CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204153Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA #:	204153
Submission Date:	December 11, 2012
Brand Name:	Luzu
Generic Name:	Luliconazole cream, 1%
Dosage Form:	Cream
Dosage Strength:	1%
Reviewer:	Chinmay Shukla, Ph.D.
Team Leader:	Doanh Tran, Ph.D.
Division Director:	Capt. E. Dennis Bashaw, Pharm.D.
OCP Division:	DCP-3
OND Division:	Division of Dermatology and Dental Products
Sponsor:	Medicis Pharmaceutical Corp.
Relevant IND(s):	076,049
Submission Type:	New-submission
Indication:	Topical treatment of interdigital tinea pedis, tinea cruris and tinea corporis in adults

Addendum to Clinical Pharmacology Review:

Correction: In the Clinical Pharmacology review for NDA 204153 dated 07/26/2013 in DARRTS, Section 2.2.7 was "What is the safety profile of efinaconazole?" and it should be "What is the safety profile of luliconazole?"

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHINMAY SHUKLA
10/17/2013

DOANH C TRAN
10/17/2013

EDWARD D BASHAW
10/19/2013
Minor editorial revision only

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1. Executive Summary

Luliconazole is a new molecular entity (NME) and belongs to azole antifungal drug class. The Sponsor has submitted this NDA via 505(b)(1) regulatory pathway and is seeking an indication of once daily topical treatment of tinea pedis, tinea cruris and tinea corporis in adult subjects 18 years of age and older. The proposed dosing duration is 7 days for tinea cruris and tinea corporis and 14 days for tinea pedis.

The clinical program consists of six Phase 1 trials which include a maximal use pharmacokinetic (PK) trial in subjects with moderate to severe tinea pedis or tinea cruris and PK assessment in TQT trial in healthy subjects, one Phase 2 safety and efficacy trial and three Phase 3 safety and efficacy trials and one Phase 3 long term open label long term safety trial. The Sponsor has also submitted reports of Japanese trials as supporting

information and this includes three Phase 1 trials, three Phase 2 trials and one Phase 3 trial.

1.1 Recommendation

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

1.2 Post-Marketing Requirements/Commitments

Post-marketing requirements:

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

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

To support this NDA the Sponsor has conducted PK assessment in the following trials:

US trials:

- MP-1007 (Max use PK trial in subjects with tinea pedis or tinea cruris)
- MP-1000-08 (TQT trial)

Supporting Japanese trials:

- 113002 (Single topical dose PK assessment in healthy subjects)
- 113003 (Multiple topical dose PK assessment in healthy subjects)

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.

Drug metabolism: Luliconazole is the R enantiomer and in the E-form (Cis). The Sponsor 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 (b) (4) 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 Sponsor 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 Sponsor 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), and the Sponsor will need to address this.

To address enzyme induction potential of luliconazole, the Sponsor 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 recommended in the *Draft Guidance for Industry: Drug Interaction Studies - Study design, data analysis, implications for dosing, and labeling recommendations (February 2012)*. The Sponsor will need to address this.

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.

Reviewer comments: *Since luliconazole is metabolized by CYP3A4 and CYP2D6, an information request (IR) was sent on 05/01/2013 asking the Sponsor to provide an assessment of luliconazole systemic safety in presence of other drugs that are strong CYP2D6 and 3A4 inhibitors. The Sponsor responded to this IR on 05/17/2013 and has provided a rationale using the > 14 fold systemic safety margin from animal toxicity studies to address the systemic safety concerns due to any potential increase in systemic exposure of luliconazole in presence of strong CYP3A4 and CYP2D6 inhibitors. This reviewer checked with the Pharmacology – Toxicology reviewer Dr. Daivender Mainigi and Dr. Mainigi concurs with the Sponsor's assessment of margin of systemic safety. Further, no systemic safety concerns in humans have surfaced thus far. Based on this information, in the opinion of this reviewer, no further in-vivo drug interaction assessment will be needed to further evaluate the effect of strong CYP3A4 and 2D6 inhibitors on systemic levels of luliconazole (see Section 2.4.2 for further details).*

Formulation used: The maximal use PK trial (MP-1007) used the formulation manufactured at another site in (b) (4) ((b) (4) and the Sponsor has provided IVRT to bridge DPT (USA) and (b) (4) (b) (4) manufacturing sites. According to Dr. Kelly Kitchens (ONDQA reviewer), the IVRT results are acceptable (for further details, see review in DARRTS by Dr. Kitchens).

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).

Note: The supporting Japanese trials were not reviewed because they were conducted in healthy subjects and this does not represent maximal use conditions. Furthermore, these trials used a formulation manufactured in (b) (4) and the Sponsor has not provided any in-vitro release test (IVRT) data to bridge the US manufacturing site (DPT) and this manufacturing site in (b) (4)

Pediatric assessment: The Sponsor has requested a waiver in pediatric subjects from birth to 1 year 11 months for tinea corporis and in pediatric subjects less than 12 years of age for tinea pedis and tinea cruris because studies are impossible or highly impractical in this population. The Sponsor has also requested for a deferral from conducting pediatric trials in subjects 2 to 17 years and 11 months old. Specifically, the Sponsor has stated that they plan to conduct a maximal use PK trial in subjects 12 to 17 years and 11 months with tinea pedis and tinea cruris and a safety and efficacy trial including PK in subjects 2 to 17 years and 11 months with tinea corporis. The Sponsor plans to work with the Agency to determine the appropriate trial designs.

At a meeting with the Pediatric Review Committee (PeRC) on 05/29/2013, PeRC agreed to the Sponsor's partial waiver request in pediatric subjects from birth to 1 year 11 months for tinea corporis and in pediatric subjects less than 12 years of age for tinea pedis and tinea cruris. The Division also requested 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 studies in adults are completed and the NDA application is being considered for approval in adults. PeRC agreed to the partial deferral request.

Clinical Pharmacology Briefing: An optional inter-division level briefing was conducted on July 17, 2013 with the following in attendance: Hae-Young Ahn, E. Dennis Bashaw, Gary Chiang, David Kettl, Balimane Praveen, Su-Young Choi, Hyewon Kim, Jing Fang, Fang Wu, Peng Duan, Sarah Dorff, Doanh Tran and Chinmay Shukla.

2. Question Based Review

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation?

Drug substance and Formulation: Luliconazole is a new azole drug with a dithiolan structure which was produced by selectively synthesizing only the *R*-enantiomer of the (b) (4) and in the E Form (Cis). Luliconazole is the international nonproprietary name (INN) for the chemical compound, (2E)-2-[(4R)-4-(2,4- dichlorophenyl)-1,3-dithiolan-2-ylidene]-2-imidazol-1-ylacetonitrile. The molecular formula is $C_{14}H_9Cl_2N_3S_2$ with a molecular weight of 354.28 g/mol and the structural formula is shown in Figure 1.

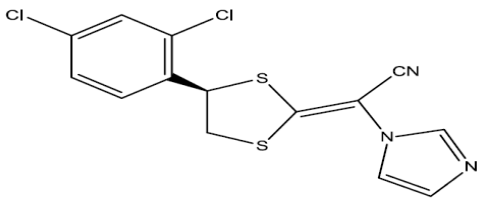


Figure 1: Structure of Luliconazole

The drug product is luliconazole, an antifungal drug, incorporated into a topical cream formulation at the strength of 1% w/w. The drug substance is [redacted] during manufacture and each gram of drug product contains 10 mg luliconazole in a white cream formulation. The composition of the cream is shown in Table 1 below.

Table 1: Qualitative and quantitative composition of Luliconazole Cream, 1%

Component	Function	Quality Standard	Quantity (% w/w)
Luliconazole	Active	In-house	1.0
Benzyl alcohol	[redacted]	NF	[redacted]
Butylated hydroxytoluene		NF	
Cetostearyl alcohol		NF	
Isopropyl myristate		NF	
Medium-chain triglyceride		NF	
Methylparaben		NF	
Polysorbate 60		NF	
Sorbitan monostearate		NF	
Propylene glycol		USP	
Purified water		USP	

qs = quantity sufficient
USP = United States Pharmacopeia
NF = National Formulary

Formulation: There are 3 formulation manufacturing sites:

1. DPT, San Antonio, TX, USA
2. [redacted]

In the US clinical program, 9 out of 11 trials used the formulation manufactured by DPT (USA). The other 2 trials which include maximal use PK trial (MP-1007) and Phase 2 trial (TP-0801) used formulations manufactured by [redacted]

The composition of the formulation from [redacted] and DPT, USA are the same. The Sponsor has also stated that during the manufacturing site change from [redacted] to US, there were minor process modifications and the Sponsor has classified this as a Level 3 change based on SUPAC-SS Guidance. An in-vitro release test (IVRT) to bridge the [redacted] and the DPT (USA) formulations was conducted. IVRT results were reviewed by Office of New Drugs Quality Assurance (ONDQA) reviewer Dr. Kelly Kitchens and according to Dr. Kitchens the IVRT results are acceptable (for further details, see review in DARRTS by Dr. Kitchens).

Luliconazole isomerism: Luliconazole was produced by selectively synthesizing only the *R*-[E Form (Cis)] enantiomer (native form) of the [redacted]. According to the Sponsor, the drug substance has been studied for the potential of [redacted] under the various conditions. [redacted]

(b) (4)

Therefore, the Sponsor concluded that the drug substance does not exhibit a propensity for (b) (4) The Sponsor further claims that the (b) (4) from drug product manufactured by both DPT (US site) and (b) (4) (b) (4) site) and analyzed by chiral HPLC were the active *R*-(*E*) Form of luliconazole. Within the limits of quantitation for the method, chiral HPLC of the isolated (b) (4) confirmed no presence of the (b) (4)

The R-[(b) (4) is a metabolite and is referred to as (b) (4)" in this review was measured in human plasma in the maximal use PK trial (MP-1007). The Sponsor had not submitted any information on R to S inter-conversion in-vivo in humans. Hence an information request (IR) was sent on 05/01/2013 (see communication in DARRTS).

The Sponsor responded to this IR on 05/17/2013 informing the Agency that they have not explored the inter-conversion between R-E (R) to S-E (S) in humans, but in dogs, there was no inter-conversion observed. The Sponsor further clarified that the non-clinical toxicology studies with S-enantiomer showed toxicology profile similar to that of the R-enantiomer with identical NOAEL (no adverse event level) values. This was verbally confirmed with the Pharmacology-Toxicology reviewer Dr. Daivender Mainigi.

Reviewer comments: *Although the potential for inter-conversion between R to S enantiomer in vivo in humans would be useful to further characterize the PK of luliconazole, the available safety data from Phase 3 and the margin of systemic safety (> 14 fold) from animal toxicity studies are adequate to support the indication. Furthermore, the Sponsor noted that the R and S enantiomer had a similar toxicity profile with identical NOAEL values.*

Note: ***Because the bioanalytical assay used by the Sponsor does not differentiate between R and S isomers, the words "luliconazole concentration" mentioned in this review would refer to both R and S isomeric forms.***

2.1.2 What are the proposed mechanism of action and the therapeutic indications?

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.

Therapeutic indication: With this application, the Sponsor is seeking an indication of 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.

2.1.3 What is the proposed route of administration and dosage?

Proposed route of administration: Topical.

Proposed dosage:

- *Interdigital tinea pedis* - When treating interdigital tinea pedis, an adequate amount of Luliconazole Cream, 1 % should be applied to the affected and immediate surrounding area(s) once daily for two weeks.
- *Tinea cruris or tinea corporis* - When treating tinea cruris or tinea corporis, an adequate amount of Luliconazole Cream, 1 % should be applied to the affected and immediate surrounding area(s) once daily for one week.

2.2 General Clinical Pharmacology

2.2.1 What were the clinical trials conducted to support this NDA?

Table 2 shows a list of all clinical trials provided to support this application.

Table 2: List of all clinical trials

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Route of Administration; Dosage Regimen	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Primary US Studies								
Phase 1 PK	MP-1000-04	To determine the potential of Luliconazole Cream 1% and its vehicle to cause irritation after repeated topical application.	Randomized, evaluator-blind, positive- and negative-controlled	Luliconazole Cream 1%; Topical; Multiple dose: 0.2 grams once daily for 3 weeks	44	Healthy subjects	3 weeks	Complete; Full
Phase 1 PK	MP-1000-05	To determine the potential of Luliconazole Cream 1% and its vehicle to cause sensitization after repeated topical application.	Randomized, evaluator-blind, positive- and negative-controlled	Luliconazole Cream 1%; Topical; Multiple dose: 0.2 grams 3 times weekly for 3 weeks and once after 10-14 day rest period	238	Healthy subjects	6 to 8 weeks	Complete; Full
Phase 1 PK	MP-1000-06	To determine the potential of Luliconazole Cream 1% and its vehicle to produce phototoxic reactions in normal use.	Randomized, evaluator-blind, vehicle-controlled	Luliconazole Cream 1%; Topical; Single dose: 20 mg left on for 24 hours	33	Healthy subjects	Single dose	Complete; Full
Phase 1 PK	MP-1000-07	To determine the potential of Luliconazole Cream 1% and its vehicle to produce photoallergenic reactions in normal use.	Randomized, evaluator-blind, vehicle-controlled	Luliconazole Cream 1%; Topical; Multiple dose: 20 mg 6 times over 3 weeks and once after 9-14 day rest period	55	Healthy subjects	6 weeks	Complete; Full
Phase 1 PK	MP-1000-08	To determine the effect of Luliconazole Cream 1% on QT/QTc interval duration and electrocardiographic morphology.	Randomized, double-blind, placebo- and active-controlled	Luliconazole Cream 1%; Topical; Multiple dose: 2 or 10 grams once daily for 7 days Note: Four-way crossover	56	Healthy subjects	4 weeks	Complete; Full
Phase 1 PK	MP-1007	To assess the systemic exposure to Luliconazole Cream 1% under maximum use conditions.	Non-randomized, open-label, single treatment group	Luliconazole Cream 1%; Topical; Multiple dose: 3 grams once daily for 15 days	30	Interdigital tinea pedis or tinea cruris	15 days	Complete; Full
Phase 2 Safety Efficacy	TP-0801	To examine the optimal duration of Luliconazole Cream 1% to achieve "complete clearance" at two weeks post-treatment.	Randomized, double-blind, parallel group, vehicle-controlled	Luliconazole Cream 1%; Topical; Multiple dose: 1 gram once daily for 2 or 4 weeks	147	Interdigital tinea pedis	2 weeks or 4 weeks	Complete; Full

Phase 3 Safety Efficacy	MP-1000-01	To evaluate the safety and efficacy of Luliconazole Cream 1% compared with vehicle in treating tinea cruris.	Randomized, double-blind, parallel group, vehicle-controlled	Luliconazole Cream 1%; Topical; Multiple dose: once daily for 1 week	483	Tinea cruris	1 week	Complete; Full
Phase 3 Safety Efficacy	MP-1000-02	To evaluate the safety and efficacy of Luliconazole Cream 1% compared with vehicle in treating interdigital tinea pedis.	Randomized, double-blind, parallel group, vehicle-controlled	Luliconazole Cream 1%; Topical; Multiple dose: once daily for 2 weeks	321	Interdigital tinea pedis	2 weeks	Complete; Full
Phase 3 Safety Efficacy	MP-1000-03	To evaluate the safety and efficacy of Luliconazole Cream 1% compared with vehicle in treating interdigital tinea pedis.	Randomized, double-blind, parallel group, vehicle-controlled	Luliconazole Cream 1%; Topical; Multiple dose: once daily for 2 weeks	322	Interdigital tinea pedis	2 weeks	Complete; Full
Phase 3 Safety	MP-1005	To evaluate the long-term safety of recurrent administration of Luliconazole Cream 1%.	Non-randomized, open-label, single treatment group	Luliconazole Cream 1%; Topical; Multiple dose: once daily for 1 or 2 weeks	604*	Tinea pedis, tinea cruris or tinea corporis	1 week or 2 weeks	Complete; Full
Supportive Japanese Studies								
Phase 1 PK	113001	To investigate the safety of Luliconazole Cream 0.25%, 0.5%, and 1% on normal skin through patch test and photopatch test.	Randomized, single-blind, placebo- and active-controlled	Luliconazole Cream 0.25%, 0.5%, and 1%; Topical; Single dose: 15 mg left on for 48 hours	30	Healthy subjects	Single dose	Complete; Legacy
Phase 1 PK	113002	To investigate the safety, PK, and transdermal absorption rate through a single high dose of Luliconazole Cream 1%.	Non-randomized, open-label, parallel group	Luliconazole Cream 1%; Topical; Single dose: 5 grams left on for 24 hours or removed immediately	9	Healthy subjects	Single dose	Complete; Legacy
Phase 1 PK	113003	To investigate the safety, PK, and transdermal absorption rate through multiple high doses of Luliconazole Cream 1%.	Non-randomized, open-label, single treatment group	Luliconazole Cream 1%; Topical; Multiple dose: 5 grams once daily for 1 week	6	Healthy subjects	1 week	Complete; Legacy
Phase 2 Safety Efficacy	113011	To investigate the safety and efficacy of Luliconazole Cream 1% through comparison between standard and short-term treatment.	Randomized, double-blind, parallel-group, vehicle-controlled	Luliconazole Cream 1%; Topical; Multiple dose: once daily for 1 or 2 weeks or once daily for 2 or 4 weeks	246	Interdigital or vesicular tinea pedis or tinea corporis	1 week, 2 weeks or 4 weeks	Complete; Legacy
Phase 2 Safety Efficacy	PR2699-P2-01	To comparatively evaluate the safety and efficacy of Luliconazole Cream 0.1%, 0.5% and 1% concentrations.	Randomized, double-blind, parallel-group, uncontrolled	Luliconazole Cream 0.1%, 0.5%, and 1%; Topical; Multiple dose: once daily for 1 or 2 weeks	341	Tinea pedis, tinea cruris or tinea corporis	1 week or 2 weeks	Complete; Legacy
Phase 2 Safety Efficacy	PR2699-P2-05	To comparatively evaluate the safety and efficacy of Luliconazole Cream 1% and Liquid 1% formulations.	Randomized, open-label, parallel-group, uncontrolled	Luliconazole Cream 1 % and Luliconazole Solution 1%; Topical; Multiple dose: once daily for 2 weeks	208	Interdigital or vesicular tinea pedis	2 weeks	Complete; Legacy
Phase 3 Safety Efficacy	PR2699-P3-01	To comparatively evaluate the safety and efficacy of Luliconazole Cream 1% and Bifonazole 1 % Cream.	Randomized, single-blind, parallel group, active-controlled	Luliconazole Cream 1%; Topical; Multiple dose: once daily for 2 weeks	511	Interdigital or vesicular tinea pedis	2 weeks	Complete; Legacy

*A total of 604 subjects (153 new subjects and 451 rollover subjects from the Phase 3 studies) were enrolled, 581 of whom were included in the safety population.

2.2.2 What are the design features of the clinical pharmacology trials used to support dosing or claims?

Design features of maximal use PK trial (MP-1007) [Formulation manufacturing site - (b) (4) - (b) (4)]: Topical drug bioavailability is a complex interaction of drug substance, formulation and the effect of disease itself on the barrier function of the skin. In order to adequately assess systemic safety, it is necessary to design trials to maximize the potential for drug absorption with the aim of capturing the worst case scenario. The Sponsor has conducted a maximal use PK trial in adult subjects with moderate to severe interdigital tinea pedis or moderate to severe tinea cruris.

A total of 15 subjects with moderate to severe interdigital tinea pedis involving both feet and 15 subjects with moderate to severe tinea cruris were enrolled. All subjects received Luliconazole Cream, 1%, once daily in the morning for 15 days. The mean amount of

formulation administered was approximately 3.5 grams per application and covered all affected and adjacent areas, including up to the ankle for tinea pedis (~ 1.5 g/foot) and the groin, thighs, and abdomen for tinea cruris.

Plasma levels of circulating luliconazole and Z-metabolite were measured prior to study drug application on Days 1, 8, and 15 and serial blood samples were also obtained at 1, 3, 6, 9, 12, and 24 hours after study drug application on Days 1, 8, and 15. 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). In addition the Sponsor has also evaluated PK on Day 1 and this would provide additional support for maximal use conditions should the skin have healed following treatment. Efficacy was not evaluated in this trial.

Reviewer comments: *For indications in tinea pedis, tinea cruris and tinea corporis, the maximal use PK trial is ideally conducted in subjects 12 years and older with both tinea pedis and tinea cruris infection; and in subjects below 12 years of age, the maximal use PK trial is conducted in subjects with tinea corporis to support all the three indications. These design elements were adopted because tinea pedis and tinea cruris infections are uncommon in subjects below 12 years of age.*

The maximal use PK trial (MP-1007) was conducted in adult subjects with tinea pedis or tinea cruris infection and not both. This "non-ideal design" was considered at the time of Pre-NDA meeting (see Clinical Pharmacology review dated 07/19/2012 and Pre-NDA meeting minutes dated 08/07/2012 in DARRTS, under IND 76049) and a decision was taken to file the NDA with the maximal use PK trial MP-1007 because, the PK results of luliconazole indicated that the mean exposure (AUC_{0-24}) was approximately 10.3 fold higher on Day 8 and 6.5 fold higher on Day 15 in subjects with tinea cruris compared to subjects with tinea pedis. Similarly, the mean maximum concentration (C_{max}) was approximately 10.0 fold and 7.9 fold higher on Day 8 and Day 15 respectively, in subjects with tinea cruris compared to tinea pedis. Hence, in the opinion of this reviewer, the overall contribution of tinea pedis to drug exposure appears to be small compared to drug exposure in subjects with tinea cruris. Furthermore, the Sponsor has deferred pediatric trials and has indicated their plan to conduct a maximal use PK trial in subjects 12 to 17 years, which the Agency will recommend to be conducted in subjects with tinea pedis and tinea cruris, and a safety and efficacy trial including PK is subjects 2 to 17 years with tinea corporis. Hence, additional systemic safety information with "ideal" experimental design will likely be produced in pediatric trials which will likely provide additional information to support systemic safety of this drug.

In addition to potential systemic safety information being generated from future trials, review of this application by Medical Officer, Dr. Gary Chiang, did not reveal any systemic safety concerns from clinical trials that might preclude approval (see review by Dr. Chiang in DARRTS).

Although, it would have been ideal if the maximal use PK trial was conducted in subjects with tinea pedis and tinea cruris, considering the overall information above, the review

team decided to accept Trial MP-1007 conducted in subjects with tinea pedis or tinea cruris as maximal use PK trial in adults in support of this NDA application.

Design features of TQT trial (MP-1000-08) [Formulation manufacturing site - DPT (USA)]: The purpose of this trial was to assess the effect of therapeutic and supra-therapeutic dose regimens of Luliconazole Cream, 1% versus vehicle cream on QTc and ECG morphology in healthy subjects and to evaluate the PD relationship between the duration of the QT/QTc intervals and plasma concentration of luliconazole. This was a randomized, double-blind, comparative, placebo- and active-controlled four-way crossover study conducted at one investigational site in the US. A brief description of treatments administered is shown in Table 3 below. There were 7 dosing days in each of the 4 crossover periods with a washout period of at least 5 days between treatment periods.

A total of up to 66 healthy adult male and female subjects between 18 to 45 years of age was planned to be enrolled in order to achieve 48 completers (47 subjects completed all 4 treatment sequences). Luliconazole PK was assessed by obtaining a single baseline PK sample prior dosing for each period and on Day 7 following last dose administration, serial blood samples were obtained approximately 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 14 and 22.5 h.

Table 3: Description of Treatments administered in Trial MP-1000-08

Group	Description
A **(Therapeutic Dose)**	2 grams of Luliconazole Cream 1% applied once daily for seven days (1 gram to the right back and 1 gram to the right groin), 8 grams of Vehicle Cream applied once daily for seven days (4 grams to the left back and 4 grams to the left groin) **plus** Oral Moxifloxacin placebo capsule once daily for seven days
B **(Supra-Therapeutic Dose)**	10 grams of Luliconazole Cream 1% applied once daily for seven days (1 gram to the right back, 1 gram to the right groin, 4 grams to the left back, and 4 grams to the left groin) **plus** Oral Moxifloxacin placebo capsule once daily for seven days
C **(Positive Control Group)**	10 grams of Vehicle Cream applied once daily for seven days (1 gram to the right back, 1 gram to the right groin, 4 grams to the left back, and 4 grams to the left groin) **plus** Oral Moxifloxacin placebo capsule once daily for six days and over-encapsulated Moxifloxacin 400 mg oral tablet on the seventh day
D **(Placebo Group)**	10 grams of Vehicle Cream applied once daily for seven days (1 gram to the right back, 1 gram to the right groin, 4 grams to the left back, and 4 grams to the left groin) **plus** Oral Moxifloxacin placebo capsule once daily for seven days

2.2.3 In which trials were PK assessed and what were the results?

Sponsor has conducted PK assessment in the following trials as shown in Table 4:

Table 4: List of trials with PK assessment

Trial #	Purpose	Formulation manufacturing site
	US Trials	
MP-1007	Maximal use PK trial in adult subjects with tinea pedis or tinea cruris	(b) (4) (b) (4)
MP-1000-08	TQT trial in healthy adult subjects	DPT (USA)
	Supporting Japanese Trials	
113002	Single dose PK assessment in healthy subjects	(b) (4)
113003	Multiple dose PK assessment in healthy subjects	

Reviewer comments: *The 2 Japanese PK trials [topical single (113002) and multiple (113003) dose] in healthy subjects used formulations manufactured by* (b) (4) *and Sponsor has not conducted any IVRT to compare formulations manufactured at* (b) (4) *and DPT (USA). Since there is no information provided regarding the similarity or difference between formulations manufactured by DPT (USA) and* (b) (4) *and furthermore, these trials were not conducted under maximal use conditions, they will not directly support the decision on this NDA and will not be reviewed (Note: Bio-analytical method validation and bioanalysis reports for the Japanese trials are not submitted with this NDA).*

Summary of PK results of Trial MP-1007 (Max use PK trial): A summary of PK parameters for luliconazole native form and (b) (4) are shown in Tables 5 and 6, respectively. Figure 2 shows the concentration versus time profile for luliconazole on Day 8 and Day 15 in subjects with tinea cruris and tinea pedis.

Table 5: Summary of Mean (SD) PK parameters for Luliconazole (Native form)

Parameter	Interdigital Tinea pedis			Tinea Cruris		
	Study Day			Study Day		
	1 N=12	8 N=11	15 N=11	1 N=8	8 N=8	15 N=8
C_{max} (ng/mL)	0.396 (0.7562)	0.565 (0.4393)	0.931 (1.2321)	4.906 (2.5053)	5.633 (2.3069)	7.358 (2.6618)
T_{max} (hr)	16.9 (9.39)	12.4 (10.29)	5.8 (7.61)	21.0 (5.55)	6.3 (4.46)	6.5 (8.25)
AUC_{0-12} (ng*hr/mL)	2.82 (6.588)	5.28 (4.164)	9.32 (13.529)	32.81 (16.006)	54.40 (30.091)	64.45 (27.780)
AUC_{0-24} (ng*hr/mL)	6.88 (14.5)	10.41 (7.878)	18.74 (27.046)	85.1 (43.695)	106.93 (57.571)	121.74 (53.361)

Notes: Since BLQ were replaced with 0.05 ng/mL, C_{max} and AUC values in a subject with no measurable concentration were 0.05 ng/mL and 1.2 ng*h/mL, respectively.

Figure 2: Concentration (Mean ± SD) versus time profile on Day 8 and Day 15 for luliconazole (Native form) for subjects with interdigital tinea pedis and subjects with tinea cruris

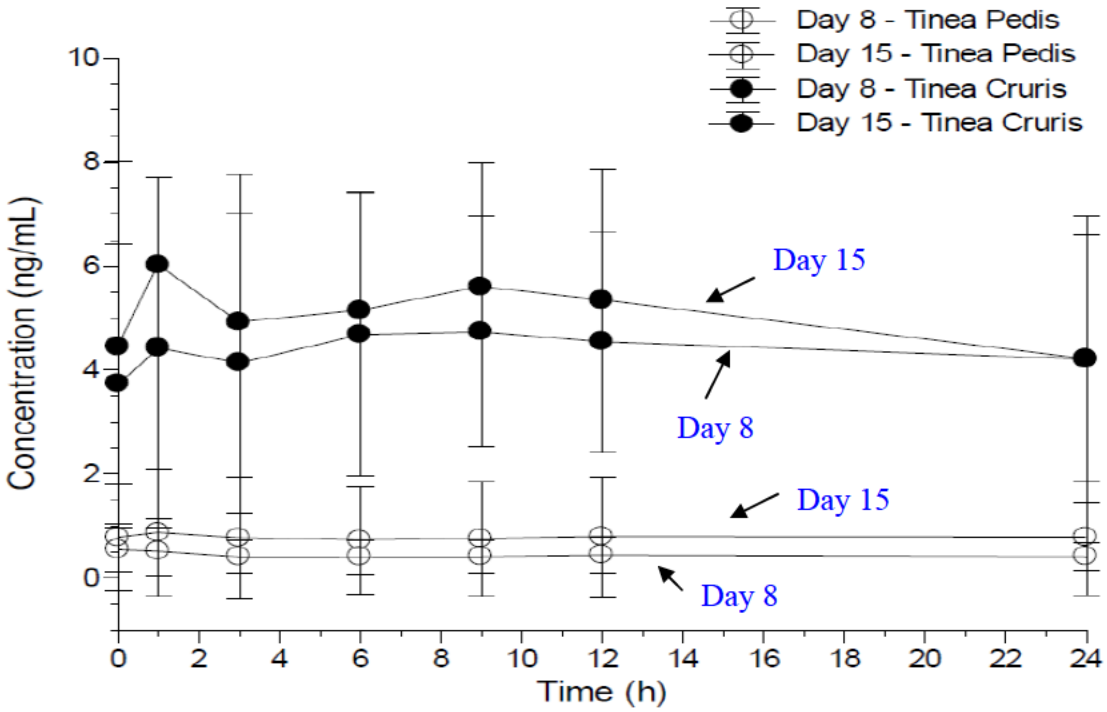


Table 6: Summary of Mean (SD) PK parameters for Luliconazole [(b) (4)] metabolite

Parameter	Interdigital Tinea Pedis			Tinea Cruris		
	Study Day			Study Day		
	1 N=12	8 N=11	15 N=11	1 N=8	8 N=8	15 N=8
C_{max} (ng/mL)	0.050 (0.0000)	0.057 (0.0223)	0.053 (0.0088)	0.054 (0.0079)	0.083 (0.0450)	0.083 (0.0409)
T_{max} (hr)	1.0 (0.00)	1.0 (0.00)	2.2 (3.31)	5.3 (8.50)	8.1 (10.51)	2.6 (3.85)
AUC_{0-12} (ng*hr/mL)	0.61 (0.004)	0.63 (0.070)	0.61 (0.014)	0.61 (0.009)	0.82 (0.475)	0.85 (0.370)
AUC_{0-24} (ng*hr/mL)	1.21 (0.004)	1.23 (0.070)	1.23 (0.066)	1.24 (0.057)	1.66 (1.005)	1.66 (0.739)

Notes: Since BLQ were replaced with 0.05 ng/mL, Cmax and AUC values in a subject with no measurable concentration were 0.05 ng/mL and 1.2 ng*h/mL, respectively.

Based on PK data in Tables 5 and 6, the [(b) (4)] metabolite was present < 7% of the native form. Specifically, the mean ratio of AUC_{0-24} of the [(b) (4)] metabolite with luliconazole on Day 8 in subjects with tinea cruris was 0.015 and similarly, the mean ratio of AUC_{0-24} on Day 15 in subjects with tinea pedis was 0.066. This indicates that further evaluation of drug interactions with the [(b) (4)] metabolite is not needed.

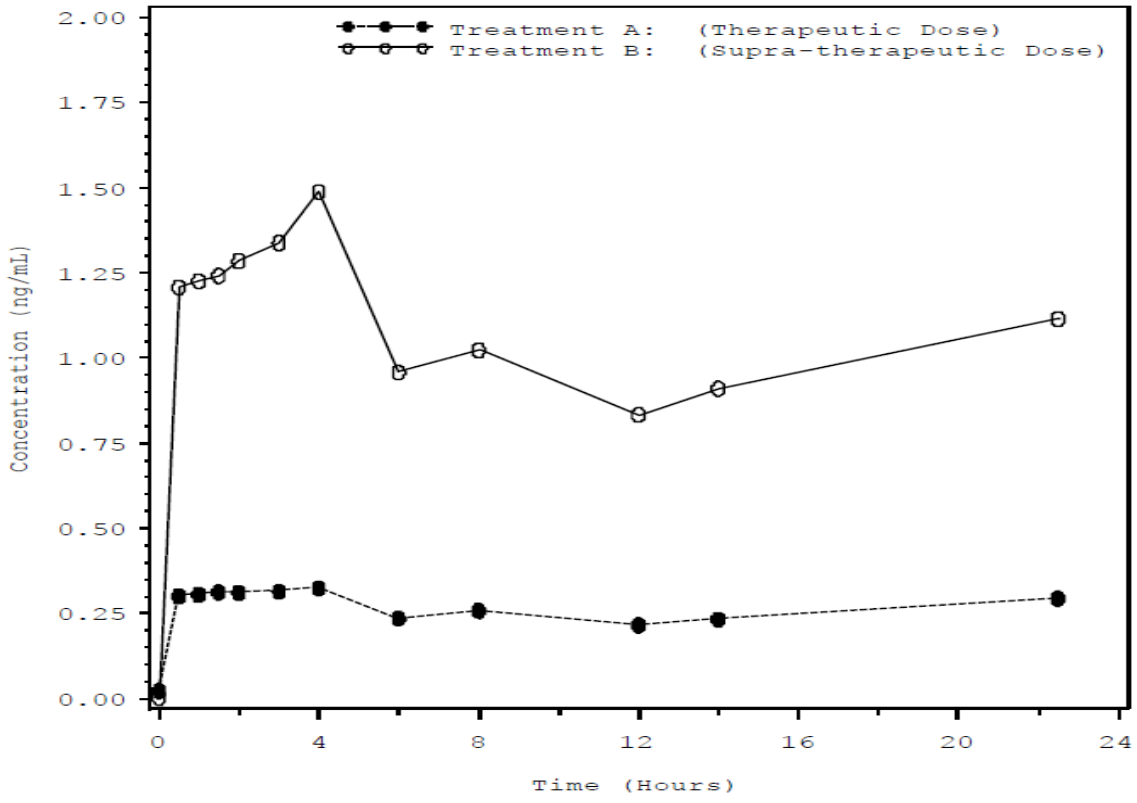
Summary of PK results of Trial MP-1000-08 (TQT trial): The PK parameters are shown in Table 7 and Figure 3 shows the concentration versus time profile for luliconazole on Day 7.

Table 7: Summary of Mean (%CV) luliconazole PK parameters on Day 7

Parameter	Treatment A: Therapeutic Dose Luliconazole Cream 1% (2 grams) (N=50)	Treatment B : Supra-Therapeutic Dose Luliconazole Cream 1% (10 grams) (N=51)
AUC_{τ} (ng·h/mL)*	5.91 (62.8)	23.62 (68.9)
C_{max} (ng/mL)	0.40 (62.0)	1.61 (73.9)
T_{max} (h)**	3.17 (0.67 – 22.68)	3.67 (0.67 – 22.68)
C_{min} (ng/mL)	0.18 (72.7)	0.77 (69.8)

*As there was no 0 hr PK value collected on Day 7, the Day 1 Hour 0 values were used for the 0 hr PK.
**Median (range)

Figure 3: Mean plasma concentrations (0-24) for luliconazole on Day 7



Comparing PK results from Trial MP-1007 (Maximal use) and Trial MP-1000-08 (TQT): A cross-trial comparison between PK parameters obtained in the maximal use PK trial (MP-1007) and TQT trial is made for qualitative purposes only. Both the trials were designed differently and were conducted in different population (diseased versus healthy)

and the PK samples were analyzed by different contract research organizations (CROs). Table 8 provides a summary of PK data.

Table 8: Mean PK parameters from Trial 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

Reviewer Comments: *Based on PK data in Table 8 (cross trial comparison), the mean C_{max} and AUC in subjects with tinea cruris under maximal use conditions on Day 8 (proposed duration of treatment) are approximately 3.5 and 4.5 fold respectively, higher compared to the C_{max} and AUC following 7 day administration of supra-therapeutic dose. This indicates that the results of TQT assessment following supra-therapeutic administration might not be adequate to cover the tinea cruris indication. The Sponsor has obtained EGC assessment in the maximal use PK trial and applicability of TQT assessment and ECG assessment to systemic safety is deferred to the Clinical reviewer and QT Interdisciplinary Review Team (QT-IRT).*

The mean C_{max} and AUC in subjects with tinea pedis under maximal use conditions on Day 15 (see Table 5) are approximately 42% and 21% lower than the C_{max} and AUC following 7 day administration of supra-therapeutic dose (see Table 7). This indicates that the results of TQT assessment following supra-therapeutic administration would be adequate to cover the tinea pedis indication.

The review by QT-IRT reviewer Dr. Qianyu Dang stated that luliconazole is not associated with QT prolongation (see review in DARRTS dated 04/30/2013). The final decision is deferred to Clinical.

2.2.4 What information is known about plasma protein binding?

Luliconazole is ~ 99% bound to plasma proteins.

2.2.5 What information is known about drug metabolism?

Luliconazole is the R enantiomer and in the E-form (Cis). The Sponsor 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. The predominant metabolic pathway involves the cleavage of the dithiolane ring to thiirane (M10) and (b) (4) into the (b) (4)). The M10 metabolite was not detectable in animals and it was not measured in any clinical trials.

The Sponsor also identified a pathway by which glutathione-conjugated compounds of M10 were metabolized to lower molecular weight metabolites (M1 - M4) or to glycine-conjugated compounds (M5) via mercapturic acid-conjugated compounds (M6 - M8), and the pathway by which M10 was metabolized to glucuronic acid-conjugated compounds via hydrolysis (M9) by epoxide hydrolase. In addition to this, another polar metabolite U1 was also identified.

In-vivo levels of the (b) (4) metabolite was measured in the maximal use PK trial (MP-1007) but the overall exposure of the (b) (4) metabolite was present at < 7 % of the native form (mean ratio of AUC_{0-24} of the (b) (4) metabolite compared to luliconazole on Day 8 in subjects with tinea cruris was 0.015 and similarly, the mean ratio of AUC_{0-24} on Day 15 in subjects with tinea pedis was 0.066) and this indicates that further evaluation of drug interactions with the (b) (4) metabolite is not needed.

The study using the human CYP expression system in microsomes suggested that CYP2D6 and CYP3A4 were primarily responsible for luliconazole metabolism with CYP2D6 and 3A4 involved in the production of (b) (4) metabolite and M10 and CYP2D6 involved in the production of U1 metabolite.

Reviewer comments: *See section 2.4.2 for information on drug interactions.*

2.2.6 What is the systemic safety margin of the drug exposure under maximal use conditions based on animal toxicity data?

According to the response to an IR dated 05/01/2013, the Sponsor has claimed that the margin of systemic safety based on animal toxicity data was > 14 fold. This reviewer checked with pharmacology-toxicology reviewer Dr. Daivender Mainigi, and Dr. Mainigi concurs with the Sponsor's assessment.

2.2.7 What is the safety profile of efinaconazole?

The Sponsor provided safety information of Luliconazole Cream, 1% based on four Phase 3 trials, a Phase 2 dose finding trial, a maximal use PK trial, a thorough QT trial and four Phase 1 provocative safety trials, conducted in USA and Central America.

A total of 1495 subjects in the US clinical studies (619 subjects with interdigital tinea pedis, 410 subjects with tinea cruris, 40 with tinea corporis, and 426 healthy volunteers) applied Luliconazole Cream 1% and were included in the safety population.

According to the Sponsor, these trials demonstrated that Luliconazole Cream, 1% had minimal potential for irritation (similar to vehicle) and did not display a potential for sensitization, phototoxicity, or photoallergenicity. The drug did not alter the constituency of blood or urine as measured by laboratory testing and a low incidence of treatment emergent adverse events (AEs), most of which were mild to moderate in severity, with very few events related to treatment. The most common AEs reported were headache and

nasopharyngitis. Of the 9 severe adverse events (SAEs) reported in the US clinical program, the Sponsor claims none of them to be treatment related.

One subject (35-447) in Study MP-1005 died as the result of myocardial infarction and according to the Sponsor, this event was not considered treatment related.

Reviewer comments: *For further information on drug safety, please see Clinical review by the Medical Officer Dr. Gary Chiang in DARRTS.*

2.2.8 Has the potential for QT prolongation adequately addressed?

The review by QT-IRT reviewer Dr. Qianyu Dang stated that luliconazole is not associated with QT prolongation (see review in DARRTS dated 04/30/2013).

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.3.1.1 Effect of gender

In the maximal use PK trial, there were only 4 female subjects in the tinea pedis group compared to 8 males. In the tinea cruris group, there were no females and all the 8 subjects were males. The Sponsor has conducted gender based analysis and showed that there was no effect of gender. In the opinion of this reviewer, since there was limited number of female subjects included in the trial and furthermore, there were no females in the tinea cruris group, no concrete conclusions on the effect of gender on PK can be made.

2.3.1.2 Pediatric subjects

The Sponsor has requested a partial waiver in pediatric subjects from birth to 1 year and 11 months and deferral from conducting pediatric trials in subjects 2 to 17 years. Further, the Sponsor has stated that they plan to conduct a maximal use PK trial in subjects 12 to 17 years with tinea pedis and tinea cruris and a safety and efficacy trial including PK is subjects 2 to 17 years with tinea corporis. The Sponsor plans to work with the Agency to determine the appropriate study designs.

At a meeting with the Pediatric Review Committee (PeRC) on 05/29/2013, PeRC agreed to the Sponsor's partial waiver request in pediatric subjects from birth to 1 year 11 months for tinea corporis and in pediatric subjects less than 12 years of age for tinea pedis and tinea cruris because studies are impossible or highly impractical in this population. The Division also requested 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 studies in adults are completed and the NDA application is being considered for approval in adults. PeRC agreed to the partial deferral request.

2.3.1.3 Renal impairment

No clinical trials have been conducted to evaluate the effect of renal impairment on the PK of luliconazole. This study is not justified given the > 14 fold margin of systemic safety based on the animal toxicity data and lack of systemic safety concerns from Phase 3 trials.

2.3.1.4 Hepatic impairment

No clinical trials have been conducted to evaluate the effect of hepatic impairment on the PK of luliconazole. This study is not justified given the > 14 fold margin of systemic safety based on the animal toxicity data and lack of systemic safety concerns from Phase 3 trials.

2.3.1.5 What pregnancy and lactation use information is there in the application?

The Sponsor has not conducted any trials in pregnant and lactating women.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or response and what is the impact of any differences in exposure or response?

The influence of extrinsic factors on dose-exposure and/or response was not explored.

2.4.2 Drug interactions

The influence of luliconazole on CYP isoforms (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) was studied using human liver microsomes.

Luliconazole inhibited the enzymatic activities of all five CYP enzymes and the inhibitory activity was highest against CYP2C19 followed by CYP3A4 and the Ki values were 0.029 and 0.13 μM, respectively.

The ratios between the mean maximum luliconazole concentration (5.63 ng/mL) from the maximal use PK trial (MP-1007) in subjects with tinea cruris following 8 day administration to subjects with tinea cruris and the Ki (i.e. [I]/Ki) for CYP2C19 and CYP3A4 were 0.548 and 0.122, respectively. The corresponding R values for CYP2C19 and CYP3A4 would be 1.548 and 1.122, respectively, indicating that the investigational drug is likely an inhibitor of CYP2C19 and CYP3A4 and the Sponsor would need to address this with appropriate clinical trials.

The Sponsor 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)*, and the Sponsor will need to address this.

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

Reviewer Comments: *Luliconazole is an NME and the Sponsor should fully characterize the drug interaction potential as recommended in the "Draft Guidance for Industry: Drug interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations - February 2012". Hence, the Sponsor should conduct in-vitro studies to address the inhibition potential of CYP2B6 and CYP2C8 and induction potential of CYP1A2, CYP2B6 and CYP3A. Based on the in-vitro results, further in-vivo drug interaction assessment may be needed.*

The potential of luliconazole to induce CYP enzyme activity would be unlikely to have any effect on luliconazole efficacy because; the drug is directly administered to the target site (skin), where it is absorbed and then distributed into the plasma. However, the effect of induction potential (if any) of luliconazole on other drugs that are substrates of CYP1A2, 2B6 and 3A needs to be adequately addressed as luliconazole might affect the plasma levels of other drugs. From Section 2.2.4 and the information provided in this section, luliconazole is a substrate of CYP2D6, a substrate and an inhibitor of CYP3A4 and an inhibitor of CYP2C19.

Effect of strong CYP3A4 and CYP2D6 inhibitors on the potential increase in systemic exposure of luliconazole: With the IR dated 05/01/2013, the Sponsor was asked to address the effect of a strong CYP3A4 and CYP2D6 inhibitors on the systemic exposure of luliconazole with the aim of further addressing systemic safety of luliconazole in the event of co-administration with strong CYP3A4 and CYP2D6 inhibitors (see communication in DARRTS).

The Sponsor responded to this IR on 05/17/2013 and provided limited comparative safety (no PK) data from their Phase 2 and Phase 3 clinical trials. Specifically, the Sponsor identified 7 subjects who were co-administered strong CYP2D6 inhibitors, however, there were no subjects identified who were co-administered strong CYP3A4 inhibitors, and only 2 subjects were identified having co-administered moderate CYP3A4 inhibitors. The Sponsor noted that there was no difference in any treatment emergent adverse events (TEAEs) between subjects that were co-administered strong CYP2D6 inhibitors or moderate CYP3A4 inhibitors and overall population. In addition to this the Sponsor has provided a rationale using the > 14 fold systemic safety margin from animal toxicity studies to address the systemic safety concerns due to any potential increase in systemic

exposure of luliconazole in presence of strong CYP3A4 and CYP2D6 inhibitors. This reviewer checked with the Pharmacology – Toxicology reviewer Dr. Daivender Mainigi and Dr. Mainigi concurs with the Sponsor's assessment of margin of systemic safety. Based on this information, in the opinion of this reviewer, no further in-vivo drug interaction assessment will be needed.

Effect of luliconazole inhibition of CYP2C19 and CYP3A4 on other drugs that are substrates of CYP2C19 and CYP3A4: The Sponsor calculated the R = 1+ [I]/Ki value based on unbound luliconazole concentration and showed that the R values for the most sensitive enzymes CYP2C19 and CYP3A4, to be below the threshold of 1.1. This estimation is not consistent with the one recommended in the "Draft Guidance for Industry: Drug interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations - February 2012", where it is recommended that the R value estimation should be based on total drug concentrations and not unbound drug concentrations.

This reviewer notes that the R = 1+ [I]/Ki values for inhibition potential of luliconazole for CYP2C19 and CYP3A4, based on the total mean luliconazole concentration observed in the maximal use PK trial (MP-1007) is above the threshold value of 1.1. Specifically, the [I]/Ki value based on concentration on Day 8 in subjects with tinea cruris under maximal use conditions are 0.548 for CYP2C19 and 0.122 for CYP3A4 and the corresponding R values are 1.548 and 1.122, respectively.

The interaction potential in subjects with tinea pedis is of less concern because the R value is below the threshold of 1.1. Specifically, the [I]/Ki value based on concentration on Day 15 (last day of treatment) (Cmax = 0.931 ng/mL) in subjects with tinea pedis under maximal use conditions are 0.091 for CYP2C19 and 0.020 for CYP3A4 and the corresponding R values are 1.091 and 1.020, respectively.

Hence based on the above assessment, the Sponsor should conduct in-vivo drug interaction trials to further evaluate the effect of luliconazole inhibition of CYP3A4 and CYP2C19 on the potential increase in exposure of co-administered drugs by using appropriate probe substrates. This trial should be conducted by applying Luliconazole Cream 1% under maximal use conditions in subjects with both tinea cruris and tinea pedis.

Amount of formulation use information: The Phase 3 trials are usually not conducted under maximal use conditions and mostly focus on general population (with respect to disease severity, area involvement, etc.) rather than capturing the "worst case scenario". For example, in the maximal use PK trial (MP-1007), subjects applied a mean daily amount of ~ 3.53 grams (median ~ 3.27 grams) of the formulation (range 2.72 – 4.90 grams) and in the Phase 3 trial conducted in subjects with tinea cruris (MP-1000-01) the mean daily amount of the formulation used was ~ 2.16 grams (range 0.17 – 4.69 grams) (median ~ 2.20 grams). This would support the concern of systemic safety due to any potential drug interactions because the mean amount of formulation used clinically appears to be only slightly (~ 1.5 fold) lower than what was used in the maximal use PK

trial, especially in subjects with tinea cruris. This would mean that there is likely going to be subjects using formulation in the clinic which will be close to the amount used in the maxima use PK trial (see the range of the amounts used above).

Lastly, the indication of tinea pedis, tinea cruris and tinea corporis are common and could affect any individual, who could be on several other co-medications. Furthermore, these indications are not considered life threatening and there are several other treatment options available. Hence, any systemic safety concerns emerging as a result of drug interactions will need to be adequately addressed by the Sponsor to support the safe use of this drug.

2.5 General Biopharmaceutics

2.5.1 Based on biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

Not Applicable

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The proposed-to-be-marketed formulation is used in the maximal use PK trial (MP-1007) and three pivotal Phase 3 clinical trials (MP-1000-01, MP-1000-02 and MP-1000-03). Hence relative bioavailability assessment is not needed. However, the formulation used in the maximal use PK trial (MP-1007) was manufactured in (b) (4) ((b) (4) while the formulation used in the Phase 3 trials were manufactured in the USA (DPT). The Sponsor has conducted IVRT to bridge the two manufacturing sites. IVRT results were reviewed by ONDQA reviewer Dr. Kelly Kitchens. According to Dr. Kitchens, the IVRT results support bridging between the two manufacturing sites, (b) (4) (b) (4) and DPT (USA). For further information, see review by Dr. Kitchens in DARRTS and see Section 2.1.1 in this review.

2.5.2.1 What data support or do not support a waiver of in vivo BE data?

A waiver of in-vivo BE is not necessary as the proposed to-be-marketed formulation was used in the three pivotal Phase 3 trials and the pivotal PK trial.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Effect of food on the BA is not evaluated for topical formulations.

2.6 Analytical Section

2.6.1 How are the active moieties identified, and measured in the plasma and urine in the clinical pharmacology and biopharmaceutics studies?

The active moiety luliconazole and the (b) (4) metabolite were identified using high performance liquid chromatography and tandem mass spectrometry (LC-MS/MS).

Reviewer comments: *The Sponsor did not use a chiral column that would distinguish between R and S enantiomer in the maximal use PK trial (MP-1007) and TQT trial (MP-1000-08). Therefore, the PK results presented in this review represent total (R + S) concentrations, if there was interconversion from R to S isomer in human.*

2.6.2 Which metabolites have been selected for analysis and why?

All metabolites were formed in minor quantities; however, the Sponsor has evaluated the systemic exposure of the (b) (4) metabolite in the maximal use PK trial (MP-1007). Based on the ratio of exposure of the (b) (4) metabolite with the parent drug, the (b) (4) metabolite was < 7 %.

Reviewer comments: *The (b) (4) metabolite was present at levels < 7 % of the parent based on the ratio of AUC from the maximal use PK trial (MP-1007). Further, according to the Sponsor, the antifungal activity of (b) (4) was 15-250 times less than luliconazole. Although the Sponsor has assessed the levels of the (b) (4) metabolite, further assessment with regards to drug interactions will not be required because the levels are < 7 % of the parent.*

2.6.3 For all moieties measured, is free, bound, or total measured?

Total concentrations for luliconazole and its (b) (4) metabolite were measured.

2.6.4 What is the range of the standard curve? How does it relate to the requirements for clinical studies?

Range for luliconazole (parent compound): 0.05 to 50 ng/mL
Range for (b) (4) metabolite: 0.05 to 50 ng/mL

This range was adequate as none of the plasma concentrations for luliconazole and Z-form metabolite in the clinical trials exceeded the upper limit of 50 ng/mL.

Reviewer comments: *The maximal use PK trial samples were analyzed by (b) (4) and the TQT trial PK samples were analyzed by (b) (4) The lower limit of quantification (LLOQ) and the range was identical for both the contract research organizations (CROs) for both luliconazole and (b) (4) metabolite.*

2.6.5 What are the accuracy and precision at LLOQ?

Trial MP-1007: Maximal use PK trial

CRO: (b) (4)

	Luliconazole	(b) (4) ***metabolite***
Within-run accuracy %	5.8	-0.8
Between-run accuracy %	0.4	-0.2
Within-run precision %	2.4	3.6
Between-run precision %	4.5	4.4

Trial MP-1000-08: TQT trial
CRO: (b) (4)

	Luliconazole	(b) (4) ***metabolite***
Within-run accuracy %	-15.3	-11.5
Between-run accuracy %	0.7	-1.7
Within-run precision %	6.3	5.4
Between-run precision %	9.8	7.5

2.6.6 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler, etc.)?

Trial MP-1007: Maximal use PK trial
CRO: (b) (4)

Parameter	***Luliconazole***	(b) (4) ***metabolite***
Freeze/Thaw cycle stability	3 cycles at - 20 and - 80ºC protected from light	3 cycles at - 20 and - 80ºC protected from light
Room temperature stability	20 hour protected from light	20 hour protected from light
Autosampler stability	84 hours protected from light	84 hours protected from light
Refrigeration stability	193 days at 2 to 8 ºC protected from light	128 days at 2 to 8 ºC protected from light
Long term stability	380 days at - 70 ºC protected from light	380 days at - 70 ºC protected from light

Trial MP-1000-08: TQT trial
CRO: (b) (4)

Parameter	***Luliconazole***
Freeze/Thaw cycle stability	3 cycles at - 80ºC
Room temperature stability	At least 6 hours
Refrigeration stability	At least 165 hours at 5 ºC
Long term stability	At least 54 days at - 80 ºC

Reviewer comments: *The sample stability data generated by* (b) (4) *will be adequate to support the stability of both the trials since storage conditions were similar across the two CROs. Further, the duration of long term PK sample stability documented by* (b) (4) *exceeded the duration of sample storage for the maximal use PK trial (MP-1007) and the TQT trial (MP-1000-08).*

Incurred sample reproducibility (ISR):
Trial MP-1007: ISR was determined for at least 10% of the samples that were originally assayed. Samples selected had concentration values near the C_{max} or from the terminal portion of the elimination phase and had sufficient volume to use the same volume used in the original analysis of the specimens. 79.7 % of the samples were within ±20 % of the original result. Results for Luliconazole met the acceptance criterion (greater than two thirds of all samples within ±20 % difference).

Trial MP-1000-08: The reliability and the reproducibility of the analytical method were confirmed as 95 out of the 122 samples (corresponding to 77.9 % of ISR) met the acceptance criteria (percentage of variability within ±20 %).

3. Detailed Labeling Recommendations

The following changes are recommended in Sponsor's proposed labeling submitted on February 26, 2013. The **bold and underlined** text indicates insertion recommended by the reviewer and the ~~strikethrough~~ text indicates recommended deletion.

7 DRUG INTERACTIONS

The potential of luliconazole to inhibit Cytochrome P-450 (CYP) enzymes 1A2, 2C9, 2C19, 2D6, and 3A4 was evaluated in vitro. Based on in vitro assessment, luliconazole at therapeutic doses, particularly when applied to patients with moderate to severe tinea cruris, may inhibit the activity of CYP2C19 and CYP3A4. However, no in vivo drug interaction trials have been conducted to evaluate the effect of luliconazole on other drugs that are substrates of CYP2C19 and CYP3A4.

Luliconazole is not expected to inhibit CYPs 1A2, 2C9 and 2D6 based on in vitro assessment. The induction potential of luliconazole on CYP enzymes has not been evaluated.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

(b) (4)

(b) (4)

12.2 Pharmacodynamics

At therapeutic doses, Luzu cream is not expected to prolong QTc to any clinically relevant extent.

(b) (4)

12.3 Pharmacokinetics

Luliconazole is the R enantiomer of a chiral molecule. The potential for inter-conversion between R and S enantiomers in humans has not been assessed. Information on the pharmacokinetics of luliconazole presented below refers to both R enantiomer and S enantiomer, if any, combined.

Luliconazole is >99% protein bound in plasma.

In a (b) (4) pharmacokinetic **trial** ~~study~~, 12 subjects with **moderate to severe** tinea pedis and 8 subjects with **moderate to severe** tinea cruris applied **a mean daily amount of approximately** 3.5 grams of Luzu Cream to the affected and surrounding areas once daily for 15 days~~,~~ (b) (4). Plasma concentrations of luliconazole on Day 15 were ~~low, but~~ measurable~~,~~ in all subjects and fluctuated little during the 24 hour interval. (b) (4)

In subjects with tinea pedis, the mean ± SD of the maximum concentration (C_{max}) was 0.40 ± 0.76 ng/mL after the first dose and 0.93 ± 1.23 ng/mL after the final dose. The mean time to reach C_{max} (T_{max}) was 16.9 ± 9.39 hours after the first dose and 5.8 ± 7.61 hours after the final dose. Exposure to luliconazole, as expressed by area under the concentration time curve (AUC_{0-24}) was 6.88 ± 14.50 ng*hr/mL after the first dose and 18.74 ± 27.05 ng*hr/mL after the final dose. In subjects with tinea cruris, the mean ± SD C_{max} was 4.91 ± 2.51 ng/mL after the first dose and 7.36 ± 2.66 ng/mL after the final dose. The mean T_{max} was 21.0 ± 5.55 hours after the first dose and 6.5 ± 8.25 hours after the final dose. Exposure to luliconazole, as expressed by AUC_{0-24} was 85.1 ± 43.69 ng*hr/mL after the first dose and 121.74 ± 53.36 ng*hr/mL after the final dose.

12.4 Microbiology

(b) (4)

4. INDIVIDUAL TRIAL REVIEW

Trial Number: MP-1007 (Maximal use PK trial)

Title: An Open-Label Study to Assess the Pharmacokinetics (PK) with Maximal Use of Luliconazole Cream, 1% in Patients with Moderate to Severe Tinea Pedis or Tinea Cruris

Bio-analytical CRO: (b) (4)

Overall Study Objectives: The objective of this study was to evaluate the PK with maximal use of Luliconazole Cream, 1%, as measured by circulating plasma levels of luliconazole in subjects with moderate to severe interdigital tinea pedis or tinea cruris.

Study Drug: Luliconazole Cream, 1% (Lot# 1009051)

Study Design: This was an open-label, non-randomized, single-treatment group, repeated-dose, maximal use, PK trial conducted at two investigator sites to determine the PK of Luliconazole Cream, 1% in subjects with either moderate to severe interdigital tinea pedis on both feet or moderate to severe tinea cruris.

A total of 15 subjects with moderate to severe interdigital tinea pedis as defined by a Physician's Global Assessment (PGA) score of 2 or 3 involving both feet and 15 subjects with moderate to severe tinea cruris as defined by a PGA score of 2 or 3 were enrolled (See Table 9).

Table 9: Physician's Global Assessment (PGA) Score

Tinea Pedis

0	Clear:	No evidence of scaling, pruritis and erythema (residual erythema may be present)
1	Mild:	Interdigital erythema and scaling are present between some toes but are mild; minimal pruritis may be present
2	Moderate:	Definite interdigital erythema and scaling are present between most toes accompanied by marked pruritis
3	Severe:	Significant erythema, scaling, and pruritis are present between most toes

Tinea Cruris

0	Clear:	No evidence of scaling, pruritis and erythema (residual erythema may be present)
1	Mild:	Erythema and scaling are present but are mild; minimal pruritis may be present
2	Moderate:	Definite erythema and scaling are present accompanied by marked pruritis
3	Severe:	Significant erythema, scaling, and pruritis are present

All subjects received Luliconazole Cream, 1%, once daily for 15 days (Days 1 through 15). All treatments were administered in the morning. On study visit Days 1, 2, 8, 9 and 15, the study staff measured and the subject applied the study drug at the clinic. Approximately 3.0 grams of the formulation was applied per application and covered all affected and adjacent areas, including up to the ankle for tinea pedis (~ 1.5 g/foot) and the groin, thighs, and abdomen for tinea cruris (average amount of actual formulation used is ~ 3.5 grams/day).

Each subject had documentation of the disease at the baseline visit with a PGA score of 2 or 3 and mycological confirmation by microscopy of tissue (KOH). Tissue samples were sent to a central laboratory for confirmation of the fungus. All subjects with a clinical diagnosis of interdigital tinea pedis or tinea cruris confirmed by the detection of fungal hyphae on a KOH wet mount, performed at the investigational site, were eligible to be included in the trial; and those subjects who subsequently showed negative baseline culture for a dermatophyte at the central laboratory were categorized as "delayed exclusions". All subjects who were enrolled, received at least one application of study drug, and had at least one post-baseline assessment were included in the analyses for safety.

Subjects identified as "delayed exclusions" were excluded from the primary analysis for PK. 15 subjects with tinea pedis and 15 subjects with tinea cruris were enrolled to provide 12 subjects with confirmed tinea pedis and 8 subjects with confirmed tinea cruris were included in the PK analyses.

Reviewer comment: *Table 10 below shows the amount of formulation applied across different clinical trials*

Table 10: Mean amount of formulation used per day

Trial #	Purpose	Mean amount in grams per day (range)
MP-1007	Maximal use PK trial in tinea pedis and cruris	3.53 (2.72 - 4.90) (median ~ 3.27)
MP-1000-01	Phase 3 trial in tinea cruris	2.16 (0.17 - 4.69) (median ~ 2.20)
MP-1000-02	Phase 3 trial in tinea pedis	0.95 (0.08 - 3.21) (median ~ 0.85)
MP-1000-03	Phase 3 trial in tinea pedis	1.31 (0.04 - 3.89) (median ~ 1.43)

Reviewer comments: *Based on the above table, the mean amount of formulation used in the maximal use PK trial is approximately 3 times higher in subjects with tinea pedis compared to the mean amount used in Phase 3 trials (MP-1000-02 and MP-1000-03). In subjects with tinea cruris the mean amount of formulation used in the maximal use PK trial was approximately 1.6 times higher than the amount of formulation used in Phase 3 trial (MP-1000-01). Hence, the Sponsor's claim that the maximal use PK trial used doses 3 times the clinical dose is not justified.*

PK Blood Sampling Time: Plasma levels of circulating luliconazole (native form and Z-metabolite) were measured at the following time points:

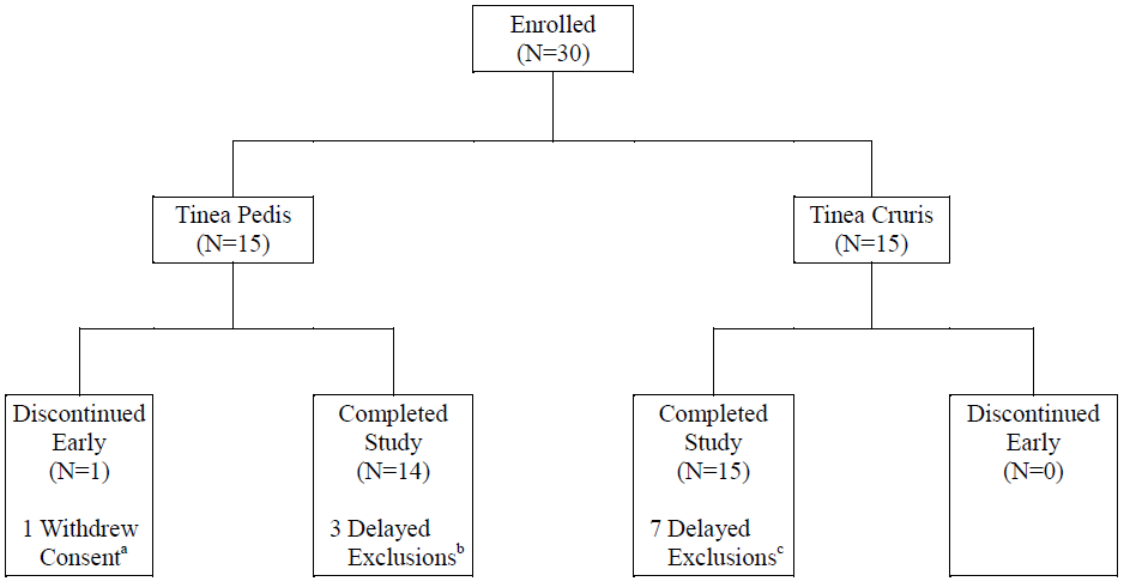
- Prior to study drug application on Days 1, 8, and 15.
- 1, 3, 6, 9, 12, and 24 hours after study drug application on Days 1, 8, and 15.

Note: The 24-hour time point was on Days 2, 9, and 16, respectively, prior to study drug application. At all sampling times, BLQ was replaced by 0.05 for subjects with no measurable concentrations.

PK Parameters: The PK parameters assessed using non-compartmental approach include AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, C_{min} and $t_{1/2}$.

Subjects: A total of 31 subjects were screened and 30 subjects were enrolled in the study and applied Luliconazole Cream, 1% topically (Figure 4).

Figure 4: Schematic representation of subject enrollment



[a] Subject 01-005 (Day 8)
[b] Subjects 02-006, 02-020, 02-023
[c] Subjects 02-009, 02-012, 02-013, 02-014, 02-017, 02-018 for negative cultures; Subject 02-016 for missing specimen

All but 1 subject (01-005) applied Luliconazole Cream, 1%, once daily for 15 days and completed the study. Subject 01-005 withdrew consent on Day 8 for non-study related reasons (Table 11). This subject is included in the safety analysis. Table 12 shows details about subject enrollment and evaluability.

Table 11: Summary of Subject Completion/Discontinuation

	Luliconazole Cream, 1%
Number of Subjects Treated	30
Number of Subjects Who Completed the Study	29
Reasons for Discontinuation from the Study	
Withdrew Consent	1
Lost to Follow-up	0
Adverse Event	0
Protocol Violation	0
Investigator Decision	0
Other	0

Table 12: Summary of Subject Enrollment and Evaluability

	Luliconazole Cream, 1%		
	Total	Tinea Pedis	Tinea Cruris
Number of Subjects Enrolled	30	15	15
Number of Subjects Failing Inclusion/Exclusion Criteria	0	0	0
Number of Subjects with Delayed Exclusion	10	3	7
Number of Subjects Treated	30	15	15
Number of Subjects Excluded from Pharmacokinetic Analyses	10	3	7
Number of Subjects Included in Pharmacokinetic Analyses	20	12	8
Number of Subjects Excluded from Safety Analyses	0	0	0
Number of Subjects Included in Safety Analyses	30	15	15

Demographics: Of the 20 subjects included in the PK analyses, 12 subjects had moderate to severe tinea pedis and 8 subjects had moderate to severe tinea cruris. The mean age of the PK subjects was 39.1 years. Most subjects (80.0% [16/20]) were male. The ethnicity for most subjects (75.0% [15/20]) was "Not Hispanic or Latino". All subjects were either white (60.0% [12/20]) or black/African American (40.0% [8/20]).

All subjects with tinea cruris were male and half (50.0% [4/8]) were black/African American. The majority of subjects with tinea pedis were male (66.7% [8/12]) and the majority (66.7% [8/12]) were white. Table 13 provides a summary on demographics.

Table 13: Demographic summary for trial MP-1007

	Luliconazole Cream, 1%		
	Subjects with Tinea Pedis (n=12)	Subjects with Tinea Cruris (n=8)	Total (N=20)
Age			
N	12	8	20
Mean	35.8	44.1	39.1
STD	10.42	12.44	11.73
Median	33.5	45.0	43.0
Min to Max	20 to 49	27 to 65	20 to 65
Gender			
N	12	8	20
Male	8 (66.7%)	8 (100.0%)	16 (80.0%)
Female	4 (33.3%)	0 (0.0%)	4 (20.0%)
Ethnicity			
N	12	8	20
Hispanic or Latino	5 (41.7%)	0 (0.0%)	5 (25.0%)
Not Hispanic or Latino	7 (58.3%)	8 (100.0%)	15 (75.0%)
Race			
N	12	8	20
American Indian / Alaskan Native	0 (0.0%)	0 (0.0%)	0 (0.0%)
Black or African American	4 (33.3%)	4 (50.0%)	8 (40.0%)
White	8 (66.7%)	4 (50.0%)	12 (60.0%)
Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)
Height (in)			
N	12	8	20
Mean	66.75	71.00	68.45
STD	3.577	1.690	3.609
Median	66.50	71.50	69.00
Min to Max	60.0 to 72.0	67.0 to 72.0	60.0 to 72.0
Weight (lbs)			
N	12	8	20
Mean	213.50	211.88	212.85
STD	29.050	50.118	37.612
Median	208.50	200.00	206.50
Min to Max	165.0 to 252.0	165.0 to 325.0	165.0 to 325.0

Baseline Characteristics with regards to disease severity: The PGA score of tinea pedis for all PK subjects with tinea pedis was moderate (83.3% [10/12] for the right foot; 58.3% [7/12] for the left foot) or severe (16.7% [2/12] for the right foot; 41.7% [5/12] for the left foot).

Similarly, the PGA score of tinea cruris for all PK subjects with tinea cruris was moderate (75.0% [6/8]) or severe (25.0% [2/8]).

Treatment Compliance: Study drug was weighed, and approximately 3.0 grams were applied to the affected area by study staff at the investigational site on Days 1, 2, 8, 9, and 15. On the remaining days, subjects applied the drug at home. On Days 8 and 15, the retrieved tubes were weighed, and subjects were queried regarding compliance with therapy.

Weights of dispensed tubes before dosing ranged from 53.9 grams to 54.1 grams on Day 1 and from 53.94 grams to 54.1 grams on Day 8. Weights of returned tubes ranged from 18.1 grams to 39.6 grams on Day 8 and from 15.6 grams to 37.6 grams on Day 15.

Based on the mean total amount of drug used, PK subjects applied 3.53 grams/day of Luliconazole, 1%, and the safety subjects applied 3.55grams/day. The mean amount of drug applied per day was similar between subjects with tinea pedis and tinea cruris (see Table 14 for details). According to the Sponsor, 10 (52.6%) PK subjects applied between 2.5 grams/day and 3.5 grams/day, 8 (42.1%) PK subjects applied between > 3.5 grams/day and 4.5 grams/day, and 1 (5.3%) PK subject applied > 4.5 grams/day. Subject (01-005) withdrew consent and did not return any tubes. Among the subjects included in safety analysis, 1 (3.4%) subject applied <2.5 grams/day, 14 (48.3%) subjects applied between 2.5 grams/day and 3.5 grams/day, 11 (37.9%) subjects applied between > 3.5 grams/day and 4.5 grams/day, and 3 (10.3%) subjects applied > 4.5 grams/day.

Table 14: Summary of drug usage

	Luliconazole Cream, 1%		
	Subjects with Tinea Pedis (n=15)	Subjects with Tinea Cruris (n=15)	Total (N=30)
Pharmacokinetic Subjects			
Amount of Study Medication Applied (g)			
N	11	8	19
Mean	53.47	52.34	52.99
SD	10.127	11.939	10.618
Median	58.50	46.05	49.10
Min to Max	40.9 to 64.9	41.8 to 73.6	40.9 to 73.6
Safety Subjects			
Amount of Study Medication Applied (g)			
N	14	15	29
Mean	54.05	52.54	53.27
SD	10.799	13.049	11.827
Median	59.00	46.20	50.00
Min to Max	38.9 to 68.4	30.8 to 74.4	30.8 to 74.4

Note: Subject 01-005 discontinued prior to study completion.

PK results for parent compound luliconazole: The PK parameters are summarized in Table 15 below and Figure 5 shows a plot of mean concentrations versus time profile of luliconazole on Day 8 and Day 15. Figure 6 shows the mean plasma luliconazole concentrations versus time profile in subjects with tinea pedis and Table 16 shows a summary of PK parameters in subjects with tinea pedis while Figure 7 shows the mean plasma luliconazole concentrations versus time profile in subjects with tinea cruris and

Table 17 shows a summary of PK parameters in subjects with tinea cruris. Individual subject profiles are shown in Figure 8.

Table 15: Mean (SD) PK parameters of luliconazole

Parameter	Interdigital Tinea pedis			Tinea Cruris		
	Study Day			Study Day		
	1 N=12	8 N=11	15 N=11	1 N=8	8 N=8	15 N=8
C_{max} (ng/mL)	0.396 (0.7562)	0.565 (0.4393)	0.931 (1.2321)	4.906 (2.5053)	5.633 (2.3069)	7.358 (2.6618)
T_{max} (hr)	16.9 (9.39)	12.4 (10.29)	5.8 (7.61)	21.0 (5.55)	6.3 (4.46)	6.5 (8.25)
AUC_{0-12} (ng*hr/mL)	2.82 (6.588)	5.28 (4.164)	9.32 (13.529)	32.81 (16.006)	54.40 (30.091)	64.45 (27.780)
$AUC_{0.24}$ (ng*hr/mL)	6.88 (14.5)	10.41 (7.878)	18.74 (27.046)	85.1 (43.695)	106.93 (57.571)	121.74 (53.361)

Notes: Since BLQ were replaced with 0.05 ng/mL, C_{max} and AUC values in a subject with no measurable concentration were 0.05 ng/mL and 1.2 ng*h/mL, respectively.

Figure 5: Concentration (Mean ± SD) versus time profile on Day 8 and Day 15 for luliconazole (Native form) for subjects with interdigital tinea pedis and subjects with tinea cruris

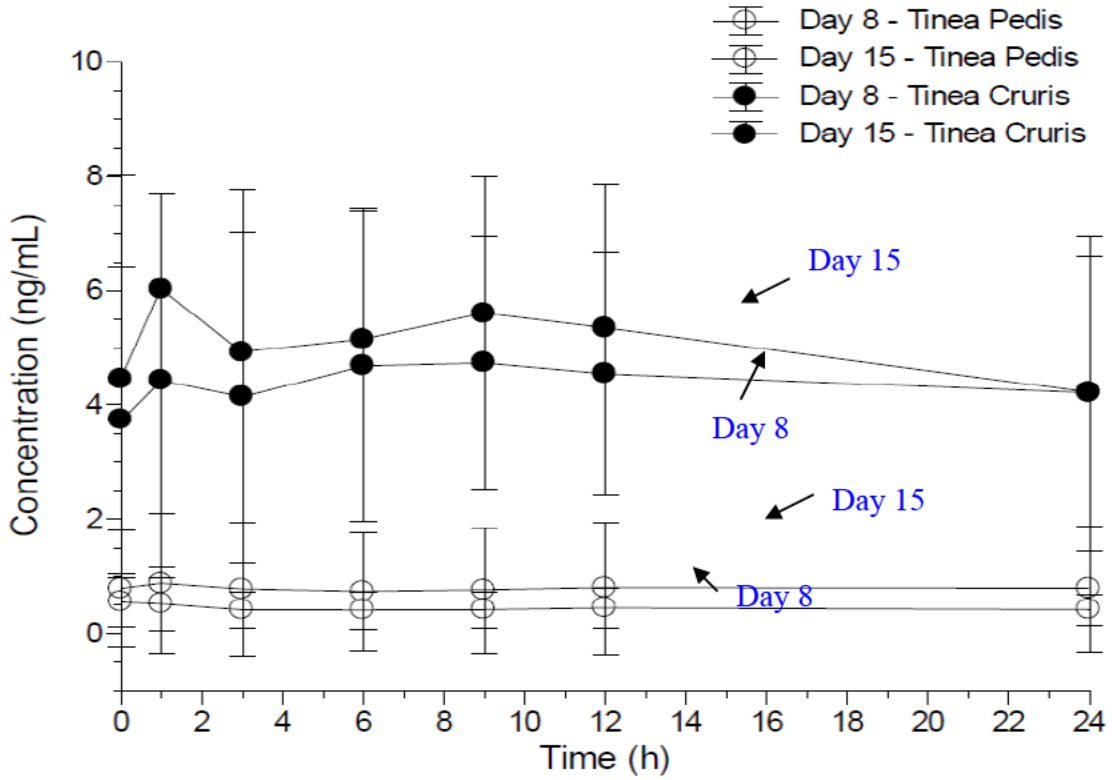
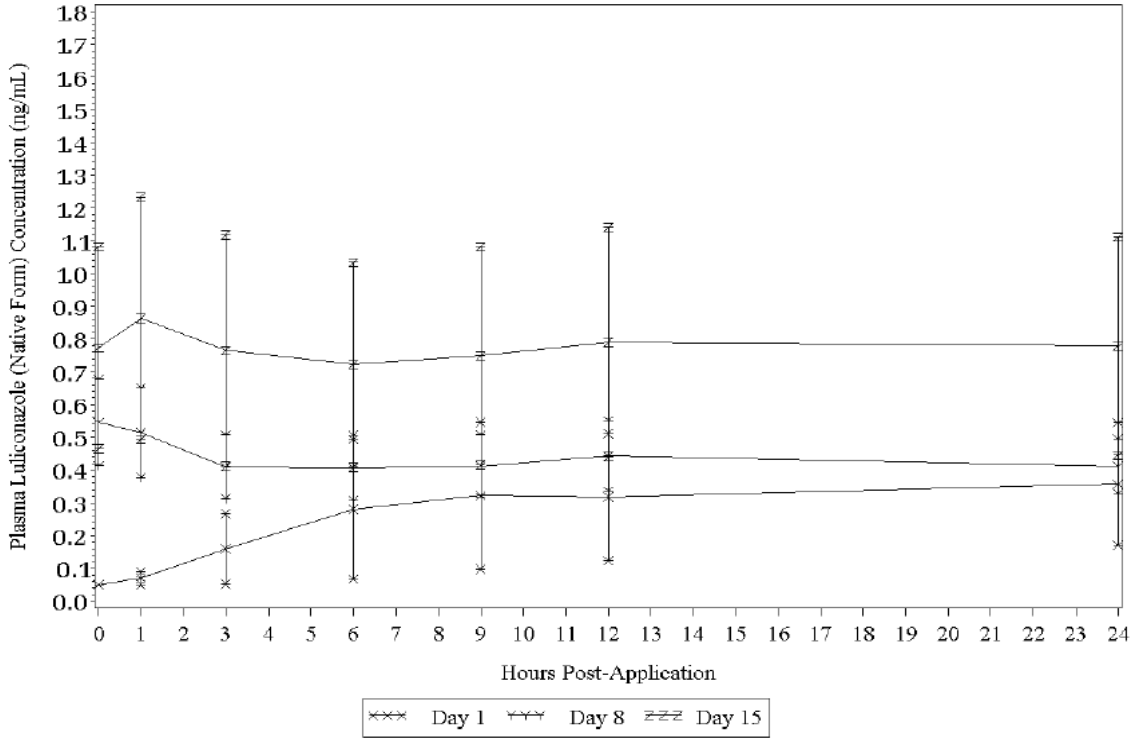
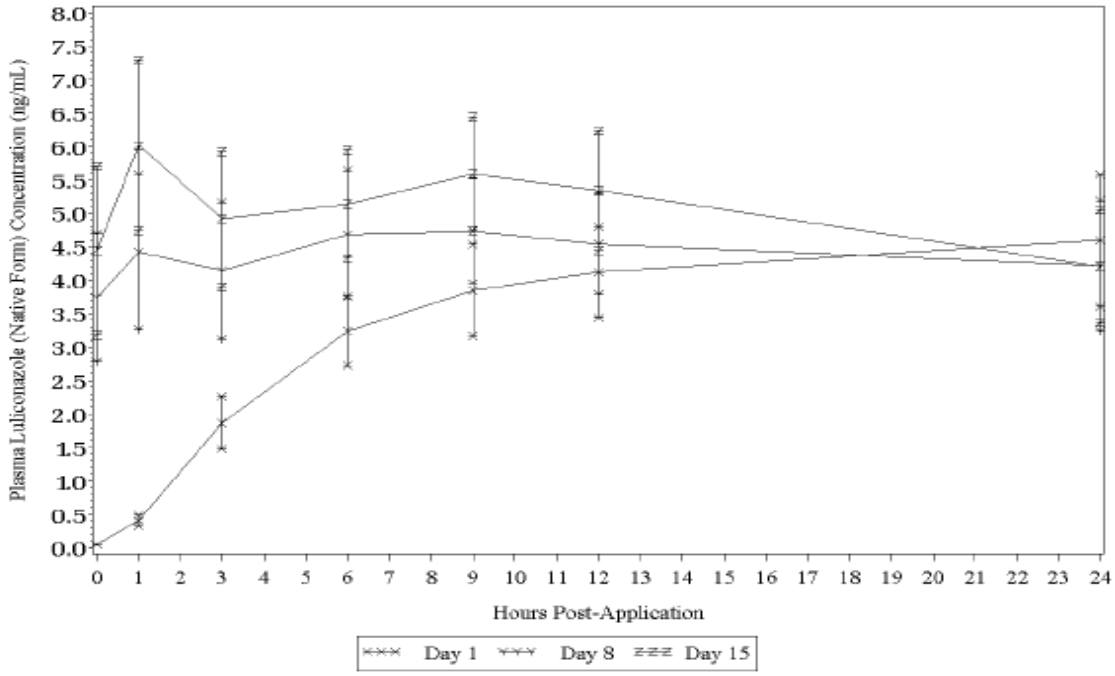


Figure 6: Plot of mean plasma luliconazole concentrations (ng/mL) versus time (hours) in subjects with tinea pedis



Note: Mean +/– standard error.

Figure 7: Plot of mean plasma luliconazole concentrations (ng/mL) versus time (hours) in subjects with tinea cruris



Note: Mean +/– standard error.

Table 16: Summary of PK parameters of luliconazole in subjects with tinea pedis

	Study Day		
	Day 1	Day 8	Day 15
C_{min} (ng/mL)			
N	12	11	11
Mean [a]	0.070	0.338	0.664
SD	0.0687	0.2691	1.0446
Median	0.050	0.282	0.337
Min to Max	0.05 to 0.29	0.06 to 0.85	0.05 to 3.72
C_{max} (ng/mL)			
N	12	11	11
Mean [a]	0.396	0.565	0.931
SD	0.7562	0.4393	1.2321
Median	0.185	0.468	0.544
Min to Max	0.05 to 2.78	0.09 to 1.55	0.10 to 4.43
T_{max} (hr)			
N	12	11	11
Mean [a]	16.9	12.4	5.8
SD	9.39	10.29	7.61
Median	24.0	12.0	1.0
Min to Max	1 to 24	1 to 24	1 to 24
$t_{1/2}$ (hr)			
N	3	7	5
Mean [b]	64.25	44.00	32.41
SD	255.490	182.958	197.749
Median	101.84	39.07	50.67
Min to Max	28.7 to 503.2	23.6 to 525.9	16.4 to 479.4
$AUC_{0 \text{ to } 12}$ (ng*hr/mL)			
N	12	11	11
Mean [a]	2.82	5.28	9.32
SD	6.588	4.164	13.529
Median	0.87	4.52	5.23
Min to Max	0.6 to 23.7	1.0 to 12.9	1.0 to 48.6
$AUC_{0 \text{ to } 24}$ (ng*hr/mL)			
N	12	11	11
Mean [a]	6.88	10.41	18.74
SD	14.500	7.878	27.046
Median	2.67	8.00	9.66
Min to Max	1.2 to 52.8	2.0 to 24.6	1.9 to 97.0
$AUC_{0 \text{ to } \infty}$ (ng*hr/mL)			
N	3		
Mean [a]	610.38		
SD	1026.02		
Median	23.42		
Min to Max	12.6 to 1795.1		

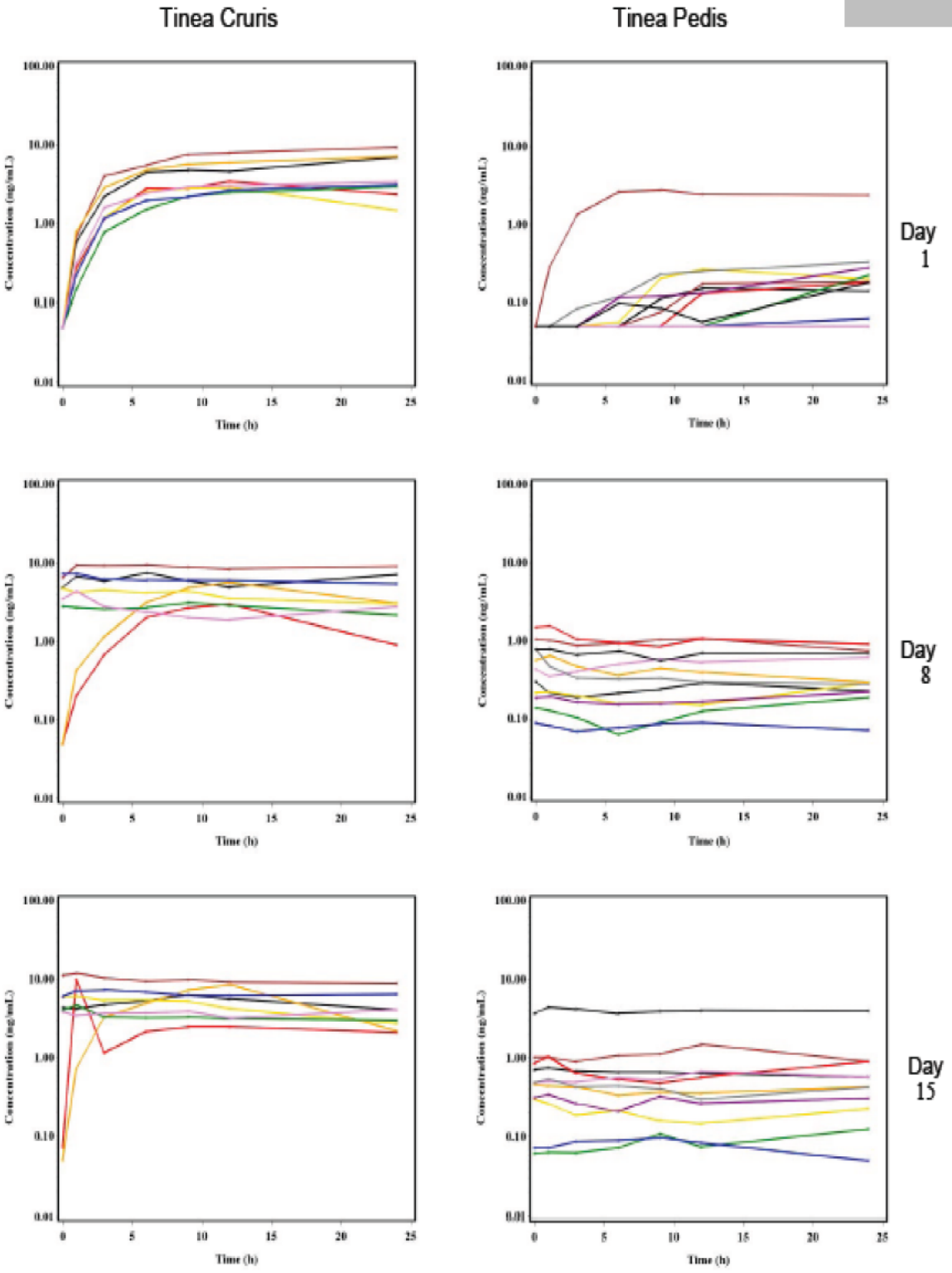
[a] Arithmetic mean
[b] Harmonic mean

Table 17: Summary of PK parameters of luliconazole in subjects with tinea cruris

	Study Day		
	Day 1	Day 8	Day 15
C_{min} (ng/mL)			
N	8	8	8
Mean [a]	0.407	3.322	3.764
SD	0.2410	2.7951	2.6994
Median	0.295	2.620	3.105
Min to Max	0.15 to 0.79	0.21 to 8.43	0.74 to 8.95
C_{max} (ng/mL)			
N	8	8	8
Mean [a]	4.906	5.633	7.358
SD	2.5053	2.3069	2.6618
Median	3.430	5.095	6.825
Min to Max	2.89 to 9.30	2.99 to 9.45	4.09 to 11.90
T_{max} (hr)			
N	8	8	8
Mean [a]	21.0	6.3	6.5
SD	5.55	4.46	8.25
Median	24.0	6.0	2.0
Min to Max	12 to 24	1 to 12	1 to 24
$t_{1/2}$ (hr)			
N	2	5	6
Mean [b]	15.90	17.95	21.15
SD	6.820	31.667	99.404
Median	17.25	29.87	38.45
Min to Max	12.4 to 22.1	7.0 to 84.7	6.2 to 260.8
$AUC_{0 \text{ to } 12}$ (ng*hr/mL)			
N	8	8	8
Mean [a]	32.81	54.40	64.45
SD	16.006	30.091	27.780
Median	25.12	43.68	61.59
Min to Max	17.1 to 62.1	20.6 to 109.4	36.2 to 122.6
$AUC_{0 \text{ to } 24}$ (ng*hr/mL)			
N	8	8	8
Mean [a]	85.10	106.93	121.74
SD	43.695	57.571	53.361
Median	61.90	89.88	114.56
Min to Max	49.5 to 165.3	44.0 to 214.5	63.8 to 231.8
$AUC_{0 \text{ to } \infty}$ (ng*hr/mL)			
N	2		
Mean [a]	105.84		
SD	41.407		
Median	105.84		
Min to Max	76.6 to 135.1		

[a] Arithmetic mean
[b] Harmonic mean

Figure 8: Individual subject concentration time profiles



Notes: Plasma concentrations BLQ were replaced with 0.05 ng/mL.

PK of luliconazole [(b) (4)] metabolite: The majority of PK subjects with tinea pedis had no measurable plasma concentrations of the [(b) (4)] metabolite throughout the study. Only 4 PK subjects with tinea pedis had quantifiable plasma levels. Specifically, 1 subject had 3 measurable concentrations on Day 8, 2 subjects had 1 measurable concentration on Day 15, and 1 subject had 2 measurable concentrations on Day 15. All plasma concentration of luliconazole [(b) (4)] metabolite was below LLOQ on Day 1, and was detectable only at pre-dose and at 1 and 3 hours post-dose on Day 8 and at pre-dose, and at 3 and 24 hours post-dose on Day 15.

Seven PK subjects with tinea cruris had quantifiable plasma concentrations of the [(b) (4)] metabolite. Mean plasma concentrations were below LLOQ until 12 hours post-dose on Day 1.

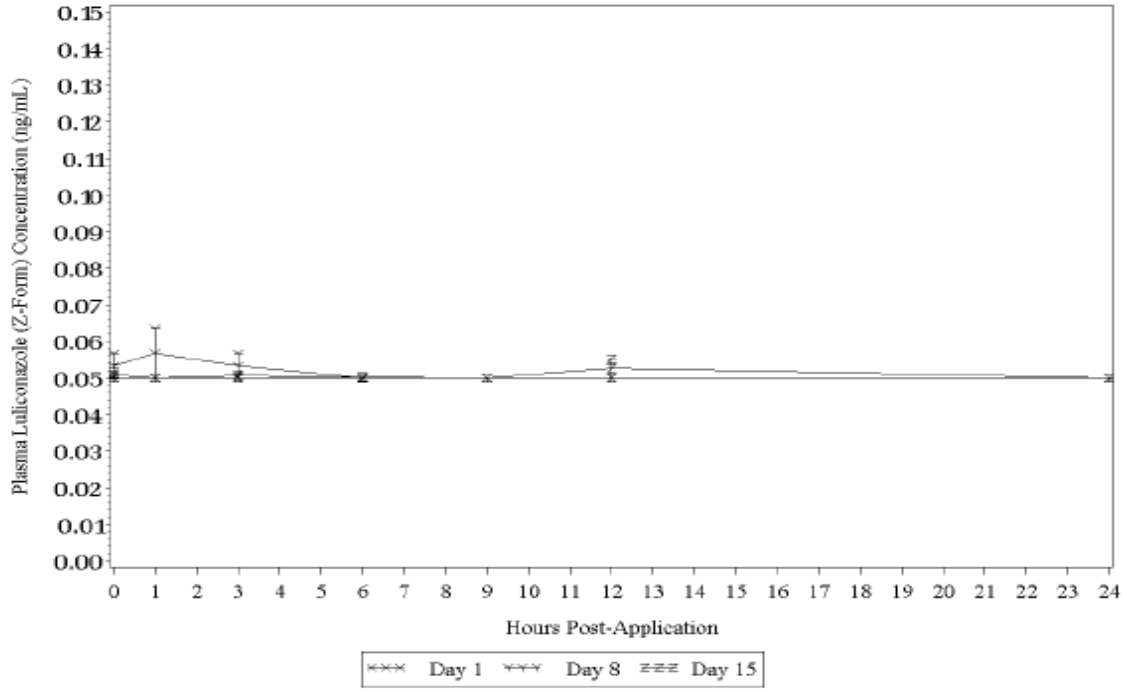
Table 18 shows a summary of PK parameters for [(b) (4)] metabolite while Figure 9 shows the mean plasma [(b) (4)] metabolite concentrations versus time profile in subjects with tinea pedis and Table 19 shows a summary of PK parameters in subjects with tinea pedis. Figure 10 shows the mean plasma [(b) (4)] metabolite concentrations versus time profile in subjects with tinea cruris and Table 20 shows a summary of PK parameters in subjects with tinea cruris.

Table 18: Summary of Mean (SD) PK parameters for Luliconazole [(b) (4)] metabolite

Parameter	Interdigital Tinea Pedis			Tinea Cruris		
	Study Day			Study Day		
	1 N=12	8 N=11	15 N=11	1 N=8	8 N=8	15 N=8
C_{max} (ng/mL)	0.050 (0.0000)	0.057 (0.0223)	0.053 (0.0088)	0.054 (0.0079)	0.083 (0.0450)	0.083 (0.0409)
T_{max} (hr)	1.0 (0.00)	1.0 (0.00)	2.2 (3.31)	5.3 (8.50)	8.1 (10.51)	2.6 (3.85)
AUC_{0-12} (ng*hr/mL)	0.61 (0.004)	0.63 (0.070)	0.61 (0.014)	0.61 (0.009)	0.82 (0.475)	0.85 (0.370)
AUC_{0-24} (ng*hr/mL)	1.21 (0.004)	1.23 (0.070)	1.23 (0.066)	1.24 (0.057)	1.66 (1.005)	1.66 (0.739)

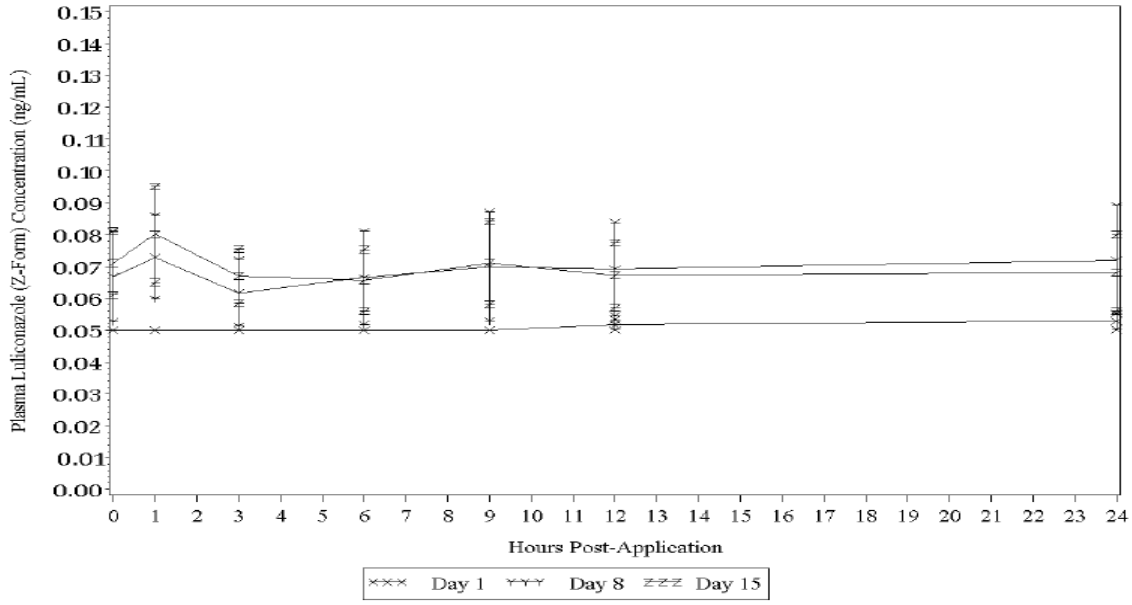
Notes: Since BLQ were replaced with 0.05 ng/mL, Cmax and AUC values in a subject with no measurable concentration were 0.05 ng/mL and 1.2 ng*h/mL, respectively.

Figure 9: Plot of mean plasma (b) (4) metabolite concentrations (ng/mL) versus time (hours) in subjects with tinea pedis



Note: Mean +/– standard error.

Figure 10: Plot of mean plasma (b) (4) metabolite concentrations (ng/mL) versus time (hours) in subjects with tinea cruris



Note: Mean +/– standard error.

Table 19: Summary of PK parameters of (b) (4) metabolite in subjects with tinea pedis

Subjects with Tinea Pedis	Luliconazole Cream, 1%		
	Day 1	Day 8	Day 15
C_{min}			
N	12	11	11
Mean [a]	0.050	0.050	0.050
STD	0.0000	0.0000	0.0000
Median	0.050	0.050	0.050
Min to Max	0.05 to 0.05	0.05 to 0.05	0.05 to 0.05
C_{max}			
N	12	11	11
Mean [a]	0.050	0.057	0.053
STD	0.0000	0.0223	0.0088
Median	0.050	0.050	0.050
Min to Max	0.05 to 0.05	0.05 to 0.12	0.05 to 0.08
T_{max}			
N	12	11	11
Mean [a]	1.0	1.0	2.2
STD	0.00	0.00	3.31
Median	1.0	1.0	1.0
Min to Max	1 to 1	1 to 1	1 to 12
$t_{1/2}$			
N	0	0	1
Mean [b]			18.03
STD			
Median			18.03
Min to Max			18.0 to 18.0
$AUC_{0 \text{ to } 12}$			
N	12	11	11
Mean [a]	0.61	0.63	0.61
STD	0.004	0.070	0.014
Median	0.61	0.61	0.61
Min to Max	0.6 to 0.6	0.6 to 0.8	0.6 to 0.7
$AUC_{0 \text{ to } 24}$			
N	12	11	11
Mean [a]	1.21	1.23	1.23
STD	0.004	0.070	0.066
Median	1.21	1.21	1.21
Min to Max	1.2 to 1.2	1.2 to 1.4	1.2 to 1.4

[a] Arithmetic mean
[b] Harmonic mean

Table 20: Summary of PK parameters of (b) (4) metabolite in subjects with tinea cruris

	Study Day		
	Day 1	Day 8	Day 15
C_{min} (ng/mL)			
N	8	8	8
Mean [a]	0.050	0.061	0.062
STD	0.0000	0.0296	0.0238
Median	0.050	0.050	0.050
Min to Max	0.05 to 0.05	0.05 to 0.13	0.05 to 0.12
C_{max} (ng/mL)			
N	8	8	8
Mean [a]	0.054	0.083	0.083
STD	0.0079	0.0450	0.0409
Median	0.050	0.073	0.075
Min to Max	0.05 to 0.07	0.05 to 0.19	0.05 to 0.17
T_{max} (hr)			
N	8	8	8
Mean [a]	5.3	8.1	2.6
STD	8.50	10.51	3.85
Median	1.0	1.0	1.0
Min to Max	1 to 24	1 to 24	1 to 12
$t_{1/2}$ (hr)			
N	1	1	2
Mean [b]	44.23	18.95	57.12
STD	-	-	235.489
Median	44.23	18.95	197.51
Min to Max	44.2 to 44.2	19.0 to 19.0	31.0 to 364.0
$AUC_{0 \text{ to } 12}$ (ng*hr/mL)			
N	8	8	8
Mean [a]	0.61	0.82	0.85
STD	0.009	0.475	0.370
Median	0.61	0.65	0.72
Min to Max	0.6 to 0.6	0.6 to 2.0	0.6 to 1.7
$AUC_{0 \text{ to } 24}$ (ng*hr/mL0			
N	8	8	8
Mean [a]	1.24	1.66	1.66
STD	0.057	1.005	0.739
Median	1.21	1.28	1.43
Min to Max	1.2 to 1.3	1.2 to 4.1	1.2 to 3.4
$AUC_{0 \text{ to } \infty}$ (ng*hr/mL)			
N	1		
Mean [a]	4.65		
STD	-		
Median	4.65		
Min to Max	4.7 to 4.7		

[a] Arithmetic mean
[b] Harmonic mean

Analysis of efficacy: Not applicable; no efficacy evaluations were performed in this trial.

Summary of safety: According to the Sponsor, there were no deaths, SAEs, or other significant AEs were reported studying this trial and none of the subjects discontinued study drug due to an AE. One severe AE i.e. back pain was reported and was considered not related to the study medication all other AEs were mild or moderate in severity. Two subjects reported 3 AEs (mild application site pruritus and mild WBC count decreased and this was considered by the Sponsor to be probably related to the study medication. The Sponsor further states that laboratory test results did not identify any safety signals. As per the Sponsor, the results of this study showed no evidence of any drug-induced effects on ventricular repolarization as manifested by prolongation of the QT interval.

Reviewer comments: *For further information on drug safety, please see review by Medical Officer Dr. Gary Chiang in DARRTS.*

Trial MP-1000-08 – TQT trial

Title: A Randomized, Double-Blinded, Placebo and Positive Controlled, Four-Group Crossover Study to Evaluate the Effect of 33525 Cream at a Projected Therapeutic and Supra-Therapeutic Dose on Cardiac Repolarization in Healthy Male and Female Subjects

Reviewer comment: *33525 cream is the same as Luliconazole Cream 1%*

Bioanalytical CRO: (b) (4)

Overall Study Objectives:

- To assess the effect of two dose regimens of topical Luliconazole Cream 1% (therapeutic and supra-therapeutic) versus Vehicle Cream on QT interval duration corrected for heart rate (QTc), and electrocardiogram (ECG) morphology in healthy subjects.
- To evaluate the pharmacodynamic (PD) relationship between the duration of the QT/QTc intervals and the plasma concentration of luliconazole.

Study Drug: Luliconazole Cream, 1% (Lot# DDE-1C)

Overall Study Design and Plan: This was a single center, randomized, double-blind, comparative, placebo and active controlled 4-way crossover thorough QT/QTc study. A total of up to 66 healthy adult subjects (approximately 33 male and 33 female) between 18 to 45 years were planned for enrollment in the study to achieve 48 completers. The active screening period lasted 23 days. There were four dosing sequences in each of the four treatment administrations (i.e., 1, 2, 3, and 4). The sequences of the Treatment Groups were (A,D,B,C), (B,A,C,D), (C,B,D,A), or (D,C,A,B). The electrocardiogram (ECG) data extracted from the Holter recorders on this day were used to calculate the subject-specific QT heart rate correction formula (QTcI). Table 21 shows the overall study design and Table 22 provides details on treatments administered.

There were seven dosing days in each of the four crossover periods and a wash-out period of at least five days between treatment periods. In order to establish the ECG

baseline, a Holter recording lasting approximately one hour was obtained prior to dosing on Day +1 of all treatment periods. During the dosing periods a 24-hour Holter recorder was used to extract ECGs on Day +7 of each Period.

PK blood samples were collected immediately following the ECG extraction time windows on the same day of the 24-hour Holter recordings.

Table 21: Major time points in the trial

Day −2 (Period 1 only)	Day -1 (Period 1 only)	Day -1 (Period 2, 3, and 4 only)	Day 1	Days 2-6	Day 7	Day 8
• Confinement to study unit • Clinical labs including urine drugs of abuse screen and a pregnancy screen (females only) collected • Safety ECG, and vital signs obtained • Brief physical exam completed	• 24-hour Holter monitoring • Seated vital signs collected prior to ECG extraction window	• Confinement to study unit • Clinical labs including urine drugs of abuse screen and a pregnancy screen (females only) collected • Safety ECG, and vital signs obtained • Brief physical exam completed	• Holter monitoring for 1 hour prior to dosing • 1 dose of study products administered • Safety ECG collected prior to dosing and at study hour 4 • Seated vital signs collected prior to dosing	• 1 dose of study products administered daily • Safety ECG collected prior to dosing and at study hour 4 (Days 3 and 5 only) • Pregnancy test (females only) collected (Day 4 only) • Seated vital signs collected prior to dosing	• 1 dose of study products administered • 24-hour Holter monitoring • Safety ECG collected prior to dosing and at study hour 4 • Seated vital signs collected prior to ECG extraction window	• Safety ECG collected • Seated vital signs collected • Clinical labs including a pregnancy screen (females only) collected • Brief physical exam completed • Subjects discharged from study unit

Table 22: Description of treatments

Group	Description
A **(Therapeutic Dose)**	2 grams of Luliconazole Cream 1% applied once daily for seven days (1 gram to the right back and 1 gram to the right groin), 8 grams of Vehicle Cream applied once daily for seven days (4 grams to the left back and 4 grams to the left groin) **plus** Oral Moxifloxacin placebo capsule once daily for seven days
B **(Supra-therapeutic Dose)**	10 grams of Luliconazole Cream 1% applied once daily for seven days (1 gram to the right back, 1 gram to the right groin, 4 grams to the left back, and 4 grams to the left groin) **plus** Oral Moxifloxacin placebo capsule once daily for seven days
C **(Positive Control Group)**	10 grams of Vehicle Cream applied once daily for seven days (1 gram to the right back, 1 gram to the right groin, 4 grams to the left back, and 4 grams to the left groin) **plus** Oral Moxifloxacin placebo capsule once daily for six days and over-encapsulated Moxifloxacin 400 mg oral tablet on the seventh day
D **(Placebo Group)**	10 grams of Vehicle Cream applied once daily for seven days (1 gram to the right back, 1 gram to the right groin, 4 grams to the left back, and 4 grams to the left groin) **plus** Oral Moxifloxacin placebo capsule once daily for seven days

Dose Preparation and Administration: On the days of dosing, subjects washed the application sites as instructed. In order to achieve supra therapeutic dose a total of 10 grams of the formulation was applied per day with 5 grams applied to the back and 5 grams to the groin. Specifically, 1 gram of study medication was applied to the right side of the back and 4 grams of study medication were applied to the left side of the back. The templates for the right side of the back and groin covered a total area of 100 cm^2 while the templates for the left side of the back and groin covered a total area of 400 cm^2. The templates for the groin areas covered the groin area and spread out towards the thigh as necessary. After dosing, the areas of application remained exposed for approximately 10 minutes before being covered with clothing.

The Moxifloxacin (either active or placebo) capsules were administered with approximately 240 mL (8 fluid ounces) of room temperature water.

Identity of products used: The identity of the products used is shown in Table 23 below.

Table 23: Identity of the products used

Product	Luliconazole Cream 1% or Vehicle Cream		Moxifloxacin or Placebo*	
Product Name	Luliconazole Cream 1%	Vehicle Cream	Over-encapsulated Moxifloxacin 400 mg Tablets	Placebo for Moxifloxacin
Manufacturer	DPT Laboratories, Ltd.	DPT Laboratories, Ltd.	Bayer HealthCare Pharmaceuticals Inc.	N/A
Lot No.	DDE-1C	DCH-C	54025X4	P-12A11-U07-001911
Manufacture Date	May 2011	March 2011	N/A	Compounded on 04/23/12 or 05/29/12
Expiration Date	None Shown	None Shown	APR14	N/A
Strength	1 gram Luliconazole Cream 1% contains 10 mg luliconazole	N/A	400 mg	N/A
Dosage Form	Cream	Cream	Capsule	Capsule
Route of Administration	Topical	Topical	Oral	Oral

*The over-encapsulated Moxifloxacin tablets, 400 mg and the placebo for Moxifloxacin were prepared by (b) (4) (b) (4) The Moxifloxacin tablets, 400 mg were over-capsulated with empty capsule 00 Blue (Lot Number CA1445-00781, Exp. Date: None Shown) on 23 April 2012. The placebo for Moxifloxacin capsules were compounded using empty capsule 00 Blue (Lot Number CA1445-000781, Exp. Date: None Shown) and Cellulose Microcrystalline, NF (Lot Number 12A11-U07-001911, Exp. Date: None Shown).

PK Assessments: On Day +7 of each period, blood samples were obtained prior to dosing (0 hour) and after dose administration at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 14, and 22.5 hours. The PK blood samples on Day +7 were obtained immediately following the 10-minute ECG extraction time windows.

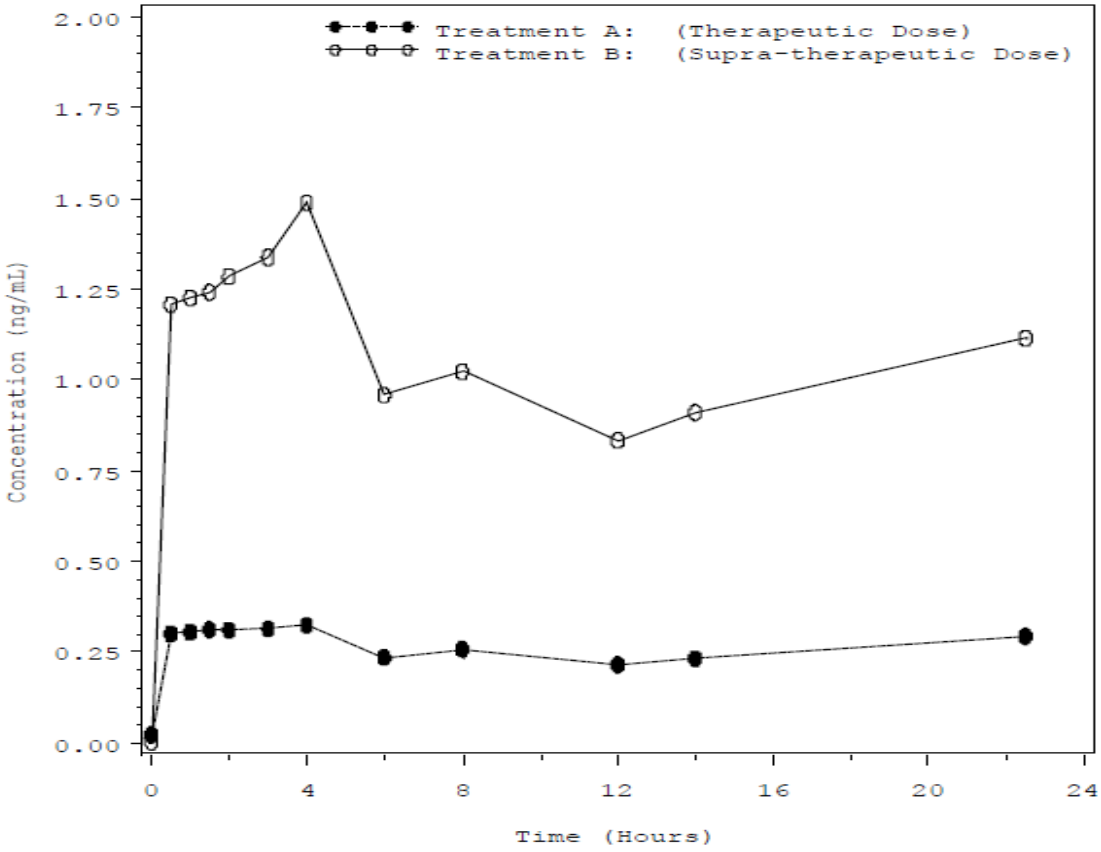
PK Results: The summary of luliconazole PK parameters is shown in Table 24 and the PK profile is shown in Figure 11.

Table 24: Summary of Mean (%CV) luliconazole PK parameters on Day 7

Parameter	Treatment A: Therapeutic Dose Luliconazole Cream 1% (2 grams) (N=50)	Treatment B : Supra-therapeutic Dose Luliconazole Cream 1% (10 grams) (N=51)
AUC_{τ} (ng·h/mL)*	5.91 (62.8)	23.62 (68.9)
C_{max} (ng/mL)	0.40 (62.0)	1.61 (73.9)
T_{max} (h)**	3.17 (0.67 – 22.68)	3.67 (0.67 – 22.68)
C_{min} (ng/mL)	0.18 (72.7)	0.77 (69.8)

*As there was no 0 hr PK value collected on Day 7, the Day 1 Hour 0 values were used for the 0 hr PK.
**Median (range)

Figure 11: Mean plasma concentrations (0-24 hours) for luliconazole



The PK results after multiple once daily supra-therapeutic doses of 10 grams of Luliconazole Cream 1% (Treatment B) showed that AUCτ, C_{max}, and C_{min} on Day 7 were approximately 4 times higher than those following the multiple once daily therapeutic doses of 2 grams of Luliconazole Cream 1% (Treatment A).

TQT results: According to the review by QT-IRT reviewer Dr. Qianyu Dang, luliconazole under conditions tested in this trial is not associated with QT prolongation (see review in DARRTS dated 04/30/2013).

Disposition of Subjects: A total of 56 healthy adult subjects were enrolled and 48 completed. Eight subjects discontinued or withdrew from the trial. Specifically subjects 06 and 07 were discontinued by the Investigator prior to Period 2, Day 1 dosing due to out of range labs. Subject 09 was discontinued by the Investigator prior to Period 1, Day 4, study hour 9 activities due to an AE (dermatitis contact at the ECG tab site) . Subject 17 was discontinued by the Investigator during Period 4, Day 3 due to an AE (left joint dislocation). Subject 29 elected to withdraw from the study prior to Period 4, Day 5, study hour 9 activities due to family emergency. Subject 39 was dropped prior to Period 2 dosing due to a positive drug screen. Subject 44 and 54 elected to withdraw from the study prior to Period 2 check-in due to personal reasons. A summary of subjects per sequence is provided in Table 25. Overall subject disposition and gender distribution is shown in Table 26 and 27.

Table 25: Summary of subject disposition by sequence

	Sequence				
	ADBC*	BACD*	CBDA*	DCAB*	Total
Subjects Who Received at Least One Dose	14	14	14	14	56
Subjects Who Completed the Study	13	12	12	11	48
Subjects Who Elected to Withdraw	0	1	0	2	3
Subjects Discontinued by the Investigator	1	1	2	1	5
Subjects Discontinued by the Sponsor	0	0	0	0	0

* See table 20 for description of treatments A, B, C and D.

Table 26: Subject disposition

Disposition	N
Number of subjects with at least one evaluable ECG in each treatment period	47
Number with any on-Drug ECGs	55
Number on Vehicle Cream	51
Number on Luliconazole Cream 1% 2 g	50
Number on Luliconazole Cream 1% 10 g	51
Number on Moxifloxacin 400 mg	50

Table 27: Gender distribution

	Males n (%)	Females n (%)
All Subjects	30 (54.6%)	25 (45.5%)
Vehicle Cream	27 (52.9%)	24 (47.1%)
Luliconazole Cream 1% 2 g	27 (54.0%)	23 (46.0%)
Luliconazole Cream 1% 10 g	27 (52.9%)	24 (47.1%)
Moxifloxacin 400 mg	26 (52.0%)	24 (48.0%)

Demographics: Demographic information is provided in Table 28.

Table 28: Demographics

Parameter	Sequence ADBC* N = 14	Sequence BACD* N = 14	Sequence CBDA* N = 14	Sequence DCAB* N = 14
Age [years] (range)	28.1 (19 - 43)	27.1 (20 - 43)	26.9 (19 - 40)	29.4 (18 - 44)
Weight [kg] (range)	74.66 (64.0 - 85.4)	69.93 (51.6 - 95.9)	69.15(43.2 - 97.8)	73.31 (53.8 - 95.0)
Height [cm] (range)	170.43 (153.37 - 184.79)	169.83 (151.74 - 187.45)	166.66 (151.84 – 182.17)	173.66 (159.82, 193.52)
BMI [kg/m^2] (range)	25.79 (23.2 - 29.5)	24.09 (20.1 - 29.0)	24.64 (18.7 - 29.5)	24.21 (19.3 - 29.7)
Gender [N (%)]				
Female:	6 (42.9%)	7 (50.0%)	7 (50.0%)	6 (42.9%)
Male:	8 (57.1%)	7 (50.0%)	7 (50.0%)	8 (57.1%)
Race [N (%)]				
American Indian / Alaska Native	-	1 (7.1%)	1 (7.1%)	-
Asian	1 (7.1%)	2 (14.3%)	3 (21.4%)	-
Black / African American	4 (28.6%)	5 (35.7%)	2 (14.3%)	3 (21.4%)
Multiple	1 (7.1%)	-	-	2 (14.3%)
Native Hawaiian / Other Pacific Islander	-	-	1 (7.1%)	-
White	8 (57.1%)	6 (42.9%)	7 (50.0%)	9 (64.3%)

* See table 22 for description of treatments A, B, C and D.

Summary of safety: According to the Sponsor, the trial was completed without any significant AEs attributable to the investigational drug. Two subjects were discontinued from the study due to AEs. Specifically one subject was discontinued by the Investigator due to of left joint dislocation. This AE was not considered to be treatment related. The second subject was discontinued by the Investigator due to contact dermatitis at ECG tab sites and this was also not considered by the Investigator to be related to the study treatments. Further, the Sponsor states that there were no clinically significant changes in clinical laboratory results, safety ECGs, vital signs or physical examinations noted.

Reviewer comments: *For further information on drug safety, please see review by Medical Officer Dr. Gary Chiang in DARRTS.*

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/s/

CHINMAY SHUKLA
07/25/2013

DOANH C TRAN
07/26/2013

EDWARD D BASHAW
07/26/2013
concur with need for requested PMC/PMRs

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 204153	**Reviewer:** Kelly M. Kitchens, Ph.D.	
Submission Date:	December 11, 2012		
Division:	Division of Dermatology and Dental Products	**Acting Team Lead:** Tapash Ghosh, Ph.D.	
Applicant:	Medicis Pharmaceutical Corporation	**Acting Supervisor:** Richard Lostritto, Ph.D.	
Trade Name:	Luzu (luliconazole) Cream, 1%	**Date Assigned:**	January 23, 2013
Established Name:	Luliconazole Cream, 1%	**Date of Review:**	July 17, 2013
Indication:	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.	**Type of Submission:** 505 (b)(1)	
Formulation/ strengths	Cream /1%		
Route of Administration	Topical		
Type of Review:	New Drug Application		

SUBMISSION SUMMARY:

Luzu (luliconazole) Cream 1% is an imidazole with antimycotic and fungicidal activity. Luzu (luliconazole) Cream 1% is proposed for the topical treatment of interdigital tinea pedis, tinea cruris and tinea corporis caused by fungal organisms such as *Trichophyton rubrum*, (b) (4) or *Epidermophyton floccosum*.

The drug product was initially developed and approved for use in Japan and has been commercially available since 2005. Since the formulation has an established safety and efficacy profile, the formulation was not changed for the US clinical development program or for the proposed US commercial drug product, except for the grade of excipients (e.g. NF or USP versus JP). Therefore, the Applicant is relying on the safety and efficacy data established with the Japanese product to support the safety and efficacy of the proposed US product. In vitro release tests (IVRT) were conducted as suggested in the SUPAC-SS guidance and results were submitted to demonstrate "sameness" of the products manufactured at two different locations

This review is focused on the following:

1. The evaluation of the in vitro release test (IVRT) study and acceptance of the bridging results from the study to qualify a level 3 drug product manufacturing site change from (b) (4) (b) (4) to DPT (DPT Laboratories Ltd., San Antonio, TX, USA). The study was conducted per the SUPAC guidance for nonsterile semisolid dosage forms (SUPAC-SS). The release rates of DPT's drug product (lot DCK,

used in Phase 3 clinical trials) were compared to those of (b) (4) commercial drug product (lot 1009051) by calculating the 90% confidence intervals of the ordered test-to-reference slope ratios for the release rates.

2. The evaluation of the IVRT studies to compare the release rates of DPT's drug product registration lots, used in the primary stability studies, to those of (b) (4) commercial drug product lot (lot 1009051). The study was conducted per the SUPAC-SS guidance. The release rates of DPT's drug product registration lots (lots DDE, DDF, and DDG) were compared to those of (b) (4) commercial drug product (lot 1009051) by calculating the 90% confidence intervals of the ordered test-to-reference slope ratios for the release rates.
3. The evaluation of the *ex vivo* skin permeation study, which compared the skin absorption profiles of two test articles from the DPT-manufactured drug product lot DDG (sub-lots DDG-7C and DDG-1C). The study was designed to evaluate the percutaneous absorption of the drug substance form the drug product in human, *ex vivo*, trunk skin, using the finite dose technique and Franz Diffusion Cells. The results from this study demonstrated the drug substance penetrated into and through human skin from both drug product samples, and both samples exhibited similar absorption and flux profiles. The *ex vivo* skin permeation study was not conducted to support the drug product manufacturing site change from (b) (4) to DPT. It was performed to demonstrate consistent skin permeation of luliconazole from two different test articles manufactured at DPT in two separate experiments.

RECOMMENDATION:

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. From the Biopharmaceutics perspective, NDA 204153 for Luzu (luliconazole) Cream, 1% is recommended for approval.

Signature
Kelly M. Kitchens, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Signature
Tapash Ghosh, Ph.D.
Acting Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc. ADorantes; RLostritto.

BIOPHARMACEUTIC ASSESSMENT

Drug Product:

The proposed drug product, luliconazole, was approved in Japan and has been commercially available in Japan since 2005. Luliconazole is an anti-fungal drug incorporated into a topical cream formulation at strength 1% w/w. Each 1 gram of product contains 10 mg luliconazole in a white cream formulation, and the drug product has the following composition:

Component	Function	Quality Standard	Quantity (% w/w)
Luliconazole	Active	In-house	1.0
Benzyl alcohol	(b) (4)	NF	(b) (4)
Butylated hydroxytoluene		NF	
Cetostearyl alcohol		NF	
Isopropyl myristate		NF	
Medium-chain triglyceride		NF	
Methylparaben		NF	
Polysorbate 60		NF	
Sorbitan monostearate		NF	
Propylene glycol		USP	
Purified water		USP	

qs = quantity sufficient
USP = United States Pharmacopeia
NF = National Formulary

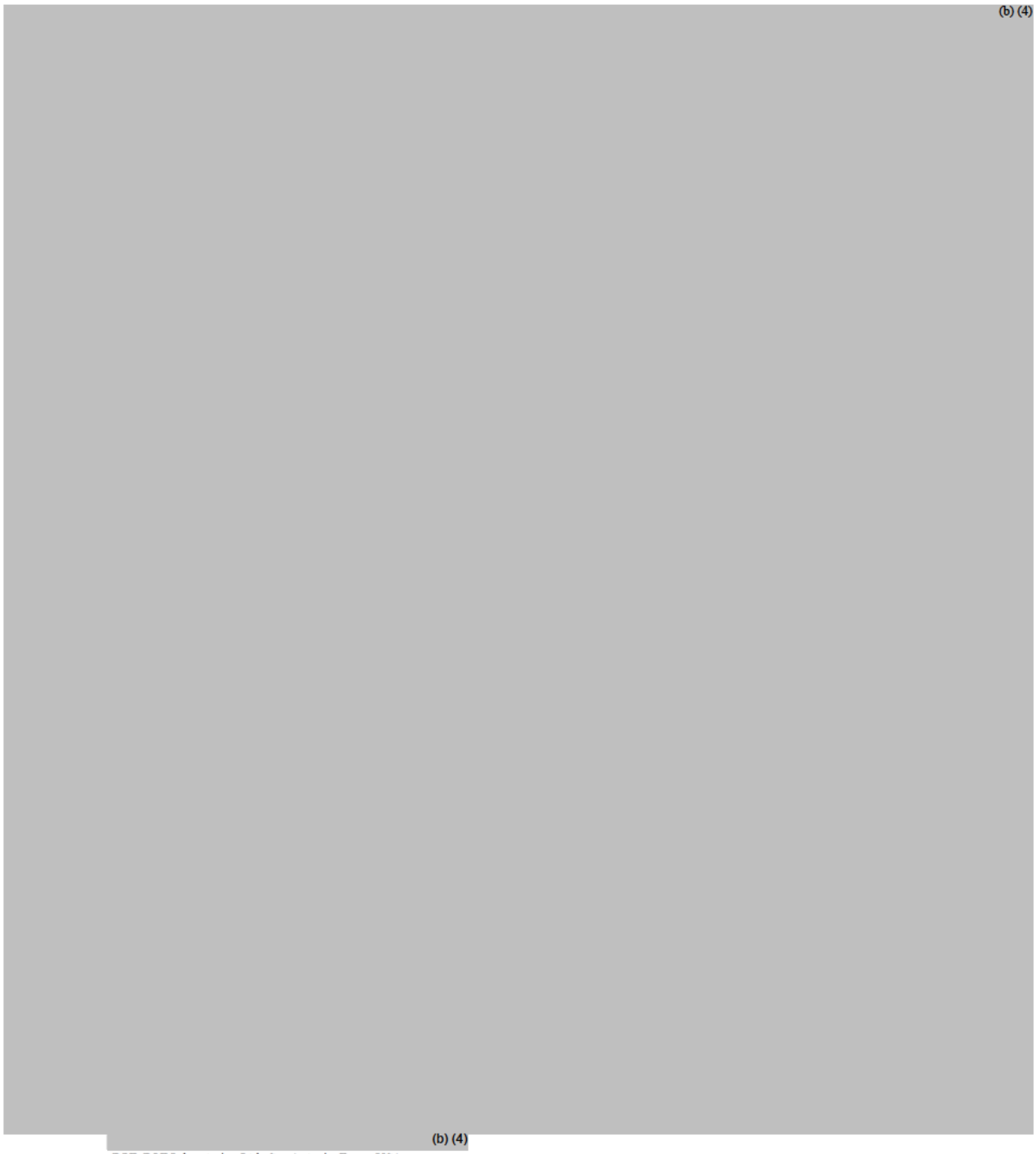
The product is contained in a blind-end aluminum tube with a 2, 30, or 60 g fill volume and a white (b) (4) cap. (b) (4)

Manufacturing Site Change:

The drug product manufacturing process was transferred from (b) (4) (b) (4) (b) (4) to the DPT site (San Antonio, TX, USA). A summary of the manufacturing process changes for the sites is provided in the following table:

Table 3. Manufacturing Process Comparability Assessment (DPT versus (b) (4)

Parameter	(b) (4)	DPT	Difference	Rationale and Quality Impact
Drug product lots		All US clinical and Registration lots and future US commercial lots	Not applicable	Not applicable
Manufacturer		DPT Laboratories, Ltd. USA	Manufacturing site	DPT is a well-established drug product manufacturer for topical dosage forms
Batch size		(b) (4)		Batch size increased to anticipate relative increase in commercial demand (US vs. Japan)
Manufacturing:				
(b) (4)				



DPT: DPT Laboratories, Ltd., San Antonio, Texas, USA

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 conducted 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. The enhancer cell method was used instead of the Franz cell method because the enhancer cell apparatus has a larger fluid volume (150 mL) than the Franz cell apparatus (7 mL). Since the Applicant observed luliconazole saturation using the Franz cell apparatus, they used

the enhancer cell apparatus for the IVRT study compare the release rates of the DPT-manufactured drug product (lot DCK) to the release rates of the (b) (4) manufactured drug product (lot 1009051). 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) (1009051).

In Vitro Release Test Method Development and Validation:

Validation Parameters	Data
(b) (4)	

(b) (4)

In Vitro Equipment

Apparatus	(b) (4) r
Receptor Fluid	
Receptor Volume	
Bath Temperature	
Speed	
Sample Amount	
Sample Volume	
Luliconazole Standards	
Time points	
Filter Membrane	

- The Applicant indicated that the report supplied by (b) (4), "Release Assessment of Lulicon Cream 1% According to SUPAC-SS, (b) (4) Test No. PQ-08-019," was used as a starting point for method optimization:
  - (b) (4)

In Vitro Release Test Results (for (b) (4) lot no. 1009051 vs. DPT's lot no. DCK)

Applicant's Results:

An *in vitro* enhancer cell study (Study 69.METH.1998.02) was performed to qualify a Level 3 (SUPAC-SS) manufacturing site change from (b) (4) to DPT, including the minor process modifications that were introduced during the transfer.

Table 3. 90% Confidence Interval Slope Ratios for Drug Substance Release Rates from Drug Product Manufactured by (b) (4) and DPT

Study	8th Individual Slope Ratio	29th Individual Slope Ratio
DCK (DPT) vs. 1009051 (b) (4)	1.1204 (112.04%)	1.2680 (126.80%)

Reviewer's Results:

The reviewer used IVRT raw data to verify the Applicant's results per the SUPAC Guidance for nonsterile semisolid dosage forms.

(b) (4)

Comments on IVRT Study Results:

- Per the SUPAC Guidance for nonsterile semisolid dosage forms, the 90% confidence intervals should fall within 75% to 133.33% at the first stage. The 90% confidence intervals (112.04%, 126.80%) meet the acceptance criteria for IVRT.
- The IVRT study results are **acceptable.**

In Vitro Release Test Results (for (b) (4) lot no. 1009051 vs. DPT's registration lot nos. DDE, DDF, DDG)

Applicant's Results:

An *in vitro* enhancer cell study (Study 69.2124.00) comparing the drug substance release rates from three drug product lots manufactured by DPT (DDE, DDF, DDG) to the drug substance release rate from a drug product lot manufactured by (b) (4) (1009051) that was used in the maximal use pharmacokinetic study.

Reviewer's Results:

The reviewer used IVRT raw data to verify the Applicant's results per the SUPAC Guidance for nonsterile semisolid dosage forms.

Reviewer-calculated slope data at first stage:

Release Rates (ug cm^{-2} h$^{-1/2}$)

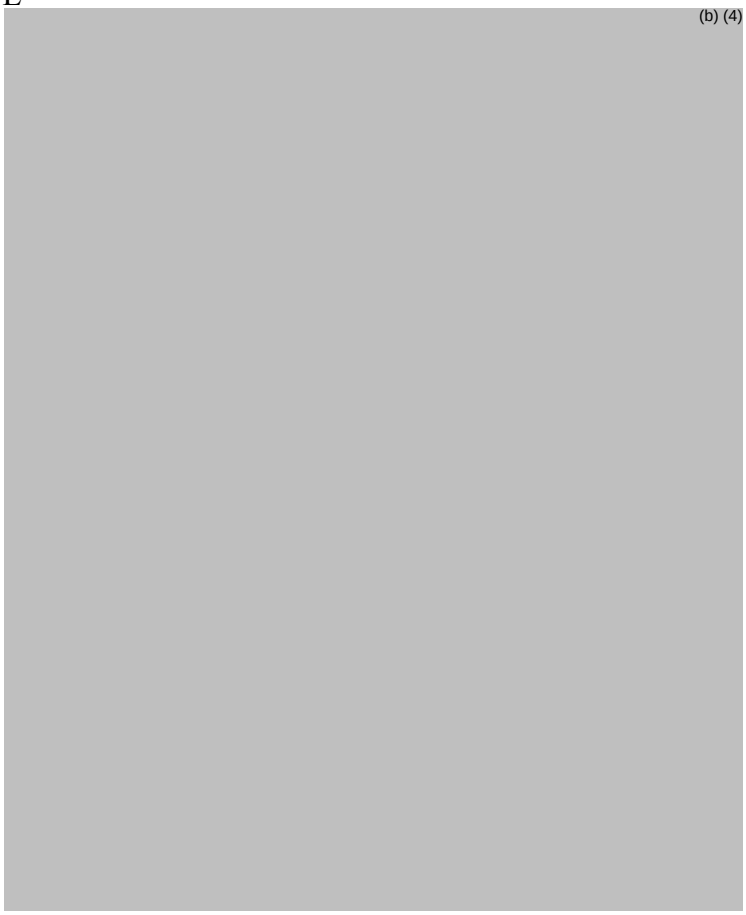
(b) (4)

(b) (4)

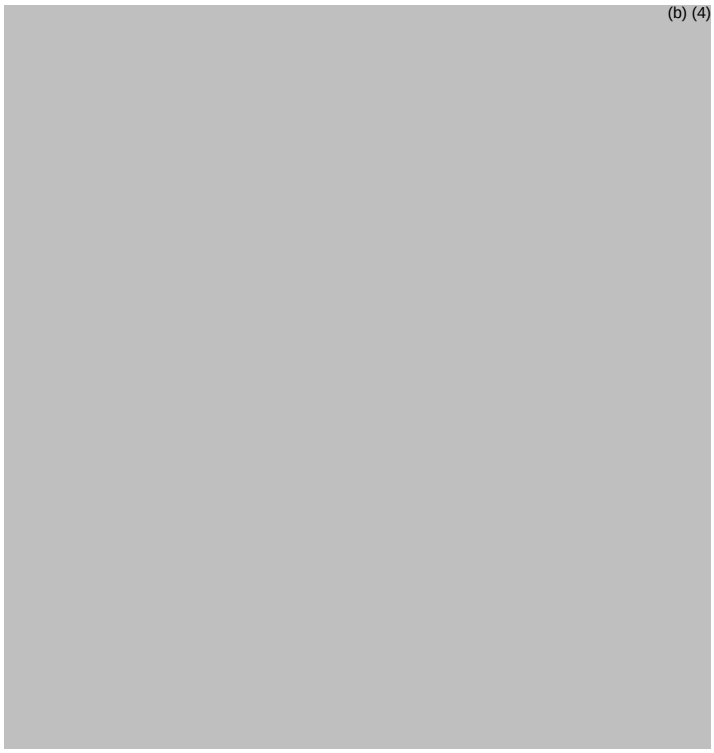
DPT lot no. DDG

Reviewer-calculated rank order of individual T/R ratios

DPT lot no. DDE



DPT lot no. DDF



DPT lot no. DDG

Comments on IVRT Study Results:

- Per the SUPAC Guidance for nonsterile semisolid dosage forms, the 90% confidence intervals should fall within 75% to 133.33% at the first stage. The 90% confidence intervals meet the acceptance criteria for IVRT.
    - Lot DDE: 103.76%, 108.88%
    - Lot DDF: 100.58%, 109.93%
    - Lot DDG: 99.38%, 113.53%
- The IVRT study results are **acceptable.**

***Ex vivo* Skin Permeation Study Design:**

On May 1, 2013, the following Information Request (IR) was submitted to the Applicant to clarify the purpose of the *ex vivo* skin permeation study:

1. ***Clarify the purpose of the ex vivo skin permeation study, and specify if the study is a supportive study of the in vitro release studies or a comparative study. If the study is comparative, explain why test articles from the*** (b) (4) ***and DPT manufacturing sites were not compared.***

2. ***In the Formulation Development sections of your original submission (Module 2.3.P.2.2.1.7 and Module 3.2.P.2.2.1.3.5), it is indicated that one test article was maintained at 25°C for 3 months and the other test article was maintained at 40°C for 3 months for Study R11-1091 (skin permeation study). However, the study report does not provide details on the treatment of the test articles prior to application to the skin samples. Please clarify the storage conditions of the test articles prior to application to the skin sample.***

On May 17, 2013, the Applicant submitted the following response to the IR:

1. The objective of supportive study R11-1091, *ex vivo* skin permeation study, was not to compare product manufactured at DPT and (b) (4) but rather to support product assessment during development.

2. The test articles were pulled from stability stations 40°C and 25°C at 3 months and shipped to the testing site under ambient conditions. (b) (4) standard operating procedure to store the test articles under controlled room temperature prior to application to the skin sample was followed in the storage of these test articles.

Study R11-1091 was conducted by (b) (4) to evaluate the percutaneous absorption pharmacokinetics of topically applied cream formulations containing Luliconazole. The rate and extent of penetration of Luliconazole was determined and compared between two test articles for the amount of penetration into the different layers of the skin, and amount absorbed through the skin. Absorption was measured in human, *ex vivo*, trunk skin, using the finite dose technique and Franz

Diffusion Cells. Two drug product test articles from drug product lot DDG manufactured by DPT were tested: sub-lot DDG-7C and sub-lot DDG-1C.

Study Design

Study Number	R11-1091
Study Title	Evaluation of the *In Vitro* Human Trunk Skin Percutaneous Absorption of Luliconazole from 1% Cream Formulations using the Franz Finite Dose Model
Clinical Site (Name, Address, Phone #)	Cetero Research – St. Charles 400 Fountain Lakes Blvd. St. Charles, MO 63301, USA (636) 947-1200
Principal Investigator	Paul A. Lehman, M.Sc.
First Chamber Dose Date	September 11, 2011
Date of Last Sample Collection	November 11, 2011
Analytical Facility	(b) (4)
Study Dates	Pilot Study: Chamber conduct: 10/18/11 – 10/21/11 Analytical conduct: 10/28/11 – 11/02/11 Pivotal Study: Chamber Conduct: 11/08/11 – 11/11/11 Analytical Conduct: 11/14/11 – 11/17/11
# Donors and Replicates per Donor	Pilot Study: 1 Donor, 6 Replicates Pivotal Study: 3 Donor, 3 Replicates
Sampling Time Points (post-dose)	Pre-dose, 4, 8, 12, 24, and 48 hours post-dose
Skin Sample Processing	Skin Type: Ex vivo human trunk skin Skin Preparations: Cryopreserved, dermatomed (nominal 500 ± 300 µm Skin Test Temperature: 32.0 ± 1.0°C Skin Integrity Test: ^3H_2O skin barrier integrity test prior to dosing Skin Diffusion Cells: Thermal jacketed, static, Franz diffusion cells Donor Chamber Dose Area: Nominal 1.0 cm^2 or 2.0 cm^2 Donor Compartment Type: Open Top (chimney) Donor-Receptor Joint: O-Ring Joint Receptor Volume: Nominal 6 mL (1.0 cm^2) or 7 mL (2.0 cm^2) Receptor Stirring: Stir bar at nominal 600 rpm Receptor Thermal Jacket: Extended at base Receptor Sampling Volume: Complete removal of receptor volume and full replacement Tape for Skin Stripping: 3M Transpore® Dosing Amount: 5 mg/cm^2 Sampling Time Points: Pre-dose, 4, 8, 12, 24, and 48 hours post-dose
Similarity Test	Differences between treatment groups were evaluated using the Student's t-test

Analytical Method

Method Name	Luliconzaole_Skin_All_NVAL_a
Name of Compound(s)	Luliconazole
Stock Solution Matrix	Acetonitrile
Standard Curve Matrix	50:50 ACN:H_2O 50:50 EtOH: H_2O
Instrument	Agilent 1100 Series LC and LC/MS Systems Diode-array Detector Wavelength 1: 298 nm – 400 nm Wavelength 2: 202 nm – 360 nm
Solvent	Isocratic 40% Solvent A, 60% Solvent B Solvent A: 0.1% Ammonium formate in H_2O Solvent B: Acetonitrile
Column	Agilent Zorbax Eclipse XDB-C18 4.6 x 50 mm, 3.5 µ Temperature: 40.0°C
Flow Rate	0.500 mL/min
Run Time	5.00 minutes (not to exceed 2 minutes)

***Ex vivo* Skin Permeation Results**

Absorption Results

Rate of percutaneous absorption is presented as the flux of Luliconazole that appears in the reservoir solution under the skin.

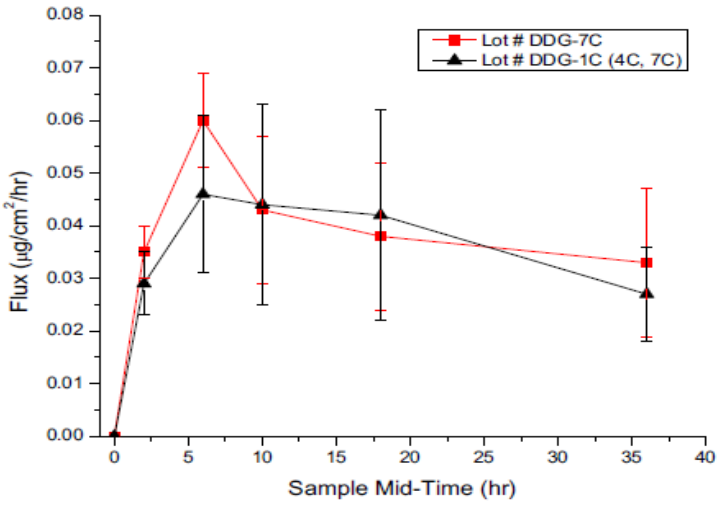
Table 1. Mean Flux (µg/cm^2/hr) Results: Across Donor Summary: Percutaneous Absorption of Luliconazole through Human, *ex vivo,* Trunk Skin over 48 hours from a Single Application (Mean ± SEM, n=3 Donors).

Time (hr)*	Luliconazole 1% Cream Lot# DDG-7C	Luliconazole 1% Cream Lot# DDG-1C (4C, 7C)
2.0	0.035 ± 0.005	0.029 ± 0.006
6.0	0.047 ± 0.010	0.046 ± 0.015
10.0	0.043 ± 0.014	0.044 ± 0.019
18.0	0.038 ± 0.014	0.042 ± 0.020
36.0	0.033 ± 0.014	0.027 ± 0.009

* Time as midpoint between samples.

Data from file:1091Luli_Med_Summary_v4.xls

Figure 1. Mean Flux (µg/cm^2/hr) Results: Percutaneous Absorption of Luliconazole through Human, *ex vivo*, Trunk Skin over 48 hours from a Single Application (Mean ± SEM, n=3 Donors).



Distribution Results

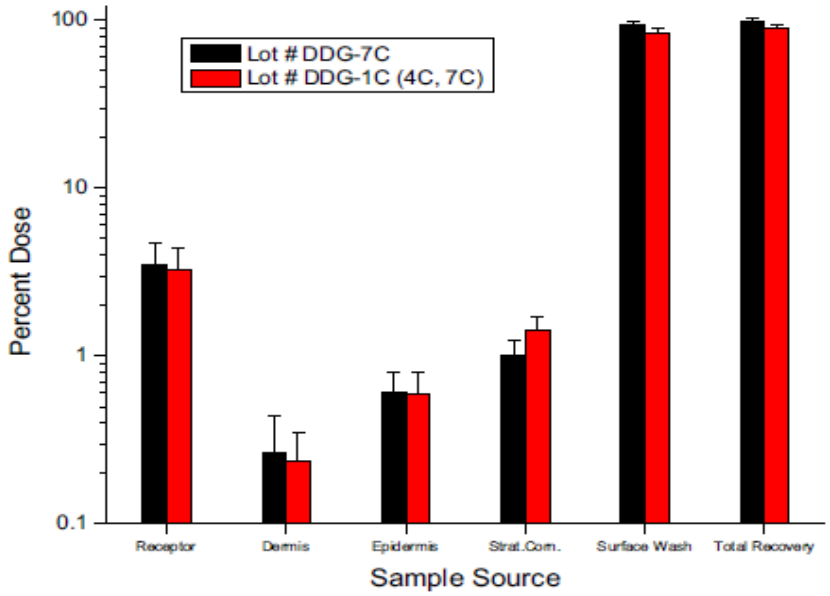
Distribution of Luliconazole is presented as mass recovered per skin section and as percent of applied dose.

Table 2. Distribution Across Skin Donors: Distribution of Luliconazole into and through, Human, *ex vivo* Trunk Skin after 48 Hours from a Single Application. Mean ± SEM (n=3 Donors) as Percent of Applied Dose and Total Mass (µg/cm^2).

Parameter	Luliconazole 1% Cream Lot# DDG-7C	Luliconazole 1% Cream Lot# DDG-1C (4C, 7C)
Total Absorption (µg/cm^2)	1.75 ± 0.62	1.64 ± 0.57
Dermis (µg/cm^2)	0.14 ± 0.09	0.12 ± 0.10
Epidermis (µg/cm^2)	0.31 ± 0.10	0.30 ± 0.10
Stratum Corneum (µg/cm^2)	0.51 ± 0.11	0.72 ± 0.16
Surface Wash (µg/cm^2)	47.18 ± 2.01	42.42 ± 3.11
Total Absorption (%)	3.46 ± 1.23	3.20 ± 1.11
Dermis (%)	0.27 ± 0.17	0.24 ± 0.11
Epidermis (%)	0.60 ± 0.19	0.59 ± 0.20
Stratum Corneum (%)	1.01 ± 0.23	1.41 ± 0.31
Surface Wash (%)	93.36 ± 3.93	82.96 ± 6.10
Total Recovery (%)	98.71 ± 5.17	88.39 ± 5.70

Data from file:1091Luli_Med_Summary_v4.xls

Figure 2. Distribution Across Skin Donors: Distribution of Luliconazole into and through Human, *ex vivo*, Trunk Skin after 48 Hours from a Single Application. Mean ± SEM, n=3 Donors as Percent Dose Recovered.



Comments on *Ex vivo* Skin Permeation:

- The absorption and distribution profiles of both Luliconazole test articles are similar. Total absorption was not significantly different between the two test articles (p=0.8456). There were no significant differences (p > 0.27) observed in the total amount of Luliconazole measured in the epidermis and dermis between the two test articles.
- The majority of the applied dose was measured on the surface of the skin after the 48 hour exposure (93.36% for sublot DDG-7C, 82.96% for sublot DDG-1C).The results from this study show that drug substance penetrated into and through human skin from both drug product samples, and both samples exhibited similar absorption and flux profiles.
- The *ex vivo* skin permeation study was not conducted to support the drug product manufacturing site change from (b) (4) to DPT. It was performed to demonstrate consistent skin permeation of luliconazole from two different test articles manufactured at DPT in two separate experiments.

Reviewer's Overall Conclusions:

- The Applicant's in vitro release test method development and validation are acceptable.
- 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.
- Per the student's t-test, there were no statistically significant differences observed between the two test articles on Luliconazole skin absorption and distribution in

human, *ex vivo*, skin. The applicant's *ex vivo* skin permeation study design and results are acceptable.

Recommendation:

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. From the Biopharmaceutics perspective, NDA 204153 for Luzu (luliconazole) Cream, 1% is recommended for approval.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KELLY M KITCHENS
07/17/2013

TAPASH K GHOSH
07/17/2013

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	204153
Submission Date	December 11, 2012
Product name, generic name of the active	Luzu (luliconazole) Cream 1%
Dosage form and strength	Cream – 1%
Route of Administration	Topical
Applicant	Medicis Pharmaceutical Corporation
Clinical Division	Division of Dermatology and Dental Products
Type of Submission	Original NDA – 505(b)(1)
Biopharmaceutics Reviewer	Kelly M. Kitchens, Ph.D.
Acting Biopharmaceutics Team Leader	Tapash Ghosh, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS **A. INITIAL** OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	**Yes**	**No**	**Comment**
1.	Does the application contain dissolution data?		X	Dissolution testing is not applicable for topical dosage forms. The application does contain **in vitro release testing (IVRT)** data. The remaining checklist parameters pertain to IVRT.
2.	Is the IVRT part of the DP specifications?		X	
3.	Does the application contain data to support the proposed IVRT acceptance criteria		X	
4.	Does the application contain the IVRT method development report?	X		Module 3.2.P.2 Pharmaceutical Development In Vitro Study 54.1493.00 – Enhancer Cell
5.	Does the application contain data on the discriminating ability of the IVRT method	X		
6.	Is there a validation package for the analytical method and IVRT methodology?	X		Module 3.2.P.2 Pharmaceutical Development Validation 69.METH.1998.02 – Enhancer Cell
7.	Does the application include a biowaiver request?		X	
8.	Does the application include an IVIVC model?		X	
9.	Is information such as BCS classification mentioned, and supportive data provided?		X	

10.	Is information on mixing the product with foods or liquids included?		X	Not applicable for topical dosage form
11.	Is there any in *vivo* BA or BE information in the submission?	X		An in vitro equivalence study was conducted to evaluate 1% solution vs. 1% cream in guinea pig plantar skin stratum corneum. This study will be evaluated by the Pharm/Tox reviewer.
12.	Does the application include in *vitro* alcohol interaction studies?		X	Not applicable for topical dosage form

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
13.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	X		
14.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.		X	Not applicable
15.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.		X	Not applicable
16.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		X	

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

BIOPHARMACEUTICS INITIAL ASSESSMENT

GENERAL SUMMARY:

Luzu (luliconazole) Cream 1% is an imidazole with antimycotic and fungicidal activity. Luzu (luliconazole) Cream 1% is proposed for the topical treatment of interdigital tinea pedis, tinea cruris and tinea corporis caused by fungal organisms such as *Trichophyton rubrum*, (b) (4) or *Epidermophyton floccosum*. The applicant conducted in vitro release testing (IVRT) to qualify a level 3 manufacturing site change from (b) (4) (b) (4) and DPT (DPT Laboratories Ltd., San Antonio, TX, USA). The applicant submitted the IVRT method development report, and the validation reports for the IVRT and HPLC analytical assay.

The Biopharmaceutics review will be focused on the evaluation and acceptability of the submitted IVRT data supporting the approval of the manufacturing site change.

Reviewer notes:

- The applicant used the confidence interval computation method per the SUPAC-SS guidance.
- The applicant evaluated the solubility of the Franz cell method for luliconazole, using a final concentration of 300 µg/ml luliconazole. Since the luliconazole solution had (b) (4) using the Franz cell apparatus, the applicant used the enhancer cell apparatus instead of the traditional Franz cell apparatus.

RECOMMENDATION:

From the ONDQA-Biopharmaceutics perspective, NDA 204153 is fileable. The ONDQA Biopharmaceutics team will further evaluate the IVRT study results.

{See appended electronic signature page}
Kelly M. Kitchens, Ph.D. — 01/25/13
Biopharmaceutics Reviewer — Date
Office of New Drug Quality Assessment

{See appended electronic signature page}
Tapash Ghosh, Ph.D. — 01/25/13
Acting Biopharmaceutics Team Leader — Date
Office of New Drug Quality Assessment

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KELLY M KITCHENS
01/31/2013

TAPASH K GHOSH
01/31/2013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**204153**	**Brand Name**	**Luzu**
OCP Division (I, II, III, IV, V)	**III**	**Generic Name**	**Luliconazole, 1%**
Medical Division	**DDDP**	**Drug Class**	**Imidazole antifungal**
OCP Reviewer	**Chinmay Shukla, Ph.D.**	**Indication(s)**	**Topical treatment of interdigital tinea pedis, tinea cruris and tinea corporis in subjects 18 years of age and older.**
OCP Team Leader	**Doanh Tran, Ph.D.**	**Dosage Form**	**Cream**
Pharmacometrics Reviewer	**NA**	**Dosing Regimen**	**Once daily for 7 days for tinea cruris and tinea corporis and once daily for 14 days for tinea pedis.**
Date of Submission	**December 11, 2012**	**Route of Administration**	**Topical**
Estimated Due Date of OCP Review	**July 26, 2013**	**Sponsor**	**Medicis Pharmaceutical Corp.**
Medical Division Due Date	**August 02, 2013**	**Priority Classification**	**Standard**
PDUFA Due Date	**December 11, 2013**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			Bioanalytical method validation and bioanalysis reports are not submitted for supporting Japanese trials 113002 and 113003
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	**X**	**1**		Trial 113002 (Single dose healthy subject Japanese trial)
multiple dose:	**X**	**3**		Trial MP-1007 (Max-use PK); Trial MP-1000-08 (TQT); Trial 113003 (Multiple dose healthy subject Japanese trial)
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				The Sponsor has applied for a deferral and has proposed to conduct pediatric trials at a later date
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**11 (USA)** **7 (Japanese)**		• **Six Phase 1** • **One Phase 2** • **Four Phase 3** **Supporting Japanese trials** • **Three Phase 1** • **Three Phase 2** • **One Phase 3**

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			The formulation used in the maximal use PK trial, TQT trial, US Phase 2 trial and the four US Phase 3 trials are to-be-marketed formulation. However, formulation used in the maximal use PK trial and the single US Phase 2 trial were manufactured in (b) (4) while the formulations used in the TQT trial and the four Phase 3 trials were manufactured in the US. The Sponsor has provided in-vitro release data comparing products manufactured in (b) (4) versus US.
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and	X			

	biopharmaceutics section of the NDA legible so that a substantive review can begin?				
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	The Sponsor has submitted a deferral to conduct pediatric trials at a later date.
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			The Sponsor has not included Drug Interactions Section in the label (Section 7). This could be added at the time of labeling.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	All reports are in English

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? __ __Yes____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.
- N.A. -

Chinmay Shukla, Ph.D.
Reviewing Clinical Pharmacologist Date

Doanh Tran, Ph.D.
Team Leader Date

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Filing Memorandum

Clinical Pharmacology Review

NDA: 204153
Compound: Luliconazole Cream, 1%
Indication: Topical treatment of tinea pedis, tinea cruris and tinea corporis in adults
Sponsor: Medicis Pharmaceutical Corp.
Date: 12/11/2012
Reviewer: Chinmay Shukla
Related IND: 076049

Background: Luliconazole is a new molecular entity and belongs to (b) (4) dazole antifungal drug class. The Sponsor has submitted this NDA via 505(b)(1) regulatory pathway and is seeking an indication of once daily topical treatment of tinea pedis, tinea cruris and tinea corporis in adult subjects 18 years of age and older. The proposed dosing duration is for 7 days for tinea cruris and tinea corporis and 14 days for tinea pedis.

Regulatory Background: Luliconazole is the R-enantiomer of the (b) (4) In Japan, the R-enantiomer luliconazole cream and solution (1% concentration) were approved on April 11, 2005 and is marketed under the trade name Lulicon® Cream, 1% and Lulicon® Solution 1%. The approved indications in Japan include:

- Tinea: Tinea pedis, tinea corporis and tinea cruris
- Candidiasis: (b) (4)
- Tinea versicolor

Pediatric Assessment: The Sponsor has requested a deferral from conducting pediatric trials. Further, the Sponsor has stated that they plan to conduct a maximal use pharmacokinetic (PK) trial in subjects 12 to 17 years with tinea pedis and tinea cruris and a safety and efficacy trial including PK is subjects 2 to 17 years with tinea corporis. The Sponsor plans to work with the Agency to determine the appropriate study designs. Deferral of pediatric trials was discussed at the Pre-NDA meeting (see Pre-NDA meeting minutes in DARRTS dated 08/07/2012 under IND 076049).

Clinical Program: Table 1 shows a tabulated list of all the clinical trials submitted to this application. The US clinical program consists of:

- Six Phase 1 trials
- One Phase 2 trial
- Three Phase 3 trials
- One long term open label Phase 3 safety trial

Additional Japanese trials include (supporting information):

- Three Phase 1 trials
- Three Phase 2 trials
- One Phase 3

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Table 1: List of all clinical trials

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Route of Administration; Dosage Regimen	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Primary US Studies								
Phase 1 PK	MP-1000-04	To determine the potential of Luliconazole Cream 1% and its vehicle to cause irritation after repeated topical application.	Randomized, evaluator-blind, positive- and negative-controlled	Luliconazole Cream 1%; Topical; Multiple dose: 0.2 grams once daily for 3 weeks	44	Healthy subjects	3 weeks	Complete; Full
Phase 1 PK	MP-1000-05	To determine the potential of Luliconazole Cream 1% and its vehicle to cause sensitization after repeated topical application.	Randomized, evaluator-blind, positive- and negative-controlled	Luliconazole Cream 1%; Topical; Multiple dose: 0.2 grams 3 times weekly for 3 weeks and once after 10-14 day rest period	238	Healthy subjects	6 to 8 weeks	Complete; Full
Phase 1 PK	MP-1000-06	To determine the potential of Luliconazole Cream 1% and its vehicle to produce phototoxic reactions in normal use.	Randomized, evaluator-blind, vehicle-controlled	Luliconazole Cream 1%; Topical; Single dose: 20 mg left on for 24 hours	33	Healthy subjects	Single dose	Complete; Full
Phase 1 PK	MP-1000-07	To determine the potential of Luliconazole Cream 1% and its vehicle to produce photoallergenic reactions in normal use.	Randomized, evaluator-blind, vehicle-controlled	Luliconazole Cream 1%; Topical; Multiple dose: 20 mg 6 times over 3 weeks and once after 9-14 day rest period	55	Healthy subjects	6 weeks	Complete; Full
Phase 1 PK	MP-1000-08	To determine the effect of Luliconazole Cream 1% on QT/QTc interval duration and electrocardiographic morphology.	Randomized, double-blind, placebo- and active-controlled	Luliconazole Cream 1%; Topical; Multiple dose: 2 or 10 grams once daily for 7 days Note: Four-way crossover	56	Healthy subjects	4 weeks	Complete; Full
Phase 1 PK	MP-1007	To assess the systemic exposure to Luliconazole Cream 1% under maximum use conditions.	Non-randomized, open-label, single treatment group	Luliconazole Cream 1%; Topical; Multiple dose: 3 grams once daily for 15 days	30	Interdigital tinea pedis or tinea cruris	15 days	Complete; Full
Phase 2 Safety Efficacy	TP-0801	To examine the optimal duration of Luliconazole Cream 1% to achieve "complete clearance" at two weeks post-treatment.	Randomized, double-blind, parallel group, vehicle-controlled	Luliconazole Cream 1%; Topical; Multiple dose: 1 gram once daily for 2 or 4 weeks	147	Interdigital tinea pedis	2 weeks or 4 weeks	Complete; Full
Phase 3 Safety Efficacy	MP-1000-01	To evaluate the safety and efficacy of Luliconazole Cream 1% compared with vehicle in treating tinea cruris.	Randomized, double-blind, parallel group, vehicle-controlled	Luliconazole Cream 1%; Topical; Multiple dose: once daily for 1 week	483	Tinea cruris	1 week	Complete; Full
Phase 3 Safety Efficacy	MP-1000-02	To evaluate the safety and efficacy of Luliconazole Cream 1% compared with vehicle in treating interdigital tinea pedis.	Randomized, double-blind, parallel group, vehicle-controlled	Luliconazole Cream 1%; Topical; Multiple dose: once daily for 2 weeks	321	Interdigital tinea pedis	2 weeks	Complete; Full
Phase 3 Safety Efficacy	MP-1000-03	To evaluate the safety and efficacy of Luliconazole Cream 1% compared with vehicle in treating interdigital tinea pedis.	Randomized, double-blind, parallel group, vehicle-controlled	Luliconazole Cream 1%; Topical; Multiple dose: once daily for 2 weeks	322	Interdigital tinea pedis	2 weeks	Complete; Full
Phase 3 Safety	MP-1005	To evaluate the long-term safety of recurrent administration of Luliconazole Cream 1%.	Non-randomized, open-label, single treatment group	Luliconazole Cream 1%; Topical; Multiple dose: once daily for 1 or 2 weeks	604*	Tinea pedis, tinea cruris or tinea corporis	1 week or 2 weeks	Complete; Full
Supportive Japanese Studies								
Phase 1 PK	113001	To investigate the safety of Luliconazole Cream 0.25%, 0.5%, and 1% on normal skin through patch test and photopatch test.	Randomized, single-blind, placebo- and active-controlled	Luliconazole Cream 0.25%, 0.5%, and 1%; Topical; Single dose: 15 mg left on for 48 hours	30	Healthy subjects	Single dose	Complete; Legacy
Phase 1 PK	113002	To investigate the safety, PK, and transdermal absorption rate through a single high dose of Luliconazole Cream 1%.	Non-randomized, open-label, parallel group	Luliconazole Cream 1%; Topical; Single dose: 5 grams left on for 24 hours or removed immediately	9	Healthy subjects	Single dose	Complete; Legacy
Phase 1 PK	113003	To investigate the safety, PK, and transdermal absorption rate through multiple high doses of Luliconazole Cream 1%.	Non-randomized, open-label, single treatment group	Luliconazole Cream 1%; Topical; Multiple dose: 5 grams once daily for 1 week	6	Healthy subjects	1 week	Complete; Legacy

Phase 2 Safety Efficacy	113011	To investigate the safety and efficacy of Luliconazole Cream 1% through comparison between standard and short-term treatment.	Randomized, double-blind, parallel-group, vehicle-controlled	Luliconazole Cream 1%; Topical; Multiple dose: once daily for 1 or 2 weeks or once daily for 2 or 4 weeks	246	Interdigital or vesicular tinea pedis or tinea corporis	1 week, 2 weeks or 4 weeks	Complete; Legacy
Phase 2 Safety Efficacy	PR2699-P2-01	To comparatively evaluate the safety and efficacy of Luliconazole Cream 0.1%, 0.5% and 1% concentrations.	Randomized, double-blind, parallel-group, uncontrolled	Luliconazole Cream 0.1%, 0.5%, and 1%; Topical; Multiple dose: once daily for 1 or 2 weeks	341	Tinea pedis, tinea cruris or tinea corporis	1 week or 2 weeks	Complete; Legacy
Phase 2 Safety Efficacy	PR2699-P2-05	To comparatively evaluate the safety and efficacy of Luliconazole Cream 1% and Liquid 1% formulations.	Randomized, open-label, parallel-group, uncontrolled	Luliconazole Cream 1 % and Luliconazole Solution 1%; Topical; Multiple dose: once daily for 2 weeks	208	Interdigital or vesicular tinea pedis	2 weeks	Complete; Legacy
Phase 3 Safety Efficacy	PR2699-P3-01	To comparatively evaluate the safety and efficacy of Luliconazole Cream 1% and Bifonazole 1 % Cream.	Randomized, single-blind, parallel group, active-controlled	Luliconazole Cream 1%; Topical; Multiple dose: once daily for 2 weeks	511	Interdigital or vesicular tinea pedis	2 weeks	Complete; Legacy

*A total of 604 subjects (153 new subjects and 451 rollover subjects from the Phase 3 studies) were enrolled, 581 of whom were included in the safety population.

Pharmacokinetic (PK) Assessment: The Sponsor has conducted PK assessment in the following trials:

US trials:

- MP-1007 (Max use PK trial in subjects with tinea pedis or tinea cruris)
- MP-1000-08 (TQT trial)

Supporting Japanese trials:

- 113002 (Single topical dose PK assessment in healthy subjects)
- 113003 (Multiple topical dose PK assessment in healthy subjects)

Maximal use PK trial: According to the Sponsor this trial was conducted in the United States in adult male or female subjects with moderate to severe tinea pedis on both feet **or** moderate to severe tinea cruris (not both indications together). Approximately 3 gram dose was administered in all the subjects once daily for 15 days in all the subjects. Plasma levels of luliconazole (native form and (b) (4) metabolite) were measured at baseline (prior drug application and at 1, 3, 6, 9, 12 and 24 hours post application on Days 1, 8 and 15. The Sponsor stated that by Day 15, luliconazole and the (b) (4) metabolite concentrations were quantifiable in most subjects with the concentrations of the metabolite close to the lower limit of quantification (LLOQ) of 0.05 ng/mL. On Day 15, the average concentration of luliconazole (Cmax) in subjects with tinea cruris appears to be about 8 fold higher than in subjects with tinea pedis.

Bioanalysis Information: Bioanalytical method validation and bioanalysis reports are submitted for the maximal use PK trial (MP-1007) and TQT trial (MP-1000-08). The bioanalytical methods for both the trials appear to be validated but stability information on internal standard Lanoconazole is not provided.

Formulation: There are 3 formulation manufacturing sites:

1. DPT, San Antonio, TX, USA
2. (b) (4) (b) (4) (b) (4)

In the US clinical program, 9 out of 11 trials used the formulation manufactured by DPT. The other 2 trials which include maximal use PK trial (MP-1007) and Phase 2 US trial (TP-0801) used formulations manufactured by (b) (4) (b) (4) The composition of the formulation from (b) (4) (b) (4) and DPT, USA are the same. The Sponsor has also stated that during the manufacturing site change from (b) (4) to US, there were minor process modifications and has classified this as a Level 3 change based on SUPAC-SS Guidance. An in-vitro release test (IVRT) to bridge the (b) (4) (b) (4) and the DPT (USA) formulations was conducted. IVRT will be reviewed by Office of New Drugs Quality Assurance (ONDQA).

Reviewer comments: *The 2 Japanese PK trials [topical single (113002) and multiple (113003) dose] in healthy subjects used formulations manufactured by (b) (4). Since these trials were not conducted under maximal use, they will not directly support the decision on this NDA. In addition to the aforementioned Japanese PK trials, the Sponsor has used the (b) (4) formulation in a Japanese Phase 1 Photopatch test (113001) and in one of the Japanese Phase 2 trials (113011).*

It should be noted that the Sponsor has not conducted any IVRT to compare formulations manufactured at DPT (US) and (b) (4)

This reviewer contacted Dr. Gary Chiang the Clinical reviewer regarding the need for information from the Japanese Phase 2 trial (113011). In the opinion of Dr. Chiang, the Japanese Phase 2 trial (113011,) would not be required to support this NDA application because information from another Japanese Phase 2 trial (PR2699-P2-01) that was conducted using formulation manufactured at (b) (4) (b) (4) would provide dosing information for tinea corporis (note – there were no Phase 3 trials conducted in adult subjects with tinea corporis). Further, according to Dr. Chiang additional safety and efficacy data will be produced in pediatric subjects with tinea pedis, tinea cruris and tinea corporis in the pediatric trials, which the Sponsor has planned to conduct later.

Hence, IVRT information between the US formulation and (b) (4) formulation will not be requested.

Recommendation: The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Human Pharmacokinetics and Bioavailability section for NDA 204153 is fileable.

Comments to be sent to the Sponsor:

1. Provide storage stability information on internal standard Lanoconazole to support the period of analysis for trials MP-1007 and MP-1000-08.

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/s/

CHINMAY SHUKLA
01/30/2013

DOANH C TRAN
01/30/2013