CLINICAL REVIEW

Application Type	Efficacy Supplement
Application Number(s)	204153/S-004
Priority or Standard	Standard
Submit Date(s)	21-APRIL-2017
Received Date(s)	21-APRIL-2017
PDUFA Goal Date	21-FEB-2018
Division / Office	DDDP/ODE III
Reviewer Name(s)	Gary Chiang MD, MPH
Review Completion Date	25-JAN-2018
Established Name	Luliconazole
(Proposed) Trade Name	LUZU
Therapeutic Class	Azole antifungal
Applicant	Valeant Pharmaceutical Corp
Formulation(s)	Cream, 1%
Dosing Regimen	Topical once daily
Proposed Indication(s)	Interdigital tinea pedis, tinea cruris, and tinea corporis
Intended Population(s)	Children 2 years of age and older

Template Version: March 6, 2009

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Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Luliconazole is available in the United States under NDA 204153 as LUZU Cream, approved November 14, 2013 for the topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organisms *Trichophyton rubrum* and *Epidermophyton floccosum*, in patients 18 years of age and older.

This "Prior Approval Labeling Supplement" (PAS) was submitted to NDA 204153 for Luzu® (luliconazole) Cream, 1%, to provide for revised clinical labeling incorporating key findings from Study V01-LUZB-401 (MP-1011), which was conducted to satisfy the required pediatric assessment 2101-1 outlined in the NDA approval letter dated 14-NOV-2013. During the review of NDA 204153, PeRC considered the applicant's Pediatric Plan to extrapolate efficacy data for pediatric patients with tinea pedis, tinea cruris, and tinea corporis. Since the adult data submitted to the NDA supported approval, the applicant agreed to post-approval studies for the pediatric populations. The agreed upon plan is outlined in the approval letter.

From a clinical prospective, an approval recommendation is made for the use of luliconazole cream, 1% applied topically onto affected areas plus a ½ inch margin of healthy surrounding skin once-daily for 2 weeks in treatment of interdigital tinea pedis, and once-daily for 1 week in the treatment of tinea cruris and tinea corporis due to *Trichophyton rubrum* and *Epidermophyton floccosum* in children ≥ 2 years of age and older. This recommendation is predicated upon the applicant's acceptance of revised labeling.

The applicant has completed the required pediatric assessments put forth in the approval letter for the original application.

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

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

The single pediatric clinical trial in tinea corporis provided sufficient evidence of safety in patients ≥ 2 years of age and older. The efficacy of luliconazole cream, 1% was previously demonstrated in the original application approved for treatment of adults with tinea pedis, tinea cruris, and tinea corporis.

1.2 Risk Benefit Assessment

Sufficient evidence of safety and efficacy is provided in this application to reason that the benefit of the drug product outweighs the risk of this product in the populations described in labeling.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

- None

1.4 Recommendations for Postmarket Requirements and Commitments

- None

2 Introduction and Regulatory Background

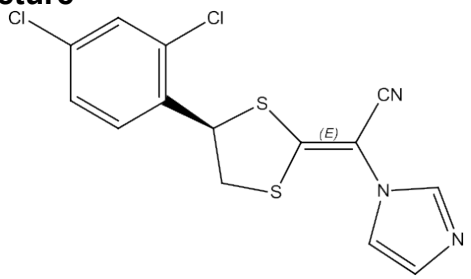
Luliconazole Cream, 1% is an imidazole antifungal with a dual mechanism of action. Luliconazole exhibits antimycotic and fungicidal activity against dermatophytes through the inhibition of ergosterol biosynthesis. In addition, luliconazole's antifungal activity includes inhibition of protease production by *Trichophyton* species.

The development plan for luliconazole cream, 1% included a Pre-IND meeting, two End-of-Phase 2 meetings, and a Pre-NDA meeting. In addition, the sponsor submitted two Special Protocol Assessments for Agency agreements. The submission includes a total of 11 U.S. clinical studies and seven clinical studies conducted in Japan to form the Japanese approval of luliconazole.

2.1 Product Information

LUZU® Cream, 1% is an imidazole antimycotic/antifungal drug with a dithiolan structure incorporated into a topical cream formulation at strength of 1% w/w. Each gram of drug product contains 10 mg luliconazole in a white cream formulation consisting of purified water, propylene glycol, methylparaben, polysorbate 60, cetostearyl alcohol, sorbitan monostearate, isopropyl myristate, medium chain triglycerides, benzyl alcohol, and butylated hydroxytoluene.

Figure 1: Molecular Structure



The product is contained in a blind-end aluminum tube with a 2, 30, or 60 gram fill volume and a (b) (4) .

The established name is luliconazole. The DMEPA approved proposed name is LUZU® (luliconazole) Cream, 1%.

Luliconazole Cream, 1% was approved on April 11, 2005 in Japan under the trade names Lulicon® Cream, 1% and Lulicon® Solution, 1%. The approved indications in Japan include the following cutaneous mycoses:

- Tinea: tinea pedis, tinea corporis, and tinea cruris
- Candidiasis: interdigital erosion and intertrigo
- Tinea versicolor

The Japanese international safety experience was considered as part of the assessment for this approval of the LUZU application.

2.2 Tables of Currently Available Treatments for Proposed Indications

It is well accepted that common tinea infections are treated with topical agents, therapeutic success is limited because of poor compliance, poor awareness regarding the disease condition by the patient, and frequent recurrence. In general, current tinea pedis therapies require once a day or twice a day treatment for up to four weeks and current tinea cruris and tinea corporis therapies require once a day or twice a day treatment for up to two weeks, and treatment should continue for at least one week after symptoms resolved to reduce recurrence. [1]

1 Fitzpatrick, T.B., Johnson, R.A., and Wolff, K. Color Atlas and Synopsis of Clinical Dermatology. Third Edition. 1997. Section 25; pg. 3-25.

Table 1: Currently Approved Topical Antifungal Cream Formulations for Treatment of Tinea Pedis, Cruris, and Corporis

Topical Antifungal Agents (Tinea Pedis)	NDA	Dosage (Tinea Pedis)	Date of Approval	Mechanism of Action
Econazole (Spectazole)	NDA 018-751	QD for 1 month	December 23, 1982	Azole: Alters fungal cell wall membrane permeability; may interfere with RNA and protein synthesis and lipid metabolism
Ciclopirox (Loprox)	NDA 018-748	BID 4 weeks	December 30, 1982	Inhibiting transport of essential elements in the fungal cell disrupting the synthesis of DNA, RNA, and protein
Sulconazole (Exelderm)	NDA 018-738	BID 4 weeks	August 30, 1985	Substituted imidazole derivative which inhibits metabolic reactions necessary for the synthesis of ergosterol, an essential membrane component.
Naftifine (Naftin) 1%	NDA 19-599	QD for 2 weeks	February 29, 1988	Interfere with sterol biosynthesis by inhibiting the enzyme squalene 2,3-epoxidase
Naftifine (Naftin) 2% Gel	NDA 204-286	QD for 2 weeks	June 27, 2013	Interfere with sterol biosynthesis by inhibiting the enzyme squalene 2,3-epoxidase
Oxiconazole (Oxistat)	NDA 019-828	QD-BID 1 month	December 30, 1988	Azole: destroys membrane integrity of fungi through inhibition of ergosterol synthesis
Clotrimazole (Lotrimin AF)	NDA 020-888	BID 2-4 weeks	October 27, 1989	Azole: Binds to phospholipids in the fungal cell membrane altering cell wall permeability resulting in loss of essential intracellular elements
Terbinafine (Lamisil Cream)	NDA 020-192	Gel: BID for 7 days Cream: BID < 4 weeks	December 30, 1992	Synthetic allylamine derivative which inhibits squalene epoxidase, a key enzyme in sterol biosynthesis in fungi
Butenafine (Mentax)	NDA 020-524	BID 1 week/QD 4 weeks	October 18, 1996	Exerts fungicidal activity against dermatophytes by blocking squalene epoxidation, resulting in inhibition of ergosterol synthesis and subsequent weakening of fungal cell membrane
Terbinafine (Lamisil Solution)	NDA 020-980	BID 1 week	October 17, 1997	Synthetic allylamine derivative which inhibits squalene epoxidase, a key enzyme in sterol biosynthesis in fungi
Butenafine (Lotrimin Ultra)	NDA 021-307	BID 1 week/QD 4 weeks	December 7, 2001	Exerts fungicidal activity against dermatophytes by blocking squalene epoxidation, resulting in inhibition of ergosterol synthesis and subsequent weakening of fungal cell membrane
Sertaconazole (Ertaczo)	NDA 021-385	BID 4 weeks	December 10, 2003	Azole: alters fungal cell wall membrane permeability; inhibits the CYP-450-dependent synthesis of ergosterol

Source: Compiled by G.Chiang form DARRTS database

2.3 Availability of Proposed Active Ingredient in the United States

Luliconazole is available in the United States under the NDA 204153 as LUZU approved November 14, 2013 for the topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organisms *Trichophyton rubrum* and *Epidermophyton floccosum*, in patients 18 years of age and older.

2.4 Important Safety Issues with Consideration to Related Drugs

Luliconazole cream, 1% is a synthetic imidazole drug unlike the currently marketed antifungals which are generally allylamine derivatives. As with all antifungal drug products, particular attention is directed at adverse events related to assessments of liver, kidney, cardiac parameters, and drug-drug interactions. The original application identified no serious safety concerns with luliconazole, cream 1%.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

LUZU® (luliconazole) Cream, 1% was approved on November 14, 2013. In the approval letter, the Agency specified several PMR/PMC for the applicant to complete.

- PMC 2101-5 Conduct in vitro assessments to evaluate the following:
  a) Inhibition potential of luliconazole for enzymes CYP2B6 and CYP2C8
  b) Induction potential of luliconazole for enzymes CYP1A2, CYP2B6 and CYP3A
  Further in vivo assessment to address drug interaction potential may be needed based on the results of these in vitro assessments.

  This PMC was completed and deemed fulfilled on 7-MAR-2016

- PMR 2101-3 Conduct an in vivo drug interaction trial using an appropriate probe substrate to evaluate the inhibition potential of luliconazole for CYP2C19 under maximal use conditions in subjects with tinea cruris and interdigital tinea pedis.

  This PMR was completed and deemed fulfilled on 17-MAY-2016

- PMR 2101-4 Conduct an in vivo drug interaction trial using an appropriate probe substrate to evaluate the inhibition potential of luliconazole for CYP3A4 under maximal use conditions in subjects with tinea cruris and interdigital tinea pedis. This trial may be omitted if the results from the trial with the CYP2C19 substrate (PMR 2101-3) indicate no significant interaction.

  A waiver was granted to release the sponsor from this PMR on 17-MAY-2016

- Approval of PAS updates to section 8 of the prescribing information to conform to the PLLR and proposed updates to section 12.3 to include information about CYP2C19 from a postmarketing study on 8-FEB-2017

The pediatric development plan for luliconazole included two postmarketing requirements.

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.

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.

This supplement proved for the completed PMR for 2101-1 to include labeling update for the information derived from the study.

2.6 Other Relevant Background Information

The majority of superficial fungal infections in the United States are tinea infections, which are primarily caused by three types of dermatophytes: *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum*. [2] The most common tinea are defined by the location of the infection as follows: tinea pedis (foot and also known as "athlete's foot"), tinea cruris (groin and surrounding issues, and also known as "jock itch"), and tinea corporis (body and commonly known as "ringworm"). These organisms are spread by human-to-human contact with infected skin scales in moist environments such as shower rooms or bathing areas. Diagnoses is usually by physical examination, in combination with laboratory evidence of the fungal organism by direct microscopic examination with potassium hydroxide (KOH) followed by culture of the dermatophyte. Tinea corporis is a superficial fungal infection of the glabrous skin (i.e., skin regions except the scalp, groin, palms, and soles) and affects persons of all age groups, but the prevalence is highest in preadolescents. [3]

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The study protocol, Informed Consent Forms (ICFs), and other information for subjects were approved by the central Institutional Review Board (IRB). The IRB was (b) (4) .

3.2 Compliance with Good Clinical Practices

According to the applicant, studies were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki, and in compliance with all International Conferences on Harmonization Good Clinical Practice (GCP) guidelines. In addition, all local regulatory requirements were followed.

2 Foster, W.K., Ghannoum M.A. and Elewski, B.E. Epideminological surveillance of cutaneous fungal infection in the United States from 1999 to 2001. *J. AM. ACAD. DERMATOL*:2004: 50 (5); 748-752.
3 Lesher, J.L. Tinea corporis. eMedicine from WebMD [Internet]. 2009 Dec [cited 2013 MAR 04].

3.3 Financial Disclosures

This study was conducted under the sponsorship of Dow Pharmaceutical Sciences, a Division of Valeant Pharmaceuticals, North America LLC. Clinical monitoring and statistical analyses were performed by (b) (4) .; clinical trial supplies were provided by Valeant - Bausch and Lomb CTM Supply group, Rochester, NY.

Table 2: Principle Investigators

Principal Investigator	Location (office)
Daisy Blanco, MD	Instituto Dermatologico Calle Federico Velazquez, Esq. Albert Thomas, Santo Domingo, Dominican Republic
Nelly Paz, MD	Hospital y Clinica Bendana, Ave. Circunvalacion, 3er Piso, local 312, San Pedro Sula, Honduras
Ynca Vasquez, MD	Instituto Dematologico y Cirugia de Piel Calle Prolongacion Sanchez, Esquina Luperon #1 San Cristobal, Dominican Republic

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There are no changes to the product as noted in the CMC review for this NDA.

4.2 Clinical Microbiology

There are no clinical microbiology safety issues in this NDA.

4.3 Preclinical Pharmacology/Toxicology

There are no Pharmacology/Toxicology safety issues in this NDA. Prior non-clinical information in the labeling is up-to-date. The minor changes in the non-clinical sections of the label have been reviewed and are deemed acceptable. Final labeling changes will be provided in the approval letter.

4.4 Clinical Pharmacology

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: 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 was 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).

Clinical Pharmacology Reviewer comments: *There were 6 subjects in the PK cohort aged 6 years and below.*

PK assessment: 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 t_{max} (6 hours after the final dose) for 15 subjects (12 active + 3 placebo).

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 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.

Table 3: Summary of PK data

Time Point		Luliconazole Cream 1% (N=12)		Vehicle Cream (N=3)	
		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

Clinical Pharmacology Reviewer comments: *In the approved label for 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 concentration 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.*

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 AEs leading to withdrawal of the subject from the study and there were no serious AEs.

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.

Clinical Pharmacology Reviewer's Recommendation: *NDA 204153/S-004 is acceptable from Clinical Pharmacology.*

5 Sources of Clinical Data

The current study investigated the safety and efficacy of luliconazole Cream 1% in pediatric subjects aged 2 years to 17 years (inclusive) with tinea corporis. The objective of this study was to evaluate the safety, efficacy, and pharmacokinetics of Luliconazole Cream 1% when applied topically for 7 days in pediatric subjects 2 years to 17 years of age (inclusive) with tinea corporis. The design of the protocol was agreed upon with the Agency prior to the start of the PMR study.

5.2 Review Strategy

The focus of this supplement will be on the single study in pediatric patients with tinea corporis.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Planned Clinical Study: MP-1011

Title: A Randomized, Multi-Center, Double-Blind, Parallel-group, vehicle-controlled study conducted at 3 investigational sites to determine the safety and efficacy of Luliconazole Cream 1% in pediatric subjects with tinea corporis, with at least moderate erythema, mild scaling, and moderate pruritus

Objective: The objective of this study was to evaluate the safety, efficacy, and pharmacokinetics of Luliconazole Cream 1% when applied topically for 7 days in pediatric subjects 2 years to 17 years of age (inclusive) with tinea corporis.

Study Design: This was a multi-center, randomized, double-blind, parallel group, vehicle-controlled study that was conducted at 3 investigator sites in Latin America to determine the safety and efficacy of Luliconazole Cream 1% in pediatric subjects with tinea corporis with at least moderate erythema, mild scaling, and moderate pruritus.

Approximately 75 male and female subjects aged 2 years to 17 years (inclusive) were recruited and randomly allocated (4:1) to treatment with either Luliconazole Cream 1% or Vehicle Cream (containing no active ingredient), once daily for 7 days. Study drug was applied once daily in the morning, at approximately the same time, for 7 days to the affected area and approximately 1 inch of the immediate surrounding area.

Number of Subjects: 75 male and female subjects aged 2 years to 17 years (inclusive)

Ages of Subjects for Inclusion: 2 years to 17 years (inclusive)

Inclusion Criteria:

1. Subjects (or legal guardian/caregiver) with the ability and willingness to sign a written informed consent and/or assent (age appropriate).

2. Subject of either gender had to be at least 2 years to < 18 years of age (2 to 17 years, inclusive).
3. Subjects with a clinical diagnosis of tinea corporis characterized by clinical evidence of a tinea infection (at least moderate erythema, mild scaling, and moderate pruritus).
4. Subjects with a mycological diagnosis of tinea corporis confirmed by the detection of fungal hyphae on a microscopic KOH wet mount.
5. Sexually active females of child-bearing potential (FOCBP) must have been willing to use:
    a. One of these highly effective contraception methods
        i. Intrauterine device (IUD); hormonal (injections, implants, transdermal patch, vaginal ring; tubal ligation; partner vasectomy,

    OR

    b. Oral contraceptives WITH a barrier method (listed below), OR
    c. Two barrier forms of contraception (listed below)
        i. Male or female condom; diaphragm with spermicides; cervical cap with spermicides; contraceptive sponge.
6. Subjects must have been in good general health and free of any disease that in the Investigator's opinion might interfere with the study evaluations.
7. Subjects/caregiver must have been able to communicate, able to understand the study procedures, and willing to comply with the study requirements.

Exclusion Criteria:

1. Subjects with active atopic or contact dermatitis in the area to be treated.
2. Subjects with severe dermatophytoses, mucocutaneous candidiasis, or bacterial skin infection.
3. Female subjects who were pregnant and/or nursing or planning a pregnancy during the course of the trial. Subjects who tested positive for pregnancy after start of test treatment were to be discontinued from test treatment but were to be followed for safety purposes.
4. Subjects who were immunocompromised (due to disease, eg, human immunodeficiency virus [HIV] or medications).
5. Subjects who had a recent history of or current drug or alcohol abuse.
6. Subjects with a history of intolerance or hypersensitivity to imidazole compounds or the inactive components of the study drug.
7. Subjects with current significant skin disease that was considered by the Investigator to be clinically important and indicative of conditions that might have complicated interpretation of study results.
8. Subjects with a life-threatening condition (eg, autoimmune deficiency syndrome, cancer, unstable angina, or myocardial infarction) within the last 6 months.
9. Subjects with abnormal findings that were considered by the Investigator to be clinically important and indicative of conditions that might have complicated interpretation of study results.
10. Subjects with uncontrolled diabetes mellitus in the judgment of the Investigator.
11. Subjects/caregivers who were unable to communicate or cooperate with the Investigator due to language problems, poor mental development, or impaired cerebral function.
12. Subjects who were currently in a clinical drug research study with other medications or had been a participant in a clinical trial within 30 days or 5 half-lives of the investigational drug (whichever was longer) prior to the Baseline visit.
13. Subjects with any other condition which, in the judgment of the investigator, would have put the subject at unacceptable risk for participation in the study, and
14. Subjects who were using the following medications;

a. topical antifungal agent within 14 days of the Baseline visit (30 days for terbinafine, butenafine, and naftifine [topical]),
b. systemic antifungal within 8 weeks or 5 half-lives of the antifungal (whichever was longer) prior to the Baseline visit (8 months for oral terbinafine),
c. topical antibiotics within 30 days of the Baseline visit,
d. systemic antibiotics within 30 days or 5 half-lives of the antibiotic (whichever was longer) prior to the Baseline visit,
e. antibacterial soaps on the affected area within 1 week of the Baseline visit,
f. topical corticosteroid in treatment area(s) within 14 days of the Baseline visit,
g. systemic of intralesional corticosteroids within 30 days of the Baseline visit,
h. any other medicated topical treatments to the treatment area(s) within 7 days of the Baseline visit,
i. any other significant treatments, except hormonal contraception and multivitamins, at the discretion of the Investigator that would have interfered with study treatment.

Study Plan:

Approximately 75 male and female subjects aged 2 years to 17 years (inclusive) were recruited and randomly allocated (4:1) to treatment with either Luliconazole Cream 1% or Vehicle Cream (containing no active ingredient), once daily for 7 days. Study drug was applied once daily in the morning, at approximately the same time, for 7 days to the affected area and approximately 1 inch of the immediate surrounding area.

The first administration of study medication was completed at the investigational site at the Baseline evaluation (Day 1). Subsequent applications of study medication were administered by the subjects/caregivers daily through Day 7. Study medication was applied at the investigational site on Day 7. Both treatment groups were followed for a 21-day post final treatment period (Day 28). Each subject had documentation of the disease at the Baseline visit with the recording of clinical parameters of the signs and symptoms of the infection and mycological confirmation by microscopy (potassium hydroxide [KOH] wet mount). Culture samples were sent to a central mycology laboratory for confirmation of the fungus. All subjects with a clinical diagnosis of tinea corporis confirmed by the detection of fungal hyphae on a KOH wet mount, performed at Screening and Baseline at the investigational site were eligible to be included in the study.

Each of the signs of tinea corporis were evaluated by scoring the severity of erythema, scaling, and pruritus on a four-point scale (0-none; 1-mild; 2-moderate; and 3-severe). Clinical and mycological testing were performed at the Baseline visit (Day 1) and repeated at the end of treatment on Day 7, and at the Day 14, Day 21, and Day 28 post treatment follow-up visits. Those who subsequently showed negative Baseline culture for a dermatophyte at the central mycology laboratory were categorized as "delayed exclusions" and excluded from the efficacy analyses.

Efficacy Assessments:

The primary analysis population, the MITT population, was defined as all subjects randomized and dispensed medication with positive baseline KOH and fungal cultures.

Primary Efficacy Endpoint:
The primary efficacy endpoint was complete cure at Day 42 (4 weeks post-treatment), defined as a negative KOH, negative culture, and no evidence of clinical disease as indicated by scores of 0 (none) on each sign or symptom (erythema, scaling, and pruritus). Each sign and symptom is evaluated on the following scale:

Table 4: Signs and Symptoms Severity Score for Study MP-1000-02 and -03

To be assessed by the Investigator at the time of the study visit:

Scaling:	
0 – None	No scaling
1 – Mild	Barely perceptible, fine scales present
2 – Moderate	Fine scale generalized to all areas
3 – Severe	Scaling and peeling of skin
Erythema:	
0 – None	No evidence of erythema present
1 – Mild	Slight pink coloration
2 – Moderate	Definite redness
3 – Severe	Marked erythema, bright red to dusky dark red in color

To be assessed by the Subject as an average of the last 24 hours:

Pruritus:	
0 – None	No itching
1 – Mild	Slight itching, not really bothersome
2 – Moderate	Definite itching that is somewhat bothersome
3 – Severe	Intense itching that may interrupt daily activities and/or sleep

These assessments will be performed at all study visits: Screening, Baseline (Day 0), Day 14, 14 days post-treatment, and at the 28-day post-treatment follow-up visit.

Secondary Efficacy Endpoints:
- Proportion of subjects who achieve "effective treatment" (defined as negative KOH and culture and at most mild erythema and/or scaling and no pruritus) at Day 42 (28 days post-treatment).
- Proportion of subjects who achieve "complete clearance" at Day 28 (14 days post-treatment).
- The proportion of subjects who achieve "mycological cure" at Day 42 (28 days post-treatment).
- The proportion of subjects who achieve "clinical cure" at Day 42 (28 days post-treatment).

Other Efficacy Endpoints:
The study will also collect clinical isolates to identity fungal organisms causing the disease to support labeling.

Safety Assessments:
At all visits, a safety evaluation and clinical grading will be performed. Local and systemic adverse event information will be collected, and blood will be drawn to obtain laboratory tests (chemistry, hematology, and urinalysis). On approximately 75 subjects enrolled at selected sites, 12-lead ECG monitoring and QT/QTc assessments will be performed. Baseline ECGs will be obtained during screening which will be compared to the 12-lead ECG obtained at the completion of treatment (Visit 2).

The safety population will include all randomized subjects who receive at least one application of study medication and who have at least one post-Baseline evaluation.

Subjects will be discontinued for adverse events as determined by the investigator, worsening of condition, and pregnancy. Urine pregnancy testing will have a minimum analytical sensitivity of 25mIU/mL. Any pregnancies which occur during the trial will be followed to term

Reviewer's comment:
The protocol for this PMR was reviewed by the Agency. The safety assessments are acceptable.

6 Review of Efficacy

Efficacy Summary
The primary objective of this study was to evaluate the safety and pharmacokinetics of Luliconazole Cream 1% when applied topically for 7 days in pediatric subjects 2 years to 17 years of age (inclusive) with tinea corporis. Efficacy was evaluated but no hypothesis testing was conducted. 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 complete clearance rate at Day 28 (mITT population) was 70.6% in the Luliconazole 1% group compared with 35.7% in the Vehicle group.

Table 5: Complete Clearance Rates at Day 28 (MITT Population)

	Luliconazole Cream 1% (N=51)		Vehicle Cream (N=14)	
	Proportion, n/N (%)	95% Confidence Interval	Proportion, n/N (%)	95% Confidence Interval
Subjects who Achieved:				
Complete Clearance	36/51 (70.6)	57.6, 83.5	5/14 (35.7)	7.0, 64.4

Note: Last observations are carried forward to provide a value for missing efficacy parameters.

6.1 Indication

LUZU® (luliconazole) Cream, 1% is indicated for the topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organisms *Trichophyton rubrum*, *Trichophyton mentagrophytes*, or *Epidermophyton floccosum*, in patients 18 years of age and older. This supplement will provide the addition of topical treatment of tinea corporis down to the age of 2 years old.

6.1.1 Methods

Efficacy was evaluated but no hypothesis testing was conducted. The primary endpoints of "Complete Clearance" were analyzed by CMH test, stratified by analysis center. The primary efficacy analysis was based on MITT population with missing data imputed using the LOCF method.

6.1.2 Demographics

Demographics and baseline characteristics are presented in the tables below for the safety population.

Table 6: Summary of Demographic Characteristics (Safety Population)

	Luliconazole Cream, 1% (N=60)	Vehicle Cream (N=15)	Total (N=75)
Age (years)			
mean (SD)	8.18 (3.87)	9.13 (5.18)	8.37 (4.14)
Min. To Max.	2.0, 16.0	2.0, 17.0	2.0, 17.0
Gender			
Male	42 (70.0)	12 (80.0)	54 (72.0)
Female	18 (30.0)	3 (20.0)	21 (28.0)
Ethnicity			
Hispanic or Latino	60 (100.)	15 (100.0)	75 (100.0)
Not Hispanic or Latino	0	0	0
Race			
White	22 (36.7)	5 (33.3)	27 (36.0)
Black	38 (63.3)	10 (66.7)	48 (64.0)

Source: Study report MP 1011, table 14.1.2.1

The overall mean age was 8.37 years and ranged from 2 to 17 years. The mean age of the subjects in the luliconazole 1% group was 8.18 years compared with 9.13 years in the Vehicle group. The majority of subjects in both treatment groups were male: 70% in the luliconazole group and 80% in the vehicle group. Most of the subjects were of Black or African American race (63.3% in the luliconazole 1% group versus 66.7% in the Vehicle group); the remaining subjects were White. All were of Hispanic or Latino ethnicity.

Table 7: Summary of Subject Baseline Signs and Symptoms (Safety Population)

	Luliconazole Cream, 1% (N=60)	Vehicle Cream (N=15)	Total (N=75)
Erythema			
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)
Scaling			
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)
Pruritus			
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)

Source: Study report MP 1011, table 14.1.2.1

Baseline symptom severity for scaling, erythema, and pruritus was moderate to severe in all subjects in both treatment groups. The majority of the subjects in both treatment groups had severe scaling (63.3% in the luliconazole 1% group versus 53.3% in the vehicle group), severe pruritus (53.3% in the luliconazole 1% group

versus 60.0% in the vehicle group), and moderate erythema (56.7% in the luliconazole 1% group versus 53.3% in the vehicle group).

Reviewer's comment: *Subject's demographics are acceptable. The age ranges in this study is appropriate.*

6.1.3 Subject Disposition

A total of 75 subjects were enrolled into the study; 60 subjects were randomly assigned to the Luliconazole 1% treatment group and 15 were randomly assigned to the Vehicle group. All of the subjects in both treatment groups completed the study.

Table 8: Subjects Disposition for MP 1011

	Luliconazole	Vehicle	All
Subjects Enrolled	60	15	75
Completed	60 (100)	15 (100)	75 (100)
Discontinued	0	0	0

Source: table 14.1.1

6.1.4 Analysis of Primary Endpoint(s)

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. Efficacy was evaluated using the following:

- Proportion of subjects who achieved "mycological cure" at Day 28 (3 weeks post-treatment).
- Proportion of subjects who achieved "clinical cure" at Day 28 (3 weeks post-treatment).
- Proportion of subjects who achieved "complete clearance" at Day 28 (3 weeks post-treatment).

Table 9: 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

Note that the mycological and clinical cure rates were similar in the luliconazole group versus the vehicle group. At Baseline, all individual symptom scores were moderate or severe for all subjects in both treatment groups.

Reviewer's comment: *Efficacy was evaluated but no hypothesis testing was conducted for this clinical study. The trend of the efficacy was similar to the data reviewed for the original adult studies.*

6.1.5 Analysis of Secondary Endpoints(s)

- Proportion of subjects who achieved "effective treatment" (defined as negative KOH and culture and at most mild erythema and/or scaling and no pruritus) at Day 28 (3 weeks post-treatment).
- Proportion of subjects who achieved "effective treatment" at Day 21 (2 weeks post-treatment).
- Proportion of subjects who achieved "effective treatment" at Day 14 (1 week post-treatment).
- Proportion of subjects who achieved "effective treatment" at Day 7 (End of Treatment).

Table 10: Effective Treatment Rates by Visit (MITT)

	Luliconazole Cream 1% (N=51)		Vehicle Cream (N=14)	
	Proportion, n/N (%)	95% Confidence Interval	Proportion, n/N (%)	95% Confidence Interval
Subjects who Achieved Effective Treatment at:				
Day 7	20/51 (39.2)	25.3, 53.1	1/14 (7.1)	0.0, 22.6
Day 14	28/51 (54.9)	40.8, 69.0	4/14 (28.6)	1.5, 55.6
Day 21	34/51 (66.7)	53.3, 80.1	6/14 (42.9)	13.2, 72.5
Day 28	39/51 (76.5)	64.4, 88.5	8/14 (57.1)	27.5, 86.8

Note: Last observations are carried forward to provide a value for missing efficacy parameters.

The effective treatment rates increase over treatment days. In all time points, the effective treatment rate was greater in the luliconazole group than in the vehicle group.

Reviewer's comment: *The secondary endpoint also trend towards efficacy of the original clinical trials for adults.*

6.1.6 Other Endpoints

No other endpoints were evaluated or explored.

6.1.7 Subpopulations

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. See Agency Biostatistical Review by Dr. Carin Kim.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

None

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

None

6.1.10 Additional Efficacy Issues/Analyses

No additional efficacy issues were explored.

Reviewer's Final Efficacy Conclusions: *This Reviewer concludes that the efficacy trend in this supplement study is sufficient to inform the PI label that luliconazole 1%, cream can be used for the treatment moderate to severe tinea corporis in the ages of 2 to 17 years. The labeling will reflect this decision. This supplement can be approved from the perspective of efficacy.*

7 Review of Safety

Safety Summary
Evidence from this single pediatric safety and efficacy study formed the database for luliconazole cream, 1%, supplement. The data for this 75 subject pediatric study did not reveal any new safety issues from the original NDA. Nine subjects (15.0%) in the Luliconazole 1% group reported 18 AEs and 2 subjects (13.3%) in the Vehicle group reported 2 AEs. All of these were TEAEs. There were no SAEs. There were no AEs leading to withdrawal of the subject from the study.

The most frequently reported TEAE was nasopharyngitis, reported in 4 subjects (6.7%) in the luliconazole 1% group and 2 subjects (13.3%) in the Vehicle group. Headache was reported in 3 subjects (5.0%) in the luliconazole 1% group and 0 subjects in the Vehicle group.

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. None of the TEAEs were related to treatment.

Reviewer's comment: *The most notable aspect of the original NDA safety review for this application is the lack of significant safety issues. No systemic safety issues were reported. No safety issues which rise to the level of "Warnings and Precautions" were identified in the safety review of this supplement. This reviewer continues to recommend that "none" more accurately describes the possibility of severe reactions for Section 5, Warnings and Precautions for this supplement.*

7.1 Methods

A total of 75 subjects (60 in the active and 15 in the placebo) were described in the safety population for this study.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

A single study was used to evaluate the safety of Luliconazole cream, 1% in the treatment of tinea corporis in subjects 2 to 17 years of age.

7.1.2 Categorization of Adverse Events

Non-serious and serious AEs were monitored throughout the studies, and incidence, severity, timing, and relationship to administration of the study medication were collected for each AE or serious AE (SAE). Adverse events are coded to MedDRA (*version 14.0*).

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

None, this is a single clinical study.

7.2 Adequacy of Safety Assessments

This Phase 3 clinical trial included assessments of AE at all visits. Safety laboratory assessments (hematology, chemistry, and urinalysis) were completed at Baseline and end-of-treatment. A urine pregnancy test at Screening, Baseline, end-of-treatment, and end-of-study was completed.

Reviewer's comment: *In general, sufficient safety assessments were completed during this clinical trial to establish pediatric safety. Minimal safety issues were identified and were confined to local application site reactions.*

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The amount of Luliconazole Cream 1% used by subjects ranged from 2.3 grams to 51.5 grams. The amount of Vehicle cream used by subjects ranged from 3.4 grams to 38.8 grams.

7.2.2 Explorations for Dose Response

None

7.2.3 Special Animal and/or In Vitro Testing

Please see original NDA for a full non-clinical analysis.

7.2.4 Routine Clinical Testing

Study MP-1011 evaluated AEs at all visits, safety laboratory (hematology, chemistry, and urinalysis) at the designated time schedule, and urine pregnancy screening.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Certain classes of AEs were identified for other currently marketed antifungal products. To monitor safety in relation to these classes of AEs, listing for AEs that occurred on-study were reviewed by the applicant's clinical review team to identify those that were related to liver function abnormalities, kidney function abnormalities, and cardiac abnormalities that were considered AEs of special interest for this development program.

7.3 Major Safety Results

Table 11: Overall Summary of Adverse Events (Safety Population)

	Luliconazole Cream 1% (N=60)		Vehicle Cream (N=15)	
	Number of Events	Number of Subjects n (%)	Number of Events	Number of Subjects n (%)
Subjects with any AEs	18	9 (15.0)	2	2 (13.3)
Subjects with any TEAE	18	9 (15.0)	2	2 (13.3)
Subjects with any SAEs	0	0	0	0
Subjects with any TEAEs Leading to Subject's Withdrawal	0	0	0	0

Note: Treatment-emergent adverse events were those AEs with an onset on or after the first application of study medication.

7.3.1 Deaths

No deaths were reported.

7.3.2 Nonfatal Serious Adverse Events

There were no SAEs reported in this clinical trial.

7.3.3 Dropouts and/or Discontinuations

A total of 18 AEs were reported in 9 subjects in the Luliconazole 1% group and a total of 2 AEs were reported in 2 subjects in the Vehicle group. All of the AEs were treatment emergent.
There were no SAEs. There were no AEs leading to withdrawal of the subject from the study.

7.4 Supportive Safety Results

The supportive safety results showed few adverse events that were related to the treatment with luliconazole cream, 1%.

7.4.1 Common Adverse Events

The overall frequency of TEAEs was approximately the same in both treatment groups (15% in the Luliconazole 1% group and 13.3% in the Vehicle group, respectively). The most frequently reported AE was nasopharyngitis, reported in 6.7% of the Luliconazole 1% group and 13.3% of the subjects in the Vehicle group.

Headache was reported in 5.0% of the subjects in the Luliconazole 1% group. All other TEAEs were reported in less than 5% of the subjects in the Luliconazole 1% group.

Table 12: Treatment-emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

	Luliconazole Cream, 1% N=60 n(%)	Vehicle Cream N=15 n(%)	Overall N=75 n(%)
Gastrointestinal disorders	**1 (1.7)**	**0**	**1 (1.3)**
Diarrhea	1 (1.7)	0	1 (1.3)
Infections and infestations	**4 (6.7)**	**2 (13.3)**	**6 (8.0)**
Naspharyngitis	4 (6.7)	2 (13.3)	6 (8.0)
Investigations	**2 (3.3)**	**0**	**2 (2.7)**
Alanine aminotransferase increased	2 (3.3)	0	2 (2.7)
Aspartate aminotransferase increased	2 (3.3)	0	2 (2.7)
Blood alkaline phosphatase increased	1 (1.7)	0	1 (1.3)
Gamma-glutamyltransferase increased	2 (3.3)	0	2 (2.7)
Nervous system disorders	**3 (5.0)**	**0**	**3 (4.0)**
Headache	3 5.0)	0	3 (4.0)

Note: Treatment-emergent adverse events are those with an onset after the initial application of luliconazole cream, 1%.
Source: Clinical Study Report, Table 14.3.2.1

Reviewer's comment: *Nearly all TEAEs reported in the luliconazole cream, 1% studies were mild intensity.*

The most frequently reported AEs was nasopharyngitis categorized in the body system category Infections and Infestations. Nasopharyngitis was reported in 6.7% of the subjects in the luliconazole 1% group and 13.3% of the subjects in the Vehicle group. Headache, in the category Nervous System Disorders was reported in 5.0% of the subjects in the luliconazole 1% group and 0 subjects in the Vehicle group. All other TEAEs were reported by subjects in the luliconazole 1% group only and included AEs in the categories of Gastrointestinal Disorders and Investigations. Three AEs in the category Investigations (alanine aminotransferase increased, aspartate aminotransferase increased, and gamma-glutamyltransferase increased) were reported once for one subject (102024), then resolved and then recurred at the next visit. These are therefore counted twice in the AE count but only once in the subject count.

7.4.2 Laboratory Findings

Clinical laboratory evaluations showed no mean changes in laboratory parameters over time, no shift in percentages of subjects who had normal values at Baseline and abnormal values at the end-of treatment, and no individually significant laboratory results reported as AEs were indicative of safety signal or indicated a clinically meaningful differences between Luliconazole cream, 1% and vehicle cream.

Table 13: Laboratory Data from Subjects with Values Considered Clinically Significant

Subject No.	Test	Normal Range	Screening Value	Day 7 Value (Clinically Significant)	Day 14 Value (Clinically Significant)
101016	ALT	5 – 20 U/L	23	57 (Yes)	35
	Alk Phos	51 – 332 U/L	362	373 (Yes)	388
	AST	0 – 36 U/L	38	88 (Yes)	109 (Yes)
	GGT	4 – -22 U/L	28	29 (Yes)	27
102024	ALT	5 – 20 U/L	101	143 (Yes)	102 (Yes)
	AST	0 – 29 U/L	108	102 (Yes)	88 (Yes)
	GGT	4 – 24 U/L	102	120 (Yes)	120 (Yes)

Abbreviations: ALT=Alanine aminotransferase; Alk Phos = Alkaline phosphatase; AST=Aspartate aminotransferase; GGT=Gamma glutamyl transferase; NA = Not available

Reviewer's comment: *This reviewer suspect the two clinically significant abnormal liver function test described in the TEAE table are due to other issues. The subjects were described to have ongoing histories of hepatitis A.*

7.4.3 Vital Signs

There was no pattern of change in the vital signs indicative of a safety signal or clinically meaningful difference between study drug and vehicle cream.

Reviewer's Conclusions:

- *A single well-controlled clinical study of luliconazole cream, 1% in the treatment of tinea corporis in subjects down to 2 years of age was completed to fulfill a PREA post-marketing requirement. The study was conducted appropriately and is adequate to fulfill the PREA PMR and provide support to update the existing labeling for pediatric populations with tinea corporis down to 2 years of age.*
- *The safety experience from this study will be added to the labeling.*
- *Clinical trial Section 14 will be updated to include the results from this study.*
- *This supplement can be approved from this Reviewer's perspective.*

8 Postmarket Experience

Annual reports for luliconazole Cream, 1% have not identified any new significant safety issues that warrant additions to product labeling.

9 Appendices

I. Physician Insert

9.2 Labeling Recommendations

The label presented in this section is the most current Agency recommended label. Final labeling will be available post-approval.

9.3 Advisory Committee Meeting

An Advisory Committee Meeting was not held for this supplement for this topical product.

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/s/

GARY T CHIANG
01/25/2018

DAVID L KETTL
01/26/2018