U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 204153 / S-04
Drug Name:	Luzu Cream, 1%
Indication(s):	For the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis
Applicant:	Valeant
Date(s):	Stamp date: 4/21/2017 PDUFA: 2/21/2018
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Carin Kim, Ph.D.
Concurring Reviewers:	Mohamed Alosh, Ph.D.
Medical Division:	Division of Dermatology and Dental Products (DDDP)
Clinical Team:	Gary Chiang, M.D. Dave Kettl, M.D.
Project Manager:	Cristina Attinello

Keywords:
Tinea Corporis, Post Marketing Requirement (PMR); pediatric subjects

Table of Contents

1. EXECUTIVE SUMMARY

In this efficacy supplement, the applicant provided the results for their Post Marketing Requirement (PMR) study in 75 pediatric subjects. The primary objective of the study was to evaluate the safety and efficacy of Luzu cream, 1% when applied topically for 7 days in pediatric subjects (2-17 years of age, inclusive) with tinea corporis. Of the 75 enrolled subjects, 65 subjects were included in the modified Intent to Treat (mITT) analysis set (51 Luzu cream, and 15 vehicle cream subjects) where mITT was defined as subjects that were randomized, dispensed medication, and had positive KOH and fungal cultures at baseline.

The same efficacy endpoints that were evaluated in the adult trials were evaluated in this PMR study as well. The endpoints are listed below:

- Complete clearance was defined as achieving mycological cure and clinical cure which are defined below
- Mycological Cure was defined as having both a negative KOH and negative fungal culture
- Clinical Cure was defined as an absence of the signs or symptoms of the tinea corporis (score of 0 for each of erythema, scaling, and pruritus)
- Effective Treatment was defined as negative KOH and culture results and at most mild erythema and/or scaling with no pruritus

The PMR study protocol specified that there would be no hypothesis testing for efficacy.

Table 1 describes the summary of results for the efficacy endpoints at Day 28.

Table 1. Efficacy results at Day 28

	Luzu 1% N=51	Vehicle N=14
Complete Clearance [(1)]	36 (70.6%)	5 (35.7%)
Mycological Cure [(2)]	41 (80.4%)	8 (57.1%)
Clinical Cure [(3)]	41 (80.4%)	6 (42.9%)
Effective Treatment [(4)]	39 (76.5%)	8 (57.1%)

Source: sponsor's table 11-3.
(1) Complete clearance was defined as achieving mycological cure and clinical cure which are defined below
(2) Mycological Cure was defined as having both a negative KOH and negative fungal culture
(3) Clinical Cure was defined as an absence of the signs or symptoms of the tinea corporis (score of 0 for each of erythema, scaling, and pruritus)
(4) Effective Treatment was defined as negative KOH and culture results and at most mild erythema and/or scaling with no pruritus

2. INTRODUCTION

2.1 Overview

The applicant proposed to update the Indications and Usage section (Section 1) to allow treatment for subjects that are "2 years of age and older" with tinea corporis as well as the

Clinical Studies section (Section 14) of the labeling with the information regarding the tinea corporis in pediatric subjects, and the safety and efficacy of Luzu cream, 1% for tinea corporis was evaluated in a PMR study.

2.2 Regulatory History

Luzu (luliconazole) cream, 1% was approved on 11/14/2013 for the topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by organisms Tichophyton rubrum and Epidermophyton floccosum in subjects 18 years of age and older. The approval letter (dated 11/14/2013) listed two Post Marketing Requirements (PMR) as shown below:

2101-1 Conduct a multi-center, randomized, blinded, vehicle-controlled study, including pharmacokinetic assessments, with luliconazole cream 1% for the treatment of tinea corporis in pediatric patients 2 years of age and older.

Final Protocol Submission:	01/2014
Study Completion:	11/2016
Final Report Submission:	04/2017

2101-2 Conduct a maximum use pharmacokinetic safety study in pediatric patients 12 years to 17 years 11 months of age with interdigital tinea pedis and tinea cruris.

Final Protocol Submission:	01/2014
Study Completion:	10/2016
Final Report Submission:	02/2017

PMR 2101-1 is the subject of this review, and the regulatory history as well as the study relevant to this PMR is summarized in this review. The protocol for PMR 2101-1 was submitted to the Agency (stamp date: 1/31/2014) for comments. In that protocol, the sponsor proposed to evaluate several efficacy endpoints, and stated that "no hypothesis testing will be conducted". A statistical review for the protocol was signed off in DARRTS (dated: 3/27/2014). In an advice letter to the sponsor (dated: 4/16/2014), the Agency commented on the adequacy of the proposed sample size, and recommended that the study enroll adequate numbers of subjects across the age spectrum.

On 4/21/2017, the applicant submitted an efficacy supplement with the intention to update the Clinical Studies section (section 14) of the labeling by including the results from the PMR pediatric trial.

2.3 Data Sources

This reviewer evaluated the applicant's clinical study reports and clinical summaries, as well as the proposed labeling. This submission was submitted in eCTD format and was

entirely electronic. Both SDTM and analysis datasets were submitted. The datasets in this review are archived at: \\cdsesub1\evsprod\nda204153\0059\m5\datasets\mp-1011\analysis\adam\datasets.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The applicant submitted electronic analysis datasets for review, and no requests for additional datasets were made to the applicant.

3.2 Evaluation of Efficacy

3.2.1 Study Design

In this efficacy supplement, the applicant provided the results for their PMR study in 75 pediatric subjects.

The primary objective of the study was to evaluate the safety and efficacy of Luzu cream, 1% when applied topically for 7 days in pediatric subjects (2-17 years of age, inclusive) with tinea corporis.

A total of 75 pediatric subjects with tinea corporis enrolled from 3 investigational sites in Latin America, and they were randomized in a 4:1 ratio to the Luzu cream, 1% or vehicle arms. Study treatment was applied to the affected area and approximately one inch of the surrounding area once daily in the morning at approximately the same time for 7 days. Subjects returned to the investigational site for safety and efficacy observations at Days 7, 14, 21, and 28.

For the analysis, the applicant used the modified Intent to Treat (mITT) population defined as subjects who had a positive KOH wet mount and a positive fungal culture at baseline. Of the 75 enrolled subjects, 65 subjects were mITT subjects.

According to the protocol, "efficacy will be evaluated, but no hypothesis testing will be conducted" for the following efficacy endpoints:

- Proportion of subjects who achieve "mycological cure" at Day 28
- Proportion of subjects who achieve "clinical cure" at Day 28
- Proportion of subjects who achieve "complete clearance" at Day 28 (mycological cure + clinical cure)
- Proportion of subjects who achieve "effective treatment" (negative KOH and culture, and at most mild erythema and/or scaling and no pruritus) at Day 28
- Proportion of subjects who achieve "effective treatment" at Day 21
- Proportion of subjects who achieve "effective treatment" at Day 14

- Proportion of subjects who achieve "effective treatment" at Day 7

The definitions of complete clearance, mycological cure, clinical cure and effective treatment are provided in Section 1 (page 3) of this review.

For handling of missing data, the protocol specified using the last observation carried forward (LOCF).

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

Table 2 presents the subject disposition of the PMR study. All subjects completed the study, and of the 75 subjects that were randomized at baseline, 65 subjects were included in the modified Intent to Treat (mITT) analysis set (51 Luzu 1%, and 15 vehicle subjects) where mITT was defined as subjects that were randomized, dispensed medication, and had positive KOH and fungal cultures at baseline.

Table 2. Subject Disposition

	Luzu 1%	Vehicle
Randomized subjects	60	15
Safety Set	60 (100%)	15 (100%)
Subjects Completed the Study	60 (100%)	15 (100%)
Subjects in the mITT (1)	51 (85%)	14 (93%)

Source: reviewer's table;
(1) mITT: all subjects who were randomized, dispensed medication, and had positive KOH and fungal cultures.

For the enrolled subjects, the mean age was 8.2 and 9.1 for Luzu 1% and vehicle cream, respectively, and the age ranged from 2 to 17 years. Approximately 72% of the subjects were male, and approximately 64% of the subjects were black. All were of Hispanic or Latino ethnicity. The baseline demographics for the mITT set were similar to the randomized set and is presented in the Appendix of this review.

Table 3. Baseline Demographics for Randomized Subjects

	Luzu 1% N=60	Vehicle N=15
Age		
Mean (SD)	8.18 (3.87)	9.13 (5.18)
Min, Max	2, 16	2, 17
Sex		
Male	42 (70%)	12 (80%)
Female	18 (30%)	3 (20%)
Race		
White	22 (37%)	5 (33%)
Black	38 (63%)	10 (67%)
Ethnicity		
Hispanic/Latino	51 (100%)	14 (100%)

Source: sponsor's table 11-2

The baseline characteristics of the randomized subjects are summarized in the table below. All enrolled subjects had moderate or severe pruritus, erythema, and scaling at baseline.

Table 4. Baseline Characteristics for Randomized Subjects

	Luzu 1% N=60	Vehicle N=15
Pruritus		
Moderate	22 (37%)	7 (47%)
Severe	38 (63%)	6 (53%)
Erythema		
Moderate	34 (57%)	8 (53%)
Severe	26 (43%)	7 (47%)
Scaling		
Moderate	28 (47%)	6 (40%)
Severe	32 (53%)	9 (60%)

Source: sponsor's table 11-2

3.2.3 Results and Conclusions

The same efficacy endpoints that were evaluated in the adult trials were evaluated in this PMR study as well.

Table 5 is a summary of results for the efficacy endpoints at Day 28.

Table 5. Efficacy results at Day 28

	Luzu 1% N=51	Vehicle N=14
Complete Clearance (1)	36 (70.6%)	5 (35.7%)
Mycological Cure (2)	41 (80.4%)	8 (57.1%)
Clinical Cure (3)	41 (80.4%)	6 (42.9%)
Effective Treatment (4)	39 (76.5%)	8 (57.1%)

Source: sponsor's table 11-3.
(1) Complete clearance was defined as achieving mycological cure and clinical cure which are defined below
(2) Mycological Cure was defined as having both a negative KOH and negative fungal culture
(3) Clinical Cure was defined as an absence of the signs or symptoms of the tinea corporis (score of 0 for each of erythema, scaling, and pruritus)
(4) Effective Treatment was defined as negative KOH and culture results and at most mild erythema and/or scaling with no pruritus

3.3 Evaluation of Safety

According to the study report, a total of 18 adverse events (AEs) were reported in 9 subjects in the Luzu cream, 1%, and a total of 2 AEs were reported in 2 vehicle subjects. The applicant reported that they were all treatment-emergent AEs. The following is a brief summary of the treatment-emergent adverse events for the enrolled subjects. For further evaluation of safety, refer to the clinical review.

Table 6. Treatment-emergent Adverse Events

	Luzu 1% N=60	Vehicle N=15
Gastrointestinal disorders	1	0
Infections and infestations	4	2
Nervous system disorders	3	0
Investigations	2	0

Source: sponsor's Table 12-2

4. FINDINGS IN SUBGROUP POPULATIONS

This was a small PMR study with a vehicle arm (15 mITT subjects) and with the majority of the mITT subjects being male, and black. Therefore, any differences in efficacy for the subgroups would be difficult to detect. Table 7 below presents the complete clearance rate for the age, sex, race subgroups.

Table 7. Complete Clearance (1) by Subgroup for the mITT subjects

	Luzu 1% N=60	Vehicle N=15
Age		
<8 years old	20/30 (67%)	4/8 (50%)
≥8 years old	16/21 (76%)	1/6 (17%)
Sex		
Male	27/35 (77%)	4/12 (33%)
Female	9/16 (56%)	1/2 (50%)
Race		
White	15/16 (94%)	1/4 (25%)
Black	21/35 (60%)	4/10 (40%)

Source: reviewer's table;
(1) Complete clearance was defined as achieving mycological cure and clinical cure which are defined below.
Mycological Cure was defined as having both a negative KOH and negative fungal culture.
Clinical Cure was defined as an absence of the signs or symptoms of the tinea corporis (score of 0 for each of erythema, scaling, and pruritus).

Subjects were enrolled from 3 sites in Latin America (2 sites in Dominican Republic and 1 in Honduras).

Table 8. Complete Clearance (1) by Sites

	Luzu 1% N=60	Vehicle N=15
Site ID		
101	11/23 (48%)	2/6 (33%)
102	11/11 (100%)	1/3 (33%)
104	14/17 (82%)	2/5 (40%)

Source: reviewer's table
(1) Complete clearance was defined as achieving mycological cure and clinical cure which are defined below.
Mycological Cure was defined as having both a negative KOH and negative fungal culture.
Clinical Cure was defined as an absence of the signs or symptoms of the tinea corporis (score of 0 for each of erythema, scaling, and pruritus).

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

This PMR study evaluated the safety and efficacy of Luzu cream, 1% in 75 pediatric subjects (age 2 to 17) with tinea corporis. The enrolled subjects had a mean age of 8.2 and 9.1 for Luzu cream, 1% and vehicle cream, respectively. Approximately 72% of the enrolled subjects were male, and approximately 64% were black. All were of Hispanic or Latino ethnicity.

It should be noted that for this PMR study that evaluated safety and efficacy, there were no hypothesis testing for efficacy. There were no statistical issues affecting the overall findings.

5.2 Conclusions

The completed study fulfilled the Post Marketing Requirements (PMR) 2101-1.

6. Appendix

For efficacy analyses, the mITT set was considered where mITT was defined as subjects that were randomized, dispensed medication, and had positive KOH and fungal cultures at baseline. The following are baseline demographics and baseline characteristics tables for the mITT subjects.

Table A1. Baseline Demographics for the mITT set

	Luzu 1% N=51	Vehicle N=14
Age		
Mean (SD)	7.69 (3.55)	8.57 (4.88)
Min, Max	2, 16	2, 17
Sex		
Male	35 (69%)	12 (86%)
Female	16 (31%)	2 (14%)
Race		
White	16 (31%)	4 (29%)
Black	35 (69%)	10 (71%)
Ethnicity		
Hispanic/Latino	51 (100%)	14 (100%)

Source: reviewer's table

Table A2. Baseline Characteristics for the mITT Subjects

	Luzu 1% N=51	Vehicle N=14
Pruritus		
Moderate	24 (47%)	6 (43%)
Severe	27 (53%)	8 (57%)
Erythema		
Moderate	30 (59%)	8 (57%)
Severe	21 (41%)	6 (43%)
Scaling		
Moderate	17 (33%)	7 (50%)
Severe	34 (67%)	7 (50%)

Source: reviewer's table

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/s/

CARIN J KIM
12/18/2017

MOHAMED A ALOSH
12/18/2017