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APPLICATION NUMBER:

204153Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505 (b)(1)
Application Number(s)	204-153
Priority or Standard	Standard
Submit Date(s)	11-DEC-2012
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Division / Office	DDDP/ODE III
Reviewer Name(s)	Gary Chiang MD, MPH
Review Completion Date	16-SEP-2013
Established Name	Luliconazole
(Proposed) Trade Name	LUZU
Therapeutic Class	Azole antifungal
Applicant	Medicis 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)	Adults 18 years of age and older

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical prospective, an approval recommendation is being 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 adults ≥ 18 years of age. This recommendation is predicated upon the applicant's acceptance of revised labeling and commitment to conduct the two Phase 4 clinical studies listed in Section 1.4. Two clinical trials in interdigital tinea pedis, and one clinical trial in tinea cruris has provided substantial evidence of safety and effectiveness for the indications since statistical superiority of the active study drug was demonstrated over vehicle.

1.2 Risk Benefit Assessment

Safety assessments for this application are based on clinical trial results as well as post-marketing experience with the Japanese luliconazole cream, 1% drug product. The risks associated with luliconazole cream, 1% treatment appear to be low in patients treated in the pivotal clinical trials. The most common adverse events associated with treatment of luliconazole cream, 1% is application site reaction and application site pain, both of which are < 1% and are comparable to vehicle in the safety population. Complete cure rates for luliconazole cream, 1% for the treatment of interdigital tinea pedis is approximately 18% and for the treatment of tinea cruris is approximately 16%. Efficacy for tinea corporis in adults is assumed in the absence of specific clinical trials based on the similarity of causative orgainisms for this condition, as has been the Agency historical precedent for these conditions.

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

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None needed.

1.4 Recommendations for Postmarket Requirements and Commitments

The applicant requested a waiver to conduct studies in pediatric subjects younger than 12 years of age for tinea pedis, and a deferral to conduct studies in pediatric subjects 12-(b) (4) years of age in tinea cruris (b) (4) In addition, a deferral was requested to conduct studies in pediatric subjects down to the age of 2 years old in tinea corporis.

The request for partial waiver and deferral was presented to the Pediatric Review Committee (PeRC) on 29-MAY-2013. The Committee agreed with the Division's recommendation that a waiver for pediatric subjects less than 12 years of age be granted for the tinea pedis indication. The Committee also agreed with the review team recommendations that a deferral to conduct studies in pediatric subjects 12-(b) (4) years in tinea cruris and pediatric subjects 2 years of age and older in tinea corporis be granted and that the following PMR be attached to the NDA approval:

- Maximum use PK safety study in pediatric subjects ≥ 12 years to 17 years, 11 months of age (b) (4) is recommended.
- Conduct of a multicenter, randomized, blinded, vehicle-controlled study with use of luliconazole cream, 1% for the treatment of tinea corporis in pediatric patients ≥ 2 years of age as a PMC/PMR.

2 Introduction and Regulatory Background

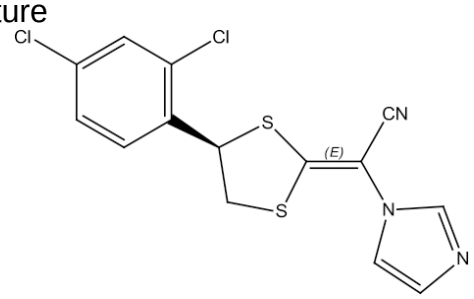
Luliconazole Cream, 1% is an imidazole antifungal with a dual mechanism of action. Luliconazole exhibits antimycotic and fungicidal activity against dermatophytes through the inhibition of ergosterol biosynthesis. In addition, luliconazole's antifungal activity includes inhibition of protease production 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: (b) (4)
- Tinea versicolor

In Japan, as of April 2011, approximately (b) (4) of Lulicon® Cream, 1% and (b) (4) Lulicon® Solution, 1% were shipped, with an estimated 10.8 million patients exposed to luliconazole. This international safety experience has been considered as part of the assessment for this 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 not available in the United States.

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, and cardiac parameters. None of these determined to be of concern during this application review.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

- 18-JUL-2012 – Pre-NDA Meeting (tinea pedis, tinea cruris, tinea corporis)
- 27-OCT-2010 – End-of-Phase 2 Meeting (tinea cruris, tinea corporis)
- 16-DEC-2009 – End-of-Phase 2 Meeting (tinea pedis)
- 16-JAN-2007 – Pre-IND Meeting (76,049)
- 7-JUL-2010 – SPA (tinea pedis)
- 17-FEB-2011 – SPA (tinea cruris)

The overall development plan for luliconazole included an extensive clinical program demonstrating safety and efficacy for the treatment of the proposed indications. The applicant conducted a Phase 2 dose ranging study, a maximal use PK study, a thorough QT study, and four dermal safety studies in addition to the two Phase 3 clinical trials in tinea pedis and one Phase 3 clinical trial in tinea cruris.

According to Agency meeting minutes, in order to obtain the desired indications of tinea pedis, corporis, and cruris, at least two studies in tinea pedis and one study in tinea cruris were recommended. Sufficient numbers of subjects will need to be assessed from tinea pedis studies and separate tinea cruris study in order to gain an additional indication for tinea corporis. When efficacy is demonstrated for tinea pedis, then efficacy at the same dosage and duration may be assumed for tinea cruris, but safety for tinea cruris may not be assumed. Efficacy and safety of the study medication may be assumed for tinea corporis at the same dosage and duration.

Reviewer's comment: *During the development of luliconazole, the Agency agreed with the sponsor's development plan of to conduct two Phase 3 clinical trials in tinea pedis and one Phase 3 clinical in tinea cruris and* (b) (4) *the safety and efficacy to the tinea corporis indication (EOP2 meeting 16-DEC-2009). However, with the Pediatric Research Equity Act of 2007 (21 U.S.C 355c), the sponsor is required to assess the safety and effectiveness of pediatric patients across all relevant populations. The Agency recommended:*

"…to demonstrate PK/safety/tolerability under maximal use conditions in subjects ages 12 year to 17 years, 11months with tinea pedis and tinea cruris, and to demonstrate safety and efficacy of luliconazole in pediatric population as young as 2 years of age for tinea corporis. In addition, pharmacokinetic information should be captured in this clinical trial to demonstrate the safety profile of your product in children as young as 2 years of age." (Pre-NDA meeting, 18, JUL-2012)

This is in line with recent topical antifungal approvals in this Division, including naftifine 2% gel and cream which were approved in the last 18 months. The sponsor agreed to submit a Pediatric Plan in the NDA during the Pre-NDA meeting.

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"). Tinea pedis involves fungal infection of the foot and is caused by dermatophytes that produce keratinase, an enzyme that breaks down keratin – a main constituent of hair, nails and the stratum corneum of skin. Tinea pedis is most commonly associated with infection manifesting between the toes (interdigital) or with widespread prolonged erythema, hyperkeratosis, and scaling on the lateral aspects and bottom of the foot (moccasin or plantar) or on the sole (vesicular and ulcerative). [3] These organisms are spread by human-to-human contact with infected skin scales in moist environments such as shower rooms or bathing areas. Diagnoses of tinea pedis 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 cruris, a pruritic superficial fungal infection of the groin and adjacent skin, is the second most common clinical presentation for dermatophytoses. It affects the upper, inner thighs and sometimes extends to the groin and the pubic area. While the condition most frequently occurs in men, it also may occur in women. Adults and adolescents are affected by tinea cruris much more commonly than are children.

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. [4]

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 Weinstein, A. and Berman, B. Topical treatment of common superficial tinea infections. *American Family Physician*. (electronic version): 2002; 65(10)
4 Lesher, J.L. Tinea corporis. eMedicine from WebMD [Internet]. 2009 Dec [cited 2013 MAR 04].

(b) (4)

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Three study sites were selected for DSI inspection due to the relatively high treatment responders and large numbers of subjects enrolled.

Site # (Name, Address, Phone number, email)	Protocol ID	Number of Subjects	Indication
#2 Alicia Barba, MD International Dermatology Research, Inc. 8370 West Flagler, Suite 200 Miami, FL 33144 (305) 225-0400	MP-1000-01-1614	15	Tinea cruris
#11 Richard Pollack, DPM, MS Endeavor Clinical Trials, PA 8042 Wrzback, Suite 420 San Antonio, TX 78229 (210) 949-0807	MP-1000-02-1614	19	Tinea pedis
#14, #10 Amaury Roman-Miranda, MD Advanced Medical Concepts, PSC Cidra, PR 00739 (787) 739-3376	MP-1000-01-1614 MP-1000-02-1614	22 36	Tinea cruris Tinea pedis

The DSI investigator noted some discrepancies between the total numbers of subjects enrolled at the sites and the mITT population. After discussions between the investigating team and the biostatistical team, it was determined that this would not affect the statistical conclusions rendered in the biostatistical review. The inspections were otherwise unremarkable.

Reviewer's comment: *The issues surrounding the inspections were thoroughly discussed with the biostatistics reviewer. The determination was that the statistical conclusion was not affected by the discrepancies in the enrollment and mITT subjects.*

No other issues were identified that might be related to investigator or data integrity during review of the application.

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.

3.3 Financial Disclosures

The applicant, Medicis Pharmaceutical Corporation, states: "As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)." Furthermore, Medicis Pharmaceutical Corporation certifies the following statements regarding the financial interest and arrangement of Clinical Investigators:

- "The Applicant did not enter into any financial agreements with a Clinical Investigator whereby, as defined in 21 CFR 54.2(a) the value of the compensation to the Clinical Investigator was affected by the outcome of the study.
- No Clinical Investigator who participated in a covered clinical study disclosed to the Sponsor any significant equity interest in the Sponsor of the covered clinical study as defined in 21 CRF 54.2(b).
- No Clinical Investigator who participated in a Covered Clinical Study disclosed to the Sponsor of the Covered Clinical Study any proprietary interest in the product, as defined in 21 CFR 54.2(c).
- No Clinical Investigator who participated in a Covered Clinical Study disclosed to the Sponsor any significant payments of other sorts received from the Sponsor as defined in 21 CFR 54.2(f)."

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The recommendation from ONDQA is for approval of the application pending resolution of labeling issues. Two main issues were at the forefront of CMC discussions:

- The pH of the drug product [redacted] (b) (4) The pH acceptance criterion in the drug product specification for the Japanese product and throughout clinical development in the US has been 5.0-7.0. [redacted] (b) (4) The applicant requested that the pH acceptance criterion in the drug product specification be expanded to [redacted] (b) (4). This was unacceptable to the Agency. After discussion with the applicant, the Agency recommended the pH acceptance criterion be maintained at 5.0-7.0 and that the expiration dating period be [redacted] (b) (4) 18 months.
- The drug product marketed in Japan and manufactured in the US exhibits [redacted] (b) (4) when subjected to microscopic examination. It was stated in the NDA submission that the [redacted] (b) (4)

Table 2: Manufacturers

(b) (4)

The applicant completed in vitro release test for comparison of data supporting the approval of the proposed drug product manufacturing site change from (b) (4) to DPT laboratories Ltd. The Agency Biopharmaceutics review states that "the in vitro drug release rate comparison data support the approval of the proposed drug manufacturing site change." The recommendation is for approval.

The primary container closure system that was used for drug product evaluated in the clinical trials will also be used for the proposed US commercial product.

The container closure system consists of the following components:

- Blind-end aluminum tube with a 2, 30 or 60 g fill volume;

(b) (4)

The Office of Compliance has issued an overall "Acceptable" recommendation for the facilities involved in manufacture of the drug product.

Reviewer's comment:

- *CMC issues were resolved with the applicant. Clinical agrees with the CMC team, keeping the pH acceptance criteria at 5.0 – 7.0.*

- *CMC labeling recommendations can be reviewed in Section 9.2. Carton and container labeling negotiations continue at this time. A finalized PI and carton & container label will be included with product approval.*

Biopharmceuticals:

ONDQA conducted a review of the in vitro release tests (IVRT) that the applicant submitted to establish safety and efficacy profile of the Japanese drug product formulation to that of the U.S. proposed commercial drug product.

The Phase 3 clinical lot (lot DCK) and registration lots (lots DDE, DDF, and DDG) used in the primary stability studies of the US NDA were manufactured at DPT Laboratories. The US commercial lots will also be manufactured at DPT Laboratories. An IVRT study was conduct to qualify the level 3 drug product manufacturing site change from (b) (4) to DPT, including the process modifications that were introduced during the transfer. An additional in vitro drug release study was conducted to compare the release rates from three drug product registration lots manufactured by DPT (DDE, DDF, DDG: the registration lots) to the release rates from the drug product manufactured by (b) (4)

The review conclusion is that the IVRT study results are acceptable. The biopharmaceutical reviewer noted "The in vitro drug release rate comparison data support the approval of the proposed drug product manufacturing site change from (b) (4) to DPT Laboratories Ltd." The recommendation is for approval.

4.2 Clinical Microbiology

Luliconazole is an imidazole antifungal agent, which inhibits fungal ergosterol biosynthesis, a constituent of fungal cell membranes. Luliconazole inhibited ergosterol synthesis in *C. albicans* with an IC_{50} of 0.014 µM and in *T. mentagrophytes* with an IC_{50} of 0.45 µM. Clinical isolates were collected mostly from hospitals geographically distributed throughout Japan; there were no surveillance studies that tested isolates within the United States. Based on these surveillance studies, the *in vitro* activity of luliconazole against *Trichophyton* species and *E. floccosum* had minimum inhibitory concentrations (MICs) values that ranged from 0.00012 to 0.02 µg/mL using the microbroth dilution method, as described by the applicant. However, there were variations in the MIC depending on the susceptibility test method used as well as culture conditions. Resistance to luliconazole has not been described.

In all three phase 3 efficacy studies, the primary endpoint was met which showed that a higher proportion of subjects in the luliconazole cream 1% arm had "complete clearance" compared to subjects in the vehicle cream group. "Complete clearance" was defined as the combination of "clinical cure" (absence of erythema, scaling and pruritus or a grade 0 for each) and "mycological

cure" (negative KOH microscopic examination and dermatophyte culture). "Mycological cure" was also evaluated as a secondary endpoint, independent of "clinical cure". The overall proportion of subjects with a "mycological cure" was significantly higher among the Luliconazole 1% cream treated subjects (58.7%) compared to vehicle treated subjects (22.4%). Most subjects were found to have *T. rubrum* as the primary fungal organism (ranging from 73.4% to 87.7%) leading to infection. This was independent of the diagnosis of interdigital tinea pedis or tinea cruris. Other dermatophytes cultured from tissue samples included *T. mentagrophytes*, *E. floccosum, T. tonsurans* and *Microsporum gypseum.* Luliconazole cream 1% was shown to be active against *T. rubrum* and *E. floccosum* in clinical trials. There was no difference in the activity of luliconazole against *T. mentagrophytes* when compared to vehicle in subjects with tinea pedis or tinea cruris. There were not enough organisms tested in the clinical trials to evaluate the activity of luliconazole against *M. gypseum* or *T. tonsurans*. No susceptibility testing interpretive criteria for luliconazole are recommended.

Recommendations from the Clinical Microbiology Review: *"From a clinical microbiology perspective the information provided by the Applicant supports the efficacy of luliconazole cream 1% for the treatment of T. rubrum and E. floccosum in the treatment of tinea pedis and tinea cruris.* (b) (4) *No susceptibility testing interpretive criteria for luliconazole are recommended."*

The following are the Clinical Microbiology Reviewer proposed recommendations for labeling revisions (only the sections pertinent to Clinical Microbiology are provided below):

(b) (4)

Mechanism of action
Luliconazole is an antifungal that belongs to the azole class. Although the exact mechanism of action against dermatophytes is unknown, luliconazole appears to inhibit ergosterol synthesis, a constituent of fungal cell membranes.

Mechanism of Resistance
To date, a mechanism of resistance to luliconazole has not been described.

LUZU Cream has been shown to be active against most isolates of the following fungi, both in vitro and in clinical infections as described in the INDICATIONS AND USAGE section:
Trichophyton rubrum
Epidermophyton floccosum

Reviewer's comment: *The labeling recommendations from the Clinical Microbiology review will be incorporated into the PI.*

4.3 Preclinical Pharmacology/Toxicology

Please see the Pharmacology/Toxicology review completed by Dr. Kumar Mainigi for detailed evaluation of the nonclinical data. A summary of the available nonclinical information is presented in this review.

The nonclinical safety profile for luliconazole cream, 1% is supported by nonclinical studies conducted in multiple species (mouse, rat, guinea pig, rabbit, and dog); most of these studies were conducted in Japan. The pivotal nonclinical studies were conducted under GLP conditions and the same studies were submitted in Japan to support the Japanese approval of Lulicon®.

Although, the clinical formulation is intended only for topical use, a number of parallel subcutaneous (intra-dermal injections) studies for greater drug exposure were also conducted. A few studies were conducted using the oral and peritoneal routes. In addition, phototoxicity, sensitization and photosensitization potentials were evaluated by more than one method.

Safety pharmacology studies were conducted in mice, rats, guinea pigs, rabbits, and dogs to investigate the effect(s) of luliconazole on the functioning of the central and autonomic nervous, respiratory and circulatory and renal systems. No significant treatment related effects were noted in these studies.

The pharmacokinetic profile of luliconazole was determined in vitro and in vivo after topical and subcutaneous administration in animals. The absorption rate after topical administration of the luliconazole cream was significantly greater in rats compared to dogs. Luliconazole was distributed primarily to the liver and adrenal glands. No qualitative differences in the metabolic profile for luliconazole were noted in rats, dogs, and humans based on in vitro studies.

In most of the pharmacokinetic studies, the to-be-marketed formulation of luliconazole cream, 1% was used. After a single percutaneous application of ^{14}C-luliconazole cream 1%, C_{max} (0.134 µg.eq/mL) in rats was achieved at T_{max} of 12 hours; drug was decreased below the detection limits (20 ng/mL) at 168 hours. After seven daily applications of the same formulation, C_{max} was 3.3 times greater; however, elimination rate was similar to that observed after the single application. The percutaneous absorption rate for cream in rats was 13.6 percent; the rate of absorption in dogs was lower.

After single and multiple applications of cream formulation, radioactivity mainly resided on the application site in the horny layer of skin. There was almost no metabolism of luliconazole in the skin. Thus, no increase in plasma drug levels would be expected as a consequence of any enzyme inhibition.

In vitro microsomal assays, luliconazole inhibited a spectrum of CYP isoforms; most strongly inhibited was CYP2C19, followed by CYP3A4. However because of very high parent drug-plasma protein binding left a very low amount of free drug in the plasma, it is highly unlikely that any significant amount luliconazole will be available for metabolism and interactions with other drugs to alter their plasma concentrations.

The general toxicity profile of luliconazole was evaluated in repeat dose toxicity studies conducted in rats and dogs. Dermal toxicity studies up to 4 weeks in rats and 26 weeks in dogs were conducted with luliconazole. Subcutaneous toxicity studies up to 26 weeks in rats were conducted with luliconazole. The primary target organ of toxicity identified in these studies was the liver. The primary toxicity noted in the liver was centrilobular hypertrophy of the liver possibly due to induction of metabolic enzymes. The liver toxicity was fully reversed after stopping drug administration.

Calculating the multiples of human exposure based on AUC comparisons for many of the nonclinical studies was problematic due to difficulties in obtaining an adequate pharmacokinetic profile in these studies. Therefore, the multiples of human exposure provided in the label are based on body surface area comparisons. Based on the suggestions of the Clinical Reviewer (Gary Chiang, MD, MPH), the maximum recommended human dose was set at 8 grams of 1% luliconazole cream per day for tinea corporis. This is equal to 1.33 mg/kg/day luliconazole for a 60 kg individual (80 mg luliconazole ÷ 60 kg = 1.33 mg/kg/day) or 49.2 mg/m^2/day based on body surface area. The multiples of human exposure for the reproductive and developmental toxicity studies incorporated into the label based on body surface area comparisons are provided in the following table.

Table 3: Comparisons of Exposure for Reproductive and Developmental Toxicity Studies

Study	Species	Route	NOAEL (mg/kg/day)	Body Surface Area Dose (mg/m^2/day)	Multiples of human exposure*
Fertility and general reproductive performance	Rats	Subcutaneous	1	6	0.1
Embryofetal study	Rats	Subcutaneous	25[a] 5[b]	150 30	3 0.6
Embryofetal study	Rabbits	Subcutaneous	100	1200	24
Peri- and post-natal development study	Rats	Subcutaneous	25[c] 5[d]	150 30	3 0.6

*Comparing to the human topical dose under maximum clinical use conditions: 49.2 mg/m^2/day, assuming 100% absorption.
a – NOAEL for maternal toxicity or malformations
b – NOAEL for skeletal variation
c – NOAEL for postnatal development
d – NOAEL for embryofetal toxicity

Luliconazole revealed no evidence of mutagenic or clastogenic potential based on the results of two *in vitro* genotoxicity tests (Ames assay and Chinese hamster lung cell chromosomal aberration assay) and one *in vivo* genotoxicity test (mouse bone marrow micronucleus test).

A waiver for conduct of carcinogenicity studies was granted for luliconazole cream, 1%.

Subcutaneous reproductive and developmental toxicity studies were conducted with luliconazole in rats and rabbits. A subcutaneous fertility study, embryofetal development study and pre-and post-natal developmental study were conducted in rats with doses of 1, 5, and 25 mg/kg/day luliconazole. In the rat fertility study, treatment related effects on reproductive function were noted in females (decreased live embryos and decreased corpus luteum) at 5 and 25 mg/kg/day and males (decreased sperm counts) at 25 mg/kg/day. No treatment related effects on fertility or reproductive performance were noted in rats at 1 mg/kg/day.

In the rat embryofetal development study, no treatment related effects on maternal toxicity or malformations were noted at 25 mg/kg/day. However, increased incidences of skeletal variation (14^{th} rib) were noted at 25 mg/kg/day. No treatment related effects on skeletal variation were noted at 5 mg/kg/day.

In the rat pre- and post-natal development study, maternal toxicity and embryofetal toxicity (increased prenatal pup mortality, reduced live litter sizes and increased postnatal pup mortality) was noted at 25 mg/kg/day. No embryofetal toxicity was noted at 5 mg/kg/day. No treatment related effects on postnatal development was noted at 25 mg/kg/day.

A subcutaneous embryofetal development study was conducted in rabbits with doses of 4, 20, and 100 mg/kg/day luliconazole. No treatment related effects on maternal toxicity, embryofetal toxicity or malformations were noted at 100 mg/kg/day.

Luliconazole cream was a weak skin irritant in rabbits and the extent of dermal irritation did not increase after 28 days of repeat daily topical exposure compared to a single application. Luliconazole cream was a weak ocular irritant in rabbits. Luliconazole cream did not express any phototoxic potential, sensitization potential, or photosensitization potential in male guinea pigs.

Overall, the nonclinical reviewer concurs that there is a margin of systemic safety based on the animal toxicity data that is >14 fold.

A comprehensive nonclinical safety profile has been determined for luliconazole cream that supports the safety of the proposed clinical dosing regimen for the topical treatment of tinea pedis, tinea cruris and tinea corporis.

Reviewer's comment: *The nonclinical data is supportive of the indications and proposed clinical dosing regimen for the treatment of tinea pedis, tinea cruris, and tinea corporis. Dr. Mainigi is recommending an approval from the Pharmacology/Toxicology perspective. There are no unresolved nonclinical issues that would impact an approval action for this application.*

Pharmacology/Toxicology recommendations for labeling:

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE

Luzu Cream is an (b) (4) antifungal indicated for the topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by *Trichophyton rubrum*, (b) (4) or *Epidermophyton floccosum*, in patients 18 years of age and older.

8.1 Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies of Luzu Cream in pregnant women. (b) (4) Luzu Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The animal multiples of human exposure calculations were based on daily dose body surface area (BSA) comparisons (mg/m2) for the reproductive toxicology studies described in this section and in Section 13.1. The Maximum Recommended Human Dose (MRHD) was set at 8 g 1% cream per day (1.33 mg/kg/day for a 60 kg individual which is equivalent to 49.2 mg/m2/day).

Systemic embryofetal development studies were conducted in rats and rabbits. Subcutaneous doses of 1, 5 and 25 mg/kg/day luliconazole were administered during the period of

organogenesis (gestational days 7-17) to pregnant female rats. No treatment related effects on maternal toxicity or malformations were noted at 25 mg/kg/day (3 times the MRHD based on BSA comparisons). Increased incidences of skeletal variation (14th rib) were noted at 25 mg/kg/day. No treatment related effects on skeletal variation were noted at 5 mg/kg/day (0.6 times the MRHD based on BSA comparisons).

Subcutaneous doses of 4, 20 and 100 mg/kg/day luliconazole were administered during the period of organogenesis (gestational days 6-18) to pregnant female rabbits. No treatment related effects on maternal toxicity, embryofetal toxicity or malformations were noted at 100 mg/kg/day (24 times the MRHD based on BSA comparisons).

In a pre- and post-natal development study in rats, subcutaneous doses of 1, 5 and 25 mg/kg/day luliconazole were administered from the beginning of organogenesis (gestation day 7) through the end of lactation (lactation day 20). In the presence of maternal toxicity, embryofetal toxicity (increased prenatal pup mortality, reduced live litter sizes and increased postnatal pup mortality) was noted at 25 mg/kg/day. No embryofetal toxicity was noted at 5 mg/kg/day (0.6 times the MRHD based on BSA comparisons). No treatment effects on postnatal development were noted at 25 mg/kg/day (3 times the MRHD based on BSA comparisons).

12.1 Mechanism of Action

Luzu Cream is an azole antifungal *[see Clinical Pharmacology (12.4)]*.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of Luzu Cream have not been conducted.

Luliconazole revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames assay and Chinese hamster lung cell chromosomal aberration assay), and one in vivo genotoxicity test (mouse bone marrow micronucleus test). (b) (4)

In a fertility study in rats, subcutaneous doses of 1, 5 and 25 mg/kg/day luliconazole were administered prior to and during mating and through early pregnancy. Treatment related effects on reproductive function were noted in females (decreased live embryos and decreased corpus luteum) at 5 and 25 mg/kg/day and males (decreased sperm counts) at 25 mg/kg/day. No treatment related effects on fertility or reproductive function were noted at 1 mg/kg/day (0.1X MRHD based on BSA comparisons).

4.4 Clinical Pharmacology

The clinical pharmacology program consisted of a maximal use pharmacokinetic (PK) study in subjects with moderate to severe tinea pedis or tinea cruris and a TQT study in healthy subjects with PK assessments. Based on the information from all the Phase 1, Phase 2, and Phase 3 clinical trials, the Clinical Pharmacology Team is recommending approval of LUZU (luliconazole) Cream, 1% for the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis in patients 18 years and older.

The Clinical Pharmacology Team has also recommended four post-marketing requirements (PMR) and one post-marketing commitment (PMC).

Post-marketing requirements:

1. PK/Safety/Tolerability trial under maximal use conditions in subjects ages 12 years to 17 years 11 months with (b) (4) both tinea pedis and tinea cruris (b) (4)

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

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

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

Post-marketing commitments:

1. Conduct in-vitro assessment 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 the in-vitro assessment.

Reviewer's comment: *The clinical team is in agreement with the proposed PMR/PMC from clinical pharmacology. The in vitro inhibition studies suggest a potential for in vivo drug interactions. This theoretical concern is not sufficient to warrant not approving the drug product if it is otherwise approvable. The data from these studies will impact labeling post-approval to*

add safety information to the clinical pharmacology and drug-drug interactions sections of the PI.

4.4.1 Mechanism of Action

Luliconazole is an azole antifungal and drugs in this class act by inhibiting the biosynthesis of ergosterol which is a constituent of fungal cell membranes. Ergosterol serves as a bioregulator of membrane fluidity and is responsible for membrane integrity of in fungal cells.

4.4.2 Pharmacodynamics

Drug metabolism: Luliconazole is the R enantiomer and in the E-form (Cis). The applicant assessed metabolism in-vitro and has reported that there were differences in the rates of metabolism of luliconazole by rat, dog and human liver microsomes, but the metabolite profiles were the same. Based on the in vitro results, the predominant metabolic pathway involves the cleavage of the dithiolane ring to thiirane (M10) and isomerization into the (b) (4)). The M10 metabolite was not detectable in animals and it was not measured in any clinical trials. In-vivo levels of the (b) (4) metabolite was assessed in the maximal use PK trial (MP-1007) and the overall exposure of the (b) (4) metabolite was present at < 7 % of the native form and this indicates that further evaluation of drug interactions with the (b) (4) metabolite is not needed.

The study using human CYP expression system in microsomes suggested that CYP2D6 and CYP3A4 were primarily responsible for luliconazole metabolism.

Drug interactions: The applicant evaluated the inhibitory potential of luliconazole on CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 using human liver microsomes. Luliconazole inhibited the enzymatic activities of all the five CYP enzymes and inhibitory activity was highest against CYP2C19 followed by CYP3A4. The ratios between the maximum luliconazole concentration [I] (5.63 ng/mL) from the maximal use PK trial (MP-1007) following 8 day administration to subjects with tinea cruris and the Ki (i.e. [I]/Ki) for CYP2C19 and CYP3A4 were 0.55 and 0.12, respectively. The corresponding R values for CYP2C19 and CYP3A4 were 1.55 and 1.12, respectively, indicating that the investigational drug is likely an inhibitor of CYP2C19 and CYP3A4 and in-vivo drug interaction trials will be needed to further address this.

The applicant has not evaluated the inhibition potential of CYP2B6 and CYP2C8 which are recommended in the *Draft Guidance for Industry: Drug Interaction Studies - Study design, data analysis, implications for dosing, and labeling recommendations (February 2012).*

To address enzyme induction potential of luliconazole, the applicant has provided information on the induction of enzyme activity by luliconazole only for CYP2B1, but have not provided information on the induction potential of CYP1A2, CYP2B6 and CYP3A, which are also recommended in the *Draft Guidance for Industry: Drug Interaction Studies - Study design, data analysis, implications for dosing, and labeling recommendations (February 2012).*

Depending on the results of in-vitro studies, further in-vivo assessment of drug interactions will be needed to assess the effect of luliconazole on other drugs that are substrates of CYP2C19 and 3A4.

4.4.3 Pharmacokinetics

PK results: The maximal use PK trial (MP-1007) was conducted in 30 adult subjects with moderate to severe interdigital tinea pedis (n=15) or moderate to severe tinea cruris (n=15). All subjects received Luliconazole Cream, 1%, once daily in the morning for 15 days. The dose administered per application covered all affected and adjacent areas, including up to the ankle for tinea pedis and the groin, thighs, and abdomen for tinea cruris. Plasma levels of luliconazole were measured on Days 1, 8, and 15 where a baseline sample was obtained prior to drug application, and post drug application, serial blood samples were obtained at 1, 3, 6, 9, 12, and 24 hours. The Sponsor has evaluated PK for the entire proposed duration of dosing (two weeks for tinea pedis and one week for tinea cruris and tinea corporis). The mean ± SD values of $AUC_{(0-t)}$ and C_{max} on Day 15 for the parent drug were 18.74 ± 27.05 ng*h/mL and 0.93 ± 1.23 ng/mL respectively, in subjects with tinea pedis, and 106.93 ± 57.57 ng*h/mL and 5.63 ± 2.31 ng/mL respectively, on Day 8 in subjects with tinea cruris. The mean $AUC_{(0-t)}$ and C_{max} in subjects with tinea cruris following 8 days of once daily application were approximately 5.7 and 6.1 fold higher, respectively, than the mean $AUC_{(0-t)}$ and C_{max} in subjects with tinea pedis following 15 days of once daily application.

TQT trial results: The TQT trial (MP-1000-08) used the to-be-marketed formulation manufactured in USA (DPT). The results of the TQT trial were review by QT-IRT reviewer Dr. Qianyu Dang and according to Dr. Dang's review, luliconazole is not associated with QT prolongation (see review in DARRTS dated 04/30/2013).

The clinical pharmacology review compared the PK results across study MP-1007 and the TQT study. Because both trials were designed and conducted on different populations, the comparison is made for qualitative purposes only.

Table 4: Mean PK parameters from MP-1007 and MP-1000-08

Mean PK parameters	Trial MP-1007 *Tinea cruris subjects*		Trial MP-1000-08 *Healthy subjects*	
	Dose =3.5 gm	Dose =3.5 gm	"Therapeutic dose" Dose =2 gm	"Supra-therapeutic dose" Dose =10 gm
	Day 8	***Day 15***	***Day 7***	***Day 7***
C_{max} (ng/mL)	5.63	7.36	0.40	1.61
AUC (ng*h/mL)	106.93	121.74	5.91	23.62

Based on the PK data from the cross comparison, the mean C_{max} and AUC in subjects with tinea cruris under maximal use conditions on Day 8 are approximately 3.5 and 4.5 fold higher, respectively, compared to the C_{max} and AUC following 7 day administration of supra-therapeutic dose to healthy subjects.

Reviewer's comment: *In this instance, the diseased skin appears to absorb more readily than in healthy skin. This data suggest that evaluation in pediatric subjects with diseased skin should be conducted for PK, safety, and efficacy.*

Although the maximal use study suggests that the TQT study may not be conclusive due to the higher C_{max} obtained in subjects with tinea cruris, the QT-IRT evaluated this issue with both studies in mind. This clinical reviewer agrees with the DCARP reviewer that it is unlikely that sufficient absorption by the topical route will potentiate a QT prolongation. Therefore, the label should reflect that it is unlikely to affect cardiac repolarization with labeled use of the product.

The Clinical Pharmacology Team recommended labeling changes are provided in Section 9.2.

5 Sources of Clinical Data

The clinical development program for luliconazole cream, 1% included 11 US clinical studies that that form the basis for safety and efficacy. These studies support the proposed labeled indication for the topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis in adults caused by fungal organisms such as *T. rubrum*, (b) (4) or *E. floccosum*.

Four Phase 3 US clinical trials were conducted for safety and efficacy determination. Two Phase 3 clinical trials in tinea pedis, one Phase 3 clinical trial in tinea cruris, and one long-term safety study in tinea pedis, tinea cruris, and tinea corporis.

5.1 Tables of Studies/Clinical Trials

Table 5: Phase 3 US Clinical Trials

Study	Objective(s) of the Study	Study Design	Subjects Population (Plan/Actual)	Number Sites (Location)	Dosing Regimen/Duration of Treatment
MP-1000-01 (Phase 3)	**To evaluate the safety and efficacy of seven days of once daily topically administered luliconazole cream 1% compared with vehicle cream in treating subjects with tinea cruris.** **To determine the fungal organism causing the infection (genus and species) from clinical isolates collected from diseased tissue.**	**Multi-center, double-blind, parallel group, vehicle-controlled study**	**Subjects with tinea cruris** **(500/483)**	**23 (US)** **1 (PR)** **3 (CA)**	**Once daily for one week**
MP-1000-02 (Phase 3)	**To evaluate the safety and efficacy of 14 days of once daily**	**Multi-center, randomized, double-blind,**	**Subjects with interdigital tinea pedis**	**11 (US)** **1 (PR)**	**Once daily for two weeks (14 days)**

	topically administered luliconazole cream 1% compared with vehicle cream in treating subjects with interdigital tinea pedis. **To determine the fungal organism causing the infection (genus and species) from clinical isolates collected from diseased tissue.**	**parallel group, vehicle-controlled study.**	**(300/321)**		
MP-1000-03 (Phase 3)	**To evaluate the safety and efficacy of 14 days of once daily topically administered luliconazole cream 1% compared with vehicle cream in treating subjects with interdigital tinea pedis.** **To determine the fungal organism causing the infection (genus and species) from clinical isolates collected from diseased tissue.**	**Multi-center, randomized, double-blind, parallel group, vehicle-controlled study.**	**Subjects with interdigital tinea pedis.** **(300/322)**	**12 (US)** **2 (CA)**	**Once daily for two weeks (14 days)**
MP-1005 (Phase 3)	**To examine the long-term safety of treating recurrent episodes of interdigital tinea pedis for 14 days and tinea corporis and tinea cruris for 7 days with luliconazole cream 1%.**	**Multi-center, non-randomized, open-label, single treatment safety study**	**Subjects with interdigital tinea pedis, tinea cruris, or tinea corporis** **(600/604)**	**33 (US)** **1 (PR)** **4 (CA)**	**Once daily for two weeks for each episode of tinea pedis.** **Once daily for one week for each episode of tinea cruris or tinea corporis.**

Source: Applicant submission section 2.7.6

5.2 Review Strategy

The main strategy will be to review the pivotal Phase 3 clinical trials in tinea pedis (2) and tinea cruris (1) for safety and efficacy.

5.3 Discussion of Individual Studies/Clinical Trials

The two Phase 3 clinical trials conducted in patients with tinea pedis are identical and will be summarized.

5.3.1 Planned Clinical Study: MP-1000-02 and -03

Title: A Randomized, Multi-Center, Double-Blind, Vehicle-Controlled Study Evaluating the Efficacy and Safety of Luliconazole Cream 1% in Patients with Tinea Pedis

Objective: To evaluate the safety and efficacy of 14 days of once daily topically administered Luliconazole Cream, 1% compared with vehicle cream in treat subjects with tinea pedis. Clinical microbiology (identify organism by genus and species) to provide clinical isolates to support labeling for specific causative organisms for tinea pedis.

Study Design: Protocol TP-1003-01, is a multi-center, randomized, double blind, vehicle-controlled, 2-arm study (Luliconazole cream vs. vehicle cream) to be conducted at twelve centers in the United States. The sponsor intends to enroll 300 subjects (randomized 1:1), with the expectation of 67% inclusion in the MITT population (based on confirmed dermatophyte infection). This will result in approximately 200 subjects (97 in the Luliconazole cream arm, 97 in the vehicle cream arm) in the MITT population.

Number of Subjects: 300 male and female subjects

Ages of Subjects for Inclusion: 12 years of age or older

Inclusion Criteria:

1. Ability and willingness to sign a written informed consent and/or ascent (age appropriate).
2. Subjects of either gender must be 12 years of age or older.
3. Subjects with a clinical diagnosis of interdigital tinea pedis on one or both feet characterized by clinical evidence of tinea infection (at least moderate erythema, moderate scaling, and mild pruritus) based on signs and symptoms.
4. Subjects with a mycological diagnosis of interdigital tinea pedis confirmed by the detection of fungal hyphae on a microscopic KOH wet mount.
5. Women of child-bearing potential (WOCBP) must have a negative urine pregnancy test and must agree to use an effective form of contraception. Effective contraception is defined as regular use of any two of the following: oral, injectable contraceptives, condoms, spermicides, diaphragm, IUD, implantable and contraceptive patches, or abstinence. (Oral contraceptives if used for at least three months and injectable contraceptives if used for at least 6 months – prior to enrollment in the study).
6. Subjects must be in good general health and free of any disease that in the Investigator's opinion might interfere with the study evaluations.

7. Subjects must be able to communicate, be able to understand the study procedures, and be willing to comply with the study requirements.

Exclusion Criteria:

1. Subjects with moccasin (dry type) tinea pedis; with concomitant onychomycosis of the fingernails and/or toenails on the evaluated foot, with severe dermatophytoses, a concurrent tinea infection or bacterial skin infection on the evaluated foot.
2. Female subjects who are pregnant and/or nursing or planning a pregnancy during the course of the trial. Subjects who test positive for pregnancy after the start of test treatment will be discontinued from test treatment but will be followed for safety purposes.
3. For sites conducting ECG assessments; subjects with an abnormal ECG morphology and/or a QTcB interval > 500ms. In addition, subjects selected for ECG follow-up, concomitant use of any drugs that are CYP3A substrates with QT interval prolongation is prohibited. A list of these drugs is provided in Appendix 1 of this clinical review on page 15. NOTE: This may not be an exhaustive list and investigators should review any concomitant medication and exclude subjects taking medications with a potential to prolong the QT interval.
4. Subjects who are immunocompromised (due to disease, e.g., HIV or medications).
5. Subjects who have a recent history of or currently known to abuse drug or alcohol.
6. Subjects with a history of intolerance or hypersensitivity to imidazole compounds or inactive components of the cream.
7. Subjects with current significant skin disease that is considered by the investigator to be clinically important and indicative of conditions that might complicate interpretation of study results.
8. Subjects who are unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function.
9. Subjects with a life-threatening condition (e.g., autoimmune deficiency syndrome, cancer, unstable angina, or myocardial infarction) within the last 6 months.
10. Subjects who are currently in a clinical drug research study with other medications or have been a participant in a clinical trial within 30 days or 5 half-lives of the investigational drug (whichever is longer) prior to the Baseline visit (8 months for oral terbinafine).
11. Subjects using the following medications:
    a. topical antifungal agent within 30 days of the Baseline visit,
    b. systemic antifungals within 8 weeks or 5 half-lives of the antifungal (whichever is 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 is longer) prior to the Baseline visit
    e. topical corticosteroid in treatment area(s) within 30 days of the Baseline visit,
    f. systemic corticosteroids within 30 days of the Baseline visit,
    g. any other medicated topical treatments to the treatment area(s) within 7 days of Baseline visit.

Study Plan:

The study will enroll approximately 300 subjects to obtain a total of 194 subjects eligible for the MITT analyses. Male and female subjects aged 12 years or older will be recruited and randomly allocated (1:1) to treatment with either Luliconazole Cream 1% or vehicle cream for two weeks.

The first administration of study medication will be completed in the clinical at the Baseline evaluation. Subsequent application of the study medication will be administered by the subjects in the evening on Days 1 through 13. Both treatment groups will be followed for a 28-day post-treatment period (Day 42).

Each subject will have documentation of disease at the Baseline visit with the recording of clinical parameters of the signs and symptoms of the infection and mycological confirmation by microscopy of tissue (KOH). One target foot will be identified at Baseline; if both feet have involvement, the foot with more severe involvement will be chosen as the target foot and evaluated throughout the duration of the study. Mycological cultures will be sent to a central laboratory for confirmation of the fungus. All subjects with a clinical diagnosis of interdigital tinea pedis confirmed by the detection of fungal hyphae on a potassium hydroxide (KOH) wet mount, performed at the investigational site, will be eligible to be included in the dermatophyte at the central laboratory will categorized as “delayed exclusions” and will be excluded from the efficacy summaries.

Each of the signs of tinea pedis will be evaluated on the target foot by scoring the severity of erythema, scaling, and pruritus, on a four-point scale (0-3, indicating none, mild, moderate, severe). Clinical and mycological assessments will be evaluated on the target foot and repeated at the end of treatment on Day 14, 12 days post-treatment (Day 28), and at the 28-day post-treatment follow-up visit (Day 42).

Table 6: Schedule of Assessment for Study MP-1000-02 and -03

Event/Procedure	Screen[a]/ Day –30 to -1 (Visit 0)	Baseline/ Day 0 (Visit 1)	Two Weeks/ End tx[b] Day 14 ±2 (Visit 2)	Four Weeks/ Two wks off tx: End tx + 14 days ± 2 (Visit 3)	Day 42 Four wks off tx: End tx + 28 days ±4 (Visit 4)
Informed Consent	X				
Inclusion/Exclusion Criteria	X	X			
Demographics	X				
Medical History	X				
Abbreviated Physical Exam	X				
Urine Pregnancy Test	X	X	X		
12-Lead Electrocardiogram[c]	X		X		
Clinical Safety Lab Tests		X	X	X[d]	X[d]
KOH[e]	X	X	X	X	X
Culture		X	X	X	X
Clinical Signs and Symptoms of *t. pedis*	X	X	X	X	X
First Study Medication Application		X[f]			
Review Subject Compliance, Weigh Tubes		X	X		
Adverse Events	X	X	X	X	X
Concomitant Medications	X	X	X	X	X

[a] If Subject has no need for washout, screening and baseline may occur on the same day.

[b] If Subject discontinues treatment early, Two Weeks / End treatment evaluations shall be performed.

[c] Electrocardiograms will be required for approximately 75 patients at selected sites. Subjects meeting the requirements for ECG testing (See Section 10.3) will also have a 12-lead ECG performed at completion of treatment (Visit 2).

[d] Only if clinically significant lab findings are present at end of treatment, repeat labs shall be performed during off-treatment period until resolution or acceptable explanation by Investigator.

[e] KOH will be performed at screening /baseline visit(s) at the site; KOH will be performed at baseline and all subsequent visits at the central lab (i.e., at baseline visit, KOH will be performed at both site and central lab)

[f] Last day of treatment is on the evening of Day 13; next visit for evaluations is on Day 14; the off-drug follow-up visit days are calculated from the last day of treatment (not from baseline).

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. The per protocol population includes MITT subjects who (1) meet all inclusion/exclusion criteria, (2) do not take interfering concomitant medications, (3) attend the Day 28 and Day 42 evaluations (unless they discontinue due to a treatment related adverse event or lack of treatment effect/worsening of condition), (4) applied 80-120% of expected doses, and (5) had the Day 28 and 42 visits within a visit window of ±4 days.

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 7: 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 the single tinea cruris study will be discussed here.*

5.3.2 Planned Clinical Study: (MP-1000-01)

Title: A Randomized, Multi-Center, Double-Blind, Vehicle-Controlled Study Evaluating the Efficacy and Safety of Product 33525 (Luliconazole Cream, 1%) in Subjects with Tinea Cruris.

Objective:

1. Evaluate the safety and efficacy of seven days of once daily topically administered Luliconazole Cream, 1% compared with Vehicle Cream in treating subjects with tinea cruris.
2. Collect clinical isolates and identify organism by genus and species to support labeling for specific causative organisms for tinea cruris.

Study Design: Protocol MP-1000-01, is a multi-center, randomized, double blind, vehicle-controlled, 2-arm study (luliconazole cream vs. vehicle cream) to be conducted at twenty centers in the United States. The sponsor intends to enroll 390 subjects (randomized 2:1), with the expectation of 219 subjects eligible for MITT analyses. Subjects will be randomly allocated to treatment with either Luliconazole Cream, 1% or Vehicle Cream for 1 week.

Number of Subjects: 390 male and female subjects

Ages of Subjects for Inclusion: 12 years of age or older

Inclusion Criteria:

8. Ability and willingness to sign a written informed consent and/or assent (age appropriate).
9. Subjects of either gender must be 12 years of age or older.
10. Subjects with a clinical diagnosis of tinea cruris characterized by clinical evidence of a tinea infection (at least moderate erythema, mild scalding, and moderate pruritis) based on signs and symptoms.

11. Subjects with a mycological diagnosis of tinea cruris confirmed by the detection of fungal hyphae on a microscopic KOH wet mount.
12. Women of child-bearing potential (WOCBP) must have a negative urine pregnancy test at Baseline and must agree to use an effective form of contraception. Effective contraception is defined as regular use of oral or intramuscular contraceptives, condoms, spermicides, diaphragm, IUD, implantable and contraceptive patches, or abstinence. (Note: Oral contraceptives if used for at least 3 months prior to enrollment in the study).
13. Subjects must be in good general health and free of any disease that in the Investigator's opinion might interfere with the study evaluations.
14. Subjects must be able to communicate, be able to understand the study procedures, and be willing to comply with the study requirements.

Exclusion Criteria:

12. Subjects with active atopic or contact dermatitis in the treated area.
13. Subjects with severe dermatophytoses, mucocutaneous candidiasis, or bacterial skin infection.
14. Female subjects who are pregnant and/or nursing or planning a pregnancy during the course of the trial. Subjects who test positive for pregnancy after the start of test treatment will be discontinued from test treatment but will be followed for safety purposes.
15. Subjects who are immunocompromised (due to disease, e.g., HIV or medications).
16. Subjects who have a recent history of or currently known to abuse drug or alcohol.
17. Subjects with a history of intolerance or hypersensitivity to imidazole compounds or inactive components of the cream.
18. Subjects with current significant skin disease that is considered by the investigator to be clinically important and indicative of conditions that might complicate interpretation of study results.
19. Subjects with a life-threatening condition (e.g., autoimmune deficiency syndrome, cancer, unstable angina, or myocardial infarction) within the last 6 months.
20. Subjects with abnormal findings that are considered by the investigator to be clinically important and indicative of conditions that might complicate interpretation of study results.
21. Subjects with uncontrolled diabetes mellitus in the judgment of the investigator.
22. Subjects who are unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function.
23. Subjects who are currently in a clinical drug research study with other medications or have been a participant in a clinical trial within 30 days or 5 half-lives of the investigational drug (whichever is longer) prior to the Baseline visit, and
24. Subjects 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 antifungals within 8 weeks or 5 half-lives of the antifungal (whichever is 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 is 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 or intralesional corticosteroids within 30 days of the Baseline visit,
h. any other medicated topical treatments to the treatment area(s) within 7 days of Baseline visit.
i. any other significant treatments, except hormonal contraception and multivitamin, at the discretion of the investigator that would interfere with study treatment.

Study Plan:

This Phase 3 clinical trial will compare the safety and efficacy of luliconazole cream, 1% to vehicle cream (placebo), in the treatment of subjects diagnosed with tinea cruris. The sponsor intends to enroll 390 subjects, randomized 2:1 to active therapy (146 MITT) in the Luliconazole arm, and 73 MITT subjects in the vehicle arm.

Each subject will have documentation of disease at the Baseline visit with the recording of clinical parameters of the signs and symptoms of the infection and mycological confirmation by microscopy (KOH). Mycology cultures will be sent to a central mycology laboratory for confirmation of the fungus. All subjects with a clinical diagnosis of tinea cruris confirmed by the detection of fungal hyphae on potassium hydroxide (KOH) wet mount, performed at the investigational site, will be eligible to be included in the study; and those who subsequently show negative baseline culture for a dermatophyte at the central mycology laboratory will be categorized as "delayed exclusion" and will be excluded from the efficacy summaries.

Each of the signs of tinea cruris will be evaluated by scoring the severity of erythema, scaling, and pruritis on a 4-point scale (0-3, indicating none, mild, moderate, severe). Clinical and mycological assessments will be evaluated and repeated at the end of treatment on Day 7, and at the 1-week, 2-week, and 3-week post-treatment follow-up visits (Day 14, 21, and 28).

Table 8: Schedule of Assessments for Study MP-1000-01

Event/Procedure	Screening[a] Day –30 to -1 (Visit 0)	Baseline Day 0 (Visit 1)	Day 3 (Telephone)	Day 7 End tx[b] + 2 days (Visit 2)	End tx + 7 days[g] (Day 14) ±2 days (Visit 3)	End tx + 14 days[g] (Day 21) ±2 days (Visit 4)	End tx + 21 days[g] (Day 28) ±2 days (Visit 5)
Informed Consent	X						
Inclusion/Exclusion Criteria	X	X					
Demographics	X						
Medical History	X						
Abbreviated Physical Exam	X						
12-Lead Electrocardiogram[c]		X		X	X		X
Urine Pregnancy Test	X	X		X			
Clinical Safety Lab Tests		X		X	X[d]	X[d]	X[d]
KOH[e]	X	X		X	X	X	X
Culture		X		X	X	X	X
Clinical Signs and Symptoms of tinea cruris	X	X		X	X	X	X
Study Medication Application		X	←	→ X[f]			
Review Subject Compliance		X	X	X			
Weigh Tubes		X		X			
Adverse Events	X	X	X	X	X	X	X
Concomitant Medications	X	X		X	X	X	X

[a] If subject has no need for washout, Screening and Baseline may occur on the same day.
[b] If subject discontinues treatment early, Day 7 / End-of-treatment evaluations will be performed.
[c] Single 12-lead ECG performed from standard ECG machine after at least 5 minutes of supine rest and before blood draw.
[d] Only if clinically significant lab findings are present at end of treatment, repeat labs will be performed during off-treatment period until resolution or acceptable explanation by investigator.
[e] KOH will be performed at the site;
[f] Last day of treatment is on Day 6; next visit for evaluations is on Day 7.
[g] The off-drug follow-up visit days are calculated from the last day of treatment (not from Baseline)

Efficacy Assessments:

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

Primary Efficacy Endpoint:

The primary efficacy endpoint will be the proportion of subjects who achieve complete clearance at Day 28 (3 weeks post-treatment). **Complete clearance** is defined as achieving both:

- "**Clinical Cure**" – absence of the signs or symptoms of tinea cruris; i.e., score of 0 (none) on each of the individual signs for erythema, scaling, and pruritis, and

- "**Mycological cure**" – negative potassium hydroxide (KOH) examination and negative fungal culture.

Table 9: Signs and Symptoms Severity Score for Study MP-1000-01

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:

Pruritis:	
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), and Days 7, 14, 21, and 28 (end-of-treatment and 1-, 2-, and 3-week follow-up).

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 28 (3 weeks post-treatment).
- Proportion of subjects who achieve "clinical cure" at Day 28 (3 weeks post-treatment).
- The proportion of subjects who achieve "mycological cure" at Day 28 (3 weeks post-treatment).
- The proportion of subjects who achieve "effective treatment" at Day 21 (2 weeks post-treatment).
- The proportion of subjects who achieve "effective treatment" at Day 14 (1 week post-treatment)
- The proportion of subjects who achieve "effective treatment" at Day 7 (end-of-treatment).

The study will also collect clinical isolates to identify 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). Laboratory tests will be conducted at Baseline and again at the end-of-treatment visit. For subjects that have clinically significant laboratory test results at the end-of-treatment visit, those test will be repeated at the off-treatment visits until resolution or stabilized as judged by the investigator.

Pregnancy Testing and Reporting:
Urine pregnancy test kits must have a minimum analytical sensitivity of 25 mIU/mL. Women of child-bearing potential (WOCBP) must have a negative urine pregnancy test at Baseline and must agree to use an effective form of contraception throughout the study. If a subject becomes pregnant during the study, the investigator must notify the Medical Monitor immediately upon learning of the pregnancy. The outcome of any pregnancies occurring on the study must be followed up to term. Any spontaneous miscarriage or congenital anomaly or birth defect must be recorded as a Serious Adverse Event and full details will be requested. Any complications during pregnancy should be recorded as an AE and may constitute SAE if they fulfill any of the specified criteria for SAE.

12 Lead ECG Assessments:
A single 12-lead ECG was performed at the Baseline and Day 7, 14, and 28 visits. All post-treatment ECGs will be compared with the Baseline ECG. ECG parameters will include HR, P-R, QT and QTc intervals, ORS duration, and overall interpretation will be reported.

Reviewer's comment: *The applicant included an open-label study in all three indications as a long-term safety study.*

5.3.3 Planned Clinical Study: MP-1005

Title: An Open-Label Study to Evaluate the Safety of Long-Term Administration of Product 33525 in subjects with Tinea Pedis, Tinea Corporis, or Tinea Cruris

Objective: To examine the long-term safety of treating recurrent episodes of tinea pedis for 14 days for each recurrence and recurrent episodes of tinea corporis or tinea cruris for 7 days for each recurrence with Product 33525 treatment.

Study Design: This is a multi-center, open-label, single-arm study. At least one hundred (100) new Subjects (at least 25 Subjects each with a diagnosis of tinea pedis, tinea corporis, and tinea cruris) will be enrolled into this study as well as approximately 500 Subjects rolled over from the phase III studies. Investigational sites that participated in Phase III efficacy studies of Product 33525 in the U.S. and Central America will enroll Subjects after the Subject's completion in the efficacy study. Each Subject evaluable for long-term safety assessment will have a confirmed clinical diagnosis of interdigital tinea pedis, tinea corporis, or tinea cruris with a KOH wet mount microscopic assessment, mycology culture confirmation and susceptibility testing. Subjects in prior efficacy studies will use the confirmation from that study. All Subjects who apply at least one dose of study medication will be included in the safety summaries.

Number of Subjects: 100 new subjects and approximately 500 subjects who completed a prior efficacy study with Product 33525

Ages of Subjects for Inclusion: males and females 12 years or older

Inclusion Criteria:

Subjects must meet all of the following criteria to be included in the study:

1. Subjects with the ability and willingness to sign a written informed consent and /or assent (age appropriate).
2. Subjects of either gender must be 12 years of age or older.
3. Subjects with a clinical diagnosis of interdigital tinea pedis on one or both feet characterized by clinical evidence of a tinea infection (at least moderate erythema, moderate scaling, and mild pruritus) based on signs and symptoms severity score of tinea pedis
   OR
   tinea corporis characterized by clinical evidence of a tinea infection (at least moderate erythema, mild scaling, and moderate pruritus) based on signs and symptoms severity score of tinea corporis
   OR
   tinea cruris characterized by clinical evidence of a tinea infection (at least moderate erythema, mild scaling, and moderate pruritus) based on signs and symptoms severity score of tinea cruris.
4. Subjects with a mycological diagnosis of interdigital tinea pedis, tinea corporis, or tinea cruris confirmed by the detection of fungal hyphae on a microscopic KOH wet mount at the time of treatment.
5. Sexually active women of child-bearing potential (WOCBP) must use:
   a. One of these highly effective contraception method
      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 be in good general health and free of any disease that in the Investigator's opinion might interfere with the study evaluations.
7. Subjects must be able to communicate, be able to understand the study procedures, and be willing to comply with the study requirements.

Exclusion Criteria:

Subjects meeting any of the following criteria will be excluded from the study:

1. For Subjects with tinea pedis: Subjects with moccasin (dry type) tinea pedis, concomitant onychomycosis of the fingernails and/or toenails, or bacterial skin infection on the feet.
2. For Subjects with tinea corporis or tinea cruris: Subjects with active atopic or contact dermatitis in the treatment area.
3. Female Subjects who are pregnant and/or nursing or planning a pregnancy during the course of the study. Subjects who test positive for pregnancy after the start of test treatment will be discontinued from test treatment but will be followed for safety purposes.
4. Subjects who are immunocompromised (due to disease, e.g., HIV or medications).

5. Subjects who have a recent history of or currently abuse drug or alcohol.
6. Subjects with a history of intolerance or hypersensitivity to imidazole compounds or the inactive components of the cream.
7. Subjects with current significant skin disease that is considered by the Investigator to be clinically important and indicative of conditions that might complicate interpretation of study results.
8. Subjects with uncontrolled diabetes mellitus in the judgment of the Investigator.
9. Subjects with a life-threatening condition (e.g., autoimmune deficiency syndrome, cancer, unstable angina, or myocardial infarction) within the last 6 months.
10. Subjects with history of cardiac disease.
11. Subjects who are unable to communicate or cooperate with the Investigator due to language problems, poor mental development, or impaired cerebral function.
12. Subjects who are currently in a clinical drug research study with other medications or have been a participant in a clinical study within 30 days or 5 half-lives of the investigational drug (whichever is longer) prior to the Baseline visit.
13. Subjects with any other condition which, in the judgment of the Investigator, would put the Subject at unacceptable risk for participation in the study.
14. Subjects 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 antifungals within 8 weeks or 5 half-lives of the anti-fungal (whichever is 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 is 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 or intralesional corticosteroids within 30 days of the Baseline visit,
    h. any other medicated topical treatments to the treatment area(s) within 7 days of Baseline visit,
    i. any other significant treatments, except hormonal contraception and multivitamin, at the discretion of the Investigator that would interfere with study treatment.

Restricted Therapies:

Information on concomitant therapies was recorded on the Concomitant Therapy Form. Any required systemic or oral drug therapy or cosmetic products on the treatment area used by the Subject will be considered concomitant therapy (e.g., aspirin, Tylenol, birth control pills, vitamins, moisturizers, sunscreens, etc.). Every attempt should be made to keep concomitant therapy dosing, if used, constant during the study. Any change to concomitant therapy should be noted on the Concomitant Therapy Form. This form should also be completed for any Subject starting a new concomitant therapy after enrollment into the study. The following medications was prohibited during the study:

- topical or systemic antifungal agents;
- topical or systemic antibiotics;

- antibacterial soaps on the treatment area;
- topical corticosteroid in treatment area(s);
- systemic or intralesional corticosteroids;
- any other medicated topical treatments to the treatment area(s);
- any other significant treatments, except hormonal contraception and multivitamin, at the discretion of the Investigator that would interfere with study treatment.

Reviewer comment: *The applicant submitted this long-term safety protocol on 14-NOV-2011 and the protocol was reviewed by the Agency. Comments regarding the acceptability of sufficient long-term exposure to the drug product were asked of the Agency at the Pre-NDA meeting on 18-JUL-2012. The Agency commented that it is likely that sufficient long-term safety data would be presented with the addition of study MP-1005. The applicant adequately met the requirements for establishing long term safety.*

6 Review of Efficacy

Efficacy Summary
The evaluation of efficacy for luliconazole cream, 1% includes two Phase 3 clinical trials in tinea pedis and one Phase 3 clinical trial in tinea cruris. These studies support the proposed labeled indication for the topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by fungal organisms such as *T. rubrum*, (b) (4) or *E. floccosum* in patients 18 years of age and older.

In MP-1000-01, the study demonstrated that seven days of once daily topically administered luliconazole cream, 1% versus vehicle cream (21.2% vs. 4.4% [$p < 0.001$], respectively) is effective in treating subjects with tinea cruris. In MP-1000-02, the study demonstrated that 14 days of once daily topically administered luliconazole cream, 1% versus vehicle cream (26.4% vs. 1.9% [$p < 0.001$)], respectively) is effective in treating subjects with tinea pedis. Similarly, MP-1000-03 showed luliconazole cream, 1% versus vehicle cream (14.0% vs. 2.8% [$p < 0.001$], respectively), was effective in treating subjects with tinea pedis.

6.1 Indication

The applicant proposed that 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*, (b) (4) or *Epidermophyton floccosum*, in patients 18 years of age and older.

Reviewer's comment: (b) (4)

6.1.1 Methods

The efficacy evaluation was based on the findings in three Phase 3 clinical trials. Study MP-1000-01 for tinea cruris will be evaluated separately for the two studies conducted in tinea pedis patients. For all three studies, 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

The study population for the US clinical trials targeted enrollment to achieve subjects representative of the to-be-treated population: male and female subjects, at least 12 years old, with a clinical diagnosis of interdigital tinea pedis or tinea cruris characterized by at least moderate erythema, moderate scaling, and mild pruritus.

A total of 1126 subjects were randomized in the Phase 3 studies (643 subjects who had interdigital tinea pedis and 483 subjects who had tinea cruris). A total of 679 subjects had positive Baseline fungal cultures and were included in the MITT populations, 616 subjects completed the study (379 subjects who had interdigitial tinea pedis and 237 subjects who had tinea cruris). The most common reason for discontinuing the study was "lost to follow-up".

MP-1000-01 (Tinea cruris)
In the Phase 3 study MP-1000-01 (tinea cruris), a total of 483 subjects were randomized (318 to luliconazole cream, 1% and 165 to the vehicle cream group). All randomized subjects had positive Baseline KOH and were dispensed medication. Two-hundred twenty seven (227) subjects (153 in luliconazole cream, 1% group and 74 subjects in the vehicle cream group) had negative Baseline fungal cultures, and, therefore, were "delayed exclusions" and excluded from the MITT population. The MITT population remaining was 256 subjects (165 in the luliconazole cream, 1% group and 91 subjects in the vehicle cream group), and of those 237 subjects (157 in the luliconazole cream, 1% group and 80 subjects in the vehicle cream group) completed the study. The 19 subjects (8 in the luliconazole cream, 1% group and 11 in the vehicle cream group) discontinued the study early. The most common reason for discontinuation was "lost to follow-up" (7), followed by "subject request/consent withdrawn" (6), and "worsening of condition" (4 in the vehicle cream group and 2 in luliconazole cream group).

Table 10: Summary of Demographic Characteristics of MP-1000-01 (MITT Population)

	Luliconazole Cream, 1% (N=165)	**Vehicle Cream (N=91)**	**Total (N=256)**
Age (years)			
N	165	91	256
mean (SD)	41.1 (17.73)	39.1 (15.78)	40.4 (17.06)
Median	41.0	40	40.5
Min. To Max.	14 to 88	16 to 87	14 to 88
Gender			
Male	137 (83.0%)	75 (82.4%)	212 (82.8%)
Female	28 (17.0%)	16 (17.6%)	44 (17.2%)
Ethnicity			
Hispanic or Latino	91 (55.2%)	47 (51.6%)	138 (53.9%)
Not Hispanic or Latino	74 (44.8%)	47 (51.6)	118 (46.1%)
Race			
White	98 (59.4%)	50 (54.9%)	148 (57.8%)
Black	52 (31.5%)	36 (39.6%)	88 (34.4%)
Native Hawaiian/Other Pacific Islander	1 (0.6%)	0 (0.0%)	1 (0.4%)
American Indian or Alaska Native	1 (0.6%)	0 (0.0%)	1 (0.4%)
Multiple/Other	13 (7.9%)	5 (5.5%)	18 (7.0%)
Geographic Location			
United States	85 (51.5%)	49 (53.8%)	134 (52.3%)
Central America	80 (48.5%)	42 (46.2%)	122 (47.7%)

Multiple/Other includes multiracial
Source: Study MP-1000-01 study report Table 15

The mean age of subject in the MITT population of study MP-1000-01 was 40.4 years. Nine subjects were < 18 years of age. Most subjects (82.8% [212/256]) were male, and the majority of subjects (53.9% [138/256]) were "Hispanic or Latino." Approximately half of the subjects were White (57.8% [148/256]), and one-third were Black or African American (34.4% [88/256]). There were little clinically significant differences in the demographics between the luliconazole cream, 1% and vehicle cream groups in the MITT population.

For the MITT population, all subjects had positive Baseline KOH and fungal cultures. Most subjects (74.6% [191/256]) tested positive for *Trichophyton rubrum*, followed by *Epidermophyton floccosum* (16.0% [41/256]) and *Trichophyton mentagrophytes* (12.5% [32/256]). There were no clinically meaningful differences between the organisms cultured from the luliconazole cream, 1% group and the vehicle cream group.

Table 11: Summary of Subject Baseline Signs and Symptoms MP-1000-01 (MITT Population)

	Luliconazole Cream, 1% (N=165)	Vehicle Cream (N=91)	Total (N=256)
Erythema			
2 - Moderate	118 (71.5%)	68 (74.4%)	186 (72.7%%)
3 - Severe	47 (28.5%)	23 (25.3%)	70 (27.3%)
Scaling			
1 - Mild	14 (8.5%)	7 (7.7%)	21 (8.2%)
2 - Moderate	101 (61.2%)	61 (67.0%)	162 (63.3%)
3 - Severe	50 (30.3%)	23 (25.3%)	73 (28.5%)
Pruritus			
2 - Moderate	102 (61.8%)	50 (54.9%)	152 (59.4%)
3 - Severe	63 (38.2%)	41 (45.1%)	104 (40.6%)

Source: MP-1000-01 Study Report Table 17

For the MITT population, most subjects (72.7% [182/256]) had moderate erythema; 27.3% 970/256) had severe erythema at Baseline. No differences were seen between the luliconazole cream, 1% group and the vehicle cream group.

MP-1000-02 and MP-1000-02 (Interdigital Tinea Pedis)
In total 643 subjects were randomized in the combined studies (321 to MP-1000-02 and 322 to MP-1000-03). All randomized subjects had positive Baseline KOH and were dispensed study medication. However, 220 subjects (112 in MP-1000-02 and 108 in MP-1000-03) had negative Baseline fungal cultures, and, therefore, were "delayed exclusions" and exclude from the MITT population. The remaining 423 subjects had positive Baseline fungal cultures and were included in the MITT population. In study MP-1000-02, 185 subjected completed the study and in MP-1000-03, 194 subjects completed the study. The most common reasons for discontinuing the study were "lost to follow-up" and "investigator decision".

Reviewer's comment: *The applicant proposed label Section 6.1, Clinical Experience, seeks to* (b) (4) (b) (4) (b) (4) *This reviewer does not agree and revised the section with the safety population. The label should have a total of 616 subjects in the safety population (305 with tinea pedis and 311 with tinea cruris). These numbers should be reflected in the labeling under Section 6.1.*

Table 12: Summary of Demographic Characteristics for Interdigital Tinea Pedis (MP-1000-02 and MP-1000-03) Pooled MITT Populations

	Luliconazole Cream, 1% (N=213)	**Vehicle Cream (N=210)**
Age (years)		
Mean [a] (SD)	41.9 (13.78)	39.2 (13.59)
Median	42	39
Min. To Max.	16 to 78	13 to 74
Gender		
Male	172 (80.8%)	173 (82.4%)
Female	41 (19.2%)	37 (17.6%)
Ethnicity		
Hispanic or Latino	88 (41.3%)	86 (41.0%)
Not Hispanic or Latino	125 (58.7%)	124 (59.0%)
Race		
White	116 (54.5%)	106 (50.5%)
Black/African American	84 (39.4%)	87 (41.4%)
Asian	1 (0.5%)	1 (0.5%)
American Indian or Alaska Native	0 (0.0%)	4 (1.9%)
Multiple [b]	12 (5.6%)	11 (5.2%)
Other [c]	0 (0.0%)	1 (0.5%)
Geographic Location		
United States	182 (85.4%)	173 (82.4%)
Central America	31 (14.6%)	37 (17.6%)

[a] Mean age of the pooled population was 40.6 years
[b] 20 Black of African American/White, 3 Black or African American/Asian
[c] Persian
Source: Integrated Summary of Efficacy, Table 32

The demographic and baseline characteristics for MP-1000-02 and MP-1000-03 were similar. The evaluation of the pooled MITT population will be discussed. The mean age of subjects was 40.6 years. Fourteen subjects in the pooled MITT population were less than 18 years of age. Most subjects (81.6% [345/423]) were male, and the majority of subjects (58.9% [249/423]) were "not Hispanic or Latino." Approximately half of the subjects were White (52.5% [222/423]); 40.4% (171/423) were Black or African American and 7.1% subjects were "multiple/other" or other. Most of the subjects (83.9%) were from the US.

Table 13: Summary of Subject Baseline Signs and Symptoms for Interdigital Tinea Pedis (Pooled MITT Populations)

	Pooled Results	
	Luliconzole Cream, 1% (N=213)	**Vehicle Cream (N=210)**
Erythema		
2 - Moderate	178 (83.6%)	173 (82.4%)
3 - Severe	35 (16.4%)	37 (17.6%)
Scaling		
2 - Moderate	133 (62.4%)	115 (54.8%)
3 - Severe	80 (37.6%)	95 (45.2%)
Pruritus		
1 - Mild	41 (19.2%)	27 (12.9%)
2 - Moderate	118 (55.4%)	122 (58.1%)
3 - Severe	54 (25.4%)	61 (29.0%)

Source: Applicant ISE Table 34

Most subjects in the pooled MITT population had moderate erythema, and 17% had severe erythema at Baseline. The majority of subjects had moderate pruritus.

Reviewer's comment: *The subject demographics for the MITT population in all three clinical trials were homogenous. No clinically significant differences were concluded between the luliconazole cream, 1% group and the vehicle group.*

6.1.3 Subject Disposition

Study 01 randomized 483 subjects and had 256 subjects (165 luliconazole, 91vehicle) in the MITT population. Subject discontinuation rate of Luliconazole cream 1% was less than vehicle (5% vs. 12%). The most common reason for discontinuation was lost to follow up. No subject dropped out due to adverse event. Study 02 randomized 321 subjects and had 209 subjects (106 luliconazole, 103 vehicle) in the MITT population. Study 03 randomized 322 subjects and had 214 (107 luliconazole, 107 vehicle) subjects in the MITT population. Subject discontinuation rate of Luliconazole cream 1% was comparable to that of vehicle in Study 02 and slightly lower than that of vehicle (6% vs. 13%) in Study 03. The most common reason for discontinuation was lost to follow up. Only one subject in Study 02 dropped out due to an adverse event. This subject was randomized to the vehicle arm.

Table 14: Subjects Disposition for All Phase 3 Clinical Trials

	Tinea Cruris		Tinea Pedis (Pooled)	
	Luliconazole	**Vehicle**	**Luliconazole**	**Vehicle**
Subjects randomized	318	165	319	324
MITT[(1)] Subjects	165	91	213	210
Completed	157 (95%)	80 (88%)	195 (91.5%)	184 (87.6%)
Discontinued[(2)]	8 (5%)	11 (12%)	18 (8.4%)	26 (12.3%)
Reasons for Discontinuation (MITT)				
Adverse Event	0	0	0	1
Lost to follow up	4 (2%)	3 (3%)	13 (6%)	20 (9.5%)
Subject withdrawal	3 (2%)	3 (3%)	1 (0.05%)	3 (0.01%)
Protocol violation	NA	NA	2 (0.01%)	0
Worsening of condition	0	4 (4%)	NA	NA
Physician decision	1 (1%)	1 (1%)	2 (0.01%)	1 (0.004%)

Source: Agency Biostatistics Review by Dr. Yuqing Tang.
(1) MITT was defined as all randomized subjects with positive baseline KOH and fungal cultures in
(2) Discontinued subjects include subjects dropped out during the treatment period or follow up period.

Reviewer's comment: *Only one AE caused discontinuation in the MITT population. Sufficient subjects completed the study for primary endpoint analyses.*

6.1.4 Analysis of Primary Endpoint(s)

The two studies evaluated subjects aged 12 years or older with clinical diagnosis of interdigital tinea pedis (moderate erythema, moderate scaling, and mild pruritus) on one or both feet, and positive KOH and fungal culture. Study 01 evaluated subjects aged 12 years or older with clinical diagnosis of tinea cruris (moderate erythema, mild scaling, and moderate pruritus), and positive KOH and fungal culture. The protocol specified primary endpoint was the proportion of subjects achieving "complete clearance" at Day 42 for tinea pedis and Day 28 for tinea cruris. "Complete clearance" was defined as both "mycological cure" (negative KOH and negative fungal culture) and "clinical cure" (scores of 0 on each individual signs for erythema, scaling, and pruritus). Efficacy results based on the modified intent to treat (MITT) population with missing data imputed using the Last Observation Carried Forward (LOCF), and efficacy results based on the per protocol (PP) population are presented in **Table 15**. In all three studies, luliconazole cream 1% demonstrated that it was statistically superior to the vehicle cream.

Table 15: Results for Primary Efficacy Endpoint (Phase 3)

	Luliconazole	Vehicle	Treatment Difference and its 95% Confidence Interval	*p*-value[3]
Tinea Cruris (Study 01)				
MITT[1] population	35/165 (21.2%)	4/91 (4.4%)	15.8%, (7.8%, 24.6%)	<0.001
PP[2] population	29/134 (21.6%)	3/68 (4.4%)	17.2%, (7.2%, 26.0%)	<0.001
Tinea Pedis (Study 02)				
MITT population	28/106 (26.4%)	2/103 (1.9%)	24.5%, (15.5%, 34%)	<0.001
PP population	26/88 (30.0%)	2/80 (2.5%)	27.0%, (16.4%, 38.1%)	<0.001
Tinea Pedis (Study 03)				
MITT population	15/107 (14.0%)	3/107 (2.8%)	11.2%, (3.7%, 19.5%)	<0.001
PP population	11/66 (16.7%)	2/60 (3.3%)	13.3%, (2.6%, 24.8%)	0.004

(1) MITT population was defined as all randomized subjects with positive baseline KOH and fungal cultures.
(2) PP population was defined as MITT subjects who completed end of treatment and post treatment evaluation without major protocol deviation.
(3) *p*-value was calculated from CMH test stratified by center
Source: Agency Biostatistics Review by Dr. Yuqing Tang

Reviewer's comment: *The efficacy finding from the three pivotal clinical trials establish that luliconazole cream, 1% was superior to vehicle gel in the treatment of tinea cruris and interdigital tinea corporis.* (b) (4)

It should also be noted that the response rate of luliconazole in Study 02 (26.4% for the MITT and 30.0% for the PP) was twice as large as that in Study 03 (14.0% for the MITT and 16.7% for the PP). The response rate was 0 in several centers in Study 03 compared to those in Study 02. The center-by-center efficacy results, ordered by the magnitude of treatment effect are presented in the figures (2-4) below.

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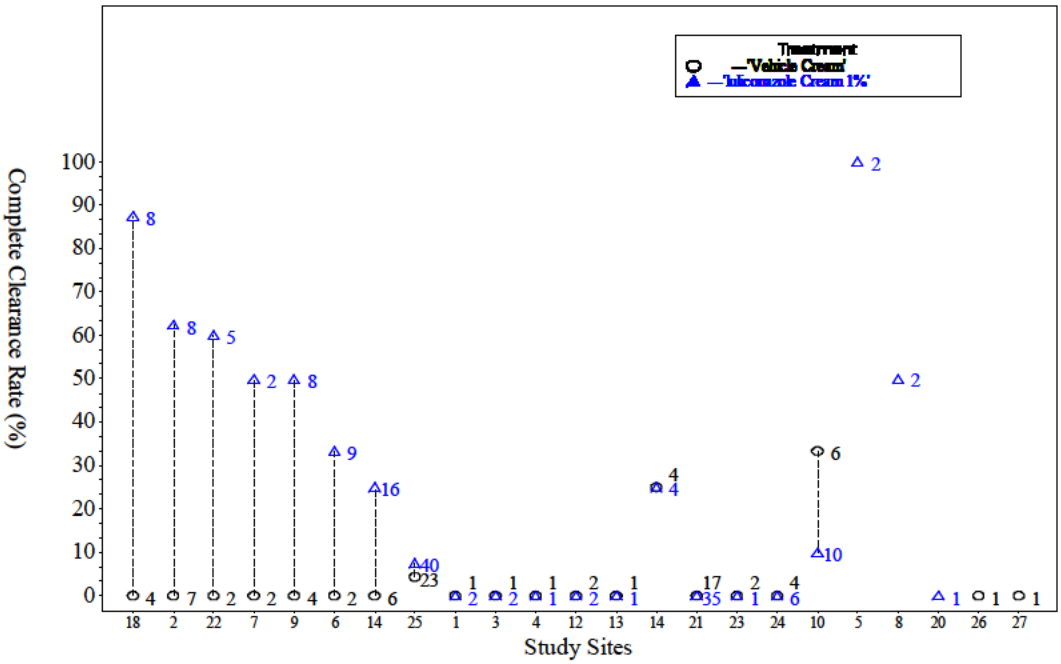
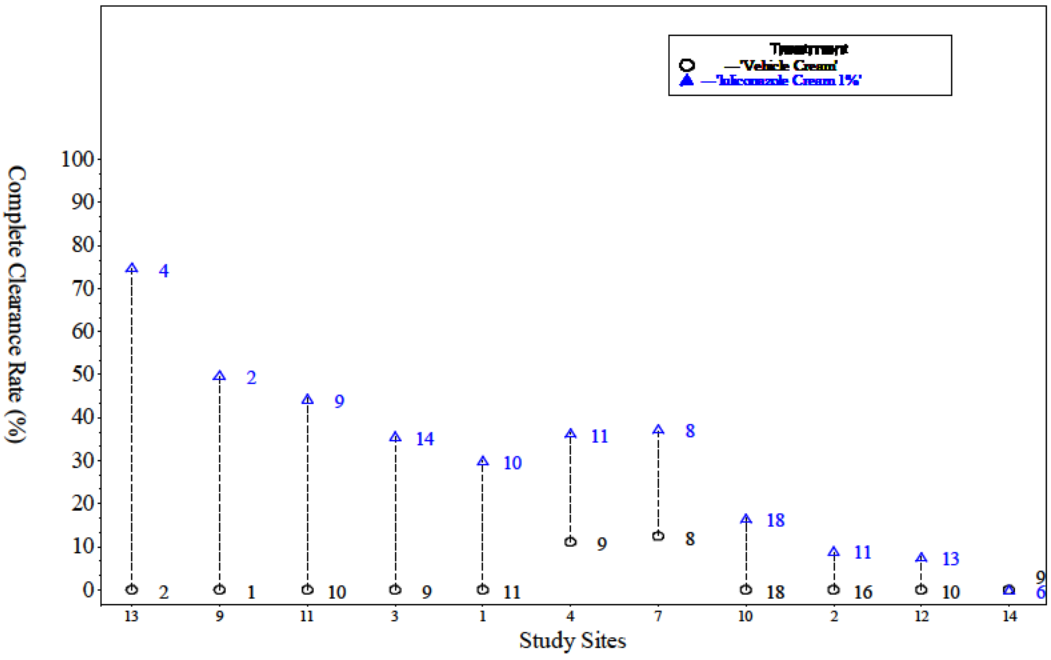
Figure 2: Efficacy by Center Results (MP-1000-01)



Source: Agency Biostatistics Review by Dr. Yuqing Tang

Figure 3: Efficacy by Center Results (MP-1000-02)



Source: Agency Biostatistics Review by Dr. Yuqing Tang

Figure 4: Efficacy by Center Results (MP-1000-03)

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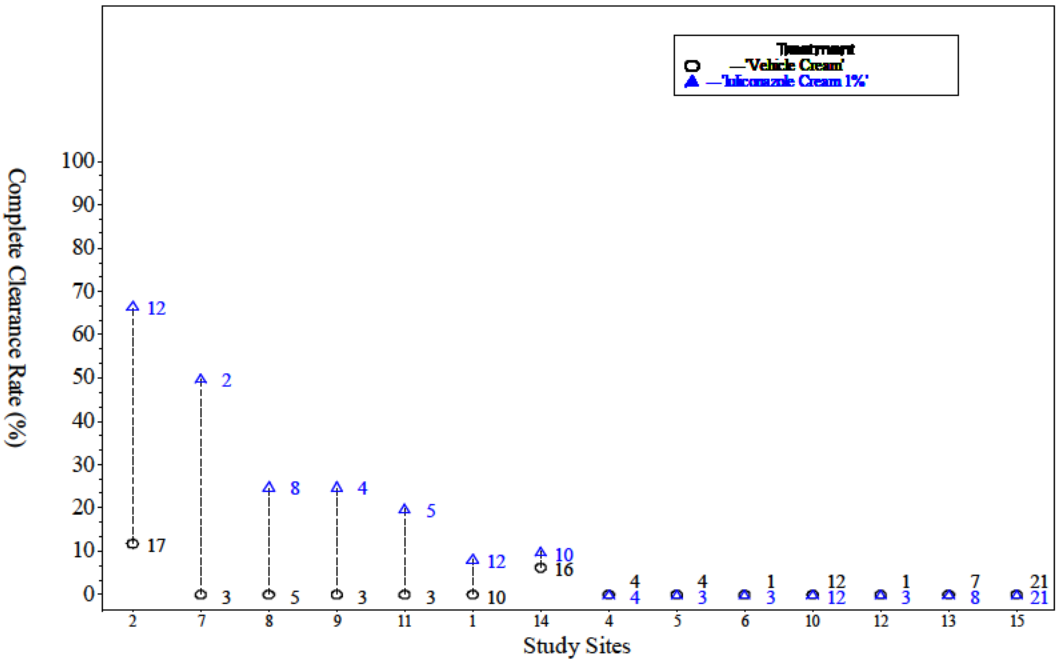

Source: Agency Biostatistics Review by Dr. Yuqing Tang

The treatment effect in Study MP-1000-02 (24.5% for MITT and 27% for PP) was twice as large as that in Study MP-1000-03 (11.2% for MITT and 13.3% for PP). Further investigation of the center-by-center variability showed that only 1 out of 11 study sites showed 0 treatment effects in MP-1000-02, in contract to 7 out of 14 study sites in MP-1000-03. The two Central American sites (sites 14 and site 15) in MP-1000-03 enrolled relatively large numbers of MITT subjects (26 in site 14 and 42 in site 15); however, these sites had relatively low treatment effect (3.75% in site 14 and 0% in site 15).

The Agency Biostatistician conducted Braslow-Day test to investigate the center-by-center variability at the significance level of 0.1. The test was not statistically significant for study MP-1000-02 and Study MP-1000-03; however, the test result was statistically significant (p-value<0.1) for Study MP-1000-01. Further examination showed that study Site 10 in Study 01 showed a negative treatment effect (36% for vehicle vs. 13% for luliconazole).

Reviewer's comment: *The analysis shows that the discrepancy in the study effects between MP1-000-02 and MP-1000-03 was a random occurrence. The treatment effects across centers were generally consistent.*

6.1.5 Analysis of Secondary Endpoints(s)

For the tinea cruris indication (study MP-1000-01), the protocol specified six secondary endpoints as follows:

- Proportion of subjects who achieved "effective treatment" (defined as negative KOH and fungal culture and at most mild erythema and/or scaling and no pruritus) at Day 28
- Proportion of subjects who achieved "clinical cure" at Day 28
- Proportion of subjects who achieved "mycological cure" at Day 28
- Proportion of subjects who achieved "effective treatment" at Day 21
- Proportion of subjects who achieved "effective treatment" at Day 14
- Proportion of subjects who achieved "effective treatment" at Day 7

For the tinea pedis indication (studies MP-1000-02 and MP-1000-03), the protocol specified four secondary endpoints as follows:

- 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;
- The proportion of subjects who achieve "complete clearance" at Day 28;
- The proportion of subjects who achieve "mycological cure" (negative KOH and culture) at Day 42;
- The proportion of subjects who achieve "clinical cure" at Day 42.

The secondary endpoints were analyzed based on the MITT population with missing data imputed using the LOCF method. All secondary endpoints showed statistically significant at the level of 0.05 except "complete clearance" rate at Day 28 in Study MP-1000-03 and "effective treatment" response rate at Day 7 in study MP-1000-01.

Table 16: Efficacy Results to Secondary Endpoints (MITT, LOCF)

	Luliconazole	**Vehicle**	***p*-value[(3)]**
Tinea Pedis (Study 02)			
Effective Treatment[(1)]	51/106 (48.1%)	10/103 (9.7%)	<0.001
Clinical cure[(1)]	31/106 (29.2%)	8/103 (7.8%)	<0.001
Mycological Cure[(1)]	66/106 (62.3%)	18/103 (17.5%)	<0.001
Complete Clearance[(1)]	15/106 (14.2%)	2/103 (1.9%)	0.001
Tinea Pedis (Study 03)			
Effective Treatment	35/107 (32.7%)	16/107 (15%)	<0.001
Clinical cure	16/107 (15%)	4/107 (3.7%)	<0.001
Mycological Cure	60/107 (56.1%)	29/107 (27.1%)	<0.001
Complete Clearance	10/107 (9.3%)	4/107 (3.7%)	0.055
Tinea Cruris (Study 01)			
Effective Treatment[(2)]	71/165 (43%)	17/91 (18.7%)	<0.001
Clinical cure[(2)]	40/165 (24.2%)	6/91 (6.6%)	<0.001
Mycological Cure[(2)]	129/165 (78.2%)	41/91 (45.1%)	<0.001
Effective Treatment at Day 21	64/165 (38.8%)	13/91 (14.3%)	<0.001
Effective Treatment at Day 14	43/165 (26.1%)	11/91 (12.1%)	0.012
Effective Treatment at Day 7	25/165 (15.2%)	6/91 (6.6%)	0.056

Source: Agency Biostatistics Review by Dr. Yuqing Tang
(1) For tinea pedis subjects, secondary endpoints of effective treatment, clinical cure, and mycological cure were evaluated at Day 42; Secondary endpoint of complete clearance was evaluated at Day 28.
(2) For Tinea cruris subjects, secondary endpoints of effective treatment, clinical cure, and mycological cure were evaluated at Day 28;
(3) *p*-value was calculated from CMH test stratified by center

Reviewer's comment: *The secondary efficacy endpoints supported the primary efficacy conclusions.* [redacted] (b) (4) (b) (4)

6.1.6 Other Endpoints

No other endpoints were evaluated or explored.

6.1.7 Subpopulations

The Phase 3 clinical trials were evaluated by subpopulation of gender, age, ethnicity, race, baseline clinical signs (erythema, scaling, and pruritus), and geographic location. The combined populations are the results for MP-1000-02 and MP-1000-03 separate from MP-1000-01.

In MP-1000-01 (tinea cruris), subject > 65 years with "Complete Clearance" was 28.6% (4/14) in the luliconazole cream, 1% treated group. None achieved "Complete Clearance" in the vehicle arm (3 subjects).

Table 17: Primary Efficacy Endpoint: Summary of Complete Clearance at Day 42 by Age Group (MITT for Interdigital Tinea Pedis MP-1000-02 and -03 Combined)

	Luliconazole Cream, 1% (N=213)	Vehicle Cream (N=210)
Age < 18 years		
Complete clearance [a]	1/4 (25%)	0/10 (0.0%)
Age 18 years to 65 years		
Complete clearance [a]	39/198 (19.7%)	5/196 (2.6%)
Age > 65 years		
Complete clearance [a]	3/11 (27.3%)	0/4 (0.0%)

[a] Complete clearance: Negative KOH and fungal culture results and severity scores of 0 (none) for erythema, scaling, and pruritus.

Based on age subgroups, few conclusions could be extrapolated from the < 18 year old group, as there are not enough subjects to determine efficacy (4 subjects) in the tinea pedis population. In the combined tinea pedis studies of the Age > 65 subgroup analysis, 27.3% (3/11 luliconazole cream, 1%) subjects in the luliconazole cream, 1% experienced "Complete Clearance". This was similar to the "Complete Clearance" primary endpoint experienced in the tinea cruris (MP-1000-01) population of 28.6% (4/14 luliconazole cream, 1%). None of the vehicle group > 65 years of age experienced "Complete Clearance" of their disease.

Reviewer's comment: *The experience in the > 65 year of age group was similar to that of the 18 years to 65 years group. The reviewer concludes that it is likely luliconazole cream, 1% is as effective for patients > 65 years of age. Labeling will reflect this conclusion.*

Table 18: Efficacy Results for Complete Cure Rate by Age, Gender, and Race

	Tinea Pedis (Study 02)		Tinea Pedis (Study 03)		Tinea Cruris (Study 01)	
	Luliconazole	**Vehicle**	**Luliconazole**	**Vehicle**	**Luliconazole**	**Vehicle**
MITT[(1)]	106	103	107	107	165	91
Gender						
Male	21/90 (23%)	1/89 (1%)	11/82 (13%)	2/84 (2%)	29/137 (21%)	3/75 (4%)
Female	7/16 (44%)	1/14 (7%)	4/25 (16%)	1/23 (4%)	6/28 (21%)	1/16 (6%)
Age						
< Median	18/50 (36%)	1/54 (2%)	8/45 (18%)	2/58 (3%)	10/82 (12%)	1/46 (2%)
≥ Median	10/56 (18%)	1/49 (2%)	7/62 (11%)	1/49 (2%)	25/83 (30%)	3/45 (7%)
Race						
White	22/55 (40%)	2/56 (4%)	10/61 (16%)	0/50 (0%)	19/98 (20%)	0/50 (0%)
Black	2/38 (5%)	0/31 (0%)	5/46 (11%)	3/56 (5%)	10/52 (19%)	4/36 (11%)
Other[(2)]	4/13 (31%)	0/16 (0%)	-	0/1 (0%)	6/15 (40%)	0/5 (0%)

Source: Page 193-197 (Study 02), Page 179-183 (Study 03), and Page 231-235 (Study 01) of sponsor's clinical study report
(1) MITT was defined as all randomized subjects with positive baseline KOH and fungal cultures.
(2)Other includes Native Hawaiian, Other Pacific Islander, American Indian, Alaska Native or Multiple.

For efficacy by gender, it appears a slight trend of female having higher success than males for subjects with tinea pedis. However, as there were over 82% males subjects, the numbers of female subjects were too small to make any inferences.

Reviewer's comment: *The response rates for each of the subgroups evaluated were generally homogeneous; it does not appear to favor race, gender, or age.*

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The US Phase 3 clinical efficacy studies demonstrated that seven days of once daily topically administered Luliconazole Cream 1% was effective in treating subjects with tinea cruris and that 14 days of once daily topically administered Luliconazole Cream 1% was effective in treating subjects with interdigital tinea pedis. The studies also demonstrated that clinical dermatophyte isolates (*T. rubrum*, *T. mentagrophytes*, and *E. floccosum*) obtained from study subjects were highly susceptible to treatment with Luliconazole Cream 1%. The US Phase 2 clinical efficacy study supports a 14-day treatment course for interdigital tinea pedis.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The US clinical program demonstrated that the efficacy of once daily dosing for seven days for subjects with tinea cruris persists for at least 21 days after the end of treatment and that the efficacy of once daily dosing for 14 days for subjects with interdigital tinea pedis persists for at least 28 days after the end of treatment.

The US Phase 3 clinical trials showed "Complete Clearance" was achieved by a significantly greater proportion of subjects in the luliconazole cream 1% group compared to subjects in the

vehicle cream group in all three studies. In an *ad hoc* analysis evaluating response at Day 42, no residual erythema was seen between the luliconazole cream, 1% for 14 days or 28 days in study TP-0801. In the MP-1005, long-term safety study, pre-treatment susceptibility testing was performed from the isolates obtained to determine if resistance had developed in any of the dermatophytes recovered. All clinical isolates were tested and no increase in MIC was detected, supporting that these dermatophytes do not become resistant to treatment with luliconazole cream, 1%

Reviewer's conclusions: *The effects of luliconazole cream showed persistence for at least 21 days after the end-of-treatment for tinea cruris and at least 28 days for tinea pedis. The data presented in the supporting studies show that no increase in erythema occurs after treatment. The targeted dermatophytes do not develop resistance to luliconazole cream and retreatment is possible.*

6.1.10 Additional Efficacy Issues/Analyses

No additional efficacy issues were explored.

Reviewer's Final Efficacy Conclusions: *The efficacy finding from the Phase 3 clinical trials established that luliconazole cream, 1% was effective in treating tinea pedis once daily for 14 days and tinea cruris once daily for 7 days. For the two tinea pedis trials, it was noted that the treatment effect in one study was twice as large as that in the second study. No specific etiology was identified for these results, although it does not appear unusual when compared to previous applications such as naftifine for the same indications. Site-by-site analysis showed that some sites had small contribution to treatment effect that was reflected in the overall study results. Treatment effects across centers were generally consistent.*

Based on the collective evidence presented by the applicant, luliconazole cream, 1% was effective and should be approved for the indications of tinea pedis and tinea cruris.

7 Review of Safety

Safety Summary
Evidence from eleven clinical studies form the safety database for luliconazole cream, 1%, these include: four Phase 3 clinical trials (two in subjects interdigital tinea pedis, one study in subjects with tine cruris, and one long-term safety study in subjects with interdigital tinea pedis, tinea cruris, tinea corporis), one Phase 2 study in subjects with tinea pedis, and six Phase 1 studies (a phototoxicity study, a photoallergenicity study, a 21-day cumulative irritation study, a human repeated insult patch test [HRIPT] study, a maximal use pharmacokinetic study in subjects with interdigital tinea pedis and tinea cruris, and a thorough QT [TQT] study). These clinical studies were conducted in the US and Central America.

In addition to the studies conducted for the NDA, seven supportive Japanese clinical studies were included in the application to support the safety database of luliconazole. The seven

supportive Japanese clinical studies were: one Phase 3 clinical study (a study in subjects with interdigital or vesicular type tinea pedis), three Phase 2 clinical studies (a study in subjects with interdigital or vesicular type tinea pedis or tinea corporis, a study in subjects with interdigital or vesicular type tinea pedis or tinea corporis/cruris, and a study in subjects with interdigital or vesicular type tinea pedis), and three Phase 1 clinical studies (two high dose PK studies and one phototoxicity study).

Reviewer's comment: *The most notable aspect of the safety review for this application is the lack of significant safety issues beyond application site reactions, and even those local reactions that did occur were judged to be mild. 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 application. The luliconazole drug product has been in use in Japan since its 2005 approval and over* (b) (4) *distributed. Few adverse events were reported in its 8 years of clinical use. As such, despite typical Agency advice to populate Section 5 of the approved labeling, this reviewer recommends that "none" more accurately describes the possibility of severe reactions for Section 5, Warnings and Precautions.*

7.1 Methods

The safety review will consist of the Phase 2 and Phase 3 US clinical trials that will from the primary basis of support for approval. The two Phase 3 studies in interdigital tinea pedis will be pooled for their safety data, as the studies were identical in design. In addition, the applicant has provided a long-term safety Phase 3 study in approximately 600 subjects (153 new subjects and 451 subjects from Phase 3 clinical trials) with tinea pedis, tinea cruris, or tinea corporis. The Phase 3 clinical trial in tinea cruris will stand alone for its safety data. The Japanese studies will be briefly reviewed for any safety signals that may exist with the use of this drug product in foreign clinical trials.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Table 19: Clinical Trials Used to Evaluate Safety

Study	Objective(s) of the Study	Study Design	Subjects Population (Plan/Actual)	Number Sites (Location)	Dosing Regimen/Duration of Treatment
MP-1000-01 (Phase 3)	**Safety and efficacy in tinea cruris**	**Multi-center, double-blind, parallel group, vehicle-controlled study**	**Subjects with tinea cruris** **(500/483)**	**23 (US)** **1 (PR)** **3 (CA)**	**Once daily for one week**
MP-1000-02 (Phase 3)	**Safety and efficacy in interdigital tinea pedis**	**Multi-center, randomized, double-blind, parallel group, vehicle-controlled study.**	**Subjects with interdigital tinea pedis** **(300/321)**	**11 (US)** **1 (PR)**	**Once daily for two weeks (14 days)**
MP-1000-03 (Phase 3)	**Safety and efficacy in interdigital tinea pedis**	**Multi-center, randomized, double-blind, parallel group, vehicle-controlled study.**	**Subjects with interdigital tinea pedis.** **(300/322)**	**12 (US)** **2 (CA)**	**Once daily for two weeks (14 days)**
MP-1005 (Phase 3)	**Long-term safety of treating recurrent episodes of interdigital tinea pedis for 14 days and tinea corporis and tinea cruris for 7 days**	**Multi-center, non-randomized, open-label, single treatment safety study**	**Subjects with interdigital tinea pedis, tinea cruris, or tinea corporis** **(600/604)**	**33 (US)** **1 (PR)** **4 (CA)**	**Once daily for two weeks for each episode of tinea pedis.** **Once daily for one week for each episode of tinea cruris or tinea corporis.**
TP-0801 (Phase 2)	**Safety and optimal duration**	**Multi-center, randomized, double-blind, duration-range, parallel group**	**Subjects with interdigital tinea pedis** **(150/147)**	**5 (US)**	**Once daily for two or four weeks (14 days or 28 days)**

Source: Table extrapolated from applicant ISS

MP-1000-01: A Phase 3, multi-center, randomized, double-blind, parallel group, vehicle-controlled study designed to evaluate the safety and efficacy of seven days of once daily topically administered luliconazole cream 1% compared with vehicle cream in treating subjects with tinea cruris. The fungal organisms causing the infection were determined (genus and species) from clinical isolates collected from diseased tissue. Subjects were randomized 2:1 to receive luliconazole cream 1% or vehicle cream. Both treatment groups were followed for 21 days post-treatment period (Day 28). Safety evaluations included:

- Adverse event (AE) assessments at all visits.

- Safety laboratory assessments (hematology, chemistry, and urinalysis) at Baseline and end-of-treatment (Day 7). For subjects who had clinically significant laboratory test

results at the end-of-treatment visit, those tests were repeated at the off-treatment visits (Days 14, 21, and 28) as necessary until resolution or stabilization as judged by the investigator.

- Urine pregnancy tests at Screening, Baseline, and end-of-treatment (Day 7), and electrocardiogram (ECG) assessments at Baseline, and Day 7, 14, and 28 [end-of-treatment and 7 and 21 days follow-up]).

MP-1000-02 and MP-1000-03: A Phase 3, multi-center, randomized, double-blind, parallel group, vehicle- controlled study designed to evaluate the safety and efficacy of 14 days of once daily topically administered luliconazole cream 1% compared with vehicle cream in treating subjects with interdigital tinea pedis. The fungal organisms causing the infection were determined (genus and species) from clinical isolates collected from diseased tissue. Subjects were randomized 1:1 to receive luliconazole cream 1% or vehicle cream. Both treatment groups were followed for 28 days post-treatment period (Day 42). Safety evaluations included:

- AE assessments at all visits.

- Safety laboratory assessments (hematology, chemistry, and urinalysis) at Baseline and end-of-treatment (Day 14). For subjects who had clinically significant laboratory test results at the end-of-treatment visit, those tests were repeated at the off-treatment visits (Days 28 and 42) as necessary until resolution or stabilization as judged by the investigator.

- Urine pregnancy tests at Screening, Baseline, and end-of-treatment (Day 14).

MP-1005: A Phase 3, multi-center, open-label study designed to examine the long-term safety of treating recurrent episodes of interdigital tinea pedis for 14 days and tinea corporis and tinea cruris for seven days with Luliconazole Cream 1%. Safety evaluations included:

- AE assessments at all visits.

- Safety laboratory assessments (hematology, chemistry, and urinalysis) at Baseline (Day 0) and at the end-of-treatment visits (Day 7 for tinea cruris/corporis or Day 14 for interdigital tinea pedis) of the initial treatment course for new subjects. Laboratory results from the end-of-treatment visit (or follow-up laboratory results) of the prior efficacy study were used for Baseline results for previously enrolled subjects who received vehicle cream in the previous efficacy study. Laboratory results from the Baseline visit of the previous efficacy study were used for baseline results for previously enrolled subjects who received luliconazole cream, 1% in the previous efficacy study. For subjects who had clinically significant laboratory test results at Baseline, those tests were to be repeated until resolution or stabilized as judged by the investigator. Safety laboratory results from all visits in the previous efficacy study also were included for previously enrolled subjects who received luliconazole cream, 1% in the previous

efficacy study. Safety laboratory tests were conducted prior to the start of treatment and end-of-treatment visit for all subsequent treatment courses for new subjects and at the quarter 4/end-of-study visit for all subjects.

- Urine pregnancy test at Screening, Baseline, End-of-Treatment, and off-treatment follow-up visits, and at initial visit, End-of-Treatment, and post-treatment visit for each retreatment for both new subjects and previously enrolled subjects.

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

The safety populations from the Phase 3 clinical trials and the long-term, open-label study will be pooled for analyses. The adverse events will be analyzed by using MedDRA (*version 14.0*) SOC and PT coding.

7.2 Adequacy of Safety Assessments

The Phase 3 clinical trials included assessments of AE at all visits. Safety laboratory assessments (hematology, chemistry, and urinalysis) were completed at Baseline and end-of-treatment (Day 7 for tinea cruris, and Day 42 for tinea pedis). A urine pregnancy test at Screening, Baseline, and end-of-treatment was completed. In addition, a 12-lead electrocardiogram assessment was completed at Baseline, and Day 7, 14, and 28 in tinea cruris subjects.

Reviewer's comment: *In general, sufficient safety assessments were completed during the Phase 3 clinical trials to establish short and long term safety. Minimal safety issues were identified and were confined to local application site reactions. In addition, the applicant completed dermal safety studies and a single Phase 2 duration of use study to complete the safety database.*

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

A total of 1495 subjects in the eleven US clinical studies (679 subjects with interdigital tinea pedis, 410 subjects with tinea cruris, 40 subjects with tinea corporis, and 426 healthy volunteers) applied luliconazole cream, 1% were included in the safety population. The long-term study MP-1005 contributed 153 new subjects and 171 previous efficacy subjects who received vehicle cream in previous studies to the safety population.

In Phase 3 US clinical trials, the combined safety population included 940 subjects who received luliconazole cream, 1% and 466 subjects who received vehicle cream.

Reviewer's comment: *The ICH E1a specifies that a minimum of 300 subjects be treated for six months and a minimum of 100 subjects be treated for one year with the investigational product at the dose level intended for clinical use. The applicant has provided three Phase 3 safety populations and a single long-term safety population treated with the investigational drug product. A total of 451 luliconazole cream, 1% treated in the MP-1005 were followed for at least six months and 126 were followed for at least one year.*

Table 20: Summary of Numbers of Subjects Included in the Phase 3 US Safety Populations

Study	Luliconazole Cream, 1%	Vehicle Cream
MP-1000-01 [a]	311	160
MP-1000-02 [b]	152	153
MP-1000-03 [b]	153	153
MP-1005 [c]	581	NA
New Subjects	153	NA
Rollover subjects Received luliconazole cream in previous efficacy study	257	NA
Received vehicle cream in previous efficacy study	171	NA
Total [d]	940	466

a. Tinea cruris
b. Interdigital tinea pedis
c. Tinea cruris, tinea corporis, or interdigital tinea pedis
d. The contribution of MP-1005 to overall safety population included new subjects plus rollover subjects who received vehicle cream in previous efficacy study and applied luliconazole cream, 1% in MP-1005.

In the three Phase 3 pivotal clinical trials (MP-1000-01, -02, -03), a total of 1126 subjects (637 subjects in the luliconazole cream, 1% group and 489 subjects in the vehicle cream group) were randomized. There were forty-four (44) subjects (21 in the luliconazole cream, 1% group and 23 subjects in the vehicle cream group) that were not included in the safety population. These subjects had no post-baseline safety evaluation and were excluded from the safety population. Therefore, a total of 1082 subjects were included in the safety population. Subjects in the MP-1000-01 (tinea cruris) were instructed to apply and adequate amount to cream to cover the affected surface and approximately 2.5 cm (1 inch) of surrounding clinically healthy skin, once daily for seven days. The subjects in the MP-1000-01 used a mean of 15.1 grams of luliconazole cream, 1% per subject. Subjects in the combined MP-1000-02 and MP-1000-03 (interdigital tinea pedis) were instructed to apply and adequate amount of cream to cover the entire area of the forefeet including all interdigital web spaces and approximately 2.5 cm (1 inch) of surrounding healthy skin, once daily for 14 days. Subjects in the combined tinea pedis trials used a mean of 15.8 grams of luliconazole cream, 1% per subject.

Table 21: Summary of Drug Exposure (Safety Population Combined)

	Luliconazole Cream, 1%			Vehicle Cream		
Study Medication Used per Subject (g) [a]	MP-1000-01 (N=311)	MP-1000-02/MP-1000-03 (N=305)	Total (N=616)	MP-1000-01 (N=160)	MP-100-02/MP-1000-03 (N=306)	Total (N=466)
N	307	297	604	158	295	453
Mean	15.1	15.8	15.5	14.7	15.9	15.5
SD	6.54	7.87	7.23	6.79	6.76	6.76
Median	15.4	15.3	15.4	15.0	15.9	15.4
Min to Max	1.2 to 32.8	0.6 to 54.4	0.6 to 54.4	0.9 to 36.6	0.8 to 29.4	0.8 to 36.6

[a] Study medication used per subject calculated as dispensed tube weight minus returned tube weight.
Source: Applicants ISS

In the open-label, long-term safety study (MP-1005), the safety population included 581 subjects (187 subjects with tinea cruris, 354 subjects with interdigital tinea pedis, and 40 subject with tinea corporis) who received luliconazole cream, 1%. Of those subjects, 153 were newly enrolled, 257 were in previous efficacy study, and 171 were previously efficacy study subjects who received vehicle cream. The application of the investigational drug product is the same as that's described above for it intended use. The mean amount of luliconazole cream, 1% used in interdigital tinea pedis, tinea corporis, and tinea cruris was 50.8 grams, 28.6 grams, and 44.1 grams, respectively.

Table 22: Summary of Drug Exposure (Mp-1005, long-term, open-label study)

Luliconazole Cream, 1% Used (g) [a]	**Interdigital Tinea Pedis (N=354)**	**Tinea Corporis (N=40)**	**Tinea Cruris (N=187)**
N	322	35	179
Mean	50.8	28.6	44.1
SD	40.58	38.79	32.25
Median	38.2	18.4	35.7
Min to Max	0.6 to 184	3.4 to 223	1.2 to 132

[a] Luliconazole Cream, 1% used calculated as dispensed tube weight minus returned tube weight.
Source: Applicant study report for MP-1005

Reviewer's conclusion: *Sufficient safety population is provided in this application to satisfy ICH E1a, and the safety profile is suggestive that the provided safety population is sufficient to evaluate long-term safety issues. Subjects in the four studies were exposed to sufficient investigational drug to provide adequate safety evaluations.*

7.2.2 Explorations for Dose Response

The exploration of dose and duration-finding was studied in a Phase 2, multi-center, randomized, double-blind, parallel group study designed to evaluate the safety and optimal duration of once daily topically administered luliconazole cream, 1% (for 14 days or 28 days). The objective of this study was to achieve "complete clearance" from interdigital tinea pedis at two weeks post-treatment. Subjects were randomly allocated (2:2:1:1) to receive luliconazole cream, 1% once daily for two weeks (14 days), luliconazole cream, 1% once daily for four weeks (28 days),

vehicle cream once daily for two weeks (14 days), or vehicle cream once daily for four weeks (28 days). Safety evaluations were similar for the Phase 3 clinical trials.

The results of the study showed that more than half of the subjects in each active treatment group achieved complete clearance by four weeks post-treatment. The extent of exposure to study drug in each treatment group was relatively identical. The AEs and skin tolerability assessments revealed no safety signal or trends. Overall, based on the review of efficacy and safety outcomes, luliconazole cream, 1% when applied once daily for two or four week was found effective and likely safe.

7.2.3 Special Animal and/or In Vitro Testing

Please see Section 4.3 for a nonclinical Pharmacology summary. No other special animal or in vitro testing was conducted with this drug product.

7.2.4 Routine Clinical Testing

Safety assessments for each of the Phase 3 clinical trial is described in section 7.1.1. Each clinical trial evaluated AEs at all visits, safety laboratory (hematology, chemistry, and urinalysis) at the designated time schedule, and urine pregnancy screening. Only MP-1000-01 evaluated ECG assessment at Baseline, Day 7, Day 14, and Day 28 (end-of-treatment and 7 and 21 days follow-up). In the maximum use PK study, the measurement of plasma levels of luliconazole subjects were measured; in addition, ECGs were done on Days 1, 8, and 15 pre-dose and prior to PK blood draws.

Reviewer's comment: *The routine clinical testing was sufficient to develop a safety database to evaluate luliconazole cream, 1%. The ECGs collected during the maximal use PK study, the Phase 3 clinical trial; along with the TQT study provides sufficient evidence for cardiac safety. The evaluation of the collected ECGs will be discussed in section 7.4.4.*

7.2.5 Metabolic, Clearance, and Interaction Workup

Please see Section 4.4 for the Clinical Pharmacology summary. Further evaluations for drug interactions in the post marketing phase are recommended for this drug product.

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

The safety of luliconazole cream, 1% was demonstrate in three Phase 3 clinical trials, a Phase 2 duration-finding study, a maximal use PK study, a long-term safety study, a thorough QT study, and four Phase 1 dermal safety studies. These studies show that there were little safety issues with irritation, sensitization, phototoxicity, or photoallergenicity. The systemic exposure demonstrated in the PK study, at doses three times the proposed clinical, dose did not induce higher AEs. The TQT study demonstrated no potential to impact cardiac safety. In addition, the AE profile in the pivotal Phase 3 clinical trials are acceptable and the drug product was generally well tolerated in the disease population.

7.3.1 Deaths

No deaths were reported in the pivotal Phase 3 clinical trials (MP-1000-01, MP-1000-02, and MP-1000-03). One subject in Study MP-1005 (35-447) died as a result of myocardial infarction. The subject was a 36 year old African American female with no relevant medical history or concomitant medications. She was reported to be obese (4ft7in height, 216 lbs. weight). The patient received a course of luliconazole cream, 1% from November 22, 2011 through December 3, 2011 during study MP-1000-03. She was advanced to the long-term safety study MP-1005 on January 6, 2012 at which time a second course of luliconazole cream, 1% was started. The second course was completed on January 21, 2012. She presented to the emergency room on (b) (6) with chest pains and vomiting. She was evaluated and discharged home on the same day. During the early morning hours of (b) (6) she was found dead in her bed. No autopsy was performed. The death certificate listed two causes of death: massive heart attack (primary) and arterial hypertension (secondary).

Reviewer's comment: *The narrative described for this death does not appear to be due to the study drug. The patient had no signs or symptoms of study drug adverse events during the two course of luliconazole cream, 1%. This reviewer concurs with the applicant's assessment that concomitant cardiovascular factors were the cause of death and it is extremely unlikely that there is a relationship to the study product.*

7.3.2 Nonfatal Serious Adverse Events

None of the SAEs in the 11 US clinical studies were deemed by the investigators to be "possibly related", "probably related", or "related" to the study medication. Eleven SAEs that were deemed "not related" to the study medication were reported by eight subjects in the US clinical studies in the luliconazole cream, 1% group. The single death event of "myocardial infarction" is discussed in the section above.

- Three SAEs were reported by two subjects in the luliconazole cream, 1% group in MP-1000-01 as "urinary tract infection" (two events) and "acute renal failure" (one event).
- Four SAEs ("loss of consciousness", "atrial fibrillation", "atrioventricular block complete", and "syncope") were reported for three subjects in MP-1005.

- Two SAEs ("asthenia" and "chest pain") were reported by one subject in the luliconazole cream, 1% for 28 days group in TP-0801.
- One SAE of joint dislocation was reported in MP-1000-08.

There were no SAEs reported in the tinea pedis Phase 3 clinical trials MP-1000-02 or MP-1000-03.

Reviewer's comment: *The three SAEs for study MP-1000-01 will be discussed under section 7.3.3. The four SAEs in the long-term safety study MP-1005 warrant further discussion.*

- *Subject 03-303 (loss of consciousness – MP-1005) was a 23 year old male with a history of head injury. This subject is not on any concomitant medications during the study. The subject received vehicle cream in his prior study (MP-1000-02) and was transitioned into the MP-1005 study on September 20, 2011, at which time the first course of luliconazole cream, 1% was started. He experienced headache and loss of consciousness, and was hospitalized on* (b) (6) *He was discharged 2 days later. The subject completed the study on August 9, 2012, but continued to have low grade headaches.*
- *Subject 34-307 (atrial fibrillation – MP-1005) was a 72 year old with a history of intermittent heart palpitations and diabetes mellitus. The subject received his first course of luliconazole cream, 1% in his prior study MP-1000-02. He did not report any AEs in that study. He was transitioned into study MP-1005 and started his second course of luliconazole cream, 1% on February 28, 2012 and subsequently had a third course on May 23, 2012. The subject was on multiple cardiac medications. He presented to his primary care physician on* (b) (6) *with dyspnea on exertion, nausea, and general weakness/dizziness. He was sent to the emergency department and diagnosed with new onset of atrial fibrillation. Due to his cardiac risk factors, he was given a cardiac work up during his hospitalization. The subject was placed on a beta-blocker for rate controlled and offered anticoagulation, but he declined. The subject then completed a fourth course of luliconazole cream, 1% and completed the study on August 14, 2012.*
- *Subject 11-205 (AV Block, syncope – MP-1005) was a 80 year old male who had an episode of syncope on May 29, 2011 after his second course of luliconazole cream, 1% was completed. The subject has a medical history that included hypertension, sleep apnea, a bundle branch block, and Merkel cell carcinoma of the left leg. The subject received his first course of luliconazole cream, 1% in his prior study MP-1000-01 which he reported no AEs. He was transitioned into MP-1005 on January 6, 2012 and received a second course of luliconazole cream, 1%. The syncope was evaluated by his cardiologist and diagnosed as a complete heart block. The subject underwent a dual chamber pacemaker and was discharged from the hospital. The subject completed the study on August 29, 2012.*

This reviewer evaluated all three narratives discussed above and found no solid associations with the investigational drug product. Each subject had an underlying medical condition that could cause the AE.

7.3.3 Dropouts and/or Discontinuations

In the tinea pedis Phase 3 clinical trials combined, only one subject in study MP-1000-02 dropped out due to an adverse event. This subject was randomized to the vehicle arm and the reason leading to study discontinuation was "dyspnea" and "application site warmth".

Table 23: Subject Disposition for Tinea Pedis Studies

	Study 02		**Study 03**	
	Luliconazole	**Vehicle**	**Luliconazole**	**Vehicle**
Subjects randomized	159	162	160	162
MITT(1) Subjects	106	103	107	107
Completed	94 (89%)	91 (88%)	101 (94%)	93 (87%)
Discontinued(2)	12 (11%)	12 (12%)	6 (6%)	14 (13%)
Reasons for Discontinuation				
Adverse Event	0	1 (1%)	0	0
Lost to follow up	7 (6%)	8 (8%)	6 (6%)	12 (11%)
Subject withdrawal	1 (1%)	3 (3%)	0	0
Protocol violation	2 (2%)	0	0	0
Physician decision	2 (2%)	0	0	1 (1%)
Other	0	0	0	1 (1%)

Source: Agency Biostatistics Review by Dr. Yuqing Tang.
(1) MITT was defined as all randomized subjects with positive baseline KOH and fungal cultures in
(2) Discontinued subjects include subjects dropped out during the treatment period or follow up period.

Across the 11 US clinical studies, only three AEs leading to study discontinuation were reported by three subjects in the luliconazole cream, 1% groups. These subjects are not included in the MITT population. These include the following:

- Two AEs ("squamous cell carcinoma" and "urinary tract infection") were reported by one subject each in the luliconazole cream, 1% group in MP-1000-01.
- One AE ("tinea versicolor on back") was reported by one subject in MP1000-07.

Table 24: Subjects Disposition for Tinea Cruris Study (MITT)

	Luliconazole	Vehicle
Subjects randomized	318	165
MITT[(1)] Subjects	165	91
Completed	157 (95%)	80 (88%)
Discontinued[(2)]	8 (5%)	11 (12%)
Reasons for Discontinuation		
Adverse Event	0	0
Lost to follow up	4 (2%)	3 (3%)
Subject withdrawal	3 (2%)	3 (3%)
Worsening of condition	0	4 (4%)
Physician decision	1 (1%)	1 (1%)

Source: Agency Biostatistics Review by Dr. Yuqing Tang.
(1) MITT was defined as all randomized subjects with positive baseline KOH and fungal cultures
(2) Discontinued subjects include subjects dropped out during the treatment period or follow up period.

The discontinuations described below are not in the MITT population and thus are not reflected in the above table, but are worth discussing.

Reviewer's comment: *Each AE leading to discontinuation was evaluated in details:*

- *Subject 16-205 (urinary tract infection – MP-1000-01) was a 75 year old male who developed a UTI after treatment with the investigational drug product. The subject has an extensive medical history, including type 2 diabetes mellitus. This reviewer agrees with the investigators assertion that this AE was not related to the investigational drug product.*
- *Subject 20-211 (urinary tract infection and acute renal failure – MP-1000-01) was a 52 year old male with stage 3 kidney disease and type 2 diabetes mellitus. This subject has significant medical conditions that predisposed him to infections. The subject was diagnosed with a UTI after completion of the investigational drug product. On hospitalization, the subject developed acute renal failure. The subject recovered and was discharged from the hospital after improvement of his infection and renal injury. This reviewer agrees with the investigators assertion that this AE was not related to the investigational drug product.*

7.3.4 Significant Adverse Events

The specific SAEs were discussed in the sections above. Other significant AEs will be discussed in the common AE section.

7.3.5 Submission Specific Primary Safety Concerns

The primary safety concerns of a topical drug product are the adverse events associated with application site reactions. Combining the safety population in the three Phase 3 clinical trials, eleven application site AEs ("application site reaction" [four events], "application site pruritus" [three events], "application site vesicles" [two events], and 'application site pain" [two events]) were reported by 10/616 subjects (1.6%) in the luliconazole cream, 1% group. Ten application site reactions ("application site reaction" [worsening of tinea cruris] [four events], "application site pain" [two events], "application site pruritus [one event], "application site vesicles" [one event], "application site erythema [one event], and "application site warmth" [one event]) were reported by 9/466 subjects (1.9%) in the vehicle group.

Table 25: Summary of Treatment-emergent Application Site Adverse Events (MP-1000-01, MP-1000-02, and MP-1000-03 Safety Populations)

	Luliconazole Cream 1%			Vehicle Cream		
System Organ Class Preferred Term	MP-1000-01 (N[a]=311)	MP-1000-02/ MP-1000-03 (N[a]=305)	Total (N[a]=616)	MP-1000-01 (N[a]=160)	MP-1000-02/ MP-1000-03 (N[a]=306)	Total (N[a]=466)
Application site reaction	1 (0.3%)	3 (1.0%)	4 (0.6%)	4 (2.5%)	0 (0.0%)	4 (0.9%)
Application site pruritus	1 (0.3%)	2 (0.7%)	3 (0.5%)	0 (0.0%)	1 (0.3%)	1 (0.2%)
Application site pain	1 (0.3%)	1 (0.3%)	2 (0.3%)	0 (0.0%)	2 (0.7%)	2 (0.4%)
Application site vesicles	0 (0.0%)	2 (0.7%)	2 (0.3%)	0 (0.0%)	1 (0.3%)	1 (0.2%)
Application site erythema	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.2%)
Application site warmth	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.2%)

[a] Number of subjects. At each level of summarization (system organ class and preferred term), subjects are only counted once.
Note: MedDRA Version: 14.0
Note: Treatment-emergent adverse events are those with an onset after the first application of study medication.
Source: Applicant submission ISS

7.4 Supportive Safety Results

The supportive safety results showed few adverse events that were related to the treatment with luliconazole cream, 1%. The applicant completed sufficient cardiac repolarization studies to evaluate the drug's potential for cardiac safety events. Laboratory results showed no clinically significant changes from vehicle cream. The dermal safety studies did not show significant irritation, sensitization, or phototoxicity/photoallergenicity.

7.4.1 Common Adverse Events

Adverse events that were common occurred at a frequency of ≥ 1%. The most frequent treatment-emergent AEs were organized by SOC and PT (MedDRA *version 14.0*) were "headache" (1.9%; 12/616 subjects) and "nasopharyngitis" (1.9%; 12/616 subjects). The most frequently reported SOC for which treatment-emergent AEs were reported was "infections and infestations" (4.4%), followed by "nervous system disorders" (1.9%), "general disorders and administration site conditions" (1.6%), "musculoskeletal and connective tissue disorder (1.1%), and "gastrointestinal disorders" (0.8%).

Table 26: Summary of Treatment-Emergent Adverse Events Occurring at a Frequency ≥ 1% in Either Treatment Group (MP-1000-01, MP-1000-02, and MP-1000-03 Safety Populations)

	Luliconazole Cream 1%			Vehicle Cream		
System Organ Class[a] Preferred Term	MP-1000-01 (N=311)	MP-1000-02/ MP-1000-03 (N=305)	Total (N=616)	MP-1000-01 (N=160)	MP-1000-02/ MP-1000-03 (N=306)	Total (N=466)
General disorders and administration site conditions	2 (0.6%)	8 (2.6%)	10 (1.6%)	4 (2.5%)	7 (2.3%)	11 (2.4%)
Infections and infestations	16 (5.1%)	11 (3.6%)	27 (4.4%)	3 (1.9%)	9 (2.9%)	12 (2.6%)
Nasopharyngitis	5 (1.6%)	7 (2.3%)	12 (1.9%)	1 (0.6%)	3 (1.0%)	4 (0.9%)
Upper respiratory tract infection	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.6%)	4 (1.3%)	5 (1.1%)
Injury, poisoning and procedural complications	1 (0.3%)	3 (1.0%)	4 (0.6%)	1 (0.6%)	4 (1.3%)	5 (1.1%)
Investigations	2 (0.6%)	2 (0.7%)	4 (0.6%)	3 (1.9%)	6 (2.0%)	9 (1.9%)
Musculoskeletal and connective tissue disorders	2 (0.6%)	5 (1.6%)	7 (1.1%)	2 (1.3%)	4 (1.3%)	6 (1.3%)
Nervous system disorders	5 (1.6%)	7 (2.3%)	12 (1.9%)	5 (3.1%)	3 (1.0%)	8 (1.7%)
Headache	5 (1.6%)	7 (2.3%)	12 (1.9%)	4 (2.5%)	3 (1.0%)	7 (1.5%)
Respiratory, thoracic and mediastinal disorders	0 (0.0%)	2 (0.7%)	2 (0.3%)	3 (1.9%)	3 (1.0%)	6 (1.3%)

[a] Counts reflect numbers of subjects reporting one or more adverse events that map to the MedDRA dictionary (Version 14.0). At each level of summarization (System Organ Class or Preferred Term) subjects are only counted once under the greatest reported severity.
Note: Treatment-emergent adverse events are those with an onset after the first application of study medication.

In the open-label, long-term clinical study (MP-1005), seven application site reactions (application site pruritus, application site vesicles, application site reaction, application site pain, and application site dryness) was reported by six subjects. Treatment was stopped for one subject (05-007) due to two events of "application site pain".

Table 27: Summary of Treatment-emergent Application Site Adverse Events by Preferred Term (MP-1005 Safety Population)

Preferred Term [a]	Interdigital Tinea Pedis (N=354)	Tinea Corporis (N=40)	Tinea Cruris (N=187)	Total (N=581)
Overall	**354**	**40**	**187**	**581**
Application site				
Dryness	0	1 (2.5%)	0	1 (0.2%)
Pain	0	1 (2.5%)	0	1 (0.2%)
Pruritus	1 (0.3%)	0	0	1 (0.2%)
Reaction	2 (0.6%)	0	0	2 (0.3%)
Vesicles	1 (0.3%)	0	0	1 (0.2%)
Initial Treatment [b]	**354**	**40**	**187**	**581**
Application site				
Dryness	0	1 (2.5%)	0	1 (0.2%)
Pain	0	0	0	0
Pruritus	1 (0.3%)	0	0	1 (0.2%)
Reaction	2 (0.6%)	0	0	2 (0.3%)
Vesicles	1 (0.3%)	0	0	1 (0.2%)
Subsequent Treatments [c]	**213**	**7**	**102**	**322**
Application site				
Dryness	0	0	0	0
Pain	0	1 (14.3%)	0	1 (0.3%)
Pruritus	0	0	0	0
Reaction	0	0	0	0
Vesicles	0	0	0	0
Off-treatment [d]	**340**	**36**	**185**	**561**
Application site				
Dryness	0	0	0	0
Pain	0	0	0	0
Pruritus	0	0	0	0
Reaction	0	0	0	0
Vesicles	0	0	0	0

[a] Counts reflect number of subjects reporting one or more adverse events that map to the MedDRA dictionary (version 14.0). At each level of summarization (Preferred Term) subjects are only counted once.
[b] The onset date is during the initial treatment/follow-up period.
[c] The onset date is during any other treatment/follow-up periods.
[d] The onset date is between treatment/follow-up periods or after the last treatment/follow-up period.
Note: Treatment-emergent adverse events are those with an onset after the initial application of luliconazole cream, 1%.
Source: MP-1005 Clinical Study Report, Table 14.3.2.2.1

Reviewer's comment: *Nearly all TEAEs reported in the luliconazole cream, 1% studies were mild or moderate in intensity. In the Phase 3 clinical trials, reactions at the site of application were relatively low. Only "site reaction" reached ≥ 2% (2.5%) in the tinea cruris population. In the open-label safety study, one subject had pain at the application site (14.3%). Due to the low subject recruitment in tinea corporis, the percentage was elevated.*

Table 28: Summary of Other Treatment-emergent Adverse Events with an Incidence ≥ 3.0% in Any Disease Type or ≥ 2.0% in the Total Group by Preferred Term, Sorted by Incidence in the Total Group (MP-1005 Safety Population)

Preferred Term [a]	Interdigital Tinea Pedis (N=354)	Tinea Corporis (N=40)	Tinea Cruris (N=187)	Total (N=581)
Overall	**354**	**40**	**187**	**581**
Headache	25 (7.1%)	0	30 (16%)	55 (9.5%)
Back pain	13 (3.7%)	0	19 (10.2%)	32 (5.5%)
Nasopharyngitis	25 (7.1%)	1 (2.5%)	6 (3.2%)	32 (5.5%)
Influenza	9 (2.5%)	0	13 (7.0%)	22 (3.8%)
Toothache	10 (2.8%)	1 (2.5%)	7 (3.7%)	18 (3.1%)
Dysmenorrhea	9 (2.5%)	0	6 (3.2%)	15 (2.6%)
Arthralgia	10 (2.8%)	0	3 (1.6%)	13 (2.2%)
Initial Treatment [b]	**354**	**40**	**187**	**581**
Headache	9 (2.5%)	0	3 (1.6%)	12 (2.1%)
Nasopharyngitis	8 (2.3%)	1 (2.5%)	3 (1.6%)	12 (2.1%)
Subsequent Treatments [c]	**213**	**7**	**102**	**322**
Headache	5 (2.3%)	0	9 (8.8%)	14 (4.3%)
Back pain	6 (2.8%)	0	3 (2.9%)	9 (2.8%)
Arthralgia	5 (2.3%)	0	2 (2.0%)	7 (2.2%)
Toothache	4 (1.9%)	1 (14.3%)	1 (1.0%)	6 (1.9%)
Tooth disorder	0	1 (14.3%)	0	1 (0.3%)
Off-treatment [d]	**340**	**36**	**185**	**561**
Headache	16 (4.7%)	0	19 (10.3%)	35 (6.2%)
Back pain	18 (5.3%)	0	3 (1.6%)	21 (3.7%)
Nasopharyngitis	6 (1.8%)	0	14 (7.6%)	20 (3.6%)
Influenza	6 (1.8%)	0	10 (5.4%)	16 (2.9%)
Toothache	5 (1.5%)	0	6 (3.2%)	11 (2.0%)
Dysmenorrhea	4 (1.2%)	0	6 (3.2%)	10 (1.8%)

[a] Counts reflect number of subjects reporting one or more adverse events that map to the MedDRA dictionary (version 14.0). At each level of summarization (Preferred Term) subjects are only counted once.
[b] The onset date is during the initial treatment/follow-up period.
[c] The onset date is during any other treatment/follow-up periods.
[d] The onset date is between treatment/follow-up periods or after the last treatment/follow-up period.
Note: Treatment-emergent adverse events are those with an onset after the initial application of luliconazole cream, 1%.
Source: MP-1005 Clinical Study Report, Table 14.3.2.2.1

The long-term study MP-1005 evaluated the safety of treatment with luliconazole cream, 1% in all three indications. Over the course of the study, the most frequently reported treatment-emergent AEs, other than application site AEs, were "headache" (9.5%), followed by "back pain" (5.5%), and "nasopharyngitis" (5.5%). The remaining treatment-emergent AEs reported by at least 2% of the subjects were "influenza" (3.8%), "toothache (3.1%), "dysmenorrhea" (2.6%), and "arthralgia" (2.2%). No clinical significant differenced were seen among subjects with interdigital tinea pedis, with tinea corporis, or with tinea cruris or among initial treatment course, subsequent treatment course, or off-treatment periods.

7.4.2 Laboratory Findings

Within the three Phase 3 clinical trials, 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.

Similarly, a review of the long-term study (MP-1005) laboratory results identified no safety signals or significant clinical laboratory changes. A single subjects abnormal laboratory result in the Phase 2 study, TP-10801, showed a high level of ALT, AST, CK, and LDH at the end of the 28-Day end-of-treatment evaluation. This abnormal result was reported as an AE and the subject was retested to within the normal limits within 2 weeks. The Phase 1 clinical studies did not collect laboratory tests.

Reviewer's comment: *This reviewer suspects the single abnormal liver function test in the Phase 2 study after 28-days of treatment with luliconazole cream, 1% was spurious. This abnormality was not seen in any of the Phase 3 clinical trials. The Clinical Pharmacology Section of the label will be sufficient to establish the investigational drugs effects on inhibition of liver enzymes.*

7.4.3 Vital Signs

Across the 11 US clinical studies conducted with luliconazole cream, 1% 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. In the long-term safety study, MP-1005, vital sign data obtained during the course of the study were consistent with that seen in the Phase 3 clinical trials. No signals were identified for those subjects followed for 1 year.

7.4.4 Electrocardiograms (ECGs)

All azole antifungals have possible adverse cardiac effects and may prolong QT intervals. During the development of luliconazole cream, 1% the applicant evaluated a maximal use PK study with ECG evaluations, in addition to conducting a thorough QT study. The applicant also submitted dog telemetry data from Japan in support of their clinical program early in the development of the drug product. All data was evaluated by the Agency QT IRT and comments were provided to the applicant. A thorough QT study was recommended to fully evaluate the potential for luliconazole to induce cardiac effects.

In nonclinical cardiovascular safety pharmacology, a hERG assay was conducted with luliconazole. The effect of luliconazole (0.2 – 7.6 μM) on the hERG potassium current was assessed in HEK 293 cells. Luliconazle produced a concentration dependent inhibition of the potassium current. The IC50 for luliconazole in this assay was 1.52 μM. It is anticipated that

the risk for QT interval prolongation for luliconazole would be minimal under clinical conditions of use due to minimal systemic exposure after topical application of luliconazole cream.

In addition, an in vivo cardiovascular safety pharmacology study was conducted in conscious telemetered dogs with luliconazole. No treatment related effects on electrocardiograms, blood pressure or heart rate were noted in this study after intravenous administration of 0.3, 1 and 3 mg/kg luliconazole.

A review of the thorough QT (TQT) study was completed by DCARP on 30-APR-2013. The overall findings of the TQT suggested no significant QTc prolongation effect by luliconazole cream, 1% (2g and 10g). The largest upper bounds of the 2-sided 90% CT for the mean difference between luliconazole cream, 1% (2g and 10g) and placebo were below 10ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CT for the ΔΔATcI for moxifloxacin was greater than 5ms, and the moxifloxacin profile over time is adequately demonstrated in the study, indicating that assay sensitivity was established. [5]

The MP-1007 maximal use study demonstrated that systemic exposure of luliconazole cream, 1% was much higher in tinea cruris subjected compared to tinea pedis subjects. Plasma concentrations of luliconazole in the plasma were established, but there was no evidence of a correlation with changes in the QT interval by ECG. Twenty-four hours after the application of luliconazole cream, 1% on Day 7 mean plasma levels in the study were on the order of 2.75 ng/mL.

Electrocardiograms were collected in the Phase 3 clinical trial MP-1000-01 (tinea cruris). The summary of the 12 lead ECGs collected showed no adverse change in QTcF or QTcB that were observed the day after the last application of luliconazole cream, 1% in subjects treated once a day for seven days. No adverse changes were observed in the PR interval, QRS complex, or heart rate at any time after treatment with luliconazole cream, 1% or vehicle cream. These results are consistent with the results of the previous ECGs collected in the maximal use study (MP-1007) that showed no adverse changes in the cardiac repolarization in subjects with tinea pedis and tinea cruris who received daily topical application of luliconazole cream, 1% at three times the clinical dose for 15 days.

Reviewer's comment*: Sufficient evidence from the TQT study, maximal use PK study, and the Phase 3 clinical trial in tinea cruris is presented to assure topical application of luliconazole cream, 1% does not affect cardiac repolarization when used clinically for the treatment of interdigital tinea pedis and tinea cruris. Because luliconazole cream, 1% was not studied in the pediatric population with tinea corporis, a separate maximal use PK study would need to be conducted to evaluate the plasma profile of this drug product in children.*

5 Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review of Luliconazole Cream, 1%. Completed Date: 30-APR-2013 by Qianyu Dan M.D.

QT-IRT proposed labeling:

Cardiac Electrophysiology
At therapeutic doses, LUZU Cream does not prolong QTc to any clinically relevant extent.

7.4.5 Special Safety Studies/Clinical Trials

Four Phase 1 dermal safety studies were performed for to demonstrate the safety of luliconazole cream, 1% for topical use.

MP-1000-04 was a Phase 1, single-center, randomized, evaluator-masked, positive and negative controlled, within-subject 21-day cumulative irritation study designed to determine the potential of luliconazole cream, 1% and its vehicle to cause irritation after repeated topical application to healthy skin of subjects under controlled conditions. Safety assessments included AE, patch site skin assessments at Baseline (Day 1), and then after each of the 21 patch applications (24 hours ± 2 hours) during the study.

A set of patches containing 0.2 g of luliconazole, 0.2 g of Vehicle cream, 0.2 mL of 0.2% SLS, and 0.2 mL of 0.9% saline was applied under occlusive patch conditions according the randomization scheme. Twenty-four hours (± 2 hours) after application, the patches were removed and assessed for dermal reactions. The procedure for removal of study materials, evaluation of test sites, and application of fresh study materials was repeated for 21 consecutive days, for a total of 21 applications of each investigational product and study control. A total of 21 post-Baseline evaluation scores were assigned to assess cumulative irritancy.

Target enrollment was 30 completed subjects evaluable for analysis; a total of 44 subjects were enrolled/randomized, and 37 subjects completed the study. The study population included 8 (18.2%) males and 36 (81.8%) females, all of whom were White. Subjects ranged in age from 21 to 73 years with a mean age of 46.9 years. There were no AEs reported during the study.

Under the exaggerated conditions of use in this study, with continuous exposure under occlusion for 21 days, luliconazole produced no evidence of irritation.

MP-1000-05 was a Phase 1, single-center, randomized, evaluator-masked, positive and negative controlled, within-subject, HRIPT study designed to determine the potential of luliconazole cream, 1% and it vehicle to induce sensitization by repeated topical application to healthy skin of subjects under controlled conditions. Safety evaluations included AE, patch site skin assessments at Baseline (Day 1), nine times during the Induction Phase, four times following challenge, and, if applicable, four times following challenge.

The majorities of subjects were White (89.9%) and female (74.4%), and ranged in age from 18 to 75 years with a mean age of 47.0 years. All 238 randomized subjects received at least one set of patches according to the randomization scheme; 224 were evaluable for sensitization.

During Induction, 2 subjects developed erythema and papules (a grade of 3) at the site treated with luliconazole. Responses were similar at the sites treated with the cream vehicle. Therefore, the investigational products appear to have minimal potential for irritancy.

There were no statistically significant differences in irritation between the luliconazole sites and the vehicle cream sites, luliconazole sites and 0.9% saline sites, or the Vehicle Cream sites and 0.9% saline sites. In comparison, the 0.1% SLS site was statistically significantly more irritated than all other sites on the study.

In the present study, the principal finding is that no subject showed evidence of sensitization at challenge to luliconazole or its vehicle. No subjects failed to complete the Induction Phase due to irritation to study products. There were no AEs reported during the study.

MP-1000-06 was a Phase 1, single-center, randomized, evaluator-masked, within-subject, phototoxicity study designed to assess the potential of luliconazole cream, 1% and it vehicle to produce phototoxicity reactions in normal use. Safety evaluations include AE and skin assessments.

There were no irritation grades of sufficient severity or patterns of irritation grades that provided evidence of potential phototoxicity, and no adverse events that were considered significant treatment effects.

MP-1000-07 was a Phase 1, single-center, randomized, evaluator-masked, within-subject, photoallergenicity study designed to assess the potential of luliconazole cream, 1% and its vehicle to produce photoallergic reactions in normal use. Safety evaluations include AE assessments and skin evaluation.

There were no irritation grades of sufficient severity or patterns of irritation grades that provided evidence of potential photoallergenicity; the most intense severity of response was Grade 3 (Definite, moderate erythema), which occurred in 1 vehicle-treated subject and in 1 subject in the control group during the induction phase. Grade 2 (definite, mild erythema) was observed a total of 8, 11, and 7 times in the active, vehicle, and control groups, respectively. No adverse events were considered significant treatment effects.

Reviewer's comment: *The Phase 1 dermal safety studies provide sufficient evidence that the drug product does not induce sensitization, cause cumulative irritation, or produce phototoxicity/photoallergenicity.*

7.4.6 Immunogenicity

No studies of immunogenicity were performed.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose dependent adverse events were not explored in the Phase 2 study or Phase 3 clinical trials.

7.5.2 Time Dependency for Adverse Events

Time dependency for adverse events was not explored in the Phase 2 study or Phase 3 clinical trials.

7.5.3 Drug-Demographic Interactions

Subset analyses of AEs by gender, race, ethnicity, and age were analyzed for the Phase 3 US studies MP-1000-01 and for the combined MP-1000-02 and MP-1000-03 population. For the long-term safety study MP-1005, subgroup summaries were performed by diagnosis type (interdigital tinea pedis, tinea cruris, and tine corporis).

Overall, the proportions of subjects with AEs were similar between treatment groups irrespective of gender, race, ethnicity, or age.

***Reviewer's comment**: No safety signals were detected in the drug-demographics evaluation. The safety population included a total of 29 subjects <18 years of age from the Phase 3 studies. There were a total of 57 subjects >65 years of age in the Phase 3 studies. Insufficient evidence of safety in the population < 18 years can be determined. However, the safety experiences in the > 65 year old patients do not seem clinically different than the adult population (18 – 65 years) experience. The label will reflect that the safety experience in patients > 65 years old appears to be the same as the adult population indicated for treatment.*

7.5.4 Drug-Disease Interactions

No other drug-disease interactions were explored in the clinical program.

7.5.5 Drug-Drug Interactions

None of the clinical studies conducted with luliconazole cream, 1% evaluated the potential for drug interactions.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity studies were conducted. A waiver for the conduct of carcinogenicity studies was granted for luliconazole cream. Conduct of a systemic carcinogenicity study was waived due to limited systemic exposure noted under clinical conditions of use. The sponsor submitted sufficient scientific rationale to warrant the waiver, and was informed on 8-MAY-2009 that the waivers were granted.

7.6.2 Human Reproduction and Pregnancy Data

The nonclinical evaluation of the reproductive and developmental data is provided in Section 4.3. The proposed labeling can be found in Section 9.2.

7.6.3 Pediatrics and Assessment of Effects on Growth

On 29-May-2013, NDA 204-153 was discussed at the PeRC meeting to introduce the applicant's pediatric plan and waiver requests.

1. The application triggers PREA as a new active ingredient.
2. A partial waiver is requested in pediatric patient's birth to 1 year 11 months for tinea corporis and a partial waiver in pediatric patients less than 12 years of age for tinea pedis and tinea cruris. The rationale provided is that the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of (b) (4) pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
   - A waiver is requested in pediatric patients less than 2 years of age in tinea corporis due to low prevalence of disease in this age group.
   - A waiver is requested in pediatric patients less than 12 years of age in tinea pedis and tinea cruris due to low prevalence of these diseases in this age group.
   - The rationale is that the prevalence of tinea corporis in pediatric patients less than 2 years of age and the prevalence of tinea pedis and cruris in pediatric patients less than 12 years of age is low and has little therapeutic advantages.
3. A partial deferral in pediatric patients 2 years to 17 years 11 months for tinea corporis and 12 years to 17 years 11 months for tinea pedis and tinea cruris because adult studies are completed and ready for approval.

The PeRC agrees to the partial waiver in pediatric patients birth to 1 year 11 months for tinea corporis and in pediatric patients less than 12 years for tinea pedis and tinea cruris because studies are impossible or highly impracticable and to the deferral in pediatric patients 2 years to 17 years 11 months for tinea corporis and 12 years to 17 years 11 months for tinea pedis and tinea cruris because adult studies are completed and ready for approval.

Additional PeRC Discussion/Recommendation(s):

- The Division has described the rationale for obtaining PK in both studies because there was higher than expected systemic exposure (compared to exposure in healthy patients in the thorough QT study) in diseased skin in the tinea pedis and tinea cruris study.
- The PeRC recommends requiring the sponsor to study a minimum number of pediatric patients in the youngest age group in the tinea corporis study.
- The PeRC recommends the protocol submission date be changed to require the sponsor to submit in 6 months instead of 1 year.
- The PeRC recommends the Division consider decreasing the number of PK samples to be collected in the youngest population in the tinea corporis study.

Reviewer's comment: *This reviewer agrees with the recommendations of the PeRC. The applicant will be asked to submit a timeline 6 months earlier than the proposed timeline and the protocols will be reviewed with the suggested reduction in sampling in mind. Appropriate comments and recommendations will be provided to the applicant once the PMR is received.*

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Due to the low systemic absorption of this topically applied product, there is little drug abuse potential for luliconazole cream, 1%.

7.7 Additional Submissions / Safety Issues

There were seven supportive Japanese clinical safety studies: one Phase 3 clinical study (PR-2699-P3-01), three Phase 2 clinical studies (113011, PR-2699-P2-01, and PR-2699-P2-05), and three Phase 1 clinical studies (113001, 113002, 113003).

The single Phase 3 clinical trial was a multi-center, randomized, single-blind, parallel group, active-control study designed to examine the safety and efficacy of luliconazole cream, 1% for interdigital or vesicular type tinea pedis as compared to bifonazole cream, 1%. Subjects were randomly allocated to luliconazole cream, 1% once daily for two weeks (14 days) followed by vehicle cream once daily for two weeks (14 days) or bifonazole cream, 1% once daily for four weeks (28 days). Safety evaluations included:

- AE assessments at all visits.
- Safety laboratory assessments at Baseline, Day 14, and Day 28.

The results of the safety determination included:

- No deaths
- One SAE (severe skin tumor) was reported in one subject in the bifonazole cream, 1% group.
- Common adverse event included application site AEs (pain, stimulation, flare)
- The most frequently reported AE for the luliconazole cream, 1% group were "eczema", "glucose positive urine", and "flu syndrome".

Reviewer's comment: *This Phase 3 clinical trial used a comparator antifungal drug, bifonazole cream, 1%, which is not approved in the US. The AEs were minimal and were consistent with the US clinical trials. No worrisome safety signals were discovered.*

In the Phase 2 and Phase 1 Japanese studies, no deaths were reported and the AE profile of the drug product was similar to the US clinical studies. No new safety signals were discovered.

Reviewer's Final Safety Conclusions:
LUZU (luliconazole) Cream, 1% was safe when used as prescribed for interdigital tinea pedis and tinea cruris. It is expected that the product is also safe for tinea corporis, as we can extrapolate the safety to that population as well. The applicant has agreed to the use of the drug product in patients 18 years and older until the PMR's show safety and efficacy in the pediatric population. The Adverse Reactions Sections of the label will include few adverse reactions seen in the clinical trials. The Warning and Precautions in the PI will be "none", as there were no safety issues that rose to the level to be included.

The pre- and post-marketing international experience of luliconazole cream was considered as part of the application safety assessments. No significant safety signals have been identified in the Japanese trials. The safety database, both in the clinical trials and in Japanese post-marketing experience is more than sufficient to conclude that there are no significant safety issues that would impact approval for this application.

During the late-cycle meeting conducted with the applicant on 11-SEP-2013, there were no substantive review issues brought up with the sponsor. The Agency discussed the PREA PMR's and the need for safety data in children treated for tinea corporis with luliconazole cream, 1%. The applicant will submit final proposed dates for the clinical pharmacology PMRs and PMC prior to the action.

8 Postmarket Experience

The applicant reports that in Japan, as of April 2011, approximately (b) (4) of luliconazole cream, 1% were shipped, with an estimated 10.8 million patients exposed to luliconazole. In the post-market experience, one report of contact dermatitis and one report of cellulitis were classified as adverse drug reactions for in-patient treatment, and the two SAEs (vertigo and chordoma) were considered unrelated to luliconazole.

A review of the literature revealed two reports of contact dermatitis in Japan that were related to luliconazole treatment. In both cases, patch testing with the formulation components as well as luliconazole indicated the reactions were elicited by luliconazole re-challenge and resolved following withdrawal.

Reviewer's comment: *The post marketing experience in Japan is useful in labeling of Section 6.2 of the PI. The included adverse reaction term will be contact dermatitis and cellulitis. The two SAEs are likely unrelated and will not be included in section 6.2.*

APPEARS THIS WAY ON ORIGINAL

9 Appendices

9.1 Literature Review/References

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.
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].
4. Weinstein, A. and Berman, B. Topical treatment of common superficial tinea infections. American Family Physician. (electronic version): 2002; 65(10)

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

9.3 Advisory Committee Meeting

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

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/s/

GARY T CHIANG
09/16/2013

DAVID L KETTL
09/17/2013

Medical Officer's Review of NDA 204-153

Type: Mid Cycle Response
Serial Amendment: 8
Supporting Document Number: 10
Correspondence date: 17-MAY-2013
CDER Stamp date: 17-MAY-2013
Review Date: 5-JUN-2013

Sponsor: Medicis Pharmaceutical Corporation
7720 North Dobson Road
Scottsdale, AZ 85256

Drug: LUZU® (luliconazole) 1%
Route of Administration: Topical
Dosage Form: Cream
Pharmacologic Category: Imidazole Antifungal
Proposed Indication: For the treatment of tinea pedis, tinea cruris, and tinea corporis in adults
Drug Development Phase: 3

Project Manager: Paul Phillips
Team Leader: David Kettl, MD
Medical Officer: Gary Chiang, MD, MPH.

Regulatory Background:

Luliconazole cream, 1% is being developed by Medicis for the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis in patients 18 years of age and older. The NDA was submitted on 11-DEC-2012. The PDUFA action date is December 13, 2013.

During the Mid-Cycle communication with the applicant on 10-MAY-2013, the issue of pH specification of the drug product was of main concern. Specifically, the applicants proposed pH acceptance criterion of (b) (4) is not acceptable. The Agency has determined that there is no clinical experience with the drug product (b) (4) and that the acceptance criterion should be revised to 5.0-7.0. As the pKa value of the drug is (b) (4) (b) (4) No clinical data related to the product with that pH has been submitted for review.

Review:

FDA COMMENT 7

Your proposal of broadening the pH acceptance criterion to (b) (4) is not acceptable. Revise the acceptance criterion in the drug product specification to pH 5.0 – 7.0 and submit the revised specification table to module 3, or provide clinical information related to the performance of your product with a pH value (b) (4) in subjects with tinea pedis, tinea cruris, and/or tinea corporis.

SPONSOR RESPONSE 7:

Based on the FDA Information Request and further clarification provided by FDA during the mid-cycle review teleconference, the concern is related to [redacted] pH specification limit [redacted] the luliconazole pKa value of [redacted] and efficacy [redacted] of luliconazole.

We propose to modify the pH specification to 4.8 – 7.0. [redacted]

The drug product specification in Section 3.2.P.5.1 has been revised to reflect an acceptance criterion of pH 4.8 – 7.0.

Reviewer's comment: [redacted] *Lowering the pH acceptance criteria any further will require supporting clinical information, which has not been provided by the applicant.*

Comment to be conveyed to applicant:

Your response (5/17/13 amendment) to FDA COMMENT 7 includes a proposal of modifying the pH specification to [redacted] without supporting clinical information. The proposal is unacceptable. Tighten the pH specification to 5.0 - 7.0 and submit the revised drug product specification with the tightened pH specification to Module 3 of the NDA, or provide clinical information related to the performance of your product with a pH value [redacted] in subjects with tinea pedis, tinea cruris, and/or tinea corporis.

Gary Chiang, M.D., M.P.H.
Medical Officer
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

GARY T CHIANG
06/05/2013

DAVID L KETTL
06/05/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 204-153 **Applicant: Medicis Pharmaceutical Corp** **Stamp Date: December 11, 2012**

Drug Name: Luliconazole **NDA/BLA Type: Standard** **The Program**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			This application is entirely in eCTD format
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			This is a 505 (b)(1) application (NME in US)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number:TP-108 Study Title: A Randomized, Multi-centered, double-blind, placebo-controlled, duration-finding study evaluating the Efficacy and Safety of two week and four week once daily treatment of luliconazole cream, 1% in patients with tinea pedis Sample Size: 147 Arms: 4 Location in submission: module 5.3.5.1	X			This product is approved and marketed in Japan with significant post-market experience. Dose-ranging is limited to length of treatment
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
15.	Randomized, Multi-Centered, Double-Blind, Vehcile-Controlled Studies Evaluating the Efficacy and SAfety of Product 33525 in Subjects with Tinea Cruris (MP-1000-01) or in Subjects with Tinea Pedis (MP 1000-2 and MP-1000-3) Pivotal Study #1 Indication: Tinea cruris Pivotal Study #2 Indication: Tinea pedis Pivotal Study #3 Indication: Tinea pedis	X			Three pivotal clinical trials were conducted to obtain the all three indications: tinea pedis, tinea cruris, and tinea corporis in adults 18 years and older.
16.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
17.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
18.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
19.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
20.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			A TQT (MP-1000-08) study was completed and reviewed by the QTIRT
21.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
22.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			A long-term safety study (MP-1005) was completed and 126 subjects followed for at least 1 year
23.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
24.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
25.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
26.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
27.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			Dermal safety and TQT studies are completed
28.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
29.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			A deferral is requested (b) (4) 17 years of age
ABUSE LIABILITY					
30.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
FOREIGN STUDIES					
31.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			As supportive safety data only
DATASETS					
32.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
33.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
34.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
35.	Are all datasets to support the critical safety analyses available and complete?	X			
36.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
37.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
38.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
39.	Has the applicant submitted the required Financial Disclosure information?	X			

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
GOOD CLINICAL PRACTICE					
40.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____YES____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

No clinical review issues at filing.

Gary Chiang, MD, MPH — 30 JAN 2013

Reviewing Medical Officer — Date

Dave Kettl, MD — 30 JAN 2013

Clinical Team Leader — Date

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/s/

GARY T CHIANG
01/30/2013

DAVID L KETTL
01/30/2013