OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 19599/S012 and 204286/S001	Submission Date(s): 12/20/2013, 1/22/2014, 1/30/2014, 1/31/2014
Brand Name	NDA 19599: Naftin cream, 2% NDA 204286: 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, LLC
Submission Type	Efficacy supplement
Formulation; Strength(s)	NDA 19599: Cream, 2% NDA 204286: Gel, 2%
Indication	NDA 19599: Treatment of tinea pedis, tinea cruris, and tinea corporis NDA 204286: Treatment of interdigital tinea pedis

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1 Executive Summary

Naftin Cream 2% (NAFT-500) is approved 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 (NDA 19599, approved 1/13/2012). There were two Pediatric Research Equity Act (PREA) post-marketing requirements included in the approval letter. The first one was:

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

Naftin Gel 2% (NAFT-600) is approved for the treatment of interdigital tinea pedis caused by the organisms Trichophyton rubrum, Trichophyton mentagrophytes, and Epidermophyton floccosum in patients 18 years of age and older (NDA 204286, approved 6/27/2013). There was one PREA post-marketing requirements included in the approval letter and it reads:

> 2050-1: 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.

The sponsor has conducted a safety/pharmacokinetic trial in pediatric subjects 12 – 17 years of age as required under the Pediatric Research Equity Act (PREA). In the current submission, the sponsor submitted the results of this trial and requested approval for use in patients 12 years of age and older.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds NDA 019599/S012 and NDA 204286/S001 acceptable pending agreement on recommended labeling changes.

These efficacy supplements also satisfy the PREA requirements 1857-1 and 2050-1 as outlined in approval letters for NDA 19599 dated 1/13/2012 and NDA 204286 dated 6/27/2013, respectively.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Bioavailability:

The sponsor submitted results from trial MUS90200/1023/0, which evaluated the systemic exposure to naftifine following multiple dose application of NAFT-500 in pediatric subjects (13 – 17 years) with tinea cruris and tinea pedis and NAFT-600 in pediatric subjects (12 – 17 years) with tinea pedis. For NAFT-600, the results showed that systemic naftifine exposures in pediatrics are similar to those in adults. For NAFT-500, systemic naftifine exposures in pediatrics are higher than adults in this trial but are similar to those observed in a previous trial in adults. The reason for the discrepancy in NAFT-500 results is not clear but may be due to the small sample size for adults in the current trial (n=6). The combined data across all trials suggest that there are no significant differences in systemic exposure between adults and pediatrics 12 – 17 years of age. A brief description and summary results from the trial are shown below.

NAFT-500:

Twenty two (22) pediatric subjects (mean 14.8 years of age, range 13 – 17 years) and 6 adult subjects with tinea cruris and tinea pedis applied approximately 8 grams NAFT-500 to both feet and groin once daily for 2 weeks. PK assessments were conducted on Day 1 and Day 14. The geometric mean (CV%) Cmax and AUC are shown in Table 1. Systemic exposure increased from Day 1 to Day 14. Systemic naftifine exposures in pediatrics are higher than adults in this trial but are similar to those observed in a previous trial in adults (trial MRZ 90200/FI/1002).

Table 1: Plasma naftifine PK parameters for NAFT-500

Parameters	Adult (n=6, mean dose 7.5 g/day)	Pediatric (n=22, mean dose 8.2 g/day)	Adult from Trial MRZ 90200/FI/1002 (n=21, mean dose 6.4 g/day)
Day 1			
AUC_{0-24} (ng*h/mL)	68.6 (95.4%)	138.3 (50.2%)	117 (41.2%)
Cmax (ng/mL)	3.98 (83.0%)	9.21 (48.4%)	7 (55.6%)
Median (range) fe (%)	0.00143 (0.0003 – 0.0159)	0.00300 (0.0005-0.0648) (n=12)	0.0016
Day 14			
AUC_{0-24} (ng*h/mL)	124.6 (49.9%)	192.5 (74.9%)	204 (28.5%)
Cmax (ng/mL)	6.83 (51.3)	12.7 (67.2%)	11 (29.3%)
Median (range) fe (%)	0.00251 (0.0006-0.0045)	0.00328 (0-0.0407) (n=20)	0.0020

NAFT-600:

Twenty two (22) pediatric subjects (mean 14.7 years of age, range 12 – 17 years) and 6 (5 provided PK data) adult subjects with tinea pedis applied approximately 4 grams NAFT-500 to both feet once daily for 2 weeks. PK assessments were conducted on Day 1 and Day 14. The geometric mean (CV%) Cmax and AUC are shown in Table 2. Systemic

exposure increased from Day 1 to Day 14. Systemic naftifine exposures in pediatrics are similar to those in adults.

Table 2: Naftifine PK parameters for NAFT-600

Parameters	Adult (n=5, mean dose 4.0 g/day)	Pediatric (n=22, mean dose 4.1 g/day)	Adult from Trial MRZ 90200/1010/1 (n=30, mean dose 3.9 g/day)
Day 1			
AUC_{0-24} (ng*h/mL)	17.2 (88.1%)	15.9 (211.6%)	10.5 (118%)
Cmax (ng/mL)	1.74 (69.2%)	1.40 (153.8%)	0.9 (92%)
Median (range) fe (%)	0.00014 (0-0.0002)	0.00031 (0-0.0016) (n=21)	≤0.01
Day 14			
AUC_{0-24} (ng*h/mL)	72.8 (71.1%)	60.0 (131.1%)	70 (59%)
Cmax (ng/mL)	3.54 (73.3%)	3.81 (153.9%)	3.7 (64%)
Median (range) fe (%)	0.00072 (0.0006-0.0035) (n=4)	0.00091 (0-0.0031) (n=21)	≤0.01

Method validation:
Assay validation and incurred sample reanalysis are acceptable for both urine and plasma naftifine assays. Storage stability was within the documented stability range (203 days for plasma and 199 days for urine).

Clinical vs. to-be-marketed formulation:
The sponsor confirmed in a letter dated 1/21/2014 (received on 1/22/2014) that the products used in trial MUS90200/1023/0, namely NAFT-500, batch numbers EBFR and ECBU and NAFT-600, batch number CFS-C, are the same (i.e., same formulation, manufacturing process and manufacturing site) as the approved marketed drug products for NDA 019599 and NDA 204286, respectively.

2 Question-Based Review

Not applicable.

3 Detailed Labeling Recommendations

The following changes are recommended for sections8.41 and 12.3 of the label for Naftin Cream, 2% and Naftin Gel, 2%. Deletion are noted as ~~strikethrough~~ and additions are noted as double underlines.

Naftin Cream, 2%:

8.4 Pediatric Use

(b) (4)

12.3 Pharmacokinetics

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

The pharmacokinetics of NAFTIN Cream, 2% was evaluated following once-daily topical application for 2 weeks to twenty one adult subjects, both males and females, with both tinea pedis and tinea cruris. The median total amount of cream applied was 6.4 g (range 5.3-7.5 g) per day. The results showed that the systemic exposure (i.e. maximum concentration (Cmax) and area under the curve (AUC)) to naftifine increased over the 2 week treatment period in all the 21 subjects. Geometric Mean (CV%) AUC0-24 was 117 (41.2) ng*hr/mL on Day 1, and 204 (28.5) ng*hr/mL on Day 14. Geometric Mean (CV %) Cmax was 7 ng/mL (55.6) on Day 1 and 11 ng/mL (29.3) on day 14. Median Tmax was 8.0 hours on Day 1 (range: 4 to 24) and 6.0 hours on Day 14 (range: 0 to 16). Accumulation after 14 days of topical application was less than two fold. Trough concentrations generally increased throughout the 14 day study period. Naftifine continued to be detected in plasma in 13/21 (62%) subjects on day 28, the mean (SD) plasma concentrations were 1.6 ± 0.5 ng/mL (range below limit of quantitation (BLQ) to 3 ng/mL). In the same pharmacokinetic (b) (4) trial conducted in patients with tinea pedis and tinea cruris, median fraction of the dose excreted in urine during the treatment period was 0.0016% on Day 1 versus 0.0020% on Day 14.

(b) (4)

(b) (4)

In a second trial, the pharmacokinetics of NAFTIN Cream, 2% was evaluated in 20 pediatric subjects 13 – 17 years of age with both tinea pedis and tinea cruris. Subjects were treated with a median dose of 8.1 g (range 6.6-10.1 g) applied to the affected areas once daily for 14 days. The results showed that the systemic exposure increased over the treatment period. Geometric Mean (CV%) AUC0-24 was 138 (50.2) ng*hr/mL on Day 1, and 192 (74.9) ng*hr/mL on Day 14. Geometric Mean (CV %) Cmax was 9.21 ng/mL (48.4) on Day 1 and 12.7 ng/mL (67.2) on day 14. Median fraction of the dose excreted in urine during the treatment period was 0.0030% on Day 1 and 0.0033% on Day 14.

Naftin Gel, 2%:

8.4 Pediatric Use

(b) (4)

12.3 Pharmacokinetics

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

Pharmacokinetic analysis of plasma samples from 32 ~~tinea pedis~~ subjects with tinea pedis treated with a mean dose ~~of~~ of 3.9 grams NAFTIN(naftifine hydrochloride) Gel, 2% applied once daily to both feet for 14 days showed increased exposure over the treatment period, with a geometric mean (CV%) AUC0-24 (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 AUC0-24 of 70 (59) ng·hr/mL on Day 14. The accumulation ratio based on AUC was approximately 6. Maximum concentration (Cmax) also increased over the treatment

period; geometric mean (CV%) Cmax after a single dose was 0.9 (92) ng/mL on Day 1; Cmax on Day 14 was 3.7 (64) ng/mL. Median Tmax 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 increased during the trial period and reached steady state after 11 days. In the same pharmacokinetic trial the fraction of dose excreted in urine was less than or equal to 0.01% of the applied dose.

(b) (4)

In a second trial, the pharmacokinetics of NAFTIN Gel, 2% was evaluated in 22 pediatric subjects 12-17 years of age with tinea pedis. Subjects were treated with a mean dose of 4.1 grams NAFTIN (naftifine hydrochloride) Gel, 2% applied to the affected area once daily for 14 days. The results showed that the systemic exposure increased over the treatment period. Geometric mean (CV%) AUC0-24 was 15.9 (212) ng·hr/mL on Day 1 and 60.0 (131) ng·hr/mL on Day 14. Geometric mean (CV%) Cmax after a single dose was 1.40 (154) ng/mL on Day 1 and 3.81 (154) ng/mL on Day 14. The fraction of dose excreted in urine was less than or equal to 0.003% of the applied dose.

4 Appendix

4.1 Individual Study Reviews

Trial MUS90200/1023/0:

Title: An Open-Label, Multi-Center, Multiple-Application Pharmacokinetic Study of NAFT-500 in Pediatric Subjects with Tinea Cruris and Tinea Pedis and NAFT-600 in Pediatric Subjects with Tinea Pedis.

Investigators, study sites: This was a multicenter study with four investigators in the Dominican Republic, Honduras, and the United States.

Objectives:

Primary Objectives:

- To quantify the pharmacokinetics of NAFT-500 in pediatric subjects aged 12 to 17 years, 11 months with tinea cruris and tinea pedis under maximal clinical use conditions for 2 weeks of once daily application in treatment group one. Maximal use condition was defined as having both feet and bikini area affected for NAFT-500.
- To quantify the pharmacokinetics of NAFT-600 in pediatric subjects aged 12 to 17 years, 11 months with tinea pedis under maximal clinical use conditions for 2 weeks of once daily application in treatment group two. Maximal use condition was defined as having both feet affected for NAFT-600.

Secondary Objectives:

The secondary objectives were to evaluate subject efficacy, tolerability, and safety after 2 weeks of once daily applications of both products (NAFT-500 and NAFT-600).

Study design and methodology:

Tinea pedis and tinea cruris (NAFT-500)

This was an open-label, multi-center, multiple-application study to quantify the pharmacokinetic (PK) profile of once daily application of NAFT-500 Cream 2% for two weeks by determining the plasma and urine concentrations of naftifine in pediatric subjects with tinea cruris and tinea pedis. It was conducted under maximal clinical use conditions where a total of 8 grams of NAFT-500 were to be applied to the affected groin area and both feet (approximately 4 grams to the groin area and 2 grams to each foot) once a day for two weeks. Additionally, approximately four PK-evaluable adult subjects with the same condition were planned to serve as controls. The efficacy, tolerability, and safety of NAFT-500 were also assessed during the study.

Tinea pedis (NAFT-600)

This was an open-label, multi-center, multiple-application study designed to quantify the PK profile of once daily application of NAFT-600 Gel 2% for 2 weeks by determining the plasma and urine concentrations of naftifine in pediatric subjects with tinea pedis. It was conducted under maximal clinical use conditions where a total of 4 grams of NAFT-600 were to be applied to both feet (approximately 2 grams to each foot) once a day for

two weeks. Additionally, approximately four PK-evaluable adult subjects with the same condition were planned to serve as controls. The efficacy, tolerability, and safety of NAFT-600 were also assessed during the study.

Number of subjects planned: It was planned to enroll 56 subjects: 22 pediatric and 6 adult subjects per treatment group.

Diagnosis and main criteria for inclusion and exclusion:

Tinea pedis and tinea cruris (NAFT-500)
Male or non-pregnant female subjects aged 12 to 17 years, 11 months old or adults of any race with tinea pedis and tinea cruris infections confirmed by a positive potassium hydroxide (KOH) analysis from both feet and the bikini area. Both cases (feet and bikini area) were required to have been characterized by clinical evidence of a tinea pedis and tinea cruris infection.

Tinea pedis (NAFT-600)
Male or non-pregnant female subjects aged 12 to 17 years, 11 months old or adults of any race with tinea pedis infection confirmed by a positive KOH analysis from both feet. Both feet were required to have been characterized by clinical evidence of a tinea pedis infection.

Test product:
NAFT-500 (naftifine hydrochloride, Cream 2%)
NAFT-600 (naftifine hydrochloride, Gel 2%)

NAFT-500 or NAFT-600 was applied once daily in the morning between 6:00 am and 9:30 am for 14 days. All doses at study visits (Days 1, 2, 7, 12, 13, and 14) were applied while the subject was on-site, and all other doses were applied at home. Subjects were provided scales for measurement of study drug. The date and time of dose and site of study medication application(s) were captured in each subject's diary. To be considered compliant, NAFT-500 or NAFT-600 use was required to have been within ± 20% of expected use.

PK assessments:
For both NAFT-500 Cream 2% (tinea pedis and tinea cruris) and NAFT-600 Gel 2% (tinea pedis only), plasma and urine samples were analyzed for concentrations of naftifine using validated analytical methods. Subjects stayed at the study center during the first and the last dosing for collection of a 24-hour PK profile. All other visits were outpatient.

- 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, and 24 hours post-application. Pre-application (trough) samples were collected on Days 2 (corresponds to the Day 1, 24-hour sample), 7, 12, 13, and 14. Samples were also collected on Day 15 (corresponds to the Day 14 24-hour sample), Day 21 (1 week after the last application), and Day 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 to 6, 6 to 12, and 12 to 24 hours after on-site application.

For non-compartmental analysis of single dose data, plasma concentrations below the lower limit of quantification (LLOQ) before tmax were replaced by zero. All plasma concentrations below LLOQ after tmax were set to missing. For non-compartmental analysis of multiple dose data, plasma concentrations below LLOQ were set to missing. For non-compartmental analysis, urine concentrations of naftifine below LLOQ were set to zero.

Efficacy and safety assessments: Please refer to Clinical review for details.

Bioanalytical methods:
Naftifine in human EDTA K_3 plasma was measured using a high performance liquid chromatography (HPLC) with tandem mass spectrometry (MS/MS) detection following automated liquid-liquid extraction. The calibration range was 99.84 – 9984.00 pg/mL. Intra-day and inter-day accuracy and precision were within acceptable range of ≤15%. Long term stability of naftifine in plasma at -20 ºC was demonstrated for 203 days. A total of 108 samples (9.38% of total samples; 2-4 samples per subject) were reanalyzed for the incurred sample reproducibility test. The results showed that 99% (107 out of 108) met the criteria of reproducibility (i.e., difference within ±20% of average of original and repeat value).

Naftifine in urine was measured using a HPLC/MS/MS assay following automated liquid-liquid extraction. The calibration range was 49.80 – 9960.00 pg/mL. Intra-day and inter-day accuracy and precision were within acceptable range of ≤15%. Long term stability of naftifine in plasma at -20 ºC was demonstrated for 199 days. A total of 49 samples (12.69 % of total samples; 2-3 samples per subject) were reanalyzed for the incurred sample reproducibility test. The results showed that 92% (45 out of 49) met the criteria of reproducibility (i.e., difference within ±20% of average of original and repeat value).

Overall, assay validation and incurred sample reanalysis are acceptable for both urine and plasma naftifine assays. Storage stability was within the documented stability range.

Results:

<u>Disposition of subjects:</u>

NAFT-500:
A total of 28 subjects were enrolled and received NAFT-500 Cream 2% in this trial: 22 pediatric subjects and six adult subjects. The majority of subjects were male (77%) and White (91%) and all were of Hispanic ethnicity (100%). Mean (±SD) pediatric subject age was 15 ± 1.5 years (range 13 – 17 years, see Figure 1). All subjects completed the

trial. Twenty pediatric subjects (91%) and all six adult subjects were included in the pharmacokinetic analysis set (PKS). The actual amount of drug applied was close to the target dose of 8 grams (see Table 3).

Figure 1: Histogram of pediatric subjects age (NAFT-500, PK data set)

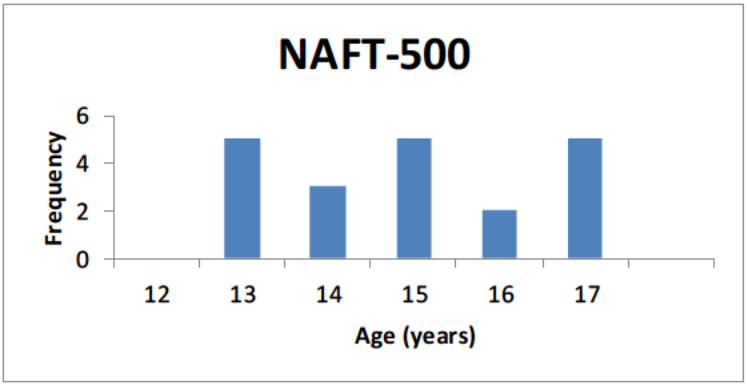

Table 3: Amount of drug applied (NAFT-500)

Compliance (g/day)	Pediatric (N=22)	Adult (N=6)	Total (N=28)
Mean (SD)	8.2 (0.6)	7.5 (0.6)	8.0 (0.7)
Median	8.12	7.41	8.1
Min, max	6.59, 10.14	6.82, 8.11	6.59, 10.14

NAFT-600:

A total of 28 subjects were enrolled and received NAFT-600 Gel 2% in this trial: 22 pediatric subjects and six adult subjects. The majority were male (82%), Black or African American (73%), and of Hispanic ethnicity (73%). Mean (±SD) pediatric subject age was 15 ± 1.7 years and ranged from 12 to 17 years (see Figure 2). All 22 pediatric subjects and five of the six adult subjects (83%) were included in the PKS. One adult subject (S1008) was excluded from the PKS as the result of protocol deviations with respect to compliance (25% at Visit 4). The actual amount of drug applied was close to the target dose of 4 grams (see Table 4).

Figure 2: Histogram of pediatric subjects age (NAFT-600, PK data set)

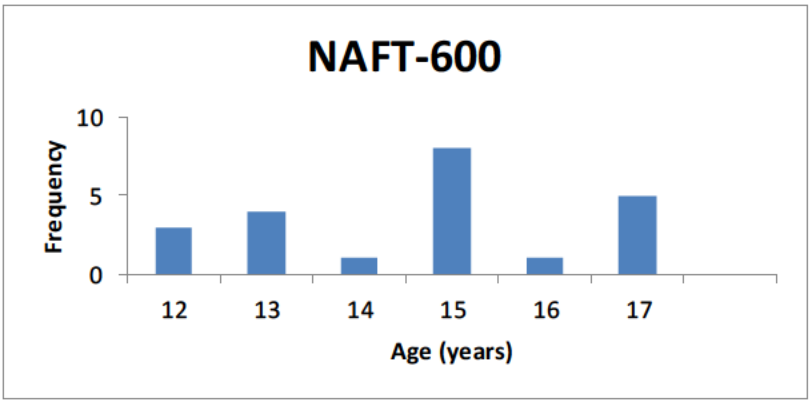

Table 4: Amount of drug applied (NAFT-600)

Compliance (g/day)	Pediatric (N=22)	Adult (N=6)	Total (N=28)
Mean (SD)	4.1 (0.2)	4.0 (0.6)	4.1 (0.3)
Median	4.06	4.05	4.05
Min, max	3.97, 4.58	2.95, 4.89	2.95, 4.89

Pharmacokinetic results:

NAFT-500:

Plasmas PK:
Exposure to naftifine increased over the 2-week treatment period with NAFT-500 Cream 2%: for pediatric subjects, geometric mean AUC0-24 (CV%) was 138262.2 pg•h/mL (50.2%) on Day 1 and AUCτ,ss was 192485.4 pg•h/mL (74.9%) on Day 14; for adult subjects, geometric mean AUC0-24 was 68634.2 pg•h/mL (95.4%) on Day 1 and AUCτ,ss was 124596.0 pg•h/mL (49.9%) on Day 14. Maximum concentration also increased over the treatment period: in pediatric subjects, geometric mean Cmax (CV%) was 9213.35 pg/mL (48.4%) on Day 1 and geometric mean Cmax was 12727.36 pg/mL (67.2%) on Day 14; in adult subjects, geometric mean Cmax was 3983.34 pg/mL (83.0%) on Day 1 and geometric mean Cmax was 6826.70 pg/mL (51.3%) on Day 14 (Tables 5 and 6). Figures 3 and 4 show the plot and whisker plots for Cmax and AUC, respectively.

In pediatric subjects, median tmax (range) was 7.0 hours (2-24 hours) after a single application on Day 1 and 6.0 hours (2-12 hours) on Day 14; in adults, median tmax was 12.0 hours (8-24 hours) after a single application on Day 1 and 7.0 hours (6-24 hours) on Day 14. Individual concentration time profiles for Day 1 are shown in Figures 5 and 6 for pediatrics and adults, respectively.

Urine PK:

For pediatric, the mean fraction of dose excreted in urine during the treatment period was 0.00859% on Day 1 and 0.00753% on Day 14 (see Table 7). The median (range) fraction of dose excreted during the treatment period was 0.00300% (0.0005 – 0.0648%) on Day 1 and 0.00328% (0 – 0.0407%) on Day 14.

For adult, the mean fraction of dose excreted in urine during the treatment period was 0.00455% on Day 1 and 0.00256% on Day 14 (see Table 7). The median fraction of dose excreted during the treatment period was 0.00143% (0.0003 – 0.0159%) on Day 1 and 0.00251% (0.0006 – 0.0045%) on Day 14.

Relative BA between pediatrics and adults:
After NAFT-500 Cream 2% application, plasma concentrations of naftifine from Day 1 (single dose) through Day 14 (multiple dose, steady state) in pediatric subjects were higher compared to those observed in adults (see Tables 5 and 6). However, the concentration in pediatric subjects was similar to those observed in a previous maximal use PK trial in adults (MRZ 90200/FI/1002). Adults in the current study had lower naftifine plasma concentrations than those observed in the pediatric subjects in the current study and in adult subjects in MRZ 90200/FI/1002. The reason for this discrepancy is not clear but may be due to the small sample size rather than true differences between the two populations as data from the NAFT-600 arm showed similar exposure between pediatrics and adults in both the current trial and a previous maximal use PK trial (see results for NAFT-600 discussed below).

Table 5: NAFT-500 plasma PK results – Day 1, single dose

Statistic	NAFT-500 Adult	NAFT-500 Pediatric
$AUC_{0\text{-}24}$ (pg•h/mL) geometric mean and geometric CV	68634.2; 95.4%	138262.2; 50.2%
C_{max} (pg/mL) geometric mean and geometric CV	3983.34; 83.0%	9213.35; 48.4%
t_{max} (h) median (minimum, maximum)	12.0 (8, 24)	7.0 (2, 24)

Table 6: NAFT-500 plasma PK results – Day 14 multiple dose

Statistic	NAFT-500 Adult	NAFT-500 Pediatric
$AUC_{\tau,ss}$ (pg•h/mL) geometric mean and geometric CV	124596.0; 49.9%	192485.4; 74.9%
$C_{max,ss}$ (pg/mL) geometric mean and geometric CV	6826.70; 51.3%	12727.36; 67.2%
$t_{max,ss}$ (h) median (minimum, maximum)	7.0 (6, 24)	6.0 (2, 12)
$T_{trough,max}$ (day) median (minimum, maximum)	13.5 (2, 15)	12.0 (2, 15)
$C_{trough,max}$ (pg/mL) geometric mean and geometric CV	6444.87; 56.8%	9274.22; 41.0%

Figure 3: Day 14 Cmax box and whisker plot

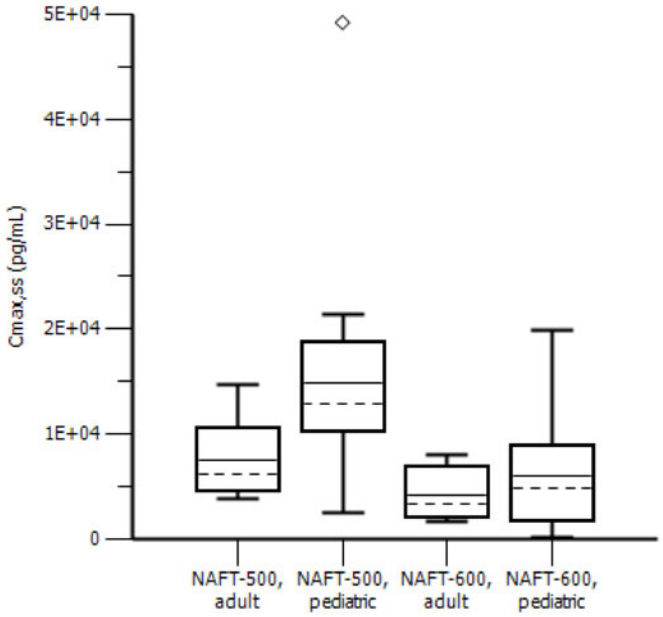

Figure 4: Day 14 AUC box and whisker plot

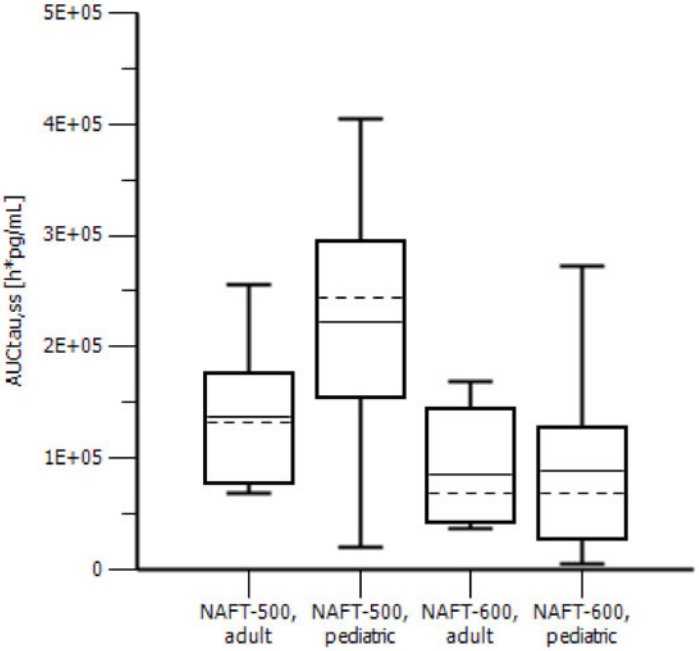

Figure 5: Individual plasma concentration time profiles (NAFT-500, pediatrics)

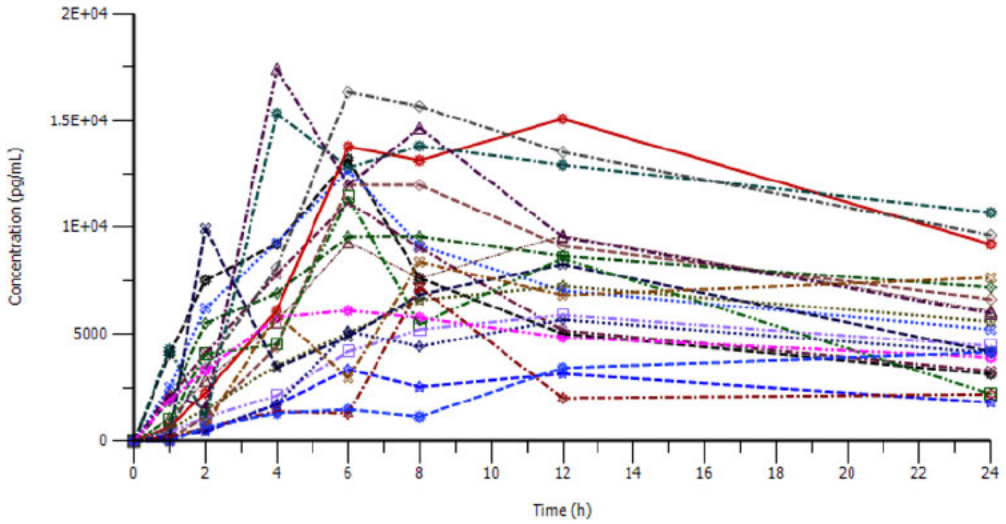

Figure 6: Individual plasma concentration time profiles (NAFT-500, adults)

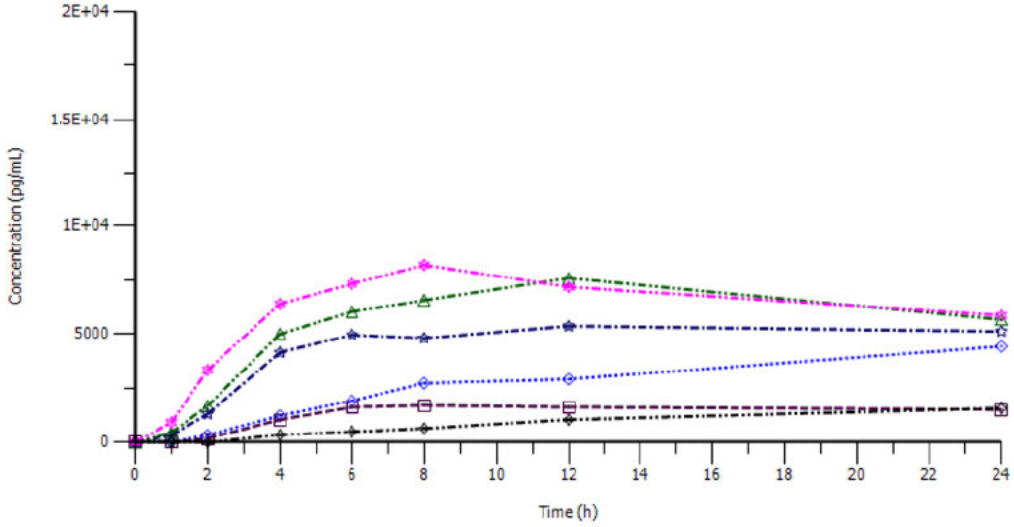

Table 7: NAFT-500 urine PK results

Statistic	NAFT-500 Adult	NAFT-500 Pediatric
Day 1		
Ae_{0-24} [ng] arithmetic mean and standard deviation	6466.1901 ± 8720.06116	12196.0750 ± 25501.83435
fe [%] arithmetic mean and standard deviation	0.00455 ± 0.006141	0.00859 ± 0.017959
CLr [mL/min] geometric mean and geometric CV	0.6707; 131.8%	0.5827; 190.1%
Day 14		
$Ae_{\tau,ss}$ [ng] arithmetic mean and standard deviation	3635.6234 ± 2422.48069	10688.5798 ± 16220.32493
fe [%] arithmetic mean and standard deviation	0.00256 ± 0.001706	0.00753 ± 0.011423
CLr [mL/min] geometric mean and geometric CV	0.3767; 78.0%	0.3760; 158.1%

Ae_{0-24} = amount of unchanged drug excreted into urine during the 24 hours after dosing, CLr = renal clearance, CV = coefficient of variation, fe (%) = fraction of orally administrated drug excreted into urine, PKS = pharmacokinetic analysis set

NAFT-600

Plasmas PK:
Exposure to naftifine increased over the 2-week treatment period with NAFT-600 Gel 2%: for pediatric subjects, geometric mean AUC0-24 (CV%) was 15890.1 pg•h/mL (211.6%) on Day 1 and AUCτ,ss was 60038.5 pg•h/mL (131.1%) on Day 14; for adult subjects, geometric mean AUC0-24 was 17213.9 pg•h/mL (88.1%) on Day 1 and AUCτ,ss was 72849.8 pg•h/mL (71.1%) on Day 14. Maximum plasma concentration also increased over the treatment period: in pediatric subjects, geometric mean Cmax (CV%) was 1397.77 pg/mL (153.8%) on Day 1 and geometric mean Cmax was 3813.38 pg/mL (153.9%) on Day 14; in adult subjects, geometric mean Cmax was 1741.02 pg/mL (69.2%) on Day 1 and geometric mean Cmax was 3538.84 pg/mL (73.3%) on Day 14 (Tables 8 and 9).

In pediatric subjects, median tmax (range) was 23.8 hours (1-24 hours) after a single application on Day 1 and 23.8 hours (4-24 hours) on Day 14; in adults, median tmax was 12.0 hours (8-24 hours) after a single application on Day 1 and 5.0 hours (4-6 hours) on Day 14. Individual concentration time profiles for Day 1 are shown in Figures 7 and 8 for pediatrics and adults, respectively.

Urine PK:
For pediatric, the mean fraction of dose excreted in urine during the treatment period was 0.00054% on Day 1 and 0.00116% on Day 14 (see Table 10). The median (range) fraction of dose excreted during the treatment period was 0.00031% (0 – 0.0016%) on Day 1 and 0.00091% (0 – 0.0031%) on Day 14.

For adult, the mean fraction of dose excreted in urine during the treatment period was 0.00011% on Day 1 and 0.00137%on Day 14 (see Table 10). The median fraction of dose

excreted during the treatment period was 0.00014% (0 – 0.0002%) on Day 1 and 0.00072% (0.0006–0.0035%) on Day 14.

Relative BA between pediatrics and adults:
After NAFT-600 Gel 2% application, plasma concentrations of naftifine from Day 1 (single dose) through Day 14 (multiple dose, steady state) in pediatric subjects were similar to those observed in the adult subjects in the current trial and in adult subjects in a previous maximal use PK trial in adults (MRZ 90200/1010/1).

Table 8: NAFT-600 plasma PK results – Day 1, single dose

Statistic	NAFT-600 Adult	NAFT-600 Pediatric
$AUC_{0\text{-}24}$ (pg•h/mL) geometric mean and geometric CV	17213.9; 88.1%	15890.1; 211.6%
C_{max} (pg/mL) geometric mean and geometric CV	1741.02; 69.2%	1397.77; 153.8%
t_{max} (h) median (minimum, maximum)	12.0 (8, 24)	23.8 (1, 24)

Table 9: NAFT-600 plasma PK results – Day 14 multiple dose

Statistic	NAFT-600 Adult	NAFT-600 Pediatric
$AUC_{\tau,ss}$ (pg•h/mL) geometric mean and geometric CV	72849.8; 71.1%	60038.5; 131.1%
$C_{max,ss}$ (pg/mL) geometric mean and geometric CV	3538.84; 73.3%	3813.38; 153.9%
$T_{max,ss}$ (h) median (minimum, maximum)	5.0 (4, 6)	23.8 (4, 24)
$T_{trough,max}$ (day) median (minimum, maximum)	7.0 (2, 13)	14.0 (2, 21)
$C_{trough,max}$ (pg/mL) geometric mean and geometric CV	3124.71; 101.8%	3485.03; 88.9%

Figure 7: Individual plasma concentration time profiles (NAFT-600, pediatrics)

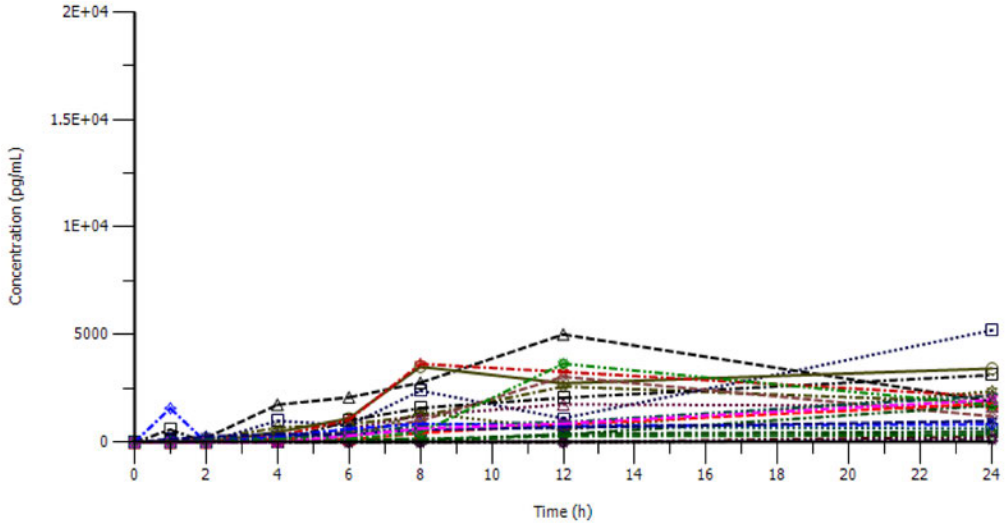

Figure 8: Individual plasma concentration time profiles (NAFT-600, adults)

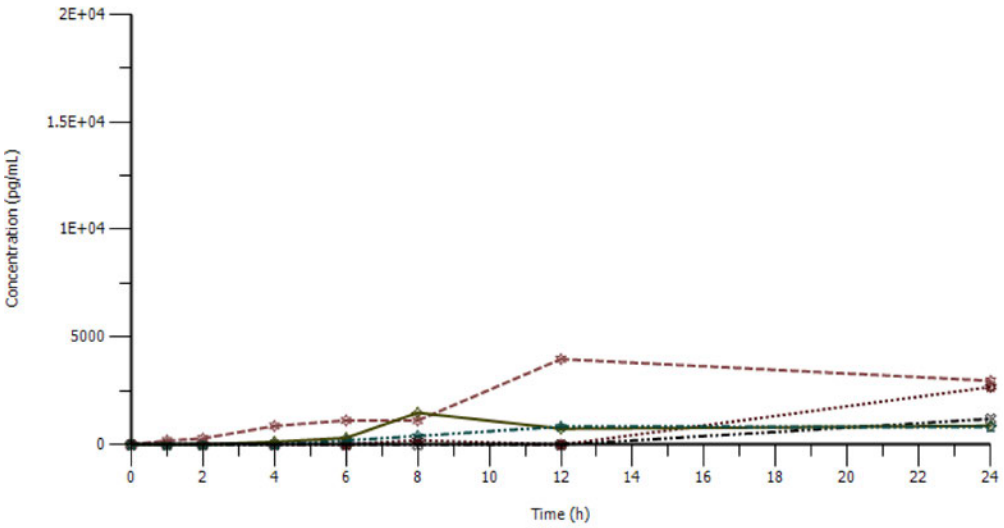

Table 10: NAFT-600 urine PK results

Statistic	NAFT-600 Adult	NAFT-600 Pediatric
Day 1		
Ae_{0-24} [ng] arithmetic mean and standard deviation	79.8651 ± 76.63244	380.9451 ± 329.80044
fe [%] arithmetic mean and standard deviation	0.00011 ± 0.000108	0.00054 ± 0.000465
CLr [mL/min] geometric mean and geometric CV	0.0933; 75.4%	0.2766; 227.5%
Day 14		
$Ae_{\tau,ss}$ [ng] arithmetic mean and standard deviation	974.5209 ± 989.08878	822.9804 ± 679.93903
fe [%] arithmetic mean and standard deviation	0.00137 ± 0.001393	0.00116 ± 0.000958
CLr [mL/min] geometric mean and geometric CV	0.1646; 33.6%	0.1546; 91.9%

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08/26/2014

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