

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204286Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 204286	Submission Date(s): 8/31/2012, 1/18/2013
Brand Name	Naftin Gel, 2%
Generic Name	Naftifine
Primary Reviewer	Doanh Tran, Ph.D.
Secondary Reviewer	Capt. E. Dennis Bashaw, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Dermatology and Dental Products
Sponsor	Merz Pharmaceuticals
Relevant IND(s)	105603
Submission Type	Original
Formulation; Strength(s)	Topical gel, 2%
Indication	Treatment of tinea pedis in patients ^{(b) (4)} years of age and older

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1 Executive Summary

Naftifine hydrochloride is a synthetic allylamine derivative topical antifungal. It is currently available as 1% gel formulation for topical treatment of tinea pedis, tinea cruris and tinea corporis. The sponsor is developing a new formulation, 2% gel, for the treatment of tinea pedis only. The proposed dosing regimen is once daily for 2 weeks. The advantage of the new higher strength formulation is that the duration of treatment is reduced from 4 weeks to 2 weeks and dosing interval from twice daily to once daily. The proposed dosing regimen for naftifine gel, 2% (also noted as NAFT-600 or NAFT-600 Gel, 2%) is the same as that of recently approved naftifine cream, 2% (NDA 19599).

This NDA includes 2 Phase 3 safety and efficacy trials and 5 Phase 1 clinical trials, including a maximal use PK trial (MRZ 90200/1010/1) and a thorough QT trial (MRZ 90200/1018/1).

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds NDA 204286 acceptable pending agreement on recommended labeling changes and postmarketing requirements as outlined in section 1.2 of this review.

1.2 Phase IV Requirements and Commitments

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.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Systemic naftifine exposure:

The sponsor conducted a maximal use pharmacokinetic (PK) trial in 32 adult male and female subjects with tinea pedis. This study administered a mean of 3.9 grams naftifine gel, 2% to both feet once daily for 2 weeks. All 32 enrolled subjects had tinea pedis on both feet and the majority of subjects (97%) had both interdigital and moccasin-type infections. Thirty subjects completed the trial. Plasma naftifine concentrations were measurable in all 30 subjects.

Plasma naftifine exposure increased over the treatment period, with a geometric mean (CV%) AUC_{0-24} (area under plasma concentration-versus-time curve from time 0 to 24 hours) of 10.5 (118) ng•hr/mL on Day 1 and an AUC_{0-24} of 70 (59) ng•hr/mL on Day 14. The accumulation ratio based on AUC was approximately 6. Maximum concentration (C_{max}) also increased over the treatment period; geometric mean (CV%) C_{max} after a single dose was 0.9 (92) ng/mL on Day 1; C_{max} on Day 14 was 3.7 (64) ng/mL. Median T_{max} was 20.0 hours (range: 8, 20 hours) after a single application on Day 1 and 8.0 hours (range: 0, 24 hours) on Day 14. Trough plasma concentrations generally

increased during the trial period and reached steady state after 11 days. The fraction of dose excreted in urine was $\leq 0.01\%$ of the applied dose.

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.

QT interval:

Review of the thorough QT trial by the Interdisciplinary Review Team for QT studies (IRT-QT) concluded that there was no significant QTc prolongation of a 600 mg oral dose of naftifine. The AUC and Cmax from the maximal use PK trial for naftifine gel, 2% (described above) were 9.4 and 46.5 fold lower, respectively, compared to the results for the 600 mg oral dose used in the TQT trial. It can be concluded that there is no concern regarding QTc prolongation with naftifine gel, 2% for treatment of tinea pedis.

Pediatrics:

The sponsor did not provide any PK data for NAFT-600 gel 2% in pediatrics. The sponsor is seeking a waiver of pediatric studies in pediatrics less than 12 years of age and deferral of pediatric studies in age range of 12-17 years to be conducted post approval. However, the sponsor has proposed an indication for treatment of patients ^{(b) (4)} years of age and older. Due to the lack of systemic bioavailability data and limited clinical experience with naftifine gel, 2% in pediatrics, it is recommended that the indication be limited to adults and the sponsor be required to conduct a PK/safety/tolerability trial as outlined in section 1.2 of this review.

Clinical vs. to-be-marketed formulation:

The to-be-marketed formulation was used in all 6 clinical trials submitted to this NDA that applied naftifine gel 2%. The remaining trial, a thorough QT trial, did not use naftifine gel, 2%; an oral capsule formulation was used in this trial.

Method validation:

Analysis of PK samples from trial MRZ 90200/1010/1 was conducted by ^{(b) (4)} using adequately validated methods.

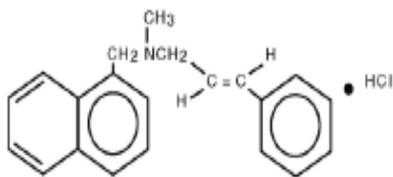
2 Question-Based Review

2.1 General Attributes

2.1.1 What is naftifine hydrochloride?

Naftifine hydrochloride, USP is the active pharmaceutical ingredient in NAFT-600 Gel, 2%. Naftifine hydrochloride has an empirical formula of $C_{21}H_{21}N \cdot HCl$ and a molecular weight of 323.86. The structural formula of naftifine hydrochloride is provided in Figure 1 below:

Figure 1: structural formula of naftifine hydrochloride



2.1.2 What are the proposed indication and dosing regimen for NAFT-600 Gel, 2%?

The proposed indication for NAFT-600 Gel, 2% is for the treatment of interdigital ^{(b) (4)} tinea pedis caused by the organism *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum* in patients ^{(b) (4)} years of age and older. NAFT-600 Gel, 2% is proposed to be applied topically once daily to the affected areas plus approximately 1/2 inch margin of healthy surrounding skin for 2 weeks.

2.1.3 What is tinea pedis?

Tinea pedis is a fungal infection of the foot caused primarily by *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum*.

2.1.4 What is the pharmacologic rationale for naftifine in the treatment of tinea pedis?

Naftifine hydrochloride is a synthetic allylamine derivative topical antifungal. Although the exact mechanism of its action against fungi is not known, naftifine hydrochloride appears to interfere with sterol biosynthesis by inhibiting the enzyme squalene 2, 3-epoxidase, the rate limiting enzyme in the cellular synthesis of ergosterol. The inhibition of enzyme activity results in decreased amount of sterols, especially ergosterol, and a corresponding accumulation of squalene in the cells.

2.2 General Clinical Pharmacology

2.2.1 What were the design features of the clinical pharmacology and clinical trials used to support NAFT-600 gel, 2%?

Naftifine hydrochloride is currently available as 1% gel formulation for topical treatment of tinea pedis, tinea cruris and tinea corporis (NDA 19356). It is also available as cream formulation at 1% and 2% strengths (NDA 19599). The sponsor is developing a new formulation, 2% gel, for the treatment of tinea pedis only in patients ^{(b)(4)} years of age and older. The proposed dosing regimen is once daily for 2 weeks. The advantage of the higher strength formulation is that the duration of treatment is reduced from 4 weeks to 2 weeks and dosing interval from twice daily to once daily. The proposed dosing regimen for naftifine gel, 2% is the same as that of recently approved naftifine cream, 2% (naftifine cream 2% is approved for use only in adults).

This NDA includes 5 Phase 1 clinical trials, including a maximal use PK trial (MRZ 90200/1010/1) and a thorough QT trial (MRZ 90200/1018/1). It also includes 2 Phase 3 safety and efficacy trials. Table 1 provides a summary of all clinical trials.

Table 1: List of all trials submitted in this NDA

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 Photoallergenicity 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

2.2.2 What is the bioavailability of NAFT-600 gel, 2% under maximal use conditions?

The sponsor submitted results of a maximal use PK trial MRZ 90200/1010/1. This study administered a mean of 3.9 grams NAFT-600 gel to both feet once daily for 2 weeks in subjects with tinea pedis. All 32 enrolled subjects had tinea pedis on both feet and the majority of subjects (97%) had both interdigital and moccasin-type infections. Pharmacokinetic blood samples were collected on Days 1 and 14 for 24 hours at 0 hour (pre-application) and 1, 2, 4, 6, 8, 12, 16, and 24 hours post-application. Pre-application

samples were collected on Days 3, 7, 11, 12, 13, and 14, and also on Days 21 (1 week after the last application), and 28 (2 weeks after the last application). Pharmacokinetic urine samples were obtained on Days 1 and 14 for 24 hours as follows: before on-site treatment application (only on Day 1), 0–6, 6–12, and 12–24 hours after on-site application.

Summary of plasma naftifine PK parameters for Day 1 and Day 14 is shown in Tables 2 and 3, respectively. Steady state individual PK profiles are shown in Figure 1 and the mean PK profile is shown in Figure 2.

Table 2: Summary of Single Dose (Day 1) Naftifine PK Parameters

Statistics	AUC ₀₋₂₄ (ng*hr/mL)	C _{max,SD} (ng/mL)	T _{max,SD} (hr)
N	32	32	32
Mean	15.520	1.220	18.9
SD	13.9159	1.0834	5.59
CV%	118.099	92.006	
Geometric Mean	10.459	0.891	
Min	1.43	0.20	8
Median	9.891	0.739	20.0
Max	47.61	4.35	24
90% C.I.(1)	(11.349, 19.691)	(0.896, 1.545)	(17.2, 20.5)
90% C.I.(2)	(7.904, 13.839)	(0.705, 1.127)	

(1) 90% CIs were based on the arithmetic mean.

(2) 90% CIs were based on the geometric mean.

Data Source: [Table 14.2.1.1](#)

Table 3: Summary of Steady State (Day 14) Naftifine PK Parameters

Statistics	AUC _{0-τ} (ng*hr/mL)	C _{max, Day 14} (ng/mL)	T _{max, Day 14} (hr)	R _{A (AUC)} (ng*hr/mL)
N	30	30	30	30
Mean	80.410	4.363	8.6	10.0444
SD	43.6681	2.5160	8.17	12.10032
CV%	58.878	63.865		117.2014
Geometric Mean	70.116	3.724		6.3347
Min	16.75	0.88	0	0.869
Median	67.415	3.503	8.0	5.8930
Max	201.60	10.28	24	57.894
90% C.I.(1)	(66.864, 93.957)	(3.582, 5.143)	(6.1, 11.2)	(6.2907, 13.7981)
90% C.I.(2)	(59.200, 83.046)	(3.106, 4.465)		(4.7475, 8.4525)

(1) 90% CIs were based on the arithmetic mean.

(2) 90% CIs were based on the geometric mean.

Data Source: [Table 14.2.1.2](#)

Figure 1: Spaghetti plot of individual naftifine plasma concentrations by time on Day 14 (source figure 14.2.5.10)

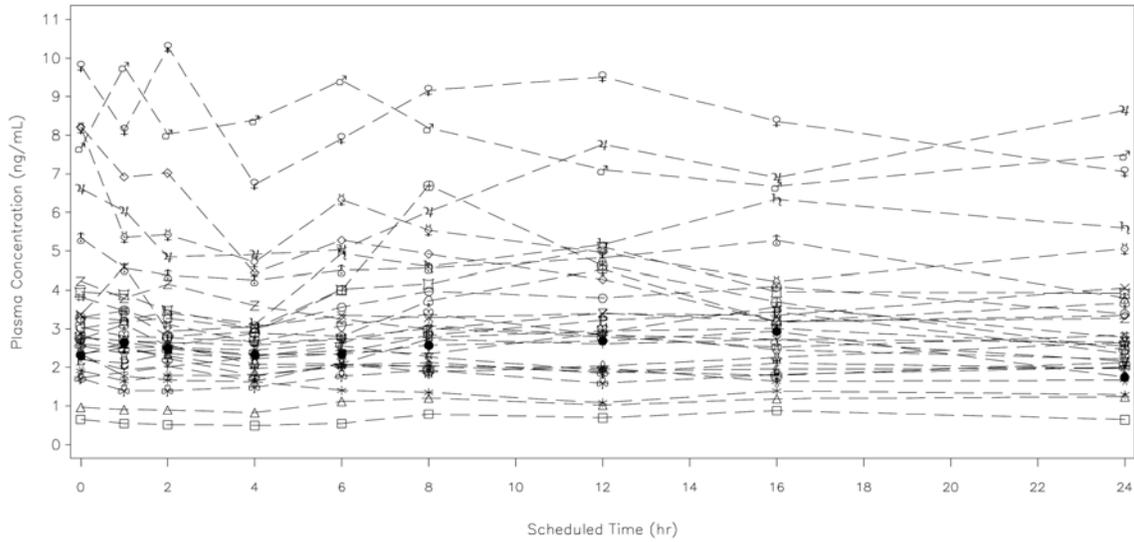
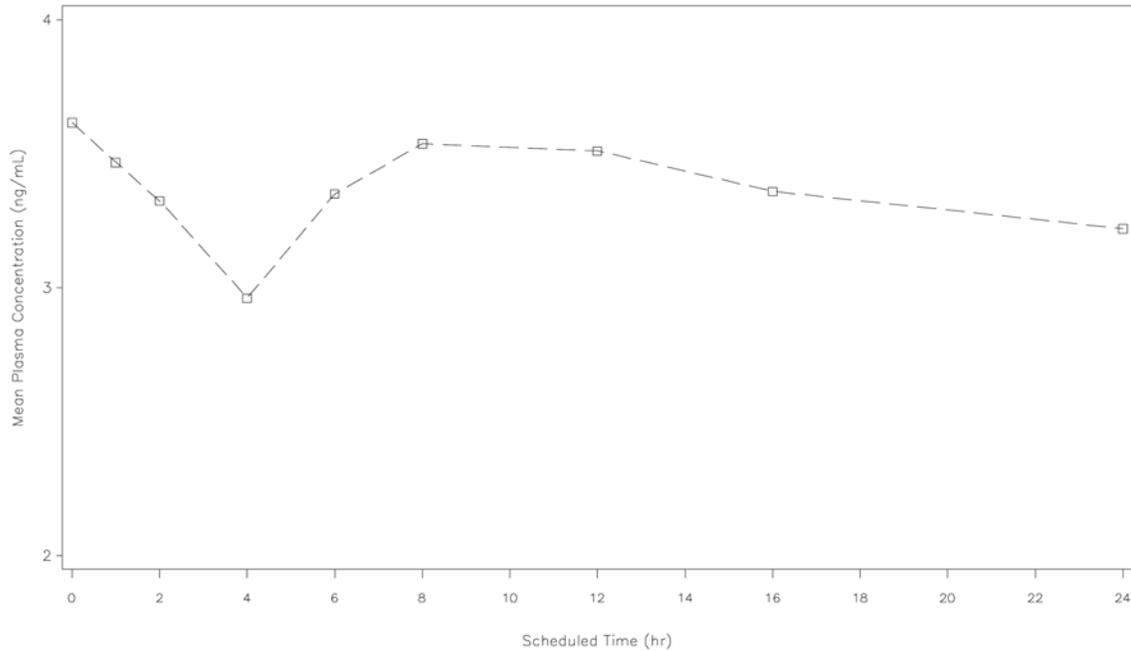


Figure 2: Mean plasma concentrations of naftifine by time on Day 14



The results showed that exposure to naftifine increased over the 2-week treatment period; geometric mean (CV%) AUC_{0-24} was 10.5 (118) ng*hr/mL on Day 1, and $AUC_{0-\tau}$ was 70 (59) ng*hr/mL on Day 14. Maximum concentration (C_{max}) also increased over the treatment period; geometric mean (CV%) C_{max} was 0.9 (92) ng/mL on Day 1; geometric mean (CV%) C_{max} on Day 14 was 3.7 (64) ng/mL. There was significant accumulation with the geometric mean (CV%) of the accumulation index ($RA_{(AUC)}$) of 6.33 (118).

Trough concentrations generally increased through the study period and approached steady state after approximately 11 days (data not shown). The mean (\pm SD) C_{trough} was 3.2 ± 1.9 ng/mL on day 15. Naftifine concentration continued to be detected in plasma in all 30 subjects at Day 28, when the geometric mean (CV%) was 0.5 (50.9) ng/mL.

The fraction of the applied dose excreted in urine over a 24 hour dosing interval was $\leq 0.01\%$. The mean (\pm SD) renal clearance (CL_r) was 6.7 ± 9.9 mL/h.

2.2.3 What are the characteristic of exposure response relationship?

No formal dose-ranging studies were conducted with NAFT-600 gel. The dose and dosing regimen evaluated in safety and efficacy trials for NAFT-600 gel are identical to that of the approved naftifine cream, 2%.

2.2.4 Does NAFT-600 gel, 2% prolong QT interval?

The sponsor submitted results of a thorough QT trial MRZ 90200/1018/1. The results from this trial were also previously submitted to NDA 19599/s011 and have been reviewed by the Interdisciplinary Review Team for QT studies (IRT-QT). IRT-QT concluded that there was no significant QTc prolongation of a 600 mg oral dose of naftifine (IRT-QT review, NDA 19599, DARRTS date 09/09/2011).

The C_{max} and AUC for naftifine gel, 2% observed in the maximal use PK trial MRZ 90200/1010/1 were 46.5 and 9.4 fold lower, respectively, than those observed following the 600 mg oral dose in the TQT trial (Table 3). Since the systemic exposure following naftifine gel, 2% application is much less than the exposure following an oral dose of 600 mg used in the thorough QT trial and the fact that there was no significant QTc prolongation with 600 mg oral dose, it can be concluded that there is no concern regarding QTc prolongation with naftifine gel, 2% for treatment of tinea pedis.

Table 4: PK comparison (geometric means)

Parameter	NAFT-600 Gel, 2%, 4 g to tinea pedis, Day 14	Oral 600 mg single dose (TQT trial)	NAFT-500 Cream, 2%, 8 g to tinea pedis and cruris, Day 14
AUC (ng*h/mL) ^a	70 (59 %CV)	657 (67% CV)	204 (28 %CV)
C_{max} (ng/mL)	3.7 (64 %CV)	172 (80 %CV)	11 (29.3 %CV)

^a $AUC_{0-\tau}$ on Day 14 for Gel and Cream and $AUC_{0-\infty}$ for single oral dose of naftifine.

2.3 Intrinsic Factors

2.3.1 What is the systemic exposure of NAFT-600 gel, 2% in pediatrics?

The sponsor did not provide any PK data for NAFT-600 gel 2% in pediatrics. The sponsor is seeking a waiver of pediatric studies in pediatrics less than 12 years of age. A waiver should be granted for pediatrics less than 12 years of age because the incidence of tinea pedis in this age group is low. A similar request was granted for naftifine cream, 2% for the same indication (NDA 19599).

The sponsor is seeking a deferral of pediatric studies in age range of 12-17 years to be conducted post approval. However, the sponsor has proposed to label for an indication for treatment of patients ^{(b) (4)} years of age and older. (b) (4)

This reviewer agrees with the recommendation from the Clinical reviewer, Dr. Milena Lolic, to approve naftifine gel, 2% only in adults until additional safety and PK information is available for pediatrics. This reviewer recommends that the sponsor conduct a trial to evaluate PK and safety of naftifine gel, 2% under maximal use conditions in subjects 12 – 17 years of age with tinea pedis as part of Pediatric Research Equity Act (PREA) post marketing requirements (PMR). This proposal will be presented to the Pediatric Review Committee on May 15, 2013.

2.4 Extrinsic Factors

There were no trials evaluating extrinsic factors with naftifine gel, 2%. Previous review of naftifine cream, 2% by Clinical Pharmacology reviewer Dr. Abimbola Adebawale concluded that there is no potential risk of drug-drug interactions following topical application of naftifine cream, 2% (NDA 19599, DARRTS dated 11/02/2011). The systemic concentration of naftifine following application of naftifine gel, 2% in subjects with tinea pedis is lower than for naftifine cream, 2% when applied for its approved indications of tinea pedis and tinea cruris. Therefore, it is also expected that there is not a potential for drug-drug interactions with naftifine cream, 2%.

2.5 General Biopharmaceutics

2.5.1 What is the product composition of NAFT-600 gel, 2%?

The drug product, NAFT-600 Gel, 2%, contains the active ingredient naftifine hydrochloride USP, in a gel base. NAFT-600 Gel, 2% will be packaged in 45g tubes. An additional 2g capacity tube will be used for physician samples. The composition of the drug product is provided in Table 5 below.

Table 5: NAFT-600 gel, 2% composition

Component	Reference	Concentration (% w/w)	Function
Naftifine hydrochloride	USP	2.00	Active Ingredient
(b) (4)	USP		(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

2.5.2 Was the to-be-marketed formulation used in the clinical trials?

The to-be-marketed formulation was used in all 6 clinical trials submitted to this NDA that applied naftifine gel 2%. The remaining trial, a thorough QT trial, administered an oral capsule formulation.

2.6 Analytical

2.6.1 What bioanalytical methods were used to assess naftifine drug concentrations and were they adequately validated?

Analyses of plasma and urine PK samples from trial MRZ 90200/1010/1 were conducted by (b) (4) using 2 separate methods. The methods were adequately validated with precision and accuracy within acceptable limits. Brief description and results of validation for these assays are summarized below.

Plasma assay:

Naftifine concentration in human EDTA K₃ plasma was measured using an high performance liquid chromatographic (HPLC) method with tandem mass spectrometry (MS/MS) detection. The method was adequately validated over a range of 99.84 to 9984.00 pg/mL. Table 6 shows the validation results.

Table 6: Summary of validation results for naftifine in plasma assay method

Assay Method	High-performance liquid chromatography with Tandem Mass Spectrometry detection
Analytical Site	(b) (4)
Compound	Naftifine in plasma
Standard Curve Range	99.84 to 9984.00 pg/mL
Lower Limit of Quantitation (LLOQ)	99.84 pg/mL

Average Recovery of Drug	84.73 to 87.64% (Internal standard recovery: 91.09%)
Intra-Batch Accuracy	-0.02 to 3.44%
Inter-Batch Accuracy	-4.83 to 2.53%
Intra-Batch Precision Range	1.03 to 3.85%
Inter-Batch Precision Range	2.93 to 5.41%
Freeze-Thaw Stability	4 cycles
Bench-Top Stability	22 hours (room temperature)
Long Term Stability	143 days at -20 °C
Dilution Integrity	Up to 20-fold

Naftifine in plasma long term storage stability was demonstrated for 143 days at -20 °C. The total time from first PK collection ((b)(4)) and end of analysis ((b)(4)) for trial MRZ 90200/1010/1 was 106 days. The samples were stored at -20 deg C until analysis. The long term storage stability for naftifine in plasma is adequate.

Urine assay:

Naftifine concentration in human urine was measured using a HPLC method with MS/MS detection. The method was adequately validated over a range of 49.92 to 4992.00 pg/mL (Note: the method was initially validated with a range of 49.80 to 9960.00 pg/mL and subsequently partially validated for the more narrow range of 49.92 to 4992.00 pg/mL). Table 7 shows the validation results.

Table 7: Summary of validation results for naftifine in urine assay method

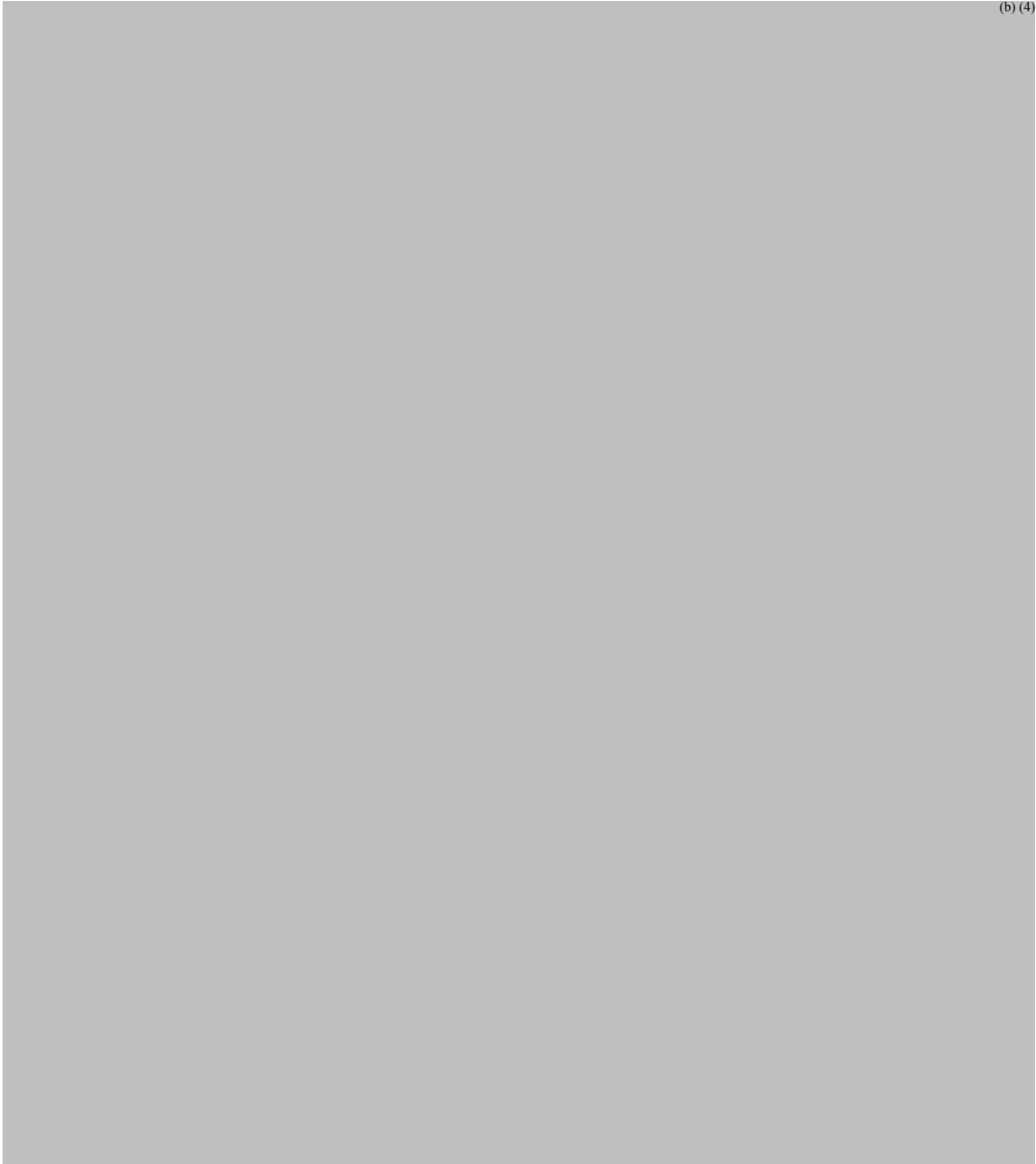
Assay Method	High-performance liquid chromatography with Tandem Mass Spectrometry detection
Analytical Site	(b)(4)
Compound	Naftifine in urine
Standard Curve Range	49.92 to 4992.00 pg/mL
Lower Limit of Quantitation (LLOQ)	49.92 pg/mL
Average Recovery of Drug	89.25 to 96.21% (Internal standard recovery: 88.59%)
Intra-Batch Accuracy	-6.58 to 5.49% ^a
Inter-Batch Accuracy	1.17 to 2.27%
Intra-Batch Precision Range	0.94 to 4.40% ^a
Inter-Batch Precision Range	2.18 to 4.24%
Freeze-Thaw Stability	4 cycles
Bench-Top Stability	24 hours at room temperature
Long Term Stability	199 days at -80 °C
Dilution Integrity	Up to 20 fold

^a These results came from partial validation for the narrower range of 49.92 to 4992.00 pg/mL. All other results came from validation of the assay with the range of 49.80 to 9960.00 pg/mL.

Naftifine in urine long term storage stability was demonstrated for 199 days at -80 °C. The total time from first PK collection ((b)(4)) and end of analysis ((b)(4)) for trial MRZ 90200/1010/1 was 113 days. The samples were stored at -80 deg C until analysis. The long term storage stability for naftifine in urine is adequate.

3 Detailed Labeling Recommendations

The following changes are recommended for sections 1 and 12 of the label. Deletion are noted as ~~striketrough~~ and additions are noted as double underlines.



(b)(4)

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4 Appendix

4.1 Individual Study Reviews

Trial MRZ 90200/1010/1:

Title: An Open-Label, Single-Center, Multiple-Application Pharmacokinetic Study of NAFT-600 in Subjects with Tinea Pedis.

Study period: Date of first enrollment: 16 Sep 2009; Date when the last subject completed the study: 07 Dec 2009

Objectives: The primary objective is to quantify the pharmacokinetics of NAFT-600 in subjects with tinea pedis under maximal clinical use conditions for 2 weeks of once daily applications. Maximal use condition is defined as applying gel to both feet. The secondary objective is to measure efficacy, tolerability, and safety of NAFT-600.

Methodology: This was an open-label, single-center, multiple-application, Phase 1 study designed to quantify the pharmacokinetic profile in plasma and urine of 2 weeks of once daily application of NAFT-600 by determining the plasma and urine concentrations of naftifine in 32 adult subjects with tinea pedis. It was conducted under maximal clinical use conditions, defined as applying gel to both feet. The applications were applied once daily in the morning between 7:00 and 9:00, totaling 4 grams of NAFT-600 (Note: The actual mean amount applied during the trial was 3.9 grams), 2 grams on each foot. The efficacy, tolerability, and safety of NAFT-600 were also assessed during the study.

Subjects stayed at the study center on Day 1 (first application) and Day 14 (last application). Pharmacokinetic blood samples were collected on Days 1 and 14 for 24 hours at 0 hour (pre-application) and 1, 2, 4, 6, 8, 12, 16, and 24 hours post-application. Pre-application samples were collected on Days 3, 7, 11, 12, 13, and 14, and also on Days 21 (1 week after the last application), and 28 (2 weeks after the last application). Pharmacokinetic urine samples were obtained on Days 1 and 14 for 24 hours as follows: before on-site treatment application (only on Day 1), 0–6, 6–12, and 12–24 hours after on-site application.

Efficacy for NAFT-600 was assessed based on KOH, dermatophyte culture, signs and symptoms, and Investigators Global Assessment results between baseline and Day 15 (24 hours after last application), and Day 28 (2 weeks after the last application and 4 weeks after the start of the study). Routine clinical laboratory assessments (serum chemistry, hematology, and urinalysis) were performed at screening and on Day 14 (end of treatment), and Day 28 (2 weeks after the last application).

ECGs were collected in triplicate on Day -1 and Day 1 (predose only). ECGs were also collected in triplicate on Day 14 for 24 hours at 0 hour (pre-application) and 1, 2, 4, 6, 8, 12, 16, and 24 hours post-application at 1- to 2-minute intervals.

Adverse events (AEs), study medication accountability, and subject compliance were reviewed at each visit.

Number of subjects: 30 subjects were to be enrolled, to ensure that 25 subjects complete the study. A total of 32 subjects were enrolled, and 30 completed the study. Enrolled subjects were healthy male and non-pregnant female ≥ 18 years of age who have tinea pedis (on one or both feet). Tinea pedis infections were confirmed by KOH analysis. All 32 (100%) subjects had tinea pedis on both feet and the majority (96.9%) of subjects had both interdigital and moccasin-type infections.

Treatment administered: Treatment consisted of once-daily morning (between 7:00 and 9:00) applications of a total of NAFT-600; 2 grams of NAFT-600 was to be applied to each foot for a total of 4 grams daily for 14 days. The applications were applied at the clinic on Days 1, 3, 7, 11–14. The treatment was applied to both feet. Subjects maintained diary cards documenting all applications at the clinic and at home.

PK sampling: Pharmacokinetic blood samples were collected on Days 1 and 14 for 24 hours at 0 hour (pre-application) and 1, 2, 4, 6, 8, 12, 16, and 24 hours post-. Pre-application samples were collected on Days 2 (corresponds to the Day 1 24-hour sample), 3, 7, 11, 12, 13, 14, and 15, (corresponds to the Day 14 24-hour sample). Samples were also collected on Days 21 (1 week after the last application), and 28 (2 weeks after the last application).

Pharmacokinetic urine samples were collected on the first and last days of treatment for 24 hours as follows: before on-site treatment application (complete void and only on Day 1), 0–6, 6–12, and 12–24 hours after on-site application.

Protocol deviations: None.

Discontinuation: Two subjects discontinued the study because of AEs; one who experienced diarrhea and vomiting on Day 13 did not apply the study medication on Day 14, and one of the subjects was hospitalized because of viral gastroenteritis.

Demographic: The majority (68.8%) of the subjects were male, white (90.6%) and of non-Hispanic ethnicity (87.5%). Mean (\pm SD) subject age was 34 ± 10.50 years and ranged from 20 to 64 years.

Table 8: Demographic
Category

NAFT-600 Gel (N=32)

Gender	
Male	22 (68.8%)
Female	10 (31.3%)
Race	
White	29 (90.6%)
Black or African American	3 (9.4%)
Asian	0
American Indian or Alaska Native	0
Native Hawaiian or Other Pacific Islander	0
Ethnicity	
Hispanic or Latino	4 (12.5%)
Not Hispanic or Latin	28 (87.5%)
Age (years)	
N	32
Mean	34.0
SD	10.50
Min	20
Median	32.0
Max	64
Height (cm)	
N	32
Mean	173.98
SD	12.200
Min	149.9
Median	175.25
Max	193.0
Weight (kg)	
N	32
Mean	98.77
SD	19.623
Min	63.6
Median	96.60
Max	146.8
Tinea Pedis Classification	
Infected Foot	
Right Foot Only	0
Left Foot Only	0
Both Right Foot and Left Foot	32 (100.0%)
Type	
Interdigital Only	0
Moccasin Type Only	1 (3.1%)
Both Interdigital and Moccasin Types	31 (96.9%)
Other	0

Treatment compliance: Overall, subjects applied approximately 98% of the intended amount of gel during the 2-week treatment period of this study, or a mean \pm SD of 3.9 ± 0.54 g per day of the intended 4 g dose (See table 9).

Table 9: Amount of drug administered

	NAFT-600 Gel		
	Average Amount (g) Dispensed from Tube (1)	NAFT-600 Gel Total Dose(g) Used (2)	Compliance (%) (3)
N	32	32	32
Mean	3.92	54.76	97.98
SD	0.536	7.624	13.390
Min	2.2	30.7	54.8
Median	4.08	57.10	101.96
Max	5.0	70.3	125.5

Note: Expected dose = 4 grams once a day for 2 weeks.

(1) Average Daily Dose = (total amount applied during the study)/(number of days in study)

(2) Total Dose Used = (total dispensed) - (total returned).

(3) Compliance = $100 * (\text{total used dose}) / (\text{total expected dose})$.

Bioanalytical Methods: Plasma and urine naftifine concentrations were analyzed using validated methods. See Question Based Review section 2.6 for details of validation results. In study method performance assessment via analysis of quality control (QC) samples during analysis of plasma and urine samples from trial MRZ 90200/1010/1 showed acceptable accuracy and precision.

Incurring sample reanalysis (ISR) was performed on 78 of 772 plasma samples and 22 of 218 urine samples. ISR for plasma sample showed a pass rate of $(b) (4)$ % being within $(b) (4)$ % of the original results. ISR for urine samples had $(b) (4)$ % pass rate with the same $(b) (4)$ % criterion.

Results:

Safety and efficacy results:

The sponsor reported that NAFT-600 gel was well-tolerated by study subjects; overall, 3 subjects reported mild AEs, and 5 reported moderate AEs. None of the TEAEs were related to study drug treatment. There were no severe AEs.

Results of the primary endpoint of complete cure are summarized in Table 10. In general, more subjects experienced complete cure on Day 28 (2-week follow up) than at the end of treatment. Complete cure was experienced by 16.7% and 59.4% of subjects on Day 15

(end of treatment) and Day 28 (2-week follow-up), respectively. For further details on safety and efficacy results, please see review by the Medical Officer.

Table 10: Number (%) of Subjects Who Experienced Complete Cure, Treatment Effectiveness, and Mycological Cure

Efficacy Endpoint	Day 7 (N=32)	Day 15 (End of Treatment) (N=30)	Day 28 (2-Week Follow-Up) (N=32)
Complete Cure (1)	0	5 (16.7%)	19 (59.4%)
90% C.I.		(6.8%, 31.9%)	(43.3%, 74.0%)
Treatment Effectiveness (2)	3 (9.4%)	13 (43.3%)	21 (65.6%)
90% C.I.	(2.6%, 22.5%)	(27.9%, 59.8%)	(49.6%, 79.4%)
Mycological Cure (3)	16 (50.0%)	19 (63.3%)	21 (65.6%)
90% C.I.	(34.4%, 65.6%)	(46.7%, 77.9%)	(49.6%, 79.4%)

Note: 90% CIs were calculated using exact methods.

(1) Complete cure is defined as negative dermatophyte culture and negative KOH results from the central laboratory and negative signs and symptoms.

(2) Treatment effectiveness is defined as negative culture and negative KOH and Investigators Global Assessment of 0 or 1.

(3) Mycological cure is defined as negative dermatophyte culture and negative KOH results from the central laboratory.

Data Source: [Table 14.3.1](#)

Pharmacokinetic results:

Plasma PK:

Exposure to naftifine increased over the 2-week treatment period; geometric mean (CV%) AUC_{0-24} was 10.5 (118) ng*hr/mL on Day 1, and $AUC_{0-\tau}$ was 70 (59) ng*hr/mL on Day 14. Maximum concentration also increased over the treatment period; geometric mean (CV%) C_{max} was 0.9 (92) ng/mL on Day 1; geometric mean (CV%) C_{max} on Day 14 was 3.7 (64) ng/mL. Geometric mean (CV%) of the accumulation index ($RA_{(AUC)}$) was 6.33 (118). Median T_{max} was 20.0 hours (range: 8, 20 hours) after a single application on Day 1 and 8.0 hours (range: 0, 24 hours) on Day 14.

Trough concentrations generally increased through the study period and approaches steady state after approximately 11 days. The mean (\pm SD) C_{trough} was 3.2 ± 1.9 ng/mL on day 15. Naftifine concentration continued to be detected in plasma in all 30 subjects at Day 28, when the geometric mean (CV%) was 0.5 ng/mL (50.9%).

Table 11: Summary of Single Dose (Day 1) Naftifine PK Parameters

Statistics	AUC ₀₋₂₄ (ng*hr/mL)	C _{max,SD} (ng/mL)	T _{max,SD} (hr)
N	32	32	32
Mean	15.520	1.220	18.9
SD	13.9159	1.0834	5.59
CV%	118.099	92.006	
Geometric Mean	10.459	0.891	
Min	1.43	0.20	8
Median	9.891	0.739	20.0
Max	47.61	4.35	24
90% C.I.(1)	(11.349, 19.691)	(0.896, 1.545)	(17.2, 20.5)
90% C.I.(2)	(7.904, 13.839)	(0.705, 1.127)	

(1) 90% CIs were based on the arithmetic mean.

(2) 90% CIs were based on the geometric mean.

Data Source: [Table 14.2.1.1](#)

Table 12: Summary of Steady State (Day 14) Naftifine PK Parameters

Statistics	AUC _{0-τ} (ng*hr/mL)	C _{max, Day 14} (ng/mL)	T _{max, Day 14} (hr)	R _{A (AUC)} (ng*hr/mL)
N	30	30	30	30
Mean	80.410	4.363	8.6	10.0444
SD	43.6681	2.5160	8.17	12.10032
CV%	58.878	63.865		117.2014
Geometric Mean	70.116	3.724		6.3347
Min	16.75	0.88	0	0.869
Median	67.415	3.503	8.0	5.8930
Max	201.60	10.28	24	57.894
90% C.I.(1)	(66.864, 93.957)	(3.582, 5.143)	(6.1, 11.2)	(6.2907, 13.7981)
90% C.I.(2)	(59.200, 83.046)	(3.106, 4.465)		(4.7475, 8.4525)

(1) 90% CIs were based on the arithmetic mean.

(2) 90% CIs were based on the geometric mean.

Data Source: [Table 14.2.1.2](#)

Figure 3: Spaghetti plot of individual naftifine plasma concentrations by time on Day 14 (source: figure 14.2.5.10)

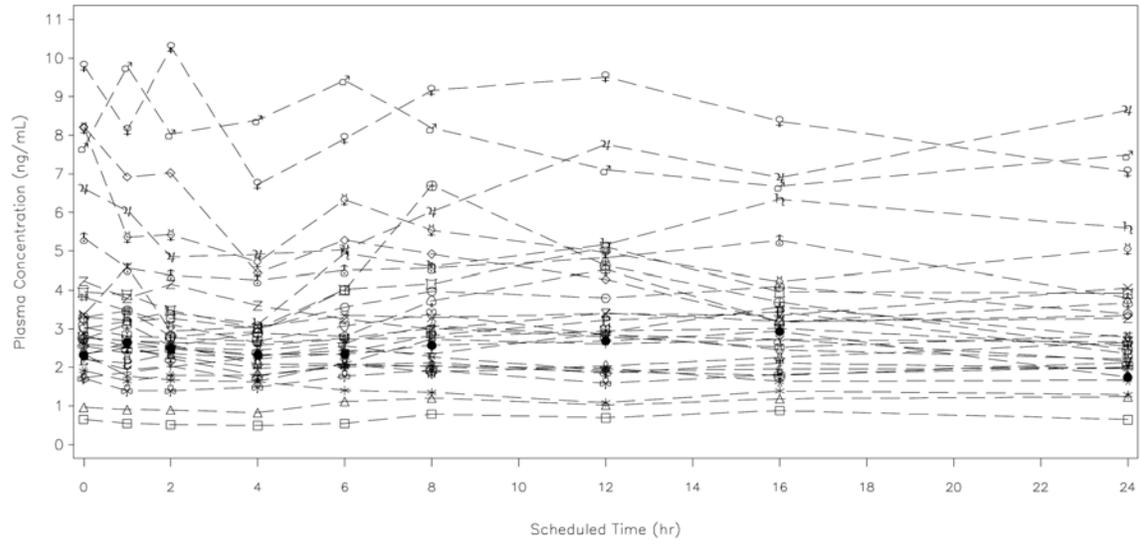


Figure 4: Mean plasma concentrations of naftifine by time on Day 14

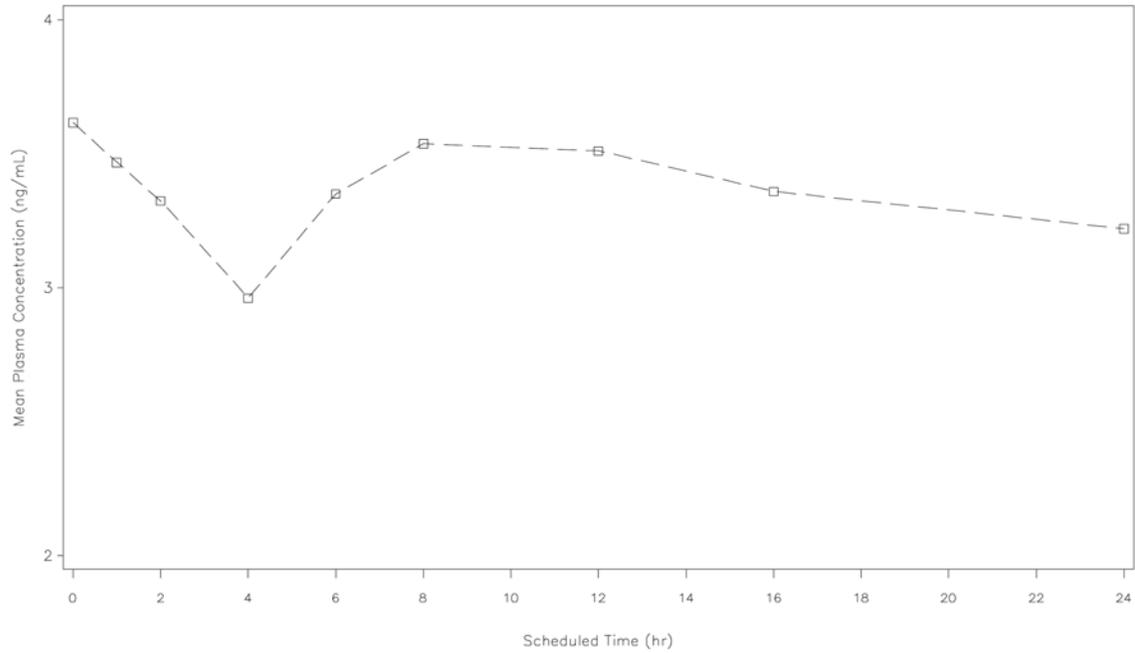


Figure 5: Mean plasma concentrations of naltifine by time

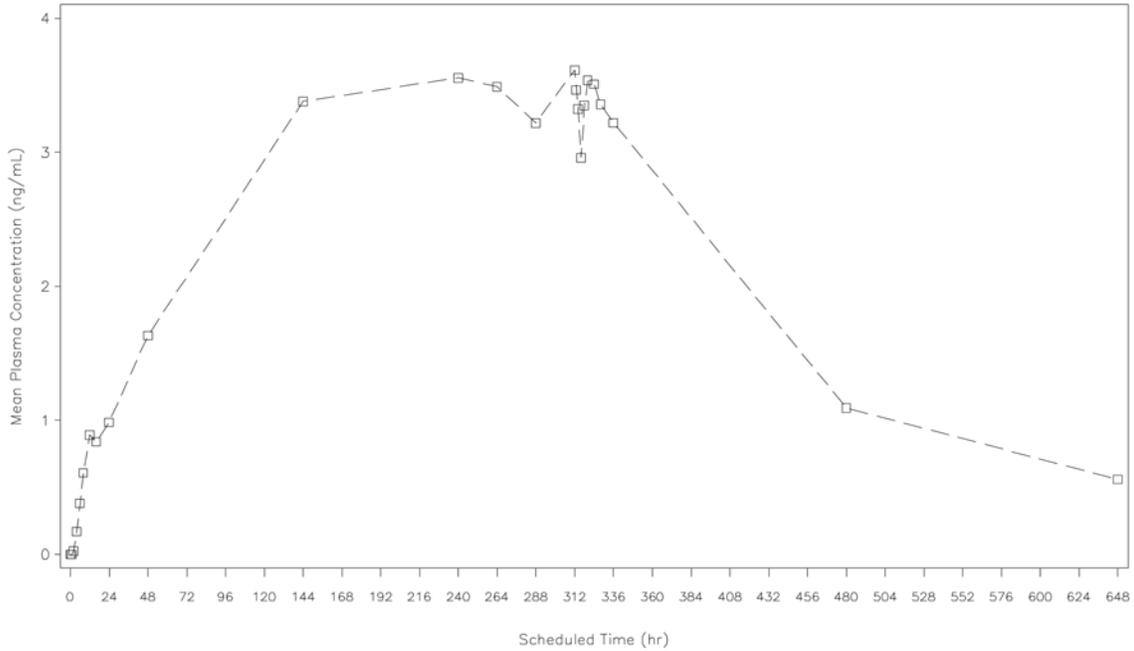


Table 13: Summary of maximal C_{trough} (i.e., highest observed trough value in each subject) naltifine PK parameters

Statistics	$T_{trough, max}$ (hr)	$C_{trough, max}$ (ng/mL)
N	32	32
Mean	228.8	4.687
SD	79.24	3.0319
CV%		70.234
Geometric Mean		3.866
Min	24	1.06
Median	240.0	3.542
Max	312	12.54
90% C.I.(1)	(205.0, 252.5)	(3.778, 5.596)
90% C.I.(2)		(3.198, 4.674)

(1) 90% CIs were based on the arithmetic mean.

(2) 90% CIs were based on the geometric mean.

Data Source: [Table 14.2.1.2](#)

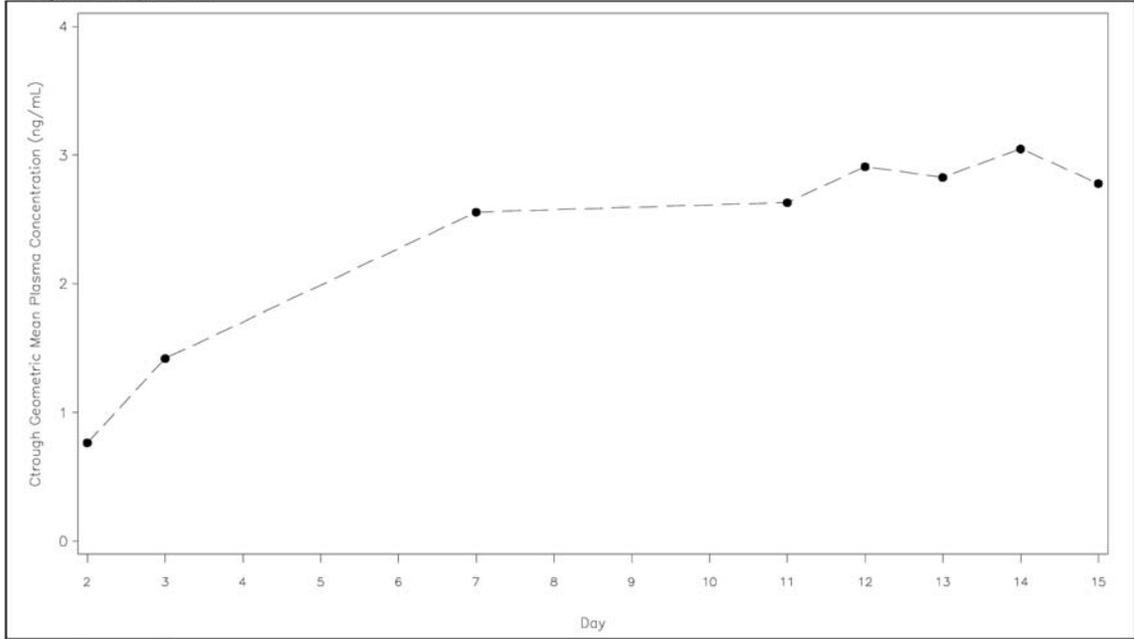
Table 14: Summary of C_{trough} plasma concentrations of naltifine over time

Statistics	Day 2 (N=32)	Day 3 (N=32)	Day 7 (N=32)	Day 11 (N=32)	Day 12 (N=32)	Day 13 (N=32)	Day 14 (N=32)	Day 15 (N=32)
N	32	32	32	31	29	31	30	30
Mean	986.038	1633.771	3380.708	3556.637	3489.452	3219.925	3616.150	3220.215
SD	833.9907	980.3398	2586.9348	2839.1135	2053.3037	1669.6658	2272.9843	1881.7842
CV%	79.000	56.419	92.001	97.521	73.089	57.228	65.723	60.088
Geo. Mean	766.630	1421.994	2556.700	2630.437	2910.367	2826.771	3048.770	2779.148
SD of Logs	2.0065	1.6916	2.1883	2.2649	1.9236	1.7028	1.8207	1.7423
Min	195.44	443.23	442.28	444.15	454.00	831.98	653.10	648.39
Median	686.690	1456.070	2564.880	2388.090	2936.900	2834.020	2803.805	2649.335
Max	4346.05	5517.79	9896.91	12535.96	8060.07	7828.62	9792.23	8647.59
90% C.I.(1)	(622.210, 944.570)	(1214.698, 1664.666)	(2021.821, 3233.081)	(2050.195, 3374.899)	(2366.982, 3578.497)	(2403.393, 3324.730)	(2531.616, 3671.568)	(2339.429, 3301.516)

(1) 90% CIs were based on the geometric mean.

Data Source: [Table 14.2.1.3](#)

Figure 6: C_{trough} geometric mean plasma concentrations of naftifine by time (Days 2-15)



Data Source: [Figure 14.2.5.9](#)

Urine PK:

Mean A_{e0-24} increased from 0.3 µg (range 0.00, 8.24 µg) on Day 1 to 0.6 µg (range 0.05, 4.64 µg) on Day 14. Correspondingly, the mean for fraction of the dose eliminated in urine over 24 hours (Fe%) increased during the treatment period from 0.0004% at Day 1 to 0.0007% at Day 14. Renal clearance (CL_r) decreased during the study period, mean results were 29.2 mL/h on Day 1 and 6.7 mL/h on Day 14.

Table 15: Urine naftifine PK parameters from Day 1 (source: corrected table 14.2.2.1)

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SUBJECT / STATISTICS	A _{e0-24} (µg)	Fe% ₀₋₂₄ (%)	CL _r (L/h)	CL _r (mL/min)
N	32	32	32	32
MEAN	0.349	0.000433	0.0292	0.4874
SD	1.4466	0.0018085	0.12626	2.10426
CV%	223.284	221.605460	185.5307	185.5307
GEO MEAN	0.126	0.000154	0.0106	0.1770
MIN	0.00	0.00000	0.000	0.000
MEDIAN	0.045	0.000055	0.0052	0.0873
MAX	8.24	0.01030	0.719	11.980
90% C.I. [1]	(-0.084, 0.783)	(-0.000109, 0.000975)	(-0.0086, 0.0671)	(-0.1433, 1.1181)
90% C.I. [2]	(0.075, 0.211)	(0.000092, 0.000257)	(0.0066, 0.0170)	(0.1104, 0.2839)

Table 16: Urine naftifine PK parameters from Day 14 (source: corrected table 14.2.2.2)

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SUBJECT / STATISTICS	Ae ₀₋₂₄ (µg)	Fe% ₀₋₂₄ (%)	CLr (L/h)	CLr (mL/min)
N	30	30	30	30
MEAN	0.568	0.000713	0.0067	0.1114
SD	0.8614	0.0010752	0.00990	0.16495
CV%	128.467	129.599376	81.5898	81.5898
GEO MEAN	0.325	0.000408	0.0046	0.0773
MIN	0.05	0.00007	0.001	0.022
MEDIAN	0.285	0.000373	0.0039	0.0657
MAX	4.64	0.00580	0.056	0.935
90% C.I. [1]	(0.301, 0.836)	(0.000380, 0.001047)	(0.0036, 0.0098)	(0.0602, 0.1626)
90% C.I. [2]	(0.240, 0.442)	(0.000300, 0.000555)	(0.0037, 0.0058)	(0.0620, 0.0965)

Naftifine excretion in urine was generally greatest over the first 6 hours of the 24-hour collection period on Day 1. On Day 14 excretion were relatively more even over the 24 hour dosing interval when the duration of urine collection is taken into account (Table 17). The results were highly variable and any conclusions should be drawn with caution.

Table 17: Summary of naftifine amount (ng) excreted in urine

Statistics	Pre-Dose (N=32)	0-6 Hours (N=32)	6-12 Hours (N=32)	12-24 Hours (N=32)	Total (N=32)
Day 1					
N	32	32	32	32	32
Mean	0.1	287.3	7.8	54.2	349.3
SD	0.59	1452.26	22.84	103.26	1446.63
CV%		411.4	83.6	121.0	223.4
Geometric Mean	3.3	149.4	39.9	71.3	125.7
Min	0	0	0	0	0
Median	0.0	0.0	0.0	3.8	45.4
Max	3	8237	107	539	8237
90% C.I.(1)		(52.1, 428.4)	(19.9, 79.9)	(47.0, 108.1)	(74.9, 210.9)
Day 14					
N		30	30	30	30
Mean		249.2	62.2	256.9	568.4
SD		689.41	78.97	238.68	861.44
CV%		225.7	99.9	114.8	128.5
Geometric Mean		95.9	57.0	173.7	325.4
Min		0	0	26	55
Median		59.6	35.1	145.7	284.5
Max		3758	376	862	4639
90% C.I.(1)		(60.5, 151.8)	(42.3, 76.8)	(130.7, 230.9)	(239.5, 442.0)

(1) 90% CIs were calculated based on the geometric mean.

Data Source: Table 14.2.3.5

The sponsor reported that there was one subject (Subject 54032) who had a much higher urine PK result at the 0–6 Hour (Day 1) collection time point (6.22 ng/mL) than all other subjects. The site confirmed that there was no cross-contamination between the administration and urinary sampling. The collection procedures and testing were all performed per protocol and no deviations have been noted. There is no medical history that would indicate any sort of contamination, and all other data collected did not suggest abnormalities that may have contributed to the abnormal results. The PK plasma values of Subject 54032 were in the mean or lower range on the study population. Therefore, the systemic exposure of this subject is not higher despite the high values of naftifine found in urine for the 0–6 hour time point.

Sponsor's PK conclusions:

Exposure to naftifine increased over the 2-week treatment period; geometric mean AUC₀₋₂₄ was 10.5 ng*hr/mL (90% CI 7.90, 13.84) on Day 1, and AUC_{0-τ} was 70 ng*hr/mL (90% CI 59.20, 83.05) on Day 14. Maximum concentration also increased over the

treatment period; geometric mean C_{\max} was 0.9 ng/mL (90% CI 0.705, 1.13) on Day 1; C_{\max} on Day 14 was 3.7 ng/mL (90% CI 3.12, 4.47). Geometric mean of the accumulation index ($RA_{(AUC)}$) was 6.33 (CI 4.747, 8.453). Median T_{\max} was 20.0 hours (range: 8, 20 hours) after a single application on Day 1 and 8.0 hours (range: 0, 24 hours) on Day 14. Trough concentrations generally increased through the study period; geometric mean $C_{\text{trough,max}}$ was 3.9 ng/mL (90% CI 3.20, 4.67) on Day 14. Maximum median $T_{\text{trough,max}}$ occurred at 240.0 hours (10 days) (range: 24, 312 hours).

Urine PK results showed one subject, Subject 54024 having traces of naftifine in his pre-dose sample of 0.07 ng/mL, and another subject, Subject 54032 had a much higher urine PK result at the 0–6 Hour collection time point (6.22 ng/mL) than all other subjects. Mean Ae_{0-24} increased from 0.3 μg (range 0.00, 8.24 μg) on Day 1 to 0.6 μg (range 0.05, 4.64 μg) on Day 14.

Reviewer's comments: *Due to a calculation error, the sponsor initially concluded that "Mean Fe% also increased during the treatment period from 8.66% at Day 1 to 14.26% at Day 14. Mean CL_r decreased during the study period from 29 L/hr (487 mL/min) on Day 1 and 7 L/hr (111 mL/min) on Day 14." Following a clarification request from this reviewer, the sponsor provided corrections as noted in tables 15 and 16 above. The results showed that the Fe% over a 24 hour interval was $\leq 0.01\%$. Renal clearance (CL_r) decreased during the study period, mean results were 29.2 mL/h on Day 1 and 6.7 mL/h on Day 14.*

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

/s/

DOANH C TRAN
05/03/2013

EDWARD D BASHAW
05/03/2013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 204286 Applicant: Merz Pharmaceuticals Stamp Date: 8/31/2012

Drug Name: Naftin (naftifine hydrochloride) gel 2% NDA/BLA Type: New original NDA

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	The to-be-marketed formulation was used in all clinical trials except for the thorough QT trial, which used an oral capsule formulation.
2	Has the applicant provided metabolism and drug-drug interaction information?		x		
Criteria for Assessing Quality of an NDA					
Data					
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g. CDISC)?	x			PK data set for max use PK trial MRZ 90200/1010/1 was submitted.
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
Studies and Analyses					
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?		x		The strength and dosing regimen is the same as that for approved naftifine cream, 2%
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?			x	
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?			x	
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Is there adequate information on the pharmacokinetics	x			

	and exposure-response in the clinical pharmacology section of the label?				
General					
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?	x			
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	x			
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	x			
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
17	Was the translation from another language important or needed for publication?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? __Yes__

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

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

None.

 Reviewing Pharmacologist

 Date

 Team Leader/Supervisor

 Date

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission				
Information		Information		
NDA Number	204286	Brand Name	Naftin Gel, 2%	
OCP Division	Division of Clinical Pharmacology 3	Generic Name	Naftifine Hydrochloride	
Medical Division	Division of Dermatology and Dental Product	Drug Class	Antifungal	
OCP Primary Reviewer	Doanh Tran, R.Ph., Ph.D	Indication(s)	Treatment of Tinea Pedis in patients ^(b) ₍₄₎ years of age and older	
OCP Secondary Reviewer	Capt. E. Dennis Bashaw, Pharm. D.	Dosage Form	Gel, 2%	
		Dosing Regimen	Apply a thin layer once daily to the affected areas plus an approximately 1/2 inch margin of healthy surrounding skin for 2 weeks.	
Date of Submission	8/31/2012	Route of Administration	Topical	
Estimated Due Date of OCP Review	4/30/2013	Sponsor	Merz Pharmaceuticals	
PDUFA Due Date	6/30/2013	Priority Classification	Standard	
Division Due Date	4/30/2013			
Clin. Pharm. and Biopharm. Information				
	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:	x	1		Thorough QT study MRZ 90200/1018/1
multiple dose:				
<i>Patients-</i>				
single dose:				
multiple dose:	x	1		Max use PK trial MRZ 90200/1010/1
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				

renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan	x			
Literature References				
Total Number of Studies		2		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable?	x	Reasons if the application <u>is not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

Filing Memorandum

Clinical Pharmacology Review

NDA: 204286
Compound: Naftifine hydrochloride (NAFT-600) gel, 2%
Sponsor: Merz Pharmaceuticals

Date: 9/21/2012
Reviewer: Doanh Tran

Background: Naftifine hydrochloride is a synthetic allylamine derivative topical antifungal. It is currently available as 1% gel formulations for topical treatment of tinea pedis, tinea cruris and tinea corporis. The sponsor is developing a new formulation, 2% gel, for the treatment of tinea pedis only in patients ^{(b)(4)} years of age and older. The proposed dosing regimen is once daily for 2 weeks. The advantage of the new higher strength formulation is that the duration of treatment is reduced from 4 weeks to 2 weeks and dosing interval from twice daily to once daily. The proposed dosing regimen for naftifine gel, 2% is the same as that of recently approved naftifine cream, 2% (naftifine cream 2% is only approved for use in adults).

This supplemental NDA (sNDA) includes 5 Phase 1 clinical trials, including a maximal use PK trial (MRZ 90200/1010/1) and a thorough QT trial (MRZ 90200/1018/1). It also includes 2 Phase 3 safety and efficacy trials.

Bioavailability: The sponsor submitted results of a maximal use PK trial MRZ 90200/1010/1. All 32 enrolled subjects had tinea pedis on both feet and the majority of subjects (97%) had both interdigital and moccasin-type infections. This study administered 4 grams NAFT-600 gel to both feet once daily for 2 weeks. Exposure to naftifine increased over the 2-week treatment period; geometric mean AUC_{0-24} was 10.5 ng*hr/mL (90% CI 7.90, 13.84) on Day 1, and $AUC_{0-\tau}$ was 70 ng*hr/mL (90% CI 59.20, 83.05) on Day 14. Maximum concentration also increased over the treatment period; geometric mean C_{maxSD} was 0.9 ng/mL (90% CI 0.705, 1.13) on Day 1; C_{max} on Day 14 was 3.7 ng/mL (90% CI 3.12, 4.47). Geometric mean of the accumulation index ($R_{A(AUC)}$) was 6.33 (90% CI 4.747, 8.453). Median T_{max} was 20.0 hours (range: 8, 20 hours) after a single application on Day 1 and 8.0 hours (range: 0, 24 hours) on Day 14. Trough concentrations generally increased through the study period and approaches steady state after approximately 11 days. The mean (\pm SD) C_{trough} was 3.2 ± 1.9 ng/mL on day 15. Naftifine concentration continued to be detected in plasma in all 32 subjects at Day 28, when the geometric mean (CV%) was 0.5 ng/mL (50.9%). Urine PK results showed mean fraction of dose excreted over 24 hours increased during the treatment period from 8.66% at Day 1 to 14.26% at Day 14.

Single dose PK information for naftifine 600 mg oral capsule is also available.

Pediatrics: The sponsor did not provide any PK data for NAFT-600 gel 2% in pediatrics. The sponsor is seeking a deferral of pediatric studies in age range of 12-17 years to be conducted post approval. (b) (4)

The sponsor is seeking a waiver of pediatric studies in pediatrics less than 12 years of age.

QT: The sponsor submitted results of a thorough QT trial MRZ 90200/1018/1. The results from this trial were previously submitted to NDA 19599/s011 and have been reviewed by the Interdisciplinary Review Team for QT studies (IRT-QT). According to the IRT-QT review, “no significant QTc prolongation effect of naftifine HCl (600 mg) was detected in this QT study.”

Clinical vs. to-be-marketed formulation: The sponsor stated that the to-be-marketed formulation was used in the 6 clinical trials submitted to this NDA that applied naftifine gel 2%. The remaining trial, a thorough QT trial, administered an oral capsule formulation.

Method validation: Analyses of PK samples from trials MRZ 90200/1010/1 and MRZ 90200/1018/1 were conducted by (b) (4), respectively, using different bioanalytical methods. Bioanalytical reports and validation reports are available for review.

Recommendation: The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Human Pharmacokinetics and Bioavailability section for NDA 204286 is fileable.

Comments for sponsor: None

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

/s/

DOANH C TRAN
10/15/2012

EDWARD D BASHAW
10/22/2012