Medical Officer's Review of NDA 19599 S-12 and NDA 204286 S-1

SDs: 276 and 47
Sponsor: Merz Pharmaceuticals, LLC
Established name: naftifine hydrochloride
Trade names: Naftin Cream 2% and Naftin Gel 2%
Route of administration: topical
Dosage forms: cream and gel
Indications: interdigital tinea pedis, tinea cruris, and tinea corporis (Naftin Cream2%)
interdigital tinea pedis (Naftin Gel 2%)

Stamp date: December 20, 2013
Review completed: September 17, 2014
PDUFA: October 20, 2014

Clinical reviewer: Milena Lolic, M.D.
Clinical team leader: David Kettl, M.D.
Project manager: Strother Dixon

I REGULATORY BACKGROUND:

Naftin Cream 2% (NAFT-500) was approved on January 13, 2012 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.

There were two PREA post-marketing requirements attached to this approval that read:

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

Naftin Gel 2% (NAFT-600) was approved on June 27, 2013 for the treatment of interdigital tinea pedis, caused by the organism *Trichophyton rubrum* in adult patients ≥18 years of age.

There was one PREA post-marketing requirement attached to this approval that 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.

Reference ID: 3629348

The applicant submitted the protocol MUS90200/1023/0 to address PMR # 1857 for Naftin Cream 2% in July 2012.The protocol had Naftin Gel 2% arm included. The review of NDA 204286 (for Naftin Gel 2%) was ongoing when the protocol was received and the review team concluded that same study appears to be adequate to address the pediatric safety needs for Naftin Gel 2%.

Current submission contains supplements for fulfillment of PMRs # 1857-1 and 2050-1 and request for an extension of regulatory exclusivity for the period of 6 months for both, Naftin Cream 2% and Naftin Gel, 2% based upon the new clinical data from study MUS90200/1023/0.

II REVIEW OF THE STUDY MUS90200/1023/0

Title: An Open-Label, Multicenter, Multiple Applications Pharmacokinetic Study of NAFT-500 in Pediatric Subjects with Tinea Cruris and Tinea Pedis and NAFT-600 in Pediatric Subjects with Tinea Pedis

Protocol: MUS90200/1023/0

Principal Investigators:

Site Number	Investigator First Name	Investigator Last Name	Institution	Specialty	Address	Phone
001261	Terry	Jones, MD	J&S Studies , Inc.	Dermatologist	1710 Crescent Pointe Pkwy College Station, TX 77802 USA	979-774-5933
504001	Nelly	Paz, MD	Hospital y Clinica Bendana	Dermatology	Ave. Circunvalacion 3 piso, local 312 San Pedro Sula Honduras	011-504-2516-2902 (site) Phone: 305-225-0400 (Martha)
180001	Daisy	Blanco, MD	Instituto Dermatológico	Dermatology	Calle Federico Velásquez Esq. Albert Thomas Ensanche Maria Auxiliadora Santo Domingo Republica Dominicana	809- 684-1376 (site) Phone: 305-225-0400 (Martha)
001272	Michael	Jarratt, MD	DermResearch Inc.	Dermatology	8140 North Mopac Expressway Building 3, Suite 120 Austin, TX 78759 USA	(512) 349-9889

The applicant certified in Form 3454 that they had not entered into any financial arrangements with any of the clinical investigators.

Study Initiation Date: September 2012
Study Completion Date: December 2013
Number of Subjects: 58

Reference ID: 3629348

Study Design: open label, multi-center (5 sites in Honduras, Dominican Republic, and United States)

Comment: Following the Filing meeting, an information request was sent to the applicant requesting a rationale for assuming the applicability of foreign data to US population/practice of medicine. The response was received on April 4, 2014 and was deemed adequate.

Study Objectives:

- to quantify the pharmacokinetics of NAFT-500 in pediatric subjects 12-17 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 is defined as having both feet and bikini area affected.
- to quantify the pharmacokinetics of NAFT-600 in pediatric subjects aged 12-17 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 is defined as having both feet affected.
- to evaluate subject efficacy, tolerability and safety after 2 weeks of once daily applications of both products (NAFT-500 and NAFT-600).

Study Plan:

Subjects applied treatment once daily for two weeks. For NAFT-500 arm total amount of drug was 8 g and for NAFT-600 it was 4g.

Figure 1: Study Flow Chart for NAFT-500 (Tinea pedis and Tinea cruris) Group

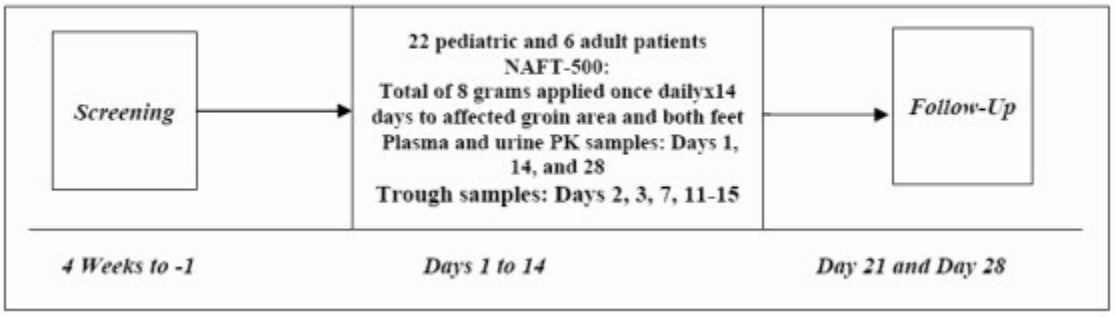

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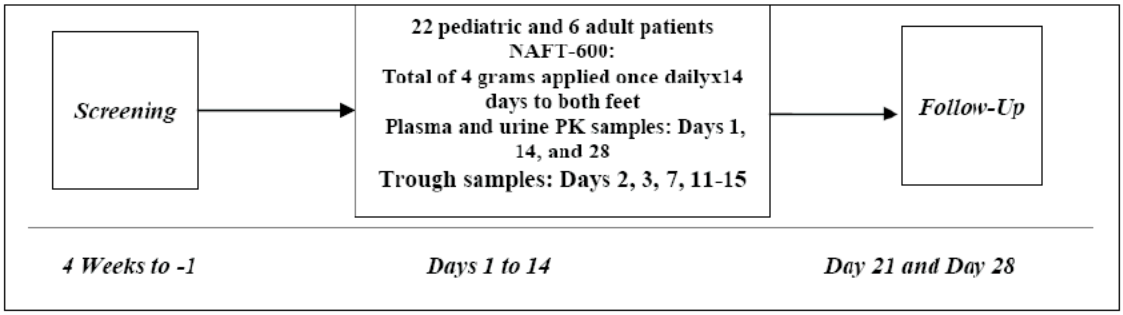
Figure 2: Study Flow Chart for NAFT-600 (Tinea pedis) Group



Comment: The protocol was reviewed in 2012 and found to be adequate to meet the stated objectives. The addition of 12 adult subjects was noted and deemed non-relevant for study interpretation.

Study Results

Table 1 Demographic data (safety population)

	NAFT-500			NAFT-600		
	pediatric	adult	total	pediatric	adult	total
Number of subjects	22	6	2 8	22	6	28
Gender **Male** **Female**	 17 (77%) 6 (23%)	N/A	N/A	 18 (82%) 4 (18%)	N/A	N/A
Age (mean)	15 (13-17)	N/A	N/A	15 (12-17)		N/A
Ethnicity **Hispanic** **Not Hispanic**	 22 (100%) 0	N/A	N/A	 16 (73%) 6 (27%)	N/A	N/A
Race **White** **Black**	 20 (91%) 2 (9%)	N/A	N/A	 6 (27%) 16 (73%)	N/A	N/A

Comment: The selected population was adequate for maximal use PK/safety study.

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Pharmacokinetics

The pharmacokinetics of NAFT-500 and NAFT-600 were assessed on Day 1 and Day 14 under maximal use condition. Systemic exposure increased from Day 1 to Day 14. The Cmax and AUC are shown in Table 2.

Table 2 Naftifine PK parameters for NAFT-500 and NAFT-500

NAFT-500		
Parameter	Day 1	Day 14
AUC (ng*h/ml)	138.3 (50.2%)	192.5 (74.9%)
Cmax (ng/mL)	9.21 (48.4%)	12.7 (67.2%)
NAFT-600		
Parameter	Day 1	Day 14
AUC(ng*h/ml)	15.9 (211.6%)	60.0 (131.1%)
Cmax (ng/mL)	1.40 (153.8%)	3.81 (153.9%)

Source: Adopted from Clinical Pharmacology review

Systemic naftifine exposures in pediatrics are similar to those observed in adults (studies MRZ 90200/FI/1002 and MRZ 90200/1010/1). Doanh Tran, Ph.D., Clinical Pharmacology reviewer commented in his review dated 8/27/14:

"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."

Comment: I agree with Dr. Tran's conclusion.

Safety results:

Total of 56 subjects comprise safety population.

Discontinuations:	One pediatric subject and 2 adults were discontinued (none for safety reasons).
Deaths:	None
Serious Adverse Events (SAE):	None

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Severe Adverse Events: None

Summary of all adverse events: There were total of 8 AEs, all mild in intensity. One AE (headache) occurred in adults.

Table 3 Summary of all AEs

	NAFT-600 (N = 28)			NAFT-500 (N = 28)		
PT	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)
Influenza	0	0	0	2	2	7.14
Urinary tract infection	0	0	0	2	2	7.14
Tonsillitis	0	0	0	1	1	3.57
Headache	1	1	3.57	0	0	0
Blood creatinine increased	1	1	3.57	0	0	0
Pharyngitis	1	1	3.57	0	0	0

Source: Reviewer's analysis using MAED. Coding was done using MedDRA 16.0

Comment: I agree with applicant's assessment that none of the AEs was treatment related.

Efficacy results

Efficacy data was not analyzed due to open label design and limited number of subjects. Statistical reviewer, Carin Kim, Ph.D., concluded in her review dated 7/25/14:

"As the completed trial was an open-label, maximal use trial that did not include a vehicle arm, efficacy results from such trial are subject to bias as no comparator arm was included. In addition, the sample size (22 pediatric subjects and 6 adult subjects) is too small to draw a reasonable conclusion about efficacy. (b) (4)

Comment: I agree with statistical comment (b) (4) .

III CONCLUSIONS

- The systemic naftifine exposures in pediatrics are similar to those in adults
- No new safety concerns were noted.
- Approved labeling needs to be revised to include new pediatric safety and pharmacokinetic data.

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IV LABELING RECOMMENDATIONS

Naftin Cream 2% labeling recommendations (deletions are crossed out, additions are underlined):

1 INDICATIONS AND USAGE

NAFTIN (naftifine hydrochloride) Cream, 2% is indicated for the treatment of: interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organism *Trichophyton rubrum.* (b) (4).

6.1 Clinical Trials Experience

In an open-label pediatric pharmacokinetics and safety trial 22 pediatric subjects 13-17 years of age with tinea pedis and tinea cruris received NAFTIN (naftifine hydrochloride) Cream, 2%. The incidence of adverse reactions in the pediatric population was similar to that observed in adult population.

8.4 Pediatric Use

(b) (4)

The safety and effectiveness of NAFTIN (naftifine hydrochloride) Cream, 2% have been established in the age group 12-18 tinea pedis and tinea cruris. Use of NAFTIN (naftifine hydrochloride) Cream, 2% in this age group is supported by evidence from adequate and well controlled studies in adults with additional safety and PK data from an open label trial, conducted in 22 adolescents ≥12 years of age who were exposed to Naftin (naftifine hydrochloride) Cream, 2% at a dose of approximately 8 g/day.

Safety and effectiveness in pediatric patients < 12 years of age has not been established.

12.3 Pharmacokinetics

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% labeling recommendations (deletions are crossed out, additions are underlined):

1 INDICATIONS AND USAGE

NAFTIN (naftifine hydrochloride) Gel, 2% is an allylamine antifungal indicated for the treatment of interdigital tinea pedis caused by the organisms *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum* (b) (4)

6.1 Clinical Trials Experience

In an open-label pediatric pharmacokinetics and safety trial 22 pediatric subjects 12-17 years of age with interdigital tinea pedis received NAFTIN (naftifine hydrochloride) Gel, 2%. The incidence of adverse reactions in the pediatric population was similar to that observed in adult population.

8.4 Pediatric Use

(b) (4)

(b) (4)

The safety and effectiveness of NAFTIN (naftifine hydrochloride) Gel 2% have been established in the age group 12-18 with interdigital tinea pedis. Use of NAFTIN (naftifine hydrochloride) Gel, 2% in this age group is supported by evidence from adequate and well controlled studies in adults with additional safety and PK data from an open label trial, conducted in 22 adolescents ≥12 years of age who were exposed to Naftin (naftifine hydrochloride) Gel, 2% at a dose of approximately 4 g/day.

Safety and effectiveness in pediatric patients <12 years of age have not been established.

12.3 Pharmacokinetics

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.

V RECOMMENDATION ON REGULATORY ACTION

1. Recommend that NDA 19599 S-12 and NDA 204286 S-1 be approved.
2. The applicant fulfilled PMRs 1857-1 and 2050-1.
3. Labeling negotiations are ongoing. The agreed upon labeling will be appended to the approval letter.
4. An extension of regulatory exclusivity for the period of 6 months for both products should be granted contingent upon labeling agreement.

Milena Lolic, MD
Medical Officer, DDDP

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/s/

MILENA M LOLIC
09/17/2014

DAVID L KETTL
09/17/2014