

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 19599	Submission Date(s): 01/13/2016, 01/21/2016, 06/09/2016, 06/30/2016
Brand Name	Naftin Cream, 2%
Generic Name	Naftifine
Primary Reviewer	Yanhui Lu, Ph.D.
Secondary Reviewer	Doanh Tran, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Dermatology and Dental Products
Sponsor	Merz Pharmaceuticals, LLC
Submission Type; Code	Efficacy supplement S013
Formulation; Strength(s)	Cream, 2%
Indication	Treatment of tinea pedis, tinea cruris, and tinea corporis

Table of Contents

1	Executive Summary	2
1.1	Recommendation	2
1.2	Phase IV Commitments	2
1.3	Summary of Important Clinical Pharmacology and Biopharmaceutics Findings ..	2
2	Question-Based Review	3
3	Detailed Labeling Recommendations	3
4	Appendix	8
4.1	Individual Study Reviews	8

1 Executive Summary

Naftin (naftifine hydrochloride) Cream 2% is approved for the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organism *trichophyton rubrum* in patients ≥ 12 years of age (NDA 19599). Two Pediatric Research Equity Act (PREA) post-marketing requirements (PMR) were included in the approval letter for NDA 19599/S011 dated 1/13/2012. The sponsor fulfilled the first PREA requirement (1857-1, letter dated 10/10/2014). The second PREA requirement that was still open is:

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

The sponsor has conducted a pharmacokinetic (PK) trial in pediatric subjects 2 to < 12 years of age with tinea corporis (trial MUS90200_4025_1) and a safety and efficacy trial in pediatric subjects 2 to < 18 years of age with tinea corporis (trial MUS90200_1024_1) to fulfill the PMR. In the current submission, the sponsor submitted the results of these trials and requested approval for use in patients 2 years of age and older.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds NDA 019599/S013 acceptable pending agreement on recommended labeling changes.

The efficacy supplement also satisfies the PREA requirements 1857-2 as outlined in the approval letter for NDA 19599/S011 dated 1/13/2012.

1.2 Phase IV Commitments

None.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Bioavailability:

The sponsor submitted results of the trial MUS90200_4025_1, which evaluated the systemic exposure of naftifine following topical application of Naftin Cream 2% in 27 pediatric subjects (2 to < 12 years) with tinea corporis affecting at least 1% of body surface area (BSA). Among the 27 subjects, 17 subjects were 2 to < 6 years of age group (also referred to as the younger group, mean 4.1 years, range 2-5 years); and 10 subjects were 6 to < 12 years of age group (also referred to as the older group, mean 9.2 years, range 7-11 years).

Naftin Cream, 2% was applied to the affected areas plus a 1/2 inch margin once daily for 14 days. The mean (standard deviation or SD) actual dose amount of Naftin Cream, 2% applied in the younger and older group was 1.6 (0.67) gram/day and 2.5 (0.61) gram/day, respectively. Only the older group had plasma PK assessment following the dose application on Day 1. Both groups had PK assessment following the dose application on

Day 14. Additionally, pre-dose plasma PK samples were collected on Days 1, 12, 13, and 14 in both groups.

All subjects had measurable levels of naftifine in plasma. Steady-state was reached within the study period for both groups. Following a single dose on Day 1 in subjects 6 to < 12 years of age, the geometric mean (coefficient of variation or CV%) values of peak plasma concentration (C_{max}) and area under the plasma concentration-time curve from time 0 to 24 hours (AUC_{0-24}) were 3.60 (76.6%) ng/mL and 49.8 (64.4%) ng*h/mL, respectively. On Day 14 in this group, the C_{max} and AUC_{0-24} were 3.31 (51.2%) ng/mL and 52.4 (49.2%) ng*h/mL, respectively. For the subjects 2 to < 6 years of age on Day 14, the C_{max} and AUC_{0-24} were 3.98 (186%) ng/mL and 54.8 (150%) ng*h/mL, respectively. In the older age group of patients 6 to < 12 years, the systemic exposures (both C_{max} and AUC_{0-24}) on Days 1 and 14 were similar. Although the dose applied in the younger group was less than that in the older group (mean(SD) dose of 1.6 (0.67) g/day versus 2.5 (0.61) g/day), the geometric mean plasma naftifine concentration-time profiles in the two groups were comparable on Day 14. The geometric mean values of C_{max} and AUC_{0-24} were lower than those observed in previous trials where Naftin Cream, 2% was investigated with different skin conditions at higher daily doses in pediatric subjects 13 to < 18 years of age or adults (**Table 1**).

Urine excretion of naftifine was only assessed in the older age group. The median fraction of dose excreted into urine ($fe\%$) over a 24-hour period after drug application was 0.0029% on Day 1 and 0.0014% on Day 14.

Method Validation:

The assay validation and incurred sample reanalysis are acceptable for both plasma and urine naftifine assays. Sample storage time was within the documented long-term matrix stability range (203 days for plasma and 397 days for urine).

Clinical vs. to-be-marketed formulation:

The sponsor confirmed in a letter dated 1/21/2016 that the products used in trials MUS90200_1024_1 and MUS90200_4025_1, namely lot# FHP-C has the same formulation as the approved marketed drug products for NDA 019599.

2 Question-Based Review

Not applicable.

3 Detailed Labeling Recommendations

The following changes are recommended for sections 8.4 and 12.3 of the label for Naftin Cream, 2%. Deletions are noted as ~~striketrough~~ and additions are noted as double underlines.

8.4 Pediatric Use

The safety and effectiveness of NAFTIN Cream have been established in ^{(b) (4)} pediatric patients age ^{(b) (4)} 12 ^{(b) (4)} and above with interdigital tinea pedis and tinea cruris and ages 2 ^{(b) (4)} and above with ^{(b) (4)} tinea corporis.

Use of NAFTIN Cream in ^{(b) (4)} is supported by evidence from adequate and well controlled studies in adults and children, and with additional safety and PK data from two open label trials, conducted in 49 ^{(b) (4)} pediatric subjects ^{(b) (4)} exposed to NAFTIN Cream [see *Clinical Pharmacology* (12.3)].

Safety and effectiveness in pediatric patients < 2 years of age have not been established.

12.3 Pharmacokinetics

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

The pharmacokinetics of NAFTIN Cream was evaluated following once-daily topical application for 2 weeks to ~~twenty-one~~ 21 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 (C_{max}) and area under the curve from time 0 to 24 hours (AUC_{0-24})) to naftifine increased over the 2 week treatment period in all the 21 subjects. Geometric mean (coefficient of variation or CV%) AUC_{0-24} was 117 (41.2) ng*hr/mL on Day 1, and 204 (28.5) ng*hr/mL on Day 14. Geometric ~~Mean~~ mean (CV %) C_{max} was 7 ng/mL (55.6) on Day 1 and 11 ng/mL (29.3) on day 14. Median time to C_{max} (T_{max}) was 8.0 hours (range 4-24 hours) on Day 1 (~~range: 4 to 24~~) and 6.0 hours (range 0-16 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 (standard deviation or SD) plasma concentrations were 1.6 ± 0.5 ng/mL (range below limit of quantitation (BLQ) to 3 ng/mL). In the same pharmacokinetic 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.

In a second trial that enrolled 22 subjects, the pharmacokinetics of NAFTIN Cream was evaluated in 20 pediatric subjects 13 to < 18 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~~ 2 weeks. The results showed that the systemic exposure increased over the treatment period. Geometric ~~Mean~~ mean (CV%) AUC_{0-24} was 138 (50.2) ng*hr/mL on Day 1, and 192 (74.9) ng*hr/mL on Day 14. Geometric ~~Mean~~ mean (CV %) C_{max} 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.

A third trial evaluated the pharmacokinetics of NAFTIN Cream in 27 pediatric subjects 2 to < 12 years of age with at least moderate tinea corporis. Subjects were divided into younger (ages 2 to < 6 years, 17 subjects) and older (6 to < 12 years, 10 subjects) groups.

Median doses of 1.3 g (range 1.0-3.1 g) and 2.3 g (range 2.2-4.2 g) were applied once-daily for 2 weeks in the younger and older groups, respectively, to the affected area plus a ½ inch margin. Plasma and urine pharmacokinetic assessments were conducted on Day 1 in the older group only and on Day 14 in both groups. All subjects showed measurable levels of naftifine in plasma after topical application of NAFTIN Cream. Following a single dose on Day 1 in subjects 6 to < 12 years of age, the geometric mean (CV%) values of C_{max} and AUC₀₋₂₄ were 3.60 (76.6) ng/mL and 49.8 (64.4) ng*h/mL, respectively. On Day 14 in this group, the C_{max} and AUC₀₋₂₄ were 3.31 (51.2) ng/mL and 52.4 (49.2) ng*h/mL, respectively. In subjects 2 to < 6 years of age on Day 14, the C_{max} and AUC₀₋₂₄ were 3.98 (186) ng/mL and 54.8 (150) ng*h/mL, respectively. In the older group of subjects 6 to 12 years of age, the systemic exposures (both C_{max} and AUC₀₋₂₄) on Days 1 and 14 were comparable. The median fraction of the dose excreted into urine over 24 hours following drug applications on Day 1 and Day 14 was 0.0029% and 0.0014%, respectively.

(b) (4)



[Redacted text block]

(b) (4)

[Redacted text block]

Table 1. A comparison of PK results from this trial MUS90200_4025_1 versus the previous two trials MRZ90200/FI/1002 and MUS90200/1023/0.

Trial		Previous Trial MUS90200/1023/0		Previous trial MRZ90200/FI/1002	Current Trial MUS90200_4025_1	
<i>Age Group Name</i>		<i>≥ 18 yr</i>	<i>13- <18 yr</i>	<i>≥ 18 yr</i>	<i>2 - <6 yr</i>	<i>6 - <12 yr</i>
<i>Number of Evaluable Subjects</i>		6	22	21	17	10
<i>Mean Dose (SD), g/day</i>		7.5 (0.6)	8.2 (0.6)	6.4 (0.73)	1.6 (0.67)	2.5 (0.61)
Day 1	AUC₀₋₂₄ (ng*h/mL)	68.6 (95.4%)	138.3 (50.2%)	117 (41.2%)	-	49.8 (64.4%)
	C_{max} (ng/mL)	3.98 (83.0%)	9.21 (48.4%)	7 (55.6%)	-	3.60 (76.6%)
	T_{max} (h)	12.0 (8-24)	7.0 (2-24)	8.0 (4-24)	-	8.0 (4.0-24)
	Median (range) fe (%)	0.00143 (0.0003-0.0159)	0.00300 (0.0005-0.0648) (n=12)	0.0016 (0.00038-0.09080)	-	0.0029 (0.00073-0.0085)
Day 14	AUC₀₋₂₄ (ng*h/mL)	124.6 (49.9%)	192.5 (74.9%)	204 (28.5%)	54.8 (150%)	52.4 (49.2%)
	C_{max} (ng/mL)	6.83 (51.3)	12.7 (67.2%)	11 (29.3%)	3.98 (186%)	3.31 (51.2%)
	T_{max} (h)	7.0 (6-24)	6.0 (2-12)	6.0 (0-16)	8.0 (4.0-24)	8.0 (4.0-12)
	Median (range) fe (%)	0.0025 (0.0006-0.0045)	0.0033 (0-0.041) (n=20)	0.0020 (0.00047-0.038)	-	0.0014 (0.000054-0.0062)

4 Appendix

4.1 Individual Study Reviews

Trial MUS90200_4025_1

Title: An Open-Label, Multi-Center, Multiple-Application Pharmacokinetic Study of Naftin® (naftifine hydrochloride) Cream, 2% in Pediatric Subjects with Tinea Corporis

Investigators, study sites: This study was conducted at two investigational sites, one each in Honduras and the Dominican Republic.

Objectives:

Primary Objective:

The primary objective was to quantify the pharmacokinetics of Naftin (naftifine hydrochloride [HCl]) Cream, 2% in pediatric subjects 2 to <12 years of age with moderate to marked tinea corporis infected up to the upper range of maximal clinical use conditions for 2 weeks of once-daily application.

Secondary Objectives:

The secondary objectives were to evaluate subject efficacy, tolerability, and safety after 2 weeks of once-daily applications of Naftin (naftifine HCl) Cream, 2%.

Study design and methodology:

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

Number of subjects planned

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

Diagnosis and main criteria for in- and exclusion

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

Test product

Naftin (naftifine HCl) Cream, 2% contained 2% naftifine HCl.

Naftin Cream, 2% was applied once daily in the morning between 6:00 am and 9:30 am for 14 days. The cream was applied at the clinic on Days 1, 2, 7, 12, 13, and 14 and at home on all other days.

In all subjects, study product was applied to all affected areas plus a ½-inch margin excluding the groin, hands, scalp, and feet and at least 1% of BSA was required to involve diseased skin with tinea corporis. In subjects aged 2 to < 6 years (referred as younger group), at least 0.5 g but no more than 3 g of Naftin Cream, 2% was applied once per day and in subjects aged 6 to < 12 years (referred as older group), at least 1g but no more than 4g of Naftin Cream, 2% was to have been applied once per day.

The study medication was weighed pre- and post-application by the site personnel during Visits 2 through 6. The date, time, and site of study medication applications were captured in each subject's diary.

Duration of study treatment

The screening period was from 4 weeks to 1 day prior to the start of treatment. Subjects received treatment with Naftin Cream, 2% for 2 weeks, and there was a follow-up visit 1 week later. Subjects participated in the study for 3 to 7 weeks.

PK assessments:

Plasma and urine samples were analyzed for concentrations of naftifine using validated analytical methods. Subjects stayed at the study center on Day 1 (first application) for older age group (6 to < 12 years) and Day 14 (last application) for both age groups (2 to < 6 years and 6 to < 12 years) for collection of a 24-hour PK profile. All other visits were outpatient.

- PK blood samples were collected on Day 1 pre-application for both age groups and at 4, 8, 12, and 24 hours post dose only for the 6 to < 12 years age group. On Day 14, PK blood samples were collected in both age groups prior to and at 4, 8, 12, and 24 hours after the dose application. In addition, a single blood sample was collected on day 21 (1 week after last application) for all subjects.
- Urine samples were collected only in the 6 to < 12 years age group. On the first and last days of treatment, urine samples were collected before on-site treatment application (complete void and on Day 1 only), 0 to 6, 6 to 12, and 12 to 24 hours after on-site application. Urine volume was determined and recorded for each collection interval.

For non-compartmental analysis of single-application data, plasma concentrations below the lower limit of quantification (LLOQ) before T_{max} were replaced by zero. All plasma concentrations below the LLOQ after T_{max} were set to missing. For non-compartmental

analysis of multiple-application data, plasma concentrations below the LLOQ were set to missing. For non-compartmental analysis, urine concentrations of naftifine below the LLOQ were set to zero.

Plasma and urine single-application PK variables (Day 1) were assessed only for the 6 to < 12 years age group. Plasma and urine multiple-application PK variables (Day 14) were assessed for both age groups.

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

Bioanalytical methods:

Naftifine in human EDTA K3 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 pg/mL. Intra-day and inter-day accuracy and precision were within acceptable range of $\pm 15\%$. Long term stability of naftifine in plasma at $-20\text{ }^{\circ}\text{C}$ was demonstrated for 203 days. This method was validated in report dated 11/18/2013 and used in the previous maximal use PK study MUS90200/1023/0 that supported the approval of NDA 19599/S012 (Clinical Pharmacology Review by Dr. Doanh C. Tran dated 05/03/2013 in DARRTS). A total of 50 samples (17.7% of 283 study samples; 2-4 samples per subject) were reanalyzed for the incurred sample reproducibility test. The results showed that 100% met the criteria of reproducibility (i.e., difference within $\pm 20\%$ 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 pg/mL. Intra-day and inter-day accuracy and precision were within acceptable range of $\pm 15\%$. This method was used for analyzing urine samples from previous maximal use PK studies MRZ 90200/FI/1002 and MUS90200/1023/0 that supported the approval of NDA 19599/S011 (Clinical Pharmacology Review by Dr. Abimbola Adebowale dated 11/02/2011 in DARRTS) and NDA 19599/S012 (Clinical Pharmacology Review by Dr. Doanh C. Tran dated 05/03/2013 in DARRTS), respectively. A partial validation (number 6, report dated 09/08/2014) extended the long term stability at $-20\text{ }^{\circ}\text{C}$ from 199 days to 397 days. A total of 50 samples (71.4% of 70 study samples; 1-6 samples per subject) were reanalyzed for the incurred sample reproducibility test. The results showed that 96% met the criteria of reproducibility (i.e., difference within $\pm 20\%$ of average of original and repeat value).

Overall, assay validation and incurred sample reanalysis are acceptable for both urine and plasma naftifine assays. Sample storage time was within the documented long-term matrix stability range.

Results

Disposition of subjects

A total of 27 pediatric subjects were enrolled and received Naftin Cream, 2% in this trial: 17 (10 male and 7 female subjects) in the younger group (2 to < 6 years of age) and 10 (4 male and 6 female subjects) in the older group (6 to < 12 years of age). All subjects were of Hispanic ethnicity (10 White and 7 Black in the younger group; and 7 White and 3

Black in the older group). Mean (SD) age was 4.1 (1.0) years (range 2-5 years) and 9.2 (1.6) years (range 7-11 years) in the younger and older groups, respectively (see **Figure 1**). All subjects completed the trial and were included in the pharmacokinetic analysis data set. The median actual amount of drug applied daily was 1.3 g (range 1.0-3.1 g) and 2.3 g (range 2.2-4.2 g) in the younger and older groups, respectively. Minimum and maximum amounts applied in both groups were close to the target dose ranges of 0.5-3 g for the younger group and 1-4 g for the older group (see **Table 2**).

Figure 1. Age distribution of the subjects enrolled in the current trial MUS90200_4025_1.

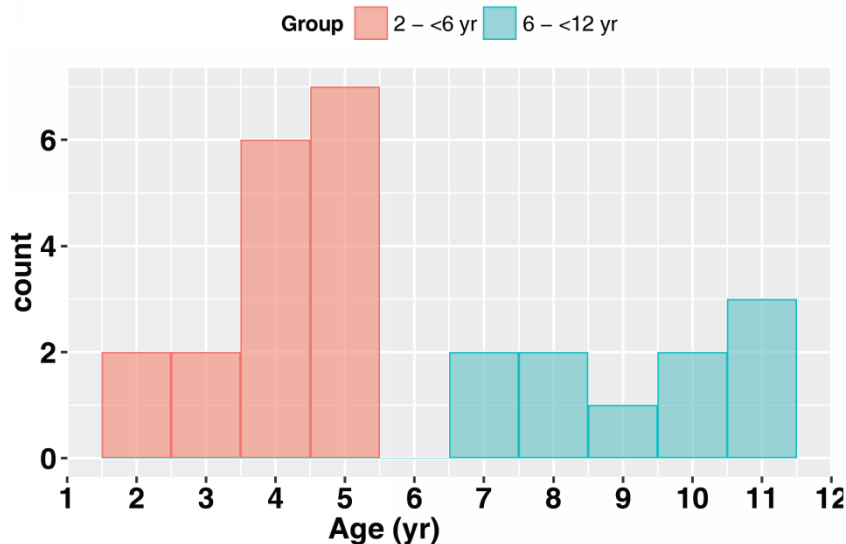


Table 2: Daily amount of Naftin Cream, 2% applied in the current trial.

Compliance (g/day)	Naftin Cream, 2%		
	2 to <6 years (N=17)	6 to <12 years (N=10)	Total (N=27)
Mean (SD)	1.6 (0.67)	2.5 (0.61)	1.9 (0.78)
Median	1.3	2.3	2.1
Min, max	1.0, 3.1	2.2, 4.2	1.0, 4.2

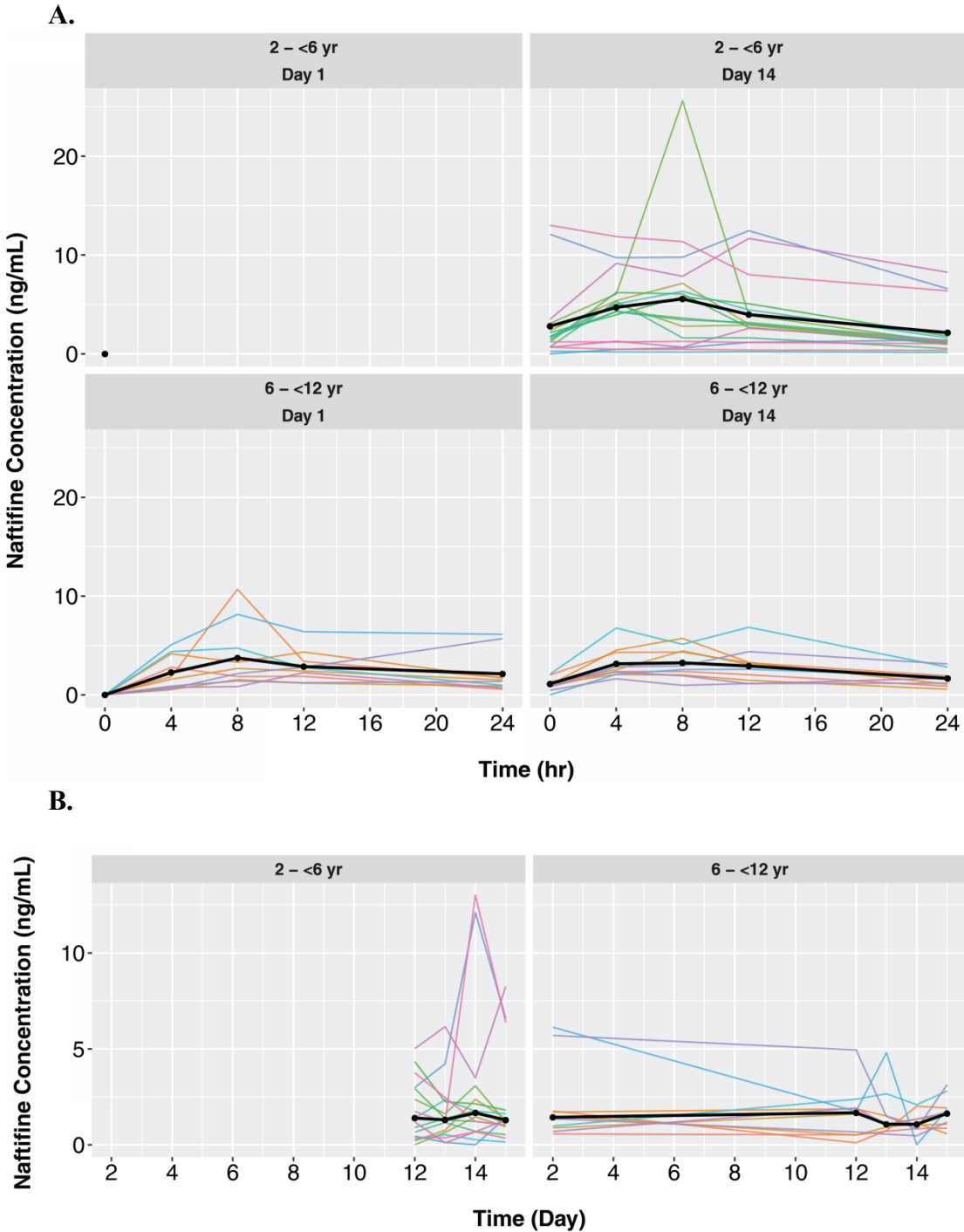
Pharmacokinetic results

Plasma PK:

All subjects had measurable levels of naftifine in plasma. Individual plasma naftifine PK profiles are shown in **Figure 3**. The median plasma concentrations were higher and the range of plasma concentrations was wider in the younger group (2 - <6 yr, N=17) than in the older group (6 - <12 yr, N=10). The trough plasma concentrations over the treatment period between the two groups were similar except that a few subjects in the younger

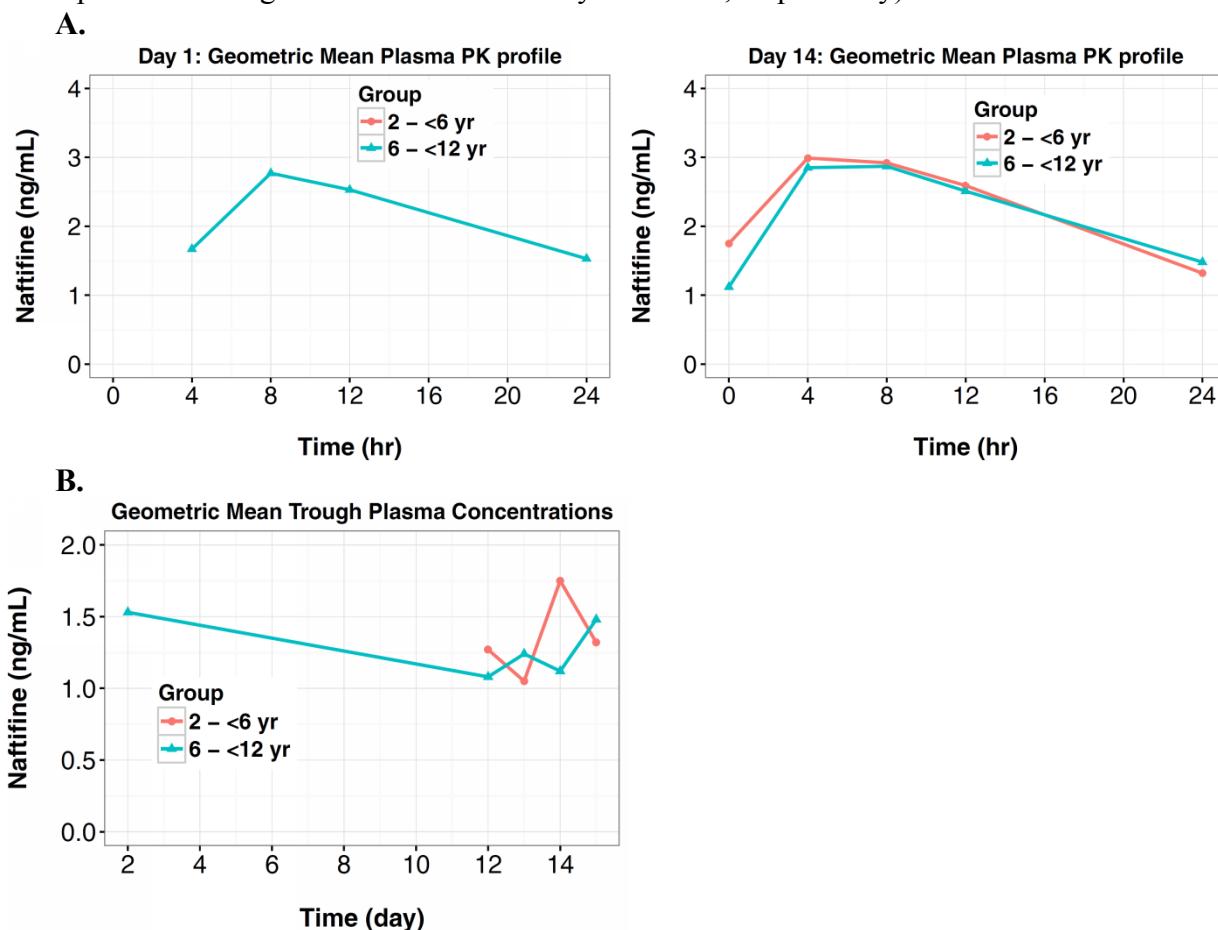
group had higher levels than others. It appears that the product has reached steady-state within the study period in both age groups.

Figure 3. Individual naftifine plasma concentration-time profiles with median profiles. **(A)** PK profiles of naftifine following dose applications on Day 1 and Day 14. **(B)** Trough plasma naftifine concentrations over the treatment period. Black lines with dots represent median profiles.



The geometric mean plasma naftifine concentrations for the two groups were comparable at the times that blood samples were collected in both groups (**Figure 4**). Since the dose applied in the younger group was lower (median: 1.3 g/day versus 2.3 g/day), the dose-normalized systemic exposure would be higher in the younger group when compared with that in the older group.

Figure 4. Geometric mean naftifine plasma concentration-time profiles on Day 1 (**A**, left panel) and Day 14 (**A**, right panel), and trough concentrations during the treatment period (**B**, plasma concentrations at 24 hours following the dose applications on Days 1 and 14 were plotted as trough concentrations for Days 2 and 14, respectively).



The PK parameters of naftifine are shown in **Table 4**. Following a single dose on Day 1 in subjects 6 to < 12 years of age, the geometric mean (CV%) values of C_{max} and AUC_{0-24} were 3.60 (76.6%) ng/mL and 49.8 (64.4%) ng*h/mL, respectively. On Day 14 in this group, the C_{max} and AUC_{0-24} were 3.31 (51.2%) ng/mL and 52.4 (49.2%) ng*h/mL, respectively. For the subjects 2 to < 6 years of age on Day 14, the C_{max} and AUC_{0-24} were 3.98 (186%) ng/mL and 54.8 (150%) ng*h/mL, respectively. The median (range) of T_{max} was 8.0 hours (4.0-24 hours) for 2 to < 6 years group on Day 14 and for 6 to < 12 years group on Day 1, and 8.0 hours (4.0-12 hours) for 6 to < 12 years group on Day 14. These values are consistent with an independent reanalysis by this reviewer. **Figures 5 and 6** show the box plots for C_{max} and AUC_{0-24} , respectively. The systemic exposures (both

C_{max} and AUC_{0-24}) on Days 1 and 14 were similar in the group (2 - < 6 years) where PK was assessed on both days. In addition, on day 21 (1 week after last dose application), the mean (SD) of naftifine plasma concentrations was 0.53 (0.66) ng/mL and 1.00 (1.54) ng/mL, respectively, in the younger and older groups.

Table 4. The summary of naftifine PK parameters from the current trial MUS90200_4025_1.

Parameters		Younger Group (2 - <6 yr, N=17)	Older Group (6 - <12 yr, N=10)
Day 1	#AUC ₀₋₂₄ , ng*h/mL	-	49.8 (64.4%)
	#C _{max} , ng/mL	-	3.60 (76.6%)
	Median (range) T _{max} , h	-	8.0 (4.0-24)
	Median (range) fe (%)	-	0.0029 (0.00073-0.0085)
Day 14	#AUC ₀₋₂₄ , ng*h/mL	54.8 (150%)	52.4 (49.2%)
	#C _{max} , ng/mL	3.98 (186%)	3.31 (51.2%)
	Median (range) T _{max} , h	8.0 (4.0-24)	8.0 (4.0-12)
	Median (range) fe (%)	-	0.0014 (0.000054-0.0062)

#C_{max} and AUC₀₋₂₄ are presented as geometric mean (%CV).

Figure 5. Box plots for C_{max}.

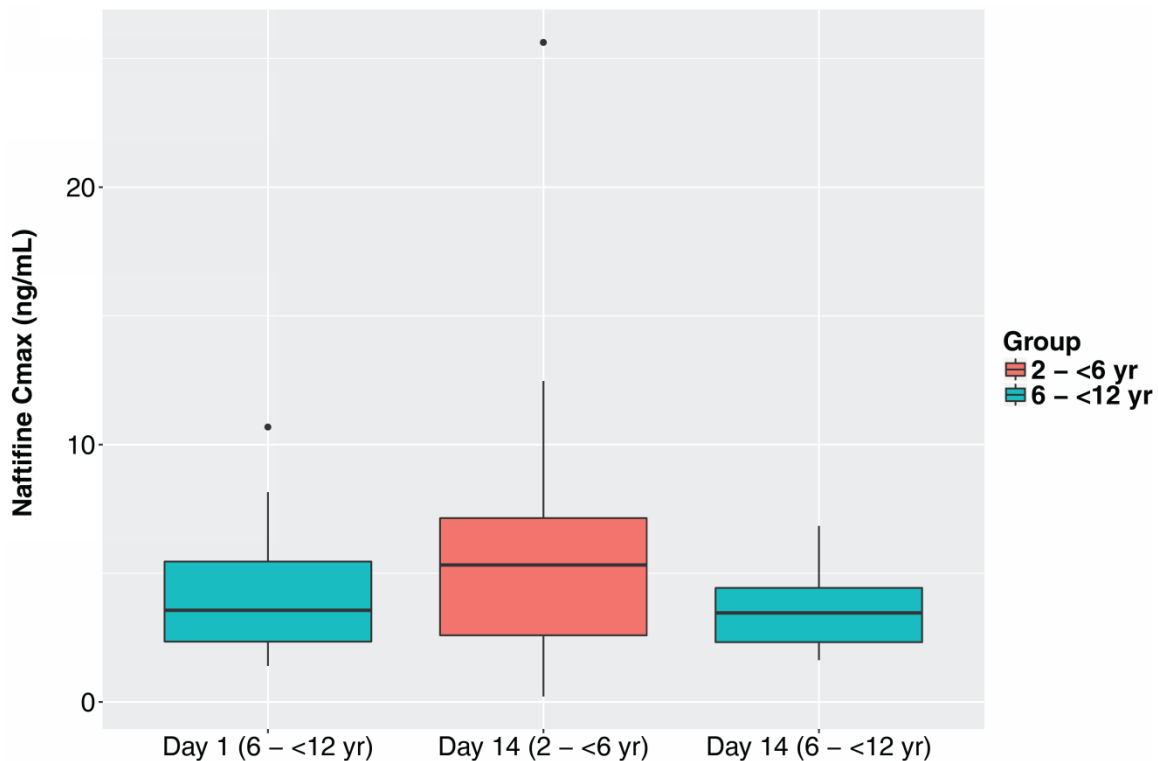
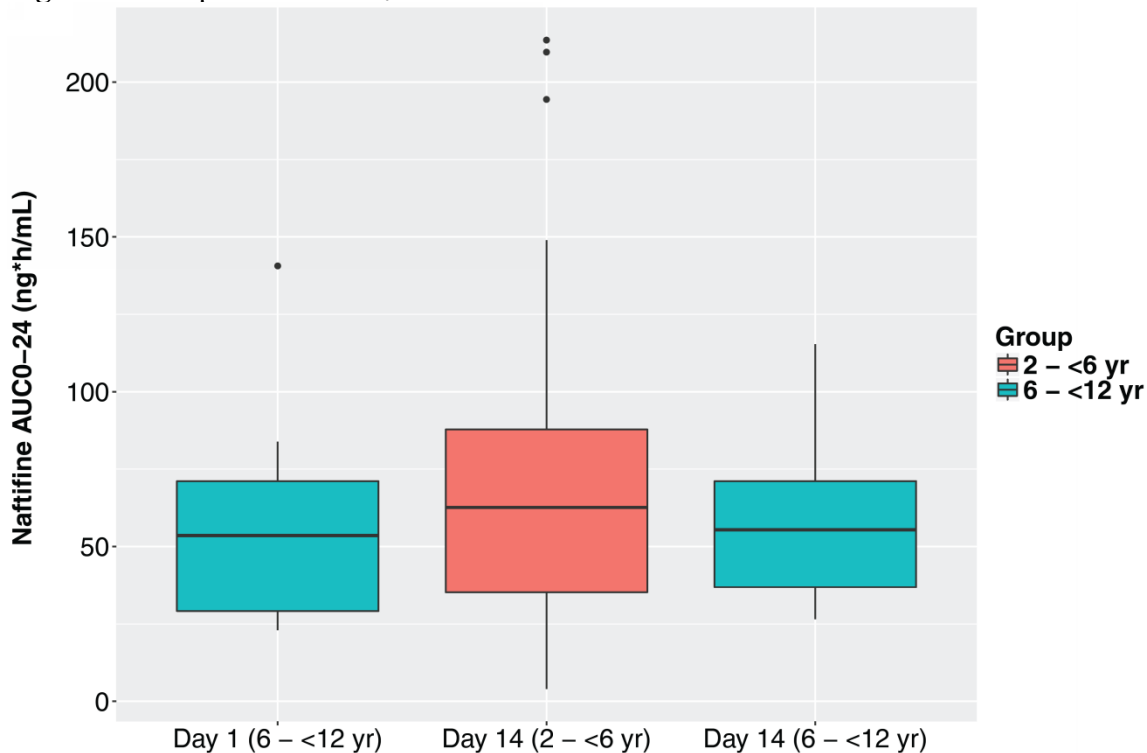


Figure 6. Box plots for AUC₀₋₂₄.



Urine PK:

Urine excretion of naftifine was only assessed in the older age group during a 24-hour period following the first dose (Day 1) and the last dose (Day 14). In the study report initially submitted by the sponsor, the mean values for fraction of drug excreted into urine (fe%) were much lower than those recalculated by the reviewer and those obtained in previous adult and pediatric trials (**Table 1**). It seems that the sponsor calculated the fe% using DOSE for Day 1 and AVGDOSSE for Day 14; however, it was not clear how these two variables were obtained based on the description that DOSE was “Dose (g)” and AVGDOSSE was “Average Dose (g)”. In addition, the AVGDOSSE values were in general several-fold higher than the daily dose applied.

An information request (IR) was sent to the sponsor on 6/2/2016 as follows:

- 1. In dataset ADPP for trial MUS90200_4025_1, it appears that most of the AVGDOSSE values are higher than the values of compliance (g/day) presented in Table 7 of the study report. Provide details on how values of DOSE were obtained and how AVGDOSSE was derived.*
- 2. The fraction excreted in urine (fe[%]) seems to be smaller than expected. For example, if we use the mean dose of 2.5 g/day and Ae₀₋₂₄ of ~823.4 ng on Day 14 in subjects 6 to < 12 years of age from Table 7 and Table 12, respectively, in the study report, then the fe[%] would be $100\% * 823.4 \text{ ng} / (2.5 \text{ g} * 2\% \text{ cream strength}) = 0.00165\%$. However, the fe[%] was presented as 0.00001241 in Table*

12. Provide details on how $fe[\%]$ values reported in Table 12 of the study report were calculated.

The applicant responded on 6/9/2016 as follows:

MERZ RESPONSE 1: DOSE in the ADaM “ADPP” dataset corresponds to the compliance calculation (g/day) in Table 7 of the CSR. This was derived using an algorithm that used the total weight of the product divided by the total number of days of exposure to the product. Using subject with identification number “S0112” (USUBJID = MUS90200_4025_1-S0112) as an example, the total weight of product used during this trial was 30.5grams, with 14 days of exposure. Therefore DOSE (also compliance) for this subject was calculated to be approximately $\sim 2.2\text{g/day}$ (after rounding to a decimal place).

For this same subject (USUBJID = MUS90200_4025_1-S0112) as example for AVGDOS; derived as 6.1 grams in the ADPP dataset. There were 5 tubes dispensed for this subject, with separate weights from the amount of product for each tube dispensed. AVGDOS is the average of the weights of products used (irrespective of the days of exposure). Therefore for this subject, AVGDOS is $30.5/5 = 6.1\text{g}$. SDTM dataset “EX” contains variable “EXDOS” which has the distribution of individual weight of amount of product used per tube that was subsequently used to derive the AVGDOS information in the ADPP dataset.

Information from the DOSE value is the more reliable of the two indices to account for exposure since the number of days in which the subject is exposed to the medication is taken into cognizance.

MERZ RESPONSE 2: An error in the data analysis program used to create the PK datasets from which the Tables, Figures, and Listings for MUS90200_4025_1 were generated has been identified. We respectfully request additional time to address this issue and will provide an answer to the question as soon as possible.

The applicant continued to respond to IR item No. 2 on 6/27/2016 as follows:

MERZ RESPONSE 2: Several errors in the data analysis conducted for study MUS90200_4025_1 have been identified and corrected.

In reference to the above question, the value in Table 12 is fe (as per the SAP), but labelled $fe(\%)$; thus it is 100 times too small for the label.

The computation of the $fe(\%)$ changed in both the single dose and multiple dose PK parameters. For the single dose data, the denominator used in the computation of this parameter was obtained from the grams of product used after a single application. For the multiple dose data, originally the denominator being used in the calculation per subject was the AVGDOS from the “ADPP” dataset which corresponds to the

cumulative weight of product used divided by the total number of tubes. For all fe(%) computations, the updated calculation utilizes the average dose based on grams per day (the compliance, or DOSE), which is the most valid denominator for the variable used for the calculation of the fe(%).

The applicant also submitted updated clinical study report, the affected datasets, PK tables, figures and listings. The updated fe% values were consistent with recalculated values by this reviewer. The median values of fe% were 0.0029% on Day 1 and 0.0014% 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/

YANHUI LU
08/05/2016

DOANH C TRAN
08/05/2016

EDWARD D BASHAW
08/08/2016