)		
	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)
Headache	22	16	2.79	6	5	1.74
Back pain	10	9	1.57	3	3	1.05
Urinary tract infection	9	9	1.57	1	1	0.35
Nasopharyngitis	7	7	1.22	3	3	1.05
Myalgia	6	6	1.05	0	0	0
Upper respiratory tract infection	6	6	1.05	4	4	1.39

**Table 21 Most Common AE in Trial 1010**

PT	NAFT-600 (N = 32)		
	Events	Number of subjects	Proportion (%)
Headache	3	3	9.4
Back pain	2	2	6.3

*Comment: Only two adverse events occurred in more than 1% of all treated subjects and those are:*

- *headache in 32 subjects (2.7%) in active arm v. 7 (1.2%) in vehicle arm*
- *back pain in 18 subjects (1.5%) in active arm v. 8 (1.4%) in vehicle arm.*

*Despite the obvious disparity between the active and vehicle arms, headache should not be considered as an adverse reaction and thus should not be included in labeling (as it is per proposed applicant's labeling). There are two reasons for that conclusion: the result of the review of all the CRF forms where headache was not considered related to the treatment in any subject and the lack of obvious plausible mechanism for causality between the treatment and AE.*

#### 7.4.2 Laboratory Findings

Overall, there were no clinically meaningful trends observed for any of the laboratory parameters. Most frequently reported shift from normal values at screening to high at the end of the trials had similar rates among active and vehicle.

#### 7.4.3 Vital Signs

There were no clinically meaningful changes in vital signs throughout any of the 3 trials.

#### 7.4.4 Electrocardiograms (ECGs)

There were no electrocardiograms recorded during Naftin-600 clinical trials. The effects of a single suprathreshold oral dose of naftifine HCl on ventricular repolarization (QT/QTc interval duration) was assessed previously in trial 1018.

This study was conducted in 3 treatment arms and healthy adult subjects were randomized to one of the following treatment groups:

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.

The oral dose of 600 mg produces mean C<sub>max</sub> values 18-fold higher than that following the therapeutic dose of Naftifine Cream 2% and is sufficient to cover high exposure clinical scenarios.

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.”

*Comment: Considering observed low systemic exposure of Naftin Gel 2% and results of suprathreshold oral dose of naftifine HCl on ventricular repolarization, there is no concern that Naftin Gel 2% may prolong QT interval.*

#### 7.4.5 Special Safety Studies/Clinical Trials

Dermal safety was evaluated in the following three studies.

1. A Study to Evaluate the Sensitization and Irritation Potential of Repeat Applications of NAFT-500 in Healthy Human Volunteers (MRZ 90200/1019/1)

This was a single-site, randomized, single-blind, controlled study conducted in 250 healthy subjects 18-65 years of age. The potential of the product to cause irritation/sensitization was tested using NAFT-600, positive irritant control (lauryl sulfate solution 0.05% w/v) and negative irritant control (sterile water for injection). Study consisted of induction phase (21 days), rest period (14 days), challenge phase and, if needed, re-challenge phase.

Induction phase:

All 250 subjects (175 females and 75 males) began the induction phase; however 14 subjects were discontinued prior to the final skin irritation assessment on day 22 (none for skin safety reasons).

During the 21 days of induction phase subjects received 3 occluded applications (test, positive and negative control) daily applied simultaneously to their upper outer arms. Approximately 30 minutes ( $\pm$  10 minutes) after test article removal on Days 2-22, a trained evaluator blinded to treatment allocation observed the application site for any signs of local irritation.

The following scoring was utilized during the irritation assessments:

Dermal 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 (with corresponding numeric score)

- A (0) = slightly glazed appearance
- B (1) = marked glazed appearance
- C (2) = glazing with peeling and cracking
- F (3) = glazing with fissures
- G (3) = film of dried serous exudates covering all or part of the patch site
- H (3) = small petechial erosions and/or scabs

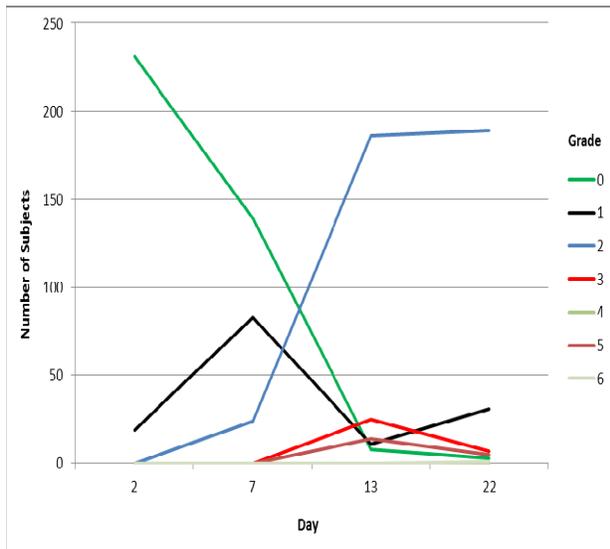
The summary of the irritation data is presented below (sponsor's Table 11.4.1. from 5.3.3.1.1):

**Table 22 Summary of Mean Cumulative Data During the Irritation Phase**

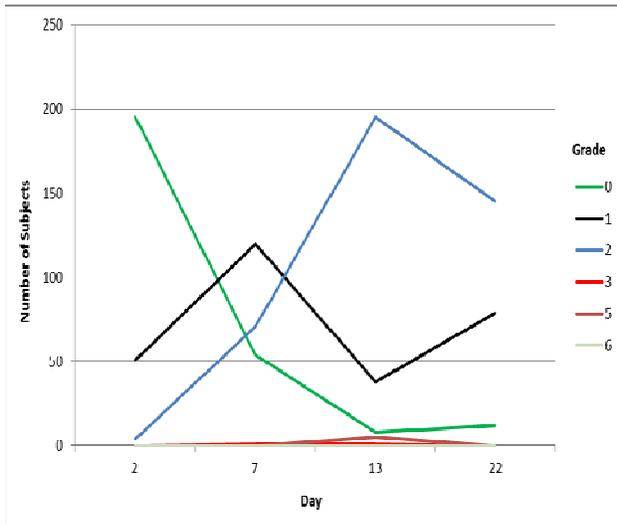
Summary of Mean Cumulative Irritation Data by Test Article (± Standard Deviation) During the Irritation Phase			
Test Article	Cumulative Dermal Response Score	Cumulative Other Effects Score	Cumulative Converted Score
NAFT-600 Gel, 2% (N=235)	28.15(± 6.96)	11.89 (± 9.03)	34.40 (± 8.48)
Positive Irritant Control (N=236)	27.09 (± 6.51)	1.70 (± 5.34)	28.78 (± 8.23)
Negative Irritant Control (N=236)	2.01 (± 4.64)	0.23 (± 2.10)	2.14 (± 5.37)

Irritation grades for each of the test articles during 3 week period are presented in Figures 3-5:

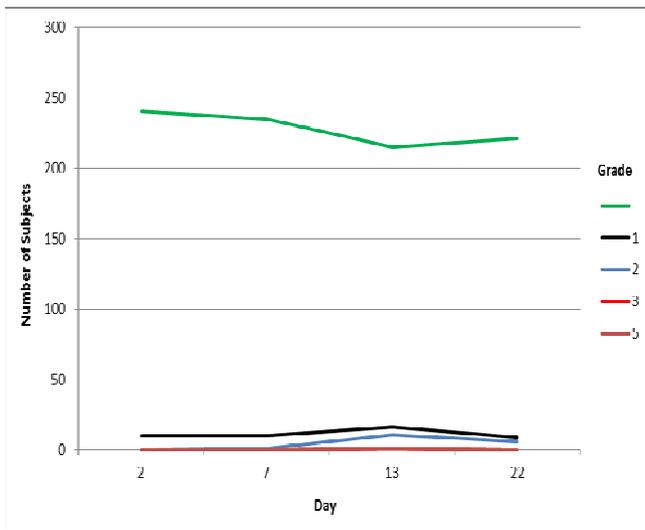
**Figure 3 Naftin-600 Irritancy Graph**



**Figure 4 Positive Irritancy Control Graph**



**Figure 5 Negative Control Irritancy Graph**



*Comment: NAFT-600 demonstrated irritation responses higher than the positive irritant control. This is also evident in the Other Effects category where more subjects in NAFT-600 arm experienced grade G and H responses than those in positive irritant control arm (data reviewed but not presented). The applicant commented in ISS (p.103) that “NAFT-600 Gel, 2% was shown to have a potential for irritation in clinical use...” however that information is not included in*

*proposed labeling.” I recommend that the irritancy potential of the Naftin-600 be included in the label.*

*Due to the lack of vehicle arm, it is not possible to conclude whether irritancy is the result of the active or excipient component of the product. It should be noted, however, that clinical reviewer of the NDA 19-599/S011 categorized NAFT-500 (Naftin cream 2%) as having a low propensity for irritation in clinical use raising the possibility that excipients in NAFT-600 may be responsible for irritation.*

*A total of 41 subjects (17%) in the irritancy/sensitization trial had application site reactions (pruritus was the most common).*

#### Challenge phase:

Following 14 days of rest period, 217 subjects began the challenge phase on Day 36. The subjects received same 3 occluded applications applied simultaneously to naïve sites on the upper back. The patches were removed after 48 hours  $\pm$  2 hours and assessments of the sites of application were made at approximately 30 minutes ( $\pm$  10 minutes) and 24, 48, and 72 hours ( $\pm$  2 hours) for any signs of local irritation. The same rating scales were used as for induction phase.

The summary of the irritation data is presented below (sponsor’s Table 11.4.2. from 5.3.3.1.1)

Test Article	Cumulative Dermal Response Score	Cumulative Other Effects Score	Cumulative Converted Score
NAFT-600 Gel, 2% (N=217)	2.67( $\pm$ 2.72)	0.28 ( $\pm$ 1.47)	2.94 ( $\pm$ 3.56)
Positive Irritant Control (N=217)	1.11 ( $\pm$ 1.35)	0.03 ( $\pm$ 0.41)	1.14 ( $\pm$ 1.52)
Negative Irritant Control (N=217)	0.34 ( $\pm$ 0.63)	0.00 ( $\pm$ 0.00)	0.34 ( $\pm$ 0.63)

The subject was considered potentially sensitized if all of the following criteria were met:

- The subject had at least 1 evaluation occurring at 48 or 72 hours ( $\pm$  2 hours) after the removal of the challenge phase patch
- The subject had a combined “Dermal Response” and “Other Effects” numeric score of at least 2 at their last evaluation during the Challenge Phase.
- The combined “Dermal Response” and “Other Effects” numeric scores obtained during the Challenge phase evaluations were observed to be generally higher than the combined “Dermal Response” and “Other Effects” numeric scores obtained during the Irritation phase

Possible sensitization was considered in 32 subjects.

#### Re-challenge phase

Of 32 subjects with possible sensitization reaction, 19 subjects participated in re-challenge phase that started on day 126 (after 28 day rest phase) using the same design as in the challenge phase

but applying the patches on new naïve site. Subject needed to meet the same 3 criteria during Re-Challenge phase as previously in the Challenge phase to confirm sensitization.

Sensitization was not confirmed in any of the 19 re-tested subjects.

*Comment: Sensitization potential of NAFT-600 was assessed using the modified Draize test<sup>3</sup> emphasizing that the test drug is capable of producing a greater response on subsequent challenges than on the initial exposure. Based on the results, it does not appear that NAF-600 is skin sensitizer.*

2. A Controlled, Open-Label, Blinded Evaluator Single Dose Study of Ultraviolet Radiation to Evaluate the Phototoxicity Potential of NAFT-600 (MRZ 90200/1021/1)

This study assessed the potential of NAFT-600 to produce phototoxic reaction by a single exaggerated exposure, with and without ultraviolet radiation (UVR) in 30 healthy subjects 18-70 years of age with Fitzpatrick skin type I, II or III. For minimal erythema dose (MED) determinations, 6 progressive, timed full-spectrum UV doses were administered in 25% intervals to 6 respective sites on the back approximately 0.8 cm in diameter. Following determination of MED, approximately 20 mg of NAFT-600 was applied to the mid-back of each subject with occlusion for 24 ±2 hours. Additional 2 untreated control sites were occluded as well. After the chambers were removed, the test products were wiped off gently, to permit visual grading of the irritation response. A small additional amount of the investigational product was then re-applied so that the UVR doses (10 J/cm<sup>2</sup> + 0.5 MED of UVA+UVB) were administered through a film of test product.

Responses of all six sites were graded immediately after removal of the chambers and 24 ±2 hours and 48 ± 4 hours after irradiation, using the 8 point irritation grading scale shown below:

Grade	Description
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

Source: Applicant's Table 4 from 5.3.3.1.1)

No irritation grades for any treatment at any evaluation were greater than 2 (definite, mild erythema). Presented below are results from NAFT-600 irradiated sites only (

Investigational Product-Irradiated Sites	Grade				
	0	1	2	3	4
Evaluation Times					
24 ± 2 hours after Application	33	0	0	0	0
Immediately After Irradiation	30	1	0	0	0
24 ± 2 hours after Irradiation	27	2	2	0	0
48 ± 4 hours after Irradiation	30	1	0	0	0

*Comment: Based on the results of this study, it is not likely that NAFT-600 can cause phototoxicity.*

3. A Controlled, Open-Label, Blinded Evaluator, Multiple Dose of Ultraviolet Radiation Study to Evaluate the Photoallergenicity Potential of NAFT-600 (MRZ 90200/1020/1)

This open-label, controlled study, consisted of a three-week Induction phase, a 9-14 day Rest period and a one week challenge Phase. Fifty-five healthy subjects 18-70 years of age received 6 24-hour application and irradiation during 3 week Induction phase and once in the challenge Phase, and the unirradiated sites were exposed to the investigational product 6 times in the Induction phase and once in the challenge Phase. Each treated site was evaluated using an 8-point irritation severity scale (same as the one used for phototoxicity assessment).

There were no irritation grades above 2 during the study on any of the application sites. Presented below are results from NAFT-600 irradiated sites only (source: Table 11 from 5.3.3.3).

Investigational Product-Irradiated Sites		Grades				
		0	1	2	3	4
Induction Phase	Pre-UV Evaluation 1-Visit 2	54	1	0	0	0
	Post-UV Evaluation 1-Visit 2	42	12	1	0	0
	Pre-UV Evaluation 2-Visit 4	52	2	0	0	0
	Post-UV Evaluation 2-Visit 4	47	7	0	0	0
	Pre-UV Evaluation 3-Visit 6	53	1	0	0	0
	Post-UV Evaluation 3-Visit 6	48	5	0	0	0
	Pre-UV Evaluation 4-Visit 8	48	5	0	0	0
	Post-UV Evaluation 4-Visit 8	41	12	0	0	0
	Pre-UV Evaluation 5-Visit 10	52	1	0	0	0
	Post-UV Evaluation 5-Visit 10	39	12	2	0	0
	Pre-UV Evaluation 6-Visit 12	51	2	0	0	0
	Post-UV Evaluation 6-Visit 12	42	8	3	0	0
	Challenge Phase	Pre-UV Evaluation Visit 13	53	0	0	0
Post UV Evaluation Visit 14		49	4	0	0	0
48 Hour Evaluation Visit 15		49	1	3	0	0
72 Hour Evaluation Visit 16		49	3	1	0	0

*Comment: There is no evidence of potential photoallergenicity of NAFT-600 based on the results of this study.*

#### 7.4.6 Immunogenicity

This drug product is not expected to induce systemic immunogenicity.

#### 7.5 Other Safety Explorations

##### 7.5.1 Dose Dependency for Adverse Events

There was only one drug concentration and only one dosing regimen applied in these studies, thus dose dependency could not be explored.

##### 7.5.2 Time Dependency for Adverse Events

Time dependency for AEs was not explored.

##### 7.5.3 Drug-Demographic Interactions

Age-related most common AEs did not show any significant differences between the groups.

**Table 23 Age-related Most Common AEs**

SUBGROUP MedDRA Preferred Term	Naftin Gel 2% (N= 1175) n (%)	Vehicle (N=571) n (%)
AGE: 12-18 years	N=20	N=6
Headache	1 (5)	0
Myalgia	1 (5)	0
AGE: 18-65 years	N=1056	N=507
Headache	31 (3)	7 (1)
Nasopharyngitis	11 (1)	5 (1)
Urinary tract infection	11 (1)	1 (<1)
AGE: 65 years and older	N=99	N=58
Myalgia	2 (2)	1(2)
Nasopharyngitis	1 (1)	0
Urinary tract infection	1 (1)	2 (3)
Sinusitis	1 (1)	1(2)

*Comment: Number of pediatric subjects is small for any meaningful conclusion on the safety of the product in that population. Additionally, there were no subjects younger than 18 years included in PK trial 1010. A PMR trial will need to be conducted according to PREA. The exposure in the geriatric population was adequate to conclude that safety does not differ from the younger subgroup.*

Gender-related AE are presented in Table 21 below:

**Table 24 Gender-related Most Common AEs**

SUBGROUP MedDRA Preferred Term	Naftin Gel 2% (N= 1175) n (%)	Vehicle (N=571) n (%)
MALE	N=892	N=435
Headache	19 (2)	3 (1)
Nasopharyngitis	10 (1)	4 (1)
FEMALE	N=283	N=136
Headache	13 (5)	4 (3)
Nasopharyngitis	2 (1)	1 (1)
Urinary tract infection	10 (4)	2 (2)
Upper respiratory infection	6 (2)	1 (1)
Sinusitis	1 (1)	1 (1)

Headaches and urinary tract infections appear to be more common in females; however that is the fact for both active, and vehicle group.

*Comment: There are no specific safety concerns related to genders.*

#### 7.5.4 Drug-Disease Interactions

Drug disease interaction was not explored.

#### 7.5.5 Drug-Drug Interactions

No evaluations of drug-drug interactions were conducted.

### 7.6 Additional Safety Evaluations

#### 7.6.1 Human Carcinogenicity

To date there is no human carcinogenicity data for naftifine HCl.

A 2-year dermal rat carcinogenicity study will be conducted as a post-marketing requirement attached to the approval of Naftin Cream 2%. The study protocol was reviewed and approved by the Executive CAC on 01/22/2013. Study completion is expected by 7/2015 and final study report by 9/2016.

#### 7.6.2 Human Reproduction and Pregnancy Data

No trials with naftifine HCl were conducted in pregnant women. There were 4 pregnancies reported in the trials with NAFT-600 (all subjects received the active):

- Subject 21/1372 (MRZ90200/3015/1) became pregnant after 14 applications. Pregnancy resulted in spontaneous abortion.
- Subject 38/5416 (MRZ90200/3016/1), became pregnant after 14 applications. Pregnancy was terminated due to ectopic pregnancy.
- Subject 083 (MRZ 90200/1019/1), became pregnant after 22 applications. Pregnancy resulted in delivery. There are no further details on the status of the child or mother.
- Subject 084 (MRZ 90200/1019/1), became pregnant after 21 applications. The outcome of the pregnancy is not known.

Naftin HCl is category B pregnancy risk based on non-clinical data.

*Comment: This drug product should be labeled to reflect the lack of data available for use in pregnant or lactating women. Pregnancy category should remain the same with the recommendation that NAFT-600 Gel, 2% should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.*

### 7.6.3 Pediatrics and Assessment of Effects on Growth

The applicant requested a waiver of the requirement to conduct studies in pediatric subjects younger than 12 years of age on the basis that “NAFT-600 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.” In addition, applicant requested a deferral for studies in pediatric subjects 12-17 years.

*Comment: It is my recommendation that a waiver be granted for pediatric subjects less than 12 years of age because the incidence of tinea pedis in this age group is low. However, as previously stated, safety information for Naftin Gel 2% in 12-17 years of age is very limited [REDACTED] (b) (4), thus I agree with the deferral of pediatric studies in pediatric subjects 12-17 years. [REDACTED] (b) (4) the labeling needs to be limited to adult population only.*

The request for partial waiver and deferral was presented to Pediatric Review Committee (PeRC) on May 22, 2013. The Committee agreed with the Division’s recommendation that both, a waiver for pediatric population less than 12 years of age and a deferral for pediatric studies in pediatric subjects 12-17 years be granted.

It should be noted that approval of Naftin Cream 2% (NDA 19599) had two PMRs attached:

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

The applicant submitted the following studies to address these PMRs:

- A Phase 4, open-label, multicenter, two-week PK/safety trial under maximal use conditions of NAFT-500 Cream, 2% in pediatric subjects with tinea cruris and tinea pedis and NAFT-600 Gel, 2% in pediatric subjects with tinea pedis.
- A Phase 4, double-blind, randomized, placebo-controlled, multicenter, parallel group trial to evaluate the PK, efficacy, and safety of NAFT-500 Cream, 2% and NAFT-600 Gel, 2% in pediatric subjects ages two years to 17 years and 11 months in the treatment of tinea corporis.

*Comment: Proposed PK/safety trial under maximal use has NAFT-600 arm included. This appears to be adequate to address the safety labeling needs for the adolescent population from age 12-17 years 11 months.*

#### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is minimal to no risk of overdose or abuse for NAFT-600 based on available data from the trials.

#### 7.7 Additional Submissions

The 120 day safety update was submitted on December 19, 2012. Per applicant “there was no new safety data available for the submission to the application.”

## **8 Postmarket Experience**

NAFT-600 is currently not marketed in any country. Application site reactions were the most common reported adverse reactions with naftifine hydrochloride products.

## 9 Appendices

### 9.1 Literature Review/References

1. Weinstein A and Berman B. Topical treatment of common superficial tinea infections. *American Family Physician* 2002;65(10): 2095-2102
2. Noble S, Forbes RC, and Stamm P. Diagnosis and management of common tinea infections. *American Family Physician* 1998;58 (1):163-174
3. Draize JH, Woodard G, and Calvery HO. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucus membranes. *J Pharmacol Expt Ther.* Vol 1944; (83) 377-390

### 9.2 Labeling Recommendations

Division of Medication Error Prevention and Analysis accepted the proposed proprietary name, Naftin Gel 2%.

Labeling recommendations are under negotiations with the applicant. Key clinical recommendations that differ from the applicants are as follows (deletions are noted as ~~strike through~~ and additions are noted as double underlines):

#### -----INDICATIONS AND USAGE-----

NAFTIN (naftifine hydrochloride) Gel, 2% is an allylamine antifungal indicated for the treatment of: interdigital <sup>(b) (4)</sup> tinea pedis caused by the organisms *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum* in patients <sup>(b) (4)</sup> 18 years of age and older.

#### -----ADVERSE REACTIONS-----

The most common adverse reactions (≥1%) ~~is headache (2.5%)~~. are application site reactions (2%). (6.1)

##### 6.1 Clinical Trials Experience

<sup>(b) (4)</sup>  
<sup>(b) (4)</sup> In two randomized, vehicle-controlled trials, 1143 <sup>(b) (4)</sup> subjects were treated with NAFTIN [naftifine hydrochloride] Gel, 2% versus 571 subjects treated with the vehicle. . The <sup>(b) (4)</sup> -trial subjects were 12 to 92 years old, primarily male (76%), 5 <sup>(b) (4)</sup>2% Caucasian, 38% Black or African American, 23% Hispanic or

Latino, and had interdigital tinea pedis only or interdigital and moccasin-type tinea pedis. 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. (b) (4)

(b) (4) he most common adverse reaction (b) (4)  
were application site reactions which occurred at the rate of 2% in NAFTIN [naftifine hydrochloride] Gel, 2% arm versus 1% in vehicle arm. Most adverse reactions were mild in severity. (b) (4)

Cumulative irritancy testing revealed the potential for NAFTIN (naftifine hydrochloride) Gel, 2% to cause irritation. There was no evidence that NAFTIN (naftifine hydrochloride) Gel, 2% causes contact sensitization, phototoxicity, or photoallergenicity in healthy skin.

14. [REDACTED] (b) (4)

NAFTIN (naftifine hydrochloride) Gel, 2% has been [REDACTED] (b) (4) evaluated for efficacy in two randomized, double-blind, vehicle-controlled, multicenter trials that included 1175 subjects with symptomatic and dermatophyte culture-positive tinea pedis. [REDACTED] (b) (4)

Subjects were randomized to receive NAFTIN (naftifine hydrochloride) Gel, 2% or vehicle. Subjects applied naftifine hydrochloride gel 2% or vehicle to the affected area of the foot once daily for 2 weeks. Signs and symptoms of tinea pedis (presence or absence of erythema, pruritus, and scaling) were assessed and potassium hydroxide (KOH) examination and dermatophyte culture were performed 6 weeks after the first treatment.

[REDACTED] (b) (4)

The mean age of the study population was 45 years; 77% were male; and 60% were Caucasian, 35% were Black or African American, and 26% were Hispanic or Latino. 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 proportion of subjects with a complete cure at 6 weeks after the start of treatment (4 weeks after the last treatment). 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 1 below. Naftin Gel demonstrated complete cure in subjects with interdigital tinea pedis, but complete cure in subjects with moccasin type tinea pedis was not demonstrated.

[REDACTED] (b) (4)

[REDACTED] (b) (4)

Table 1 Interdigital Tinea Pedis: Number (%) of Subjects With Complete Cure, Effective Treatment, and Mycological Cure at Week 6 Following Treatment With NAFTIN Gel, 2% (Full Analysis Set, Missing Values Treated as Treatment Failure)

Endpoint	Trial 1		Trial 2	
	NAFTIN Gel, 2% N=382 n (%)	Vehicle N=179 n (%)	NAFTIN Gel, 2% N=400 n (%)	Vehicle N=213 n (%)
Complete Cure <sup>a</sup>	64 (17%)	3 (2%)	104 (26%)	7 (3%)

Treatment Effectiveness <sup>b</sup>	207 (54%)	11 (6%)	203 (51%)	15 (7%)
Mycological Cure <sup>c</sup>	250 (65%)	25 (14%)	235 (59%)	22 (10%)

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.



### 9.3 Advisory Committee Meeting

Advisory Committee meeting was deemed not necessary.

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

/s/  
-----

MILENA M LOLIC  
06/03/2013

DAVID L KETTL  
06/04/2013





## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			Yes, dermal safety studies
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included ( <i>e.g.</i> , label comprehension, self selection and/or actual use)?			x	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	All studies were done in USA.
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			6 individual datasets are missing for MRZ 016 trial, however those are included in the pooled datasets.
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	Division requested CRF for deaths, serious adverse events, and adverse dropouts.
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	x			

as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes**

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

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

Applicant should submit the following missing individual datasets for trial 0316:  
adae.xpt ; adcm.xpt ; adlb.xpt ; adeff.xpt ; adpe.xpt ; advs.xpt .

Milena Lolic October 11, 2012  
 \_\_\_\_\_  
 Reviewing Medical Officer Date

\_\_\_\_\_  
 Clinical Team Leader Date

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

/s/  
-----

MILENA M LOLIC  
10/19/2012

DAVID L KETTL  
10/19/2012