Clinical Pharmacology Review

NDA #:	204153/S-004
Submission Date:	April 21, 2017
Generic Name:	Luliconazole cream, 1%
Dosage Form:	Cream
Dosage Strength:	1%
Reviewer:	Chinmay Shukla, Ph.D.
Secondary Reviewer:	CAPT. E. Dennis Bashaw, Pharm. D.
Sponsor:	Valent Pharmaceuticals LLC.
Relevant IND(s):	076,049
Submission Type:	Efficacy Supplement
Indication:	Topical treatment of tinea pedis, tinea cruris and tinea corporis in adults

Background: Luliconazole Cream, 1% was approved on November 14, 2013 for the topical treatment of interdigital tinea pedis, tinea cruris and tinea corporis caused by organisms *Trichophyton rubrum* and *Epidermophyton floccosum* in subjects 18 years of age and older.

At the time of original approval one of the Post Marketing Requirements (PMR) was to conduct a multi-center, randomized, blinded, vehicle-controlled study, including pharmacokinetic (PK) assessments, with luliconazole cream 1% for the treatment of tinea corporis in pediatric patients 2 years of age and older. This supplement includes the final study report of the aforementioned PMR and subsequent labeling revisions.

Summary of the clinical study report (Study V01-LUZB-401, MP-1011): This was a randomized multi-center, double-blind, vehicle controlled study evaluating the safety, efficacy and pharmacokinetics (PK) of Luliconazole cream, 1% in pediatric subjects 2 to 17 years of age with tinea corporis.

Study design: Approximately 75 male and female subjects aged 2 years to 17 years with tinea cruris were randomized (4:1) to treatment with either Luliconazole Cream 1% or Vehicle Cream once daily for 7 days. The diagnosis of tinea corporis was confirmed by the detection of fungal hyphae on a KOH wet mount test.

Study drug was applied once daily in the morning for 7 days to the affected area and approximately 1 inch of the immediate surrounding area. The first and last (Day 7) administration of study medication was completed at the investigational site and rest of the applications of study medication were administered by the subjects/ caregivers at home. Subjects were instructed to allow the treated area(s) to remain exposed for 5 minutes prior to putting on clothes, and not to wash the treated area(s) for at least 4 hours after application. Both treatment groups were followed for a 21-day post final treatment period (Day 28).

Identity of the investigational product:

- Luliconazole Cream, 1% (Lot No. HFFE-1C). Manufactured by DOP Laboratories, Ltd., San Antonio, TX 78215
- Vehicle Cream, 1% (Lot No. HDH-C). Manufactured by DOP Laboratories, Ltd., San Antonio, TX 78215

Pharmacokinetic assessment: Pharmacokinetic (PK) assessment was performed in approximately 15 subjects (12 active + 3 vehicle) at selected sites. Plasma levels of luliconazole and z-luliconazole (metabolite) were obtained on Day 7 within 15 minutes prior to the final dose of the drug and at approximately near the expected Tmax based on prior PK experience in adult subjects with tinea cruris (6 hours after the final dose).

Reviewer comments: *The applicant did not record the % body surface area (% BSA) that was treated, the number of lesions that were treated and the anatomical sites of the lesions that were treated subjects in the PK cohort. However, using daily dose information that was recorded and assuming thin layer to constitute 2 mg/cm^2, this reviewer back calculated the % BSA as shown in Table 1below. It should be noted that this is an estimation.*

Table 1: Estimation of % BSA

Subject	Age (years)	BSA m^2	BSA cm^2	Total amount of dose used over 7 days (g)	Daily dose (g)	Daily dose (mg)	Assuming 2 mg/cm^2 this dose corresponds to BSA (cm^2)	%BSA
101018	12	1.3	13000	6.1	0.87	871.43	435.71	3.35
101020	6	0.8	8000	10.6	1.51	1514.29	757.14	9.46
101021	3	0.6	6000	8.6	1.23	1228.57	614.29	10.24
101022	5	0.71	7100	11.1	1.59	1585.71	792.86	11.17
101023	5	0.71	7100	7.3	1.04	1042.86	521.43	7.34
101024	2	0.53	5300	23.5	3.36	3357.14	1678.57	31.67
101029	7	0.88	8800	43.5	6.21	6214.29	3107.14	35.31
101030	3	0.6	6000	30.9	4.41	4414.29	2207.14	36.79
101031	5	0.71	7100	12.3	1.76	1757.14	878.57	12.37
101034	6	0.8	8000	21.8	3.11	3114.29	1557.14	19.46
101035	6	0.8	8000	39.5	5.64	5642.86	2821.43	35.27
101036	6	0.8	8000	23.7	3.39	3385.71	1692.86	21.16
Mean	5.50				2.84	2844.05	1422.02	19.47
SD	2.54				1.82	1823.22	911.61	12.30

Note: Pediatric subject BSA was calculated based on BSA calculator on http://www-users.med.cornell.edu/~spon/picu/calc/bsacalc.htm

Pharmacokinetic results: Of the 12 subjects in the Luliconazole 1% treatment group who had blood drawn for PK determinations, all 12 had quantifiable levels of the parent compound at the pre-dose and 6-hour post-dose time points. Eleven had quantifiable levels of the Z form of luliconazole at the pre-dose time point and at the 6-hour post-dose time point. On Day 7, the mean (±SD) plasma concentrations of luliconazole were similar at pre-dose and 6 hours post-dose and the values were 4.63 (± 2.93) ng/mL and 4.84 (± 3.33) ng/mL, respectively. All 12 subjects had quantifiable concentrations.

Mean (±SD) plasma concentrations of the metabolite Z form of luliconazole were lower than the mean concentrations of the parent form at both time points and the values were 0.34 (±0.43) ng/mL and 0.46 (± 0.54) ng/mL, respectively. PK results are summarized in Table 2.

Table 2: Summary of PK data

		Luliconazole Cream 1% (N=12)		Vehicle Cream (N=3)	
Time Point		Parent Form Luliconazole	Z-Form Luliconazole	Parent Form Luliconazole	Z-Form Luliconazole
Day 7 Pre-dose	N	12	12	3	3
	N_{quant}	12	11	0	0
	Arithmetic Mean	4.63	0.34	0.00	0.00
	SD	2.93	0.43	0.00	0.00
	Minimum, Maximum	0.8, 9.7	0.0, 1.4	0.0, 0.0	0.0, 0.0
Day 7 6 hr Post-dose	N	12	12	3	3
	N_{quant}	12	11	1	0
	Arithmetic Mean	4.84	0.46	0.07	0.00
	SD	3.33	0.54	0.12	0.00
	Minimum, Maximum	0.4, 11.5	0.0, 1.9	0.0, 0.2	0.0, 0.0

Note: Concentration below the limit of quantitation (<0.0500 ng/mL) are reported as "0.00" for calculating summary statistics.

N_{quant}: number of samples in the N population with quantifiable levels of analyte; SD = Standard Deviation

Reviewer comments: *Of the 3 subjects from the Vehicle group who had blood drawn for PK determinations, none of the subjects had a quantifiable level of the parent compound at the pre-dose time point. However, one had a quantifiable level of the parent compound at the 6-hour post-dose time point. The reason for this is unknown and could have been due to sample contamination during bioanalysis. None of the subjects had a quantifiable level of the Z form of luliconazole at either time point.*

Drug interactions: In the approved label of Luliconazole Cream, the mean (± SD) C_{max} in subjects with tinea pedis and tinea cruris after the final dose was 0.93 (± 1.23) ng/mL and 7.36 (± 2.66) ng/mL. The observed systemic concentrations of luliconazole in this study in subjects with tinea corporis is lower than in subjects with tinea cruris. Hence there appears to be no additional concerns of drug interaction potential in this new population.

Disposition of subjects: 75 subjects (60 active + 15 vehicle) enrolled in this study and all subjects completed the study.

Demographic and baseline characteristics: Demographics and baseline characteristics are shown in Table 3.

Table 3: Demographic and baseline characteristics

		Luliconazole 1% (n=60)	Vehicle (n=15)	All (n=75)
Age (years)	Mean (SD)	8.18 (3.87)	9.13 (5.18)	8.37 (4.14)
	Minimum, Maximum	2.0, 16.0	2.0, 17.0	2.0, 17.0
Sex, n (%)	Male	42 (70.0)	12 (80.0)	54 (72.0)
	Female	18 (30.0)	3 (20.0)	21 (28.0)
Race, n (%)	White	22 (36.7)	5 (33.3)	27 (36.0)
	Black or African American	38 (63.3)	10 (66.7)	48 (64.0)
Ethnicity, n (%)	Hispanic or Latino	60 (100.0)	15 (100.0)	75 (100.0)
	Not Hispanic or Latino	0	0	0
Scaling, n (%)	0=None	0	0	0
	1=Mild	0	0	0
	2=Moderate	22 (36.7)	7 (46.7)	29 (38.7)
	3=Severe	38 (63.3)	8 (53.3)	46 (61.3)
Erythema, n (%)	0=None	0	0	0
	1=Mild	0	0	0
	2=Moderate	34 (56.7)	8 (53.3)	42 (56.0)
	3=Severe	26 (43.3)	7 (46.7)	33 (44.0)
Pruritus, n (%)	0=None	0	0	0
	1=Mild	0	0	0
	2=Moderate	28 (46.7)	6 (40.0)	34 (45.3)
	3=Severe	32 (53.3)	9 (60.0)	41 (54.7)

Summary of Safety: Nine of the subjects (15.0%) in the Luliconazole group reported 18 adverse events (AEs) and 2 subjects (13.3%) in the Vehicle group reported 2 AEs. There were no serious AEs and there were no AEs leading to withdrawal of the subject from the study.

The most frequently reported treatment-emergent adverse event (TEAE) was nasopharyngitis reported in 4 (6.7%) subjects in the Luliconazole group and 2 (13.3%) subjects in the Vehicle group. Headache was reported in 3 (5.0%) of the subjects in the Luliconazole group and no subjects in the Vehicle group reported this.

None of the TEAEs were severe, but 2 of the TEAEs reported in the Luliconazole 1% group, one case of nasopharyngitis and one case of headache, were of moderate severity. The applicant concluded that none of the TEAEs were related to treatment.

Reviewer comments: *See clinical summary for additional analysis of adverse events.*

Bioanalytical method validation: The bioanalytical method used was similar to the one used earlier with the exception that the range of luliconazole and Z-luliconazole was 0.05 ng/mL to 10 ng/mL (the range used earlier was 0.05 ng/mL to 50 ng/mL). The method was validated and long term stability established earlier was adequate to support the storage stability of the PK samples in this study (Details of original bioanalytical method validation can be found in Clinical Pharmacology review dated 07/26/2013 in DARRTS). The method validation parameters for the standard curve is shown in Table 4.

Table 4: Method validation parameters of standard curve

	Luliconazole	***Z-form metabolite***
Between-run accuracy %	-3.8 to 5.0	-2.9 to 4.5
Between-run precision %	4.2 to 7.5	1.8 to 5.9

Reviewer comment: *The inter-run % accuracy and precision for the quality control samples for luliconazole was -3.3% to 1.9% and 4.3% to 11.2% and for Z-form metabolite was -5.3 % to -2.1% and 2.4% to 6.4%, respectively. Incurred sample reanalysis was conducted for 20 out of 30 samples (~ 66.7 % of the samples) and 19 out of 20 (95%) samples were within the ± (b) (4) % acceptable limit.*

Labeling: The following changes are recommended in the applicant's proposed labeling that was submitted where **bold and underlined** text indicates insertion recommended by the reviewer and the ~~strikethrough~~ text indicates reviewer recommended deletion.

(b) (4)

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Recommendation: From a Clinical Pharmacology standpoint, this application is acceptable provided the labeling comments are adequately addressed by the Sponsor.

Post marketing requirement or commitment: None.

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/s/

CHINMAY SHUKLA
12/20/2017

EDWARD D BASHAW
12/20/2017