

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204153Orig1s000**

**MICROBIOLOGY REVIEW(S)**

**Division of Anti-Infective Products**  
**Clinical Microbiology Review**  
Dermatology and Dental Consult

**NDA#: 204,153**  
**Luliconazole, 1% Cream**  
**Tinea Pharmaceuticals, Inc.**

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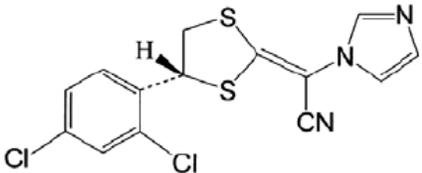
**NDA:** 204,153 (Orig: 001)  
Date Company Submitted: 12/11/2012  
Date received by CDER: 12/11/2012  
Date Assigned: 1/26/2013

**NAME AND ADDRESS OF APPLICANT:**

Tinea Pharmaceuticals, Inc.  
435 Tasso Street, Suite 325  
Palo Alto, CA 94301

Contact Person: Diane Stroehmann  
Director, Regulatory Affairs  
Phone: 480-291-5611

**DRUG PRODUCT NAMES:**

Proprietary Name:	Luzu Cream
Code Name:	NND-502; luliconazole
Established Name:	Luliconazole, 1% Cream
Chemical Name:	(-)-(E)-[(4R)-(2,4-dichlorophenyl)-1,3-dithiolan-2-ylidene](1H-imidazol-1-yl)acetonitrile
Molecular Weight:	354.28
Molecular Formula:	C <sub>14</sub> H <sub>9</sub> Cl <sub>2</sub> N <sub>3</sub> S <sub>2</sub>
Structural Formula:	

**DRUG CATEGORY**

Anti-fungal (topical)

**PROPOSED INDICATION**

Topical treatment of interdigital tinea pedis, tinea cruris and tinea corporis caused by *Trichophyton rubrum*, (b) (4) or *Epidermophyton floccosum*.

**PROPOSED DOSAGE FORM, STRENGTH AND ROUTE OF ADMINISTRATION:**

Dosage Form:	Cream
Route of Administration:	Topical
Dose Strength:	1% (10 mg/g)
Frequency:	Once daily
Duration:	7 days (tinea cruris) 14 days (tinea pedis)

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**DISPENSED**

Prescription Product

**RELATED DOCUMENTS**

IND 76,049

**REMARKS**

The applicant in this submission is seeking approval to market Luliconazole Cream 1%. The applicant has conducted four Phase 3 efficacy studies (two studies in subjects with interdigital tinea pedis, one study in subjects with tinea cruris and one long-term study in subjects with interdigital tinea pedis, tinea cruris or tinea corporis) to support the safety and efficacy of Luliconazole Cream 1% in the treatment of interdigital tinea pedis, tinea cruris and tinea corporis.

**SUMMARY AND RECOMMENDATIONS**

The Division of Dermatology and Dental Products (DDDP) requested the following consult:

**Please evaluate the clinical microbiology data proposed to support claims in the sponsor submitted draft labeling as well as any applicable study results.**

*From a clinical microbiology perspective the information provided by the Applicant supports the efficacy of luliconazole cream 1% for the treatment of *T. rubrum* and *E. floccosum* in the treatment of tinea pedis and tinea cruris.*

(b) (4)

*No susceptibility testing interpretive criteria for luliconazole are recommended.*

*See Section 6 of this review for the proposed labeling of the clinical microbiology subsection of the Luliconazole cream 1% package insert. There are several recommendations proposed that should be communicated to the sponsor.*

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**EXECUTIVE SUMMARY**

Tinea Pharmaceuticals, Inc is seeking approval to market Luliconazole cream 1% for the treatment of tinea pedis, tinea cruris and tinea corporis in subjects <sup>(b)</sup><sub>(4)</sub> years of age and older. Tinea infections are usually caused by dermatophytes such as *Trichophyton rubrum*, <sup>(b)</sup><sub>(4)</sub> and *Epidermophyton floccosum*.

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

In guinea pig models of tinea infection, dermal application of luliconazole cream 1% for either four or eight days showed decrease in infection intensity, decreased lesion scores and no growth of microorganisms. Therapeutic efficacy of luliconazole cream 1% was similar to lanoconazole cream; however, was more effective than terbinafine cream 1% or bifonazole cream 1%. The luliconazole 1% solution showed similar results to the luliconazole cream 1%.

In all three phase 3 efficacy studies, the primary endpoint was met which showed that a higher proportion of subjects in the luliconazole cream 1% arm had “complete clearance” compared to subjects in the vehicle cream group. “Complete clearance” was defined as the combination of “clinical cure” (absence of erythema, scaling and pruritus or a grade 0 for each) and “mycological cure” (negative KOH microscopic examination and dermatophyte culture). “Mycological cure” was also evaluated as a secondary endpoint, independent of “clinical cure”. The overall proportion of subjects with a “mycological cure” was significantly higher among the Luliconazole 1% cream treated subjects (58.7%) compared to vehicle treated subjects (22.4%). Most subjects were found to have *T. rubrum* as the primary fungal organism (ranging from 73.4% to 87.7%) leading to infection. This was independent of the diagnosis of interdigital tinea pedis or tinea cruris. Other dermatophytes cultured from tissue samples included *T. mentagrophytes*, *E. floccosum*, *T. tonsurans* and *Microsporum gypseum*. Luliconazole cream 1% was shown

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to be active against *T. rubrum* and *E. floccosum* in clinical trials. There was no difference in the activity of luliconazole against *T. mentagrophytes* when compared to vehicle in subjects with tinea pedis or tinea cruris. There were not enough organisms tested in the clinical trials to evaluate the activity of luliconazole against *M. gypseum* or *T. tonsurans*. No susceptibility testing interpretive criteria for luliconazole are recommended.

The following are the Agency's proposed recommendations for labeling (only the sections pertinent to Clinical Microbiology are provided below):

**12.1. Mechanism of Action**

Luzu Cream is a topical antifungal drug [See Clinical Pharmacology (12.4)]

(b) (4)

**12.4. Microbiology**

(b) (4)

**Mechanism of action**

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

**Mechanism of Resistance**

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

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

*Trichophyton rubrum*

*Epidermophyton floccosum*

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**1. INTRODUCTION**

The subject of this NDA is luliconazole, an imidazole antifungal drug for the proposed topical treatment of tinea pedis, tinea cruris and tinea corporis in subjects <sup>(b)</sup><sub>(4)</sub> years of age and older.

Tinea pedis involves fungal infection of the foot and is usually caused by dermatophytes. Dermatophytes are aerobic fungi that produce keratinase, an enzyme that breaks down keratin – a main constituent of hair, nails and the stratum corneum of the skin. Three genera are responsible for the infection – *Trichophyton*, *Epidermophyton* and *Microsporum*. The vast majority of tinea pedis cases are caused by *T. rubrum*, *E. floccosum* or *T. mentagrophytes*. Most infections are acquired directly through contact with an infected person or by self-infection by transfer from another body part (anthrophilic), animals (zoophilic) or indirectly from exposure to contaminated fomites or the soil (geophilic). The clinical manifestations of tinea pedis usually present as a pruritic, erythematous, inflamed region most often seen between the fourth and fifth toes (interdigital type) or a more severe, prolonged form that covers the bottom and lateral aspects of the foot (moccasin type) or sometimes located on the sole (vesicular type). Diagnosis of tinea pedis is usually by physical examination, in combination with laboratory evidence of the fungal organisms by direct microscopic examination with potassium hydroxide (KOH) followed by culture of the dermatophyte (*Masri-Fridling 1996, Pray 2007, Hansan 2004, Andrews 2008, Kosinski 2007, McNeely 1998*).

Tinea cruris involves fungal infection of the groin and adjacent skin. It is the second most common clinical presentation caused by dermatophytes. It affects the upper, inner thighs and sometimes extends to the groin and the pubic area. The most common organisms associated with this disease are *T. rubrum* and *E. floccosum*; less commonly *T. mentagrophytes* are involved. Tinea corporis involves fungal infection of the arms and legs, especially on glabrous skin; however it may occur on any part of the body.

**REGULATORY HISTORY**

Luliconazole cream 1% is a novel analog of the antifungal compound, “Ianoconazole”. It is an imidazole drug with a dithiolan structure which was produced by selectively synthesizing on the *R*-enantiomer of the optical isomer. The *R*-enantiomer luliconazole cream and solution (1% concentration) is approved in Japan under the trade name Lulicon® Cream 1% and Lulicon® Solution 1% for the treatment of tinea (tinea pedis, tinea corporis and tinea cruris), candidiasis <sup>(b)</sup><sub>(4)</sub> and tinea versicolor. However, luliconazole is not marketed in the United States.

**2. IN VITRO ACTIVITY**

The azole anti-fungal agents inhibit the fungal enzyme lanosterol 14 $\alpha$ -demthylase; the

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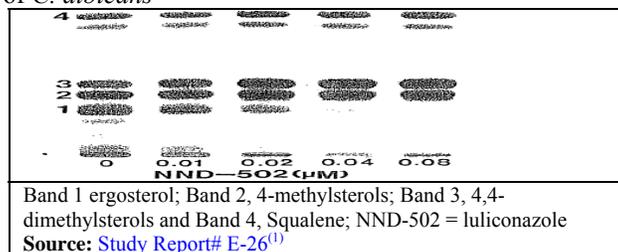
enzyme necessary to convert lanosterol to ergosterol. The depletion of the ergosterol in the fungal membrane disrupts the structure and many functions of the fungal cell membrane and buildup of ergosterol precursors resulting in increased cell permeability with leakage of cell contents and disruption of the cell wall integrity leading to inhibition of fungal growth.

Luliconazole has been shown to share many basic chemical and biological characteristics with azole class of antifungal agents. Several studies were conducted that evaluated the *in vitro* activity of luliconazole in comparison with other imidazoles. A summary of data from unpublished and published studies and from other data sources on the activity of luliconazole is provided below.

### 2.1. Mechanism(s) of action

The *in vitro* inhibitory effect of luliconazole on ergosterol biosynthesis was evaluated in cell-free extracts of *Candida albicans*. *C. albicans* IFO1270 strain was grown on pYG medium with shaking at 30°C for 15 hours. Cells were harvested by centrifugation and homogenized using glass beads. After low speed centrifugation to remove cell debris, the supernatant was centrifuged at 10,000 g for 30 minutes to separate membranes plus ribosomes from cytoplasmic components. Serial dilutions of luliconazole dissolved in dimethyl sulfoxide (DMSO) were added to 40 µL of [2-<sup>14</sup>C] mevalonate and cell free extracts of *C. albicans* IFO 1270 strain. The S-enantiomer of luliconazole, lanoconazole and bifonazole were used as comparators. The reaction mixture was incubated at 30°C for 3 hours. The reaction was stopped by the addition of the saponification reagent followed by incubation at 80°C for 30 minutes and then centrifuged. The pellet was washed and the lipid solvent extracted. The extracted lipid was dissolved in chloroform:methanol (6:1 v/v) and developed in toluene:diethyl ether (9:1 v/v). Radioactivity of each fraction was analyzed and identified using standards for ergosterol, lanosterol and squalene using a bio-imaging analyzer (FUJIX BAS-2000, Fuji Film Co., Tokyo, Japan). The results in Figure 1 showed a reduction in the radioactivity incorporated into ergosterol by addition of increasing amounts of luliconazole.

Figure 1 : Activity of luliconazole on [2-<sup>14</sup>C] mevalonate incorporation into sterols and its precursors in cell free extracts of *C. albicans*



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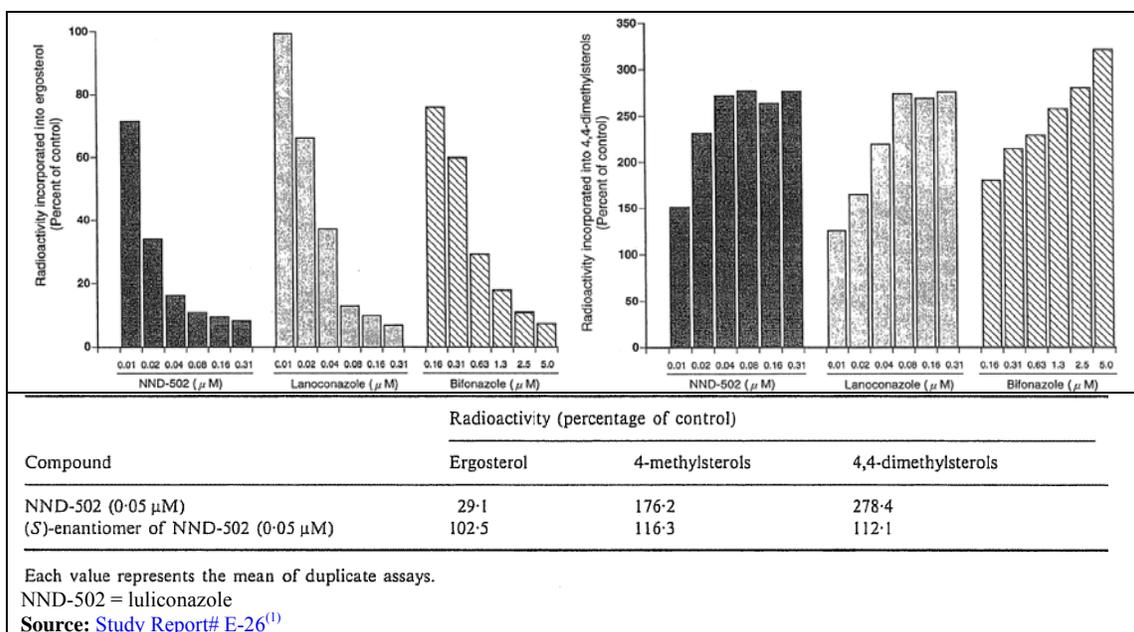
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Similar to lanoconazole and bifonazole, there was a concentration-dependent decrease in ergosterol synthesis when exposed to treatment with luliconazole (Figure 2). In contrast, the radioactivity incorporated into precursor molecules 4,4-dimethylsterol was increased. A similar concentration (0.05  $\mu\text{M}$ ) of the S-enantiomer of luliconazole exhibited almost no effect of the sterol synthesis of the three sterols. Overall, luliconazole inhibited ergosterol synthesis at concentrations lower than those of lanoconazole and bifonazole.

Figure 2: Effect of luliconazole and comparators on the incorporation of [2-<sup>14</sup>C] mevalonate into ergosterol and 4,4-dimethylsterol of cell free extracts of *C. albicans*



The inhibitory concentration (IC<sub>50</sub>) values for the inhibition of ergosterol based on the percentage of control value were calculated using a probit method. Luliconazole inhibited ergosterol synthesis in *C. albicans* with an IC<sub>50</sub> of 0.014 $\mu\text{M}$  (Table 1). The IC<sub>50</sub> of luliconazole was 2.5 lower than lanoconazole and 28 times lower than bifonazole

Table 1: Activity (IC<sub>50</sub>) of luliconazole and comparators for incorporation of [2-<sup>14</sup>C] mevalonate into ergosterol sterol synthesis in cell free extracts of *C. albicans*

Compound	IC <sub>50</sub> ( $\mu\text{M}$ )	95% fiducial limit ( $\mu\text{M}$ )
NND-502	0.014	0.0014 ~ 0.029
Lanoconazole	0.036	0.017 ~ 0.063
Bifonazole	0.39	0.32 ~ 0.47

NND-502 = luliconazole

Source: Study Report# E-26<sup>(1)</sup>

The *in vitro* inhibitory effect of luliconazole on ergosterol biosynthesis was also

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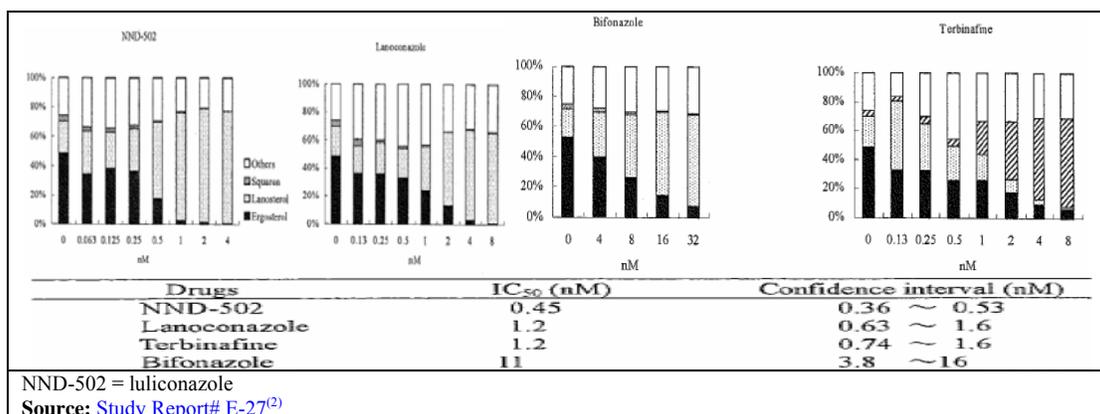
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evaluated against conidia of *T. mentagrophytes* TIMM 2789 strain. The experimental methods were similar as described previously. Briefly, serial dilutions of luliconazole dissolved in DMSO and 100  $\mu$ L of [2-<sup>14</sup>C] mevalonate were added to germinated conidial suspensions of *T. mentagrophytes* TIMM 2789 and incubated at 30°C for 3 hours. The reaction was stopped by the additions of phosphate buffer and the samples centrifuged. The pellet was washed and the lipid solvent extracted. The extracted lipid was dissolved in chloroform:methanol (6:1 v/v) and developed in toluene:diethylether (9:1 v/v). The radioactivity of each fraction was analyzed and identified using standards for ergosterol, lanosterol and squalene. The IC<sub>50</sub> values were calculated for the inhibition of ergosterol biosynthesis based on the percentage of control value. Luliconazole inhibited ergosterol synthesis in *T. mentagrophytes* with an IC<sub>50</sub> of 0.45  $\mu$ M which was lower than lanoconazole, terbinafine and bifonazole (Figure 3).

Figure 3: Effect of luliconazole and comparators on the incorporation of [2-<sup>14</sup>C] mevalonate into ergosterol and 4,4-dimethylsterol of cell free extracts of *T. mentagrophytes* TIMM 2789



#### Reviewer's comments:

Like other imidazole anti-fungal agents, luliconazole inhibits the enzyme involved in the demethylation of the 14 $\alpha$  position of lanosterol, which is necessary to convert lanosterol to ergosterol. Luliconazole inhibited ergosterol synthesis in *T. mentagrophytes* with an IC<sub>50</sub> of 0.45 nM and in *C. albicans* with an IC<sub>50</sub> of 0.014  $\mu$ M. Overall, luliconazole inhibited ergosterol synthesis at concentrations lower than those of lanoconazole and bifonazole.

#### 2.2. Antimicrobial spectrum of activity

The activity of luliconazole against common dermatophytes and fungal organisms associated with cutaneous infections was examined in various laboratories.

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**2.2.1. Dermatophytes**

The *in vitro* activity of luliconazole was evaluated against dermatophyte laboratory strains and fresh clinical isolates. Isolates were collected from (b) (4) and from hospitals geographically distributed throughout Japan. The MICs were determined using either the macrobroth or a microbroth dilution method developed by the applicant. Luliconazole were compared to lanoconazole, terbinafine and bifonazole.

**2.2.1.1. Macrobroth dilution method**

For the macrobroth dilution method, (b) (4)

Drug concentration ranges tested were 0.004 – 8 µg/mL for luliconazole, 0.004 – 8 µg/mL for lanoconazole, 0.004 – 8 µg/mL for bifonazole and 0.001 – 2 µg/mL for terbinafine. The MIC was determined as the lowest concentration which prevented visual fungal growth at 7 days after incubation at 27°C. The luliconazole MICs against 10 *T. mentagrophytes* isolates ranged from 0.0025 to 0.02 µg/mL and from 0.00063 to 0.0025 µg/mL against 10 *T. rubrum* isolates (Table 2). Overall, luliconazole showed similar activity as lanoconazole, however, the MIC values were lower than terbinafine.

Table 2: Activity of luliconazole and comparators against *T. mentagrophyte* and *T. rubrum* laboratory isolates

Strain	MIC (µg/mL)		
	NND-502	Lanoconazole	Terbinafine
<i>T. mentagrophytes</i>			
IFO 5466	0.020	0.040	0.020
IFO 5809	0.0050	0.010	0.010
IFO 5810	0.0050	0.010	0.0050
IFO 5811	0.010	0.040	0.010
IFO 5929	0.010	0.020	0.010
TIMM 1189	0.010	0.040	0.010
TIMM 1814	0.020	0.040	0.010
TIMM 1815	0.020	0.040	0.020
TIMM 1817	0.010	0.040	0.010
TIMM 2789	0.0025	0.010	0.0025
Geometric mean	0.0093	0.025	0.0093
<i>T. rubrum</i>			
IFO 5467	0.0025	0.0050	0.0050
IFO 5807	0.0025	0.010	0.0050
IFO 5808	0.0025	0.010	0.0050
IFO 6203	0.0013	0.0050	0.0025
IFO 6204	0.0025	0.010	0.0050
IFO 9185	0.0013	0.0025	0.0025
TIMM 1822	0.00063	0.0050	0.0025
TIMM 1823	0.0013	0.010	0.0025
TIMM 1824	0.0013	0.0050	0.0013
TIMM 1830	0.00063	0.0013	0.00063
Geometric mean	0.0015	0.0054	0.0027

NND-502 = Luliconazole  
 Source: Study Report#E-1<sup>(9)</sup>

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The *in vitro* activity of luliconazole and comparators were evaluated against clinical isolates of dermatophytes obtained from patients at the (b) (4). The MICs were determined by the macrobroth dilution method as described previously. All dermatophytes tested had luliconazole MICs that were  $\leq 0.008 \mu\text{g/mL}$  (Table 3). The activity of luliconazole was closely similar to that of lanoconazole and lower than bifonazole (MIC range, 0.016 – 2  $\mu\text{g/mL}$ ) and terbinafine (MIC range, 0.008 – 0.125  $\mu\text{g/mL}$ ).

Table 3: Activity of luliconazole and comparators against dermatophyte stock cultures

Species (no of strains)	MIC or MIC range ( $\mu\text{g/ml}$ )			
	Luliconazole	Lanoconazole	Bifonazole	Terbinafine
Dermatophytes				
<i>Trichophyton rubrum</i> (10)	$\leq 0.004$	$\leq 0.004$	0.031–0.25	0.008–0.016
<i>T. mentagrophytes</i> (10)	$\leq 0.004$ –0.008	$\leq 0.004$ –0.008	0.25–2	0.016–0.031
<i>T. violaceum</i> (1)	$\leq 0.004$	$\leq 0.004$	0.125	0.016
<i>T. verrucosum</i> (1)	$\leq 0.004$	$\leq 0.004$	0.125	0.016
<i>T. tonsurans</i> (1)	$\leq 0.004$	$\leq 0.004$	0.016	0.004
<i>Microsporum canis</i> (2)	$\leq 0.004$	$\leq 0.004$	0.125, 1	0.016, 0.031
<i>M. gypseum</i> (2)	$\leq 0.004$	$\leq 0.004$	0.25, 0.5	0.016, 0.031
<i>Epidermophyton floccosum</i> (2)	$\leq 0.004$	$\leq 0.004$	0.031, 0.063	0.031, 0.125

Source: Study Report# E-5<sup>(4)</sup>

**2.2.1.2. Microbroth dilution method**

For the microbroth dilution method, (b) (4)



The MICs were determined as the minimum drug concentration to lower the OD at 20% or lower than the value of the positive control. The MICs for luliconazole against 10 *T. mentagrophytes* ranged from 0.0005 to 0.002  $\mu\text{g/mL}$  and 0.0024  $\mu\text{g/mL}$  to 0.001  $\mu\text{g/mL}$  against *T. rubrum* (Table 4). Overall, the luliconazole MICs by the microbroth dilution method were 10-fold to 100-fold lower than the macrobroth dilution method against *T. mentagrophytes* and *T. rubrum*, the reasons for the differences in the MICs are unclear.

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Table 4: Activity of luliconazole and comparators against *T. mentagrophytes* and *T. rubrum*

Strains	MIC( $\mu$ g/mL)			
	NND-502	Lanconazole	Terbinafine	Bifonazole
<i>T. mentagrophytes</i>				
ATCC 18748	0.00050	0.0010	0.016	0.50
TIMM 1189	0.0020	0.0040	0.016	1.0
TIMM 1814	0.0010	0.0020	0.016	0.50
TIMM 1815	0.0010	0.0010	0.016	0.25
TIMM 1817	0.0010	0.0010	0.0040	0.25
TIMM 2789	0.0010	0.0020	0.016	>1.0
IFO 5466	0.00050	0.0010	0.0040	0.13
IFO 5809	0.0020	0.0020	0.060	>1.0
IFO 5810	0.0010	0.0020	0.030	1.0
IFO 5811	0.0010	0.0010	0.016	0.13
Geometric mean*	0.0010	0.0015	0.015	0.50
<i>T. rubrum</i>				
TIMM 1822	0.0010	0.0020	0.016	>1.0
TIMM 1824	0.00024	0.00050	0.0040	0.13
TIMM 1830	0.00024	0.0010	0.0040	0.060
IFO 5467	0.00050	0.0010	0.0080	0.25
IFO 5807	0.00050	0.0010	0.0080	0.50
IFO 5808	0.00050	0.0010	0.0080	0.50
IFO 6203	0.0010	0.0010	0.016	>1.0
IFO 6204	0.00050	0.0010	0.016	0.25
IFO 9185	0.00050	0.0010	0.0080	0.060
Geometric mean*	0.00050	0.0010	0.0086	0.31

\*MIC value of > 1  $\mu$ g/mL was estimated to be 2  $\mu$ g/mL for geometric mean calculation  
NND-502 = luliconazole  
Source: Study Report E-2<sup>(5)</sup>

The *in vitro* activity of luliconazole and comparators against clinical isolates of *T. rubrum*, *T. mentagrophytes* and *E. floccosum* obtained from patients attending the (b) (4) [redacted]. The isolates were collected from January to May 2000. The MICs were determined by the microbroth dilution method for dermatophytes as described previously. The luliconazole MICs values against *T. rubrum*, *T. mentagrophytes* and *E. floccosum* were  $\leq 0.004 \mu$ g/mL (Table 5). The MIC<sub>90</sub> of luliconazole against both *Trichophyton* spp. were the same (0.001  $\mu$ g/mL), which was 4-times lower than lanconazole (0.004  $\mu$ g/mL), 30-times lower than terbinafine (0.03  $\mu$ g/mL) and more than 1000 times lower than bifonazole (>1  $\mu$ g/mL).

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Table 5: Activity of luliconazole and comparators against 76 dermatophyte clinical isolates

Species (number of isolates tested)	Drugs	MIC (µg/ml)		
		Range	50%	90%
<i>Trichophyton rubrum</i>	(59) Luliconazole	0.00012–0.004	0.00024	0.001
	Lanconazole	0.00024–0.016	0.0005	0.004
	Terbinafine	0.002–>0.25	0.008	0.03
	Bifonazole	0.008–>1	0.03	>1
<i>T. mentagrophytes</i>	(26) Luliconazole	0.00024–0.002	0.001	0.001
	Lanconazole	0.0005–0.004	0.001	0.004
	Terbinafine	0.001–0.06	0.004	0.03
	Bifonazole	0.016–1	0.13	1
<i>Epidermophyton floccosum</i> <sup>a</sup>	(1) Luliconazole	0.001	–	–
	Lanconazole	0.001	–	–
	Terbinafine	0.004	–	–
	Bifonazole	0.13	–	–

Source: Study Report# E-4<sup>(6)</sup>

**2.2.2. Yeast and Yeast-like fungi**

The *in vitro* activity of luliconazole was evaluated against *Candida albicans*. All isolates were obtained from (b) (4). The MICs were determined using the standard microbroth dilution method in accordance with CLSI M27-A guidelines using a spectrophotometric endpoint determination. Briefly, test and comparative antifungal agents were dissolved in DMSO (100 µL) and 100 µL of the fungal inoculum was added to flat bottled 96-well microplates containing RPMI. A positive growth control well of drug-free media and a negative control well of drug-free medium without inoculation were prepared. Each drug was tested using a series of two-fold dilutions, the dilution range tested for luliconazole was not specified. Microplates were incubated at 35°C for 48 hours and were read using a spectrophotometer at an OD of 630 nm. The MICs was determined as the minimum drug concentration to lower the OD at 20% or lower than the value of the positive control. The luliconazole MICs against the *C. albicans* tested ranged from 0.063 to 0.25 µg/mL which was lower than lanconazole, fluconazole and terbinafine (Table 6).

Table 6: Activity of luliconazole and comparators against *C. albicans* isolates

Strain	MIC (µ g/mL)			
	NND-502	Lanconazole	Terbinafine	Fluconazole
IFO 0197	0.13	0.25	>32	0.25
IFO 0579	0.063	0.063	>32	0.13
IFO 1269	0.063	0.13	4.0	0.25
IFO 1270	0.25	1.0	>32	0.25
IFO 1385	0.13	0.50	>32	1.0
IFO 1386	0.13	0.25	>32	0.50
Range	0.063~	0.063~	4.0~	0.13~
	0.25	1.0	>32	1.0
Geometric mean*	0.11	0.25	40	0.32

\*: >32 (µ g/mL) was estimated to be 64 (µ g/mL) for geometric mean calculation.

NND-502 = luliconazole

Source: Study Report# E-3<sup>(7)</sup>

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The *in vitro* activity of luliconazole and comparators was evaluated against clinical isolates of *C. albicans* obtained from patients attending the (b) (4)

The isolates were collected from January to May 2000. The MICs were determined by the broth microdilution method as described previously. The MIC of luliconazole against *C. albicans* ranged from 0.03 to 0.25 µg/mL similar to that of lanoconazole (0.063 – 0.25 µg/mL) but lower than terbinafine (2 – >64 µg/mL) and bifonazole (0.5 – 4 µg/mL; Table 7).

Table 7: Activity of luliconazole and comparators against *C. albicans*

Species (number of isolates tested)	Drugs	MIC (µg/ml)		
		Range	50%	90%
<i>Candida albicans</i> <sup>a</sup> (5)	Luliconazole	0.031-0.25	-	-
	Lanoconazole	0.063-0.25	-	-
	Terbinafine	2->64	-	-
	Bifonazole	0.5-4	-	-

<sup>a</sup>MIC<sub>50</sub> and MIC<sub>90</sub> values not recorded because of the limited number of strains tested

Source: Study Report# E-4<sup>(6)</sup>

In another study, the *in vitro* activity of luliconazole and comparators were evaluated against *Candida* spp. obtained from the (b) (4)

The MICs were determined by the microbroth dilution method as described previously. Against yeast and yeast-like fungi, the luliconazole ranged from 0.125 to 4 µg/mL which were comparable to lanoconazole and more active than bifonazole and terbinafine (Table 8).

Table 8: Activity of luliconazole and comparators against yeast and yeast-like fungi

Species (no of strains)	MIC or MIC range (µg/ml)			
	Luliconazole	Lanoconazole	Bifonazole	Terbinafine
Yeastlike fungi				
<i>Candida albicans</i> (5)	0.125-0.5	0.125-0.5	4-8	>2
<i>C. tropicalis</i> (1)	4	2	>8	>2
<i>C. parapsilosis</i> (1)	4	2	>8	1
<i>C. glabrata</i> (1)	1	1	4	>2
<i>Cryptococcus neoformans</i> (2)	0.25	0.25, 1	4, 8	>2
<i>Trichosporon asahii</i> (2)	0.125, 0.25	0.125, 0.25	4, 8	>2

Source: Study Report# E-5<sup>(4)</sup>

### 2.2.3. Dematiaceous fungi

The *in vitro* activity of luliconazole and comparators were evaluated against five dematiaceous fungi obtained from patients at a university medical center (Japan). The MIC values were determined using the macrobroth dilution method. (b) (4)

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(b) (4) The final drug concentration ranges tested were 0.004 – 8 µg/mL for luliconazole, 0.004 – 8 µg/mL for lanoconazole, 0.004 – 8 µg/mL for bifonazole and 0.001 – 2 µg/mL for terbinafine. (b) (4)

The luliconazole MIC values against dematiaceous fungi ranged from ≤ 0.004 to 0.063 µg/mL, which was similar to luliconazole; however, were lower than bifonazole and terbinafine (Table 9).

Table 9: Activity of luliconazole and comparators against dematiaceous fungi

Species (no of strains)	MIC or MIC range (µg/ml)			
	Luliconazole	Lanoconazole	Bifonazole	Terbinafine
Dematiaceous fungi				
<i>Hortaea werneckii</i> (3)	≤0.004–0.008	0.008–0.016	4–8	0.125–0.25
<i>Alternaria alternata</i> (2)	0.063	0.125	4	0.25, >2

Source: Study Report# E-5<sup>(4)</sup>

#### 2.2.4. Filamentous fungi

The *in vitro* activity of luliconazole and comparators were evaluated against 12 filamentous fungi obtained from patients at a university medical center (Japan). The MIC values were determined by the microbroth dilution method using a spectrophotometric endpoint determination (OD<sub>570nm</sub>). Drug concentration ranges tested were 0.004 – 8 µg/mL for luliconazole, 0.004 – 8 µg/mL for lanoconazole, 0.004 – 8 µg/mL for bifonazole and 0.001 – 2 µg/mL for terbinafine. Microplates were incubated at 30 - 35°C and evaluated every 24 hours for up to 7 days. The MICs for luliconazole against most filamentous fungi ranged from ≤ 0.004 µg/mL to 0.125 µg/mL with the exception of zygomycetes fungi *M. circinelloides* which was not inhibited by luliconazole even at the highest concentration tested (Table 10). Overall, the luliconazole MICs against the filamentous fungi were similar to luliconazole; however, were lower than bifonazole and terbinafine.

Table 10: Activity of luliconazole and comparators against filamentous fungi

Species (no of strains)	MIC or MIC range (µg/ml)			
	Luliconazole	Lanoconazole	Bifonazole	Terbinafine
Hyaline hyphomycetes				
<i>Aspergillus fumigatus</i> (3)	≤0.004	≤0.004	1	0.125
<i>A. flavus</i> (1)	0.008	0.016	>8	0.031
<i>A. terreus</i> (1)	≤0.004	0.008	2	0.031
<i>Paecilomyces lilacinus</i> (2)	0.031	0.125	4, 8	0.125, 0.25
<i>Fusarium solani</i> (2)	0.125	0.25	>8	1, >2
<i>Scopulariopsis brevicaulis</i> (1)	≤0.004	0.008	2	0.5
Zygomycetes				
<i>Mucor circinelloides</i> (2)	>8	>8	4	0.5, >2

Source: Study Report# E-5<sup>(4)</sup>

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**2.2.3. Malassezia spp.**

The *in vitro* activity of luliconazole and comparators were evaluated against major strains of *Malassezia* spp. The isolates were obtained commercially or were clinical isolates obtained from the medical university (Japan). The MICs were determined by the agar dilution method using modified Dixon media. Briefly, test and comparator drug concentrations were dissolved in DMSO and diluted using a series of two-fold dilutions to obtain the required concentration. The final concentrations tested for luliconazole ranged from 0.0078 to 16 µg/mL, lanoconazole (range, 0.0078 to 16 µg/mL), terbinafine (range, 0.03125 to 64 µg/mL) and bifonazole (range, 0.0625 to 128 µg/mL). Plates were incubated at 30°C for 4 days. The MICs were defined as the lowest concentration of the drug tested in which showed no colony formation. There was marked difference in MIC values to the luliconazole depending on the strain (Table 11). Luliconazole was most active against *M. sympodialis* > *M. slooffiae* > *M. furfur*. Overall, the activity of luliconazole against *Malassezia* spp. was similar to lanoconazole; whereas higher MICs were observed for terbinafine and bifonazole.

Table 11: Activity of luliconazole and comparators against *Malassezia* spp. using the agar dilution method on modified Dixon agar

Organism (No. of strains)	Drug	MIC range <sup>a</sup> (mg/l)	MIC <sub>50</sub> (mg/l)	MIC <sub>90</sub> (mg/l)	Geometric mean MIC (mg/l)
<i>M. furfur</i> (25)	NND-502	0.13–8	2	4	1.357
	LCZ	0.13–8	2	4	1.320
	BFZ	1–16	8	16	5.579
	TBF	0.25–16	4	16	3.891
<i>M. sympodialis</i> (15)	NND-502	0.03–0.25	0.06	0.25	0.091
	LCZ	0.06–0.25	0.13	0.25	0.125
	BFZ	0.13–2	1	2	0.758
	TBF	0.13–0.5	0.25	0.5	0.287
<i>M. slooffiae</i> (10)	NND-502	0.5–2	1	1	1.000
	LCZ	0.5–2	1	1	0.933
	BFZ	64–128	64	64	68.593
	TBF	1–2	2	2	1.866

<sup>a</sup> MIC values were read after 4 days of incubation at 30 °C.  
 NND-502 = luliconazole; LCZ = lanoconazole; BFZ = bifonazole; TBF = terbinafine  
 Source: Study Report# E-6<sup>(8)</sup>

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**2.3. Fungicidal Activity**

The fungicidal activity of luliconazole was assessed by various methods - neutral red assay, semi-permeable membrane method and macrobroth dilution method.

**2.3.1. Neutral Red Assay**

The *in vitro* fungicidal activity of luliconazole was evaluated against ten isolates of *T. mentagrophytes* and *T. rubrum* using the neutral red method. Neutral red is a supravital dye and accumulates in the vacuoles of viable fungal cells. In this assay, germinating conidia (1 x 10<sup>6</sup> conidia/mL) were inoculated into Sabouraud dextrose broth (SDB) with luliconazole (0.00016 – 8 µg/mL), lanoconazole (0.00031 – 8 µg/mL), terbinafine (0.0013 – 8 µg/mL) or bifonazole (0.08 – 8 µg/mL) at 27°C for 7 days. The hyphae were

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collected and treated with neutral red solution (50 µg/mL in PBS) at 27°C for 1 hour. Fungal fixation and neutral dye extraction was performed and the OD<sub>540nm</sub> of the extract was measured using a spectrophotometer (Hitachi 220 A). The minimum fungicidal concentration (MCC) was determined as the minimum concentration of the test drug inhibiting the uptake of the dye into the fungal cells. The MIC were determined against select strains and defined as the minimum drug concentration in which no visual fungal growth was observed. The luliconazole MCCs ranged from 0.0025 to 0.01 µg/mL against *T. mentagrophytes* and 0.00031 to 0.01 µg/mL against *T. rubrum* (Table 12).

Luliconazole MIC values against select strains were similar or within 2-fold dilution of the MCC suggesting fungicidal activity (Table 13). Overall, luliconazole MCCs were lower than lanoconazole, terbinafine and bifonazole.

Table 12: *In vitro* fungicidal activity of luliconazole and comparators against *T. mentagrophytes* and *T. rubrum* isolates using neutral red assay.

Strain	MCC (µg/mL)			
	NND-502	Lanoconazole	Terbinafine	Bifonazole
<i>T. mentagrophytes</i>				
IFO 5466	0.010	0.020	0.020	1.3
IFO 5809	0.0050	0.010	0.020	2.6
IFO 5810	0.0025	0.0050	0.080	1.3
IFO 5811	0.010	0.020	0.080	1.3
TIMM 1189	0.0050	0.010	0.040	2.6
TIMM 1814	0.010	0.010	0.040	2.6
TIMM 1815	0.010	0.020	0.080	1.3
TIMM 1816	0.010	0.020	0.040	1.3
TIMM 1817	0.0050	0.010	0.040	0.64
TIMM 2789	0.0050	0.010	0.080	1.3
Geometric mean	0.0071	0.013	0.046	1.5
<i>T. rubrum</i>				
IFO 5467	0.010	0.020	0.020	1.3
IFO 5807	0.0050	0.0050	0.020	5.1
IFO 5808	0.0025	0.010	0.040	0.32
IFO 6203	0.0025	0.010	0.040	1.3
IFO 6204	0.0025	0.0050	0.080	1.3
IFO 9185	0.0025	0.010	0.040	2.6
TIMM 1822	0.00031	0.0025	0.040	0.64
TIMM 1823	0.0013	0.0025	0.010	0.32
TIMM 1824	0.00063	0.0025	0.020	0.32
TIMM 1830	0.00063	0.0025	0.010	0.16
Geometric mean	0.0018	0.0054	0.026	0.79

NND-502 = luliconazole

Source: Study Report# E-9<sup>(9)</sup>

Table 13: *In vitro* MIC and MCC of luliconazole and comparators against select *T. mentagrophytes* and *T. rubrum* isolates

Compounds	<i>T. mentagrophytes</i>				<i>T. rubrum</i>			
	IFO 5809		IFO 5810		IFO 6203		IFO 6204	
	MIC <sub>MCC</sub>	MIC <sub>CON</sub>	MIC <sub>MCC</sub>	MIC <sub>CON</sub>	MIC <sub>MCC</sub>	MIC <sub>CON</sub>	MIC <sub>MCC</sub>	MIC <sub>CON</sub>
NND-502	0.0050	0.0050	0.0050	0.0050	0.0025	0.0013	0.0025	0.0025
Lanoconazole	0.010	0.010	0.010	0.01	0.0050	0.0025	0.0050	0.010
Terbinafine	>0.040	0.010	>0.040	0.005	0.16	0.0025	0.080	0.0050
Bifonazole	1.3	-	1.3	-	1.3	-	0.64	-

MIC<sub>MCC</sub> : MIC was measured by the MCC-assay method.

MIC<sub>CON</sub> : MIC was measured by the conventional macro-broth dilution method<sup>2, 19)</sup>

NND-502 = luliconazole

Source: Study Report# E-9<sup>(9)</sup>

### 2.3.2. Semi-permeable membrane method

In the semi-permeable membrane method, a cellophane (20 x 20 mm) was placed on the surface of a SDA drug free plate. Briefly, conidia were inoculated onto the cellophane

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and incubated at 27°C for 24 hours. The inoculated cellophane was transferred onto SDA containing a series of two-fold dilution of luliconazole (0.02 – 1.3 µg/mL), lanconazole (0.02 – 1.3 µg/mL), terbinafine (0.02 – 0.64 µg/mL) or bifonazole (1.3 – 82 µg/mL) and further incubated at 27°C for 24 hours. The cellophane was transferred on newly prepared SDA (drug free) plated and incubated at 27°C for 14 days. The colony formation of fungal organisms that survived was observed visually. The minimum fungicidal concentration (MCC) was defined as the minimum drug concentration showing no fungal growth visually at day 14. The MCCs for luliconazole against *T. mentagrophytes* isolates ranged from 0.64 to 2.6 µg/mL and for *T. rubrum* 0.08 to 0.16 µg/mL (Table 14). Overall, luliconazole MCCs were generally lower than lanconazole and bifonazole

Table 14: Fungicidal activity of luliconazole and comparators against dermatophyte isolates using the agar dilution cellophane method.

Strains	MCC( µ g/mL)				
	NND-502	Lanconazole	Terbinafine	Bifonazole	
<i>T.mentagrophytes</i>	IFO 5809	0.64	1.3	0.16	41
	IFO 5810	0.64	1.3	0.16	41
	TIMM1189	0.64	2.6	0.32	82
	TIMM 1816	1.3	10	0.16	41
	TIMM 2789	2.6	5.1	0.16	41
Geometric mean	0.98	3.0	0.18	47	
<i>T.rubrum</i>	IFO 5467	0.080	0.64	0.16	41
	IFO 6203	0.080	0.64	0.16	41
	IFO 6204	0.080	0.32	0.16	82
	TIMM 1822	0.080	0.32	0.16	41
	TIMM 1823	0.16	1.3	0.16	20
Geometric mean	0.092	0.56	0.16	41	

NND-502 = luliconazole  
 Source: Study Report# E-10<sup>(10)</sup>

**2.3.3. Macrobroth dilution method**

For the macrobroth dilution method, conidia were inoculated to SDB containing a series of two-fold dilution of luliconazole (0.00031 – 0.064 µg/mL), lanconazole (0.00031 – 0.064 µg/mL), terbinafine (0.00031 – 0.16 µg/mL) or bifonazole (0.16 – 82 µg/mL) in the test tube and incubated at 30°C for 7 days with shaking. The test tube of inoculated broth without fungal growth observed visually was transferred into a new SDB (drug-free) media and incubated at 30°C for 7 days with shaking. The MCC was defined as the minimum drug concentration in which no fungal growth was observed at day 7. The MCCs for luliconazole against *T. mentagrophytes* ranged from 0.02 to 0.08 µg/mL and against *T. rubrum* from 0.0025 to 0.08 µg/mL (Table 15). Generally, luliconazole MCCs were lower than lanconazole and bifonazole. Overall, luliconazole MCCs by the microbroth dilution were significantly lower than the macrobroth dilution and semi-permeable membrane methods; the macrobroth dilution method was 6- to 27-fold lower than the semi-permeable membrane method.

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Table 15: Fungicidal activity of luliconazole and comparators against dermatophyte isolates using the macrobroth dilution method.

Strains		MCC( $\mu$ g/mL)			
		NND-502	Lanocanazole	Terbinafine	Bifonazole
<i>T.mentagrophytes</i>	ATCC18748	0.040	0.040	0.0050	5.1
	IFO 5809	0.040	0.080	0.0050	5.1
	IFO 5810	0.020	0.080	0.0050	2.6
	IFO 5811	0.040	0.080	0.0050	2.6
	TIMM 1189	0.040	0.16	0.0025	1.3
	TIMM 1816	0.080	0.080	0.0025	1.3
	TIMM 2789	0.020	0.020	0.0025	1.3
	Geometric mean	0.036	0.066	0.0037	2.3
<i>T.rubrum</i>	IFO 5467	0.080	0.16	0.0025	1.3
	IFO 5808	0.040	0.16	0.0025	2.6
	IFO 6203	0.040	0.16	0.0025	1.3
	IFO 6204	0.010	0.080	0.0025	0.64
	IFO 9185	0.040	0.080	0.0025	1.3
	TIMM 1822	0.0025	0.010	0.0025	0.64
	TIMM 1823	0.0050	0.020	0.0025	0.64
	TIMM 1824	0.0025	0.010	0.0025	0.64
	Geometric mean	0.014	0.052	0.0025	0.99

NND-502 = luliconazole  
 Source: Study Report# E-10<sup>(10)</sup>

**2.3.4. Electron microscope studies**

Morphological changes were assessed to examine the effect of luliconazole on the microstructure and cell wall of germinating hypha of *T. rubrum* using scanning electron microscopy (SEM) and transmission electron microscopy (TEM). Varying concentrations of luliconazole (0.004 – 80 ng/mL) were added to germinating *T. rubrum* strain IFO 6204 strain and incubated for 24 hours. In comparison, the effect of enzymes concentration (zymolase, lysozyme or chitinase) on the germinated fungi was also investigated at concentration of 1, 3 and 5 mg/mL. Cell changes were observed in a dose-dependent manner with the addition of luliconazole (Figure 4). Using SEM, swelling of the tip region of hypha was observed at 0.0049 ng/mL (1/1024 MIC), heterogenous width of hypha, multiple branched and cleavage of hypha were observed at 0.31 ng/mL (1/16 MIC), while spreading, cracking and thickening of the hypha were observed at 5ng/mL (MIC). Using TEM, detachment of the outer layer of the cell wall and high density granular structures located between the cell membrane and cell wall were observed at 0.0049 ng/mL (1/1024 MIC), ablation of the hypha and efflux of cytoplasm to the outside of the cells walls were observed at 0.31 ng/mL (1/16 MIC), and ablation, breakage of the cell membrane and swelling of the vacuoles were observed at 5 ng/mL (MIC). No clear differences were observed in the morphology of the microstructure of hyphae when pre-treated with degradation enzymes such as zymolase, lysozyme and chitinase (data not shown). Though, cleavage and swelling of hypha was observed at lower concentrations of luliconazole when added with chitinase.

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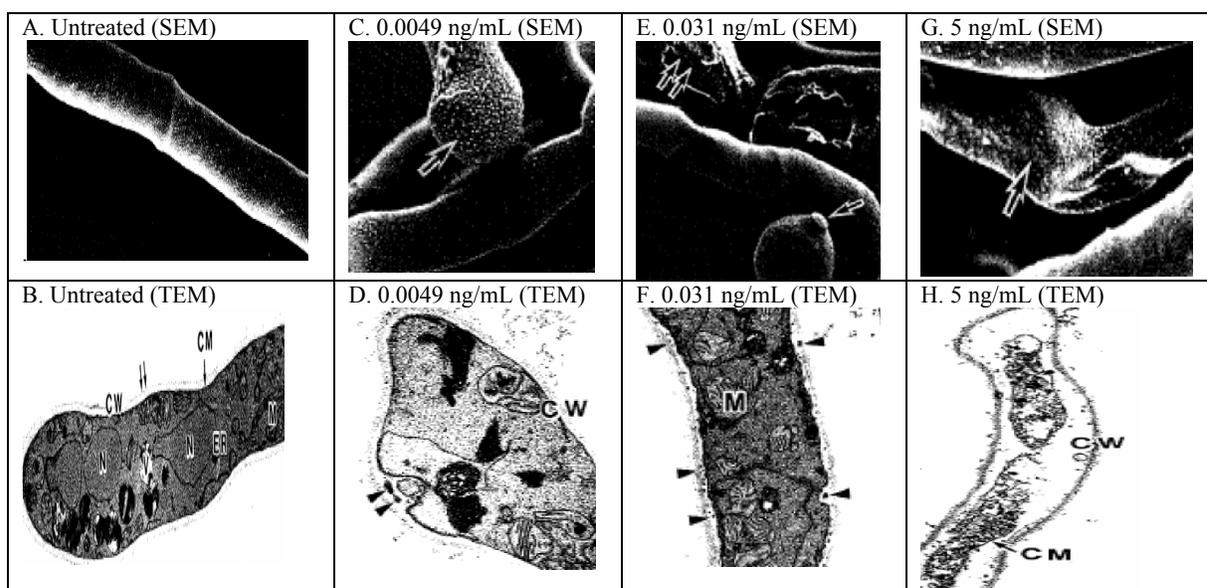
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Figure 4 : Morphological changes on the microstructure and cell wall of the germinating *T. rubrum* IFO 6204 strain after treatment with luliconazole upon examination by SEM and TEM



Top: Scanning Electron Microscopy - A. untreated germinating *T. rubrum*; C. 0.0049 ng/mL swelling tip region of hypha; E. 0.31 ng/mL heterogenous width, winding and multiple branches of hypha, cleavage of hypha at septum, G. 5ng/mL cracks, thickness and flatterting;

Bottom: Transmission Electron Microscopy- B. Untreated organelles such as nuclear (N), mitochondria (M), vacuole (V) and endoplasmic reticulum (ER) clearly observed and outer layer cell wall (CW); D. 0.0049 ng/mL no significant changes observed except outer layer of cell wall detached; F. 0.31 ng/mL cleavages of hypha and enlarged ER, more lesions of granular structures between cell membrane and cell wall; H. 5 ng/mL ghost image of dead fungal hypha with melted cytoplasm and breaking of cell membrane (CM) and swelled endoplasmic reticulum

Source: [Study Report# E-28<sup>\(11\)</sup>](#)

#### 2.4. Skin Penetration Studies

*In vitro* penetration studies to assess the effect of luliconazole and comparators on the invasion of *T. mentagrophytes* into the stratum corneum were evaluated using reconstituted human skin culture system. In this study, drug solutions (0.1%) dissolved in DMSO or the vehicle control were added to human skin culture system (TESTSKIN LSE-d) along with 50  $\mu$ L of *T. mentagrophytes* strain TIMM 2789 conidial suspension. The mixture was incubated at 37°C for 48 hours. The reconstituted skin was fixed with formalin, embedded in paraffin and sections perpendicular to the surface of the reconstituted skin were prepared. The sections were stained with Periodic acid-Schiff (PAS) stain and examined by light microscopy. The sections were assessed for germinating hyphae formation and for the invasion of *Trichophyton* into the reconstituted skin model. The results showed that in the untreated control group numerous hyphae developed from conidia were observed at the surface and inside of the corneum with some penetration extending into the basal layer (Figure 5). In the presence of luliconazole, elongation of hyphae on the surface of corneum was observed at drug

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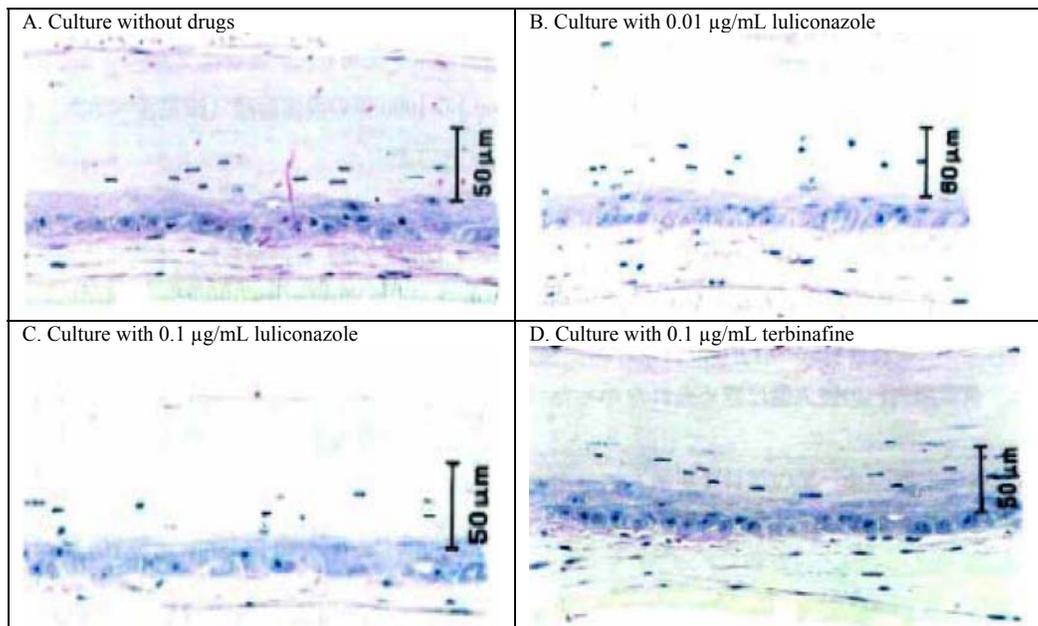
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concentrations up to 0.01  $\mu\text{g}/\text{mL}$  but invasion into the corneum was not detected. At concentrations of 0.1  $\mu\text{g}/\text{mL}$  or higher, hyphae elongation was inhibited and only conidia or short rod shaped fungi were observed on the surface of the corneum but invasion into the corneum was not detected. In comparison, skin samples cultured with 0.0001 – 0.1  $\mu\text{g}/\text{mL}$  of terbinafine were similar to the results observed in untreated control group; however, at 1  $\mu\text{g}/\text{mL}$  terbinafine, only conidia or short rod shaped fungus were observed on the surface of the corneum and invasion of the hyphae was not detected.

Figure 5: Histopathological findings in luliconazole treated and comparators after 48 hours inoculation using *in vitro* reconstituted human skin culture system (PAS stain)



Source: Study Report E-30<sup>(13)</sup>

To determine whether luliconazole affected protease production and protease activity in *Trichophyton* species, conidial solutions of *T. mentagrophytes* TIMM 2789 strain were cultured in the presence or absence of luliconazole added to a buffer solution containing keratin. The extracellular protease production of *T. mentagrophytes* was measured by measuring the protein content using a bicinchoninic acid assay. The 50% inhibition concentration was calculated determining the level of protease activity in drug-treated cells relative to controls. Luliconazole inhibited the production of protease by 27.3% at 1  $\text{ng}/\text{mL}$  and 100% at 3  $\text{ng}/\text{mL}$  (Figure 6). The  $\text{IC}_{50}$  value for luliconazole was 1.6  $\text{ng}/\text{mL}$  which was lower than lanoconazole, terbinafine and bifonazole.

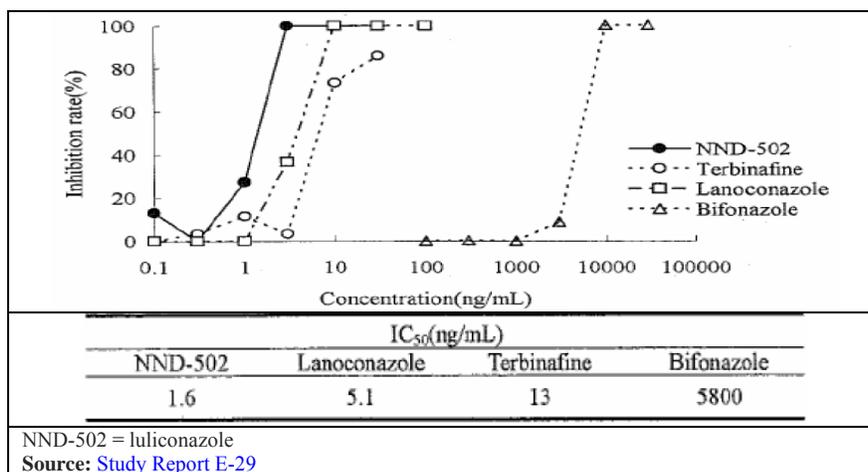
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Figure 6: Inhibitory effect and IC<sub>50</sub> values of luliconazole and comparators on extracellular protease production of *Trichophyton mentagrophytes* TIMM 2789



**2.5. Development of Resistance and Resistance Mechanisms**

No information was provided.

**2.6. Effect of medium, inoculum size, pH and serum on *in vitro* activity**

The effects of testing conditions (culture media, media pH, amount of fungi inoculated and addition of serum or urea) were evaluated on antifungal activities of luliconazole.

**2.6.1. Dermatophytes**

The effect of various testing conditions was determined using the agar dilution method against *T. mentagrophytes* IFO 5811 and *T. rubrum* IFO 6204 isolates. Conidia cells were inoculated onto Sabouraud dextrose agar (SDA) at pH 7 (no serum or urea added) using an inoculum of 1 x 10<sup>6</sup> conidia/mL and incubated at 27°C for 7 days. Plates contained a series of two fold dilutions of luliconazole, lanoconazole, or terbinafine at 0.00031 – 64 µg/mL or bifonazole at 0.005 – 82 µg/mL. The MIC was determined as the lowest concentration of the test materials which prevented visual fungal growth. To evaluate the effects of inoculum size, plates were inoculated from conidial suspensions of 1 x 10<sup>4</sup> conidia/mL, 1 x 10<sup>5</sup> conidia/mL and 1 x 10<sup>7</sup> conidia/mL. To evaluate the effect of culture medium, organisms were grown in SDA, Sabouraud dextrose broth (SDB), Bact-yeast morphology agar (YMA) and Casitone Agar (CA). To evaluate the effects of medium pH, SDA media was adjusted to a pH between 5 and 9. To evaluate the effects of serum, SDA media was supplemented with human serum (Type AB, Cosmobio) at 10% or 20% (v/v). To evaluate the effect of addition of urea, SDA media was supplemented with 1.25% to

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5% urea (Katayama Chemical). The results in Table 16 show that:

- Luliconazole MICs against *T. mentagrophytes* and *T. rubrum* isolates were not affected by using SDA, SDB or YMA media, however, luliconazole MICs were 4-fold lower in Casitone agar compared to SDA.
- The effect of pH against the dermatophytes tested showed no change in the MIC of luliconazole.
- The inoculum concentration of  $10^4$ ,  $10^5$  or  $10^7$  conidia/mL showed no change or within 2-fold change of luliconazole MICs compared to the standard inoculum ( $10^6$  conidia/mL). The greatest effect was shown at concentrations  $10^8$  conidia/mL that resulted in a 4-fold or 8-fold increase in luliconazole MICs against the *T. mentagrophytes* or *T. rubrum* isolate, respectively.
- The MICs of luliconazole increased 8-fold or greater when evaluated in the presence of 10% or 20% serum relative to standard conditions (no serum).
- The effect of 1.25% or 2.5% of urea showed no change in luliconazole MIC compared to without urea. When 5% of urea was added the luliconazole MICs decreased 4-fold.

Table 16: Effect of culture conditions on MIC values of luliconazole and comparators against *Trichophyton* species.

Factors	<i>T. mentagrophytes</i> IFO 5811				<i>T. rubrum</i> IFO 6204			
	NND-502	LCZ	TBF	BFZ	NND-502	LCZ	TBF	BFZ
Standard Conditions <sup>a</sup>	0.02	0.04	0.01	2.6	0.005	0.01	0.01	2.6
Culture Media								
SDB	0.02	0.04	0.005	1.3	0.01	0.02	0.04	2.6
YMA	0.02	0.04	0.01	5.1	0.0025	0.01	0.005	2.6
CA	0.005	0.01	0.0025	1.3	0.0013	0.005	0.0013	0.32
pH								
pH 5	0.01	0.04	0.02	2.6	0.005	0.02	0.02	2.6
pH 6	0.01	0.04	0.01	2.6	0.005	0.01	0.01	2.6
pH 8	0.01	0.04	0.01	2.6	0.005	0.02	0.01	2.6
pH 9	0.01	0.02	0.01	2.6	0.005	0.02	0.01	2.6
Inoculum size								
$10^4$	0.01	0.02	0.01	--	0.0013	0.005	0.005	1.3
$10^5$	0.02	0.04	0.01	--	0.0025	0.005	0.005	1.3
$10^7$	0.04	0.08	0.02	--	0.005	0.02	0.02	2.6
$10^8$	0.04	0.08	0.02	--	0.02	0.08	0.02	5.1
Addition of serum								
0→10%	0.32	0.64	0.04	82	0.02	0.16	0.04	82
0→20%	0.64	1.3	0.08	>82	0.02	0.16	0.04	82
Addition of urea								
0→1.25%	0.02	0.04	0.01	2.6	0.005	0.02	0.01	2.6
0→2.5%	0.02	0.02	0.01	1.3	0.005	0.02	0.01	1.3
0→5%	0.005	0.01	0.005	0.64	0.0025	0.01	0.01	0.64

NND-502=luliconazole; LCZ = Iaconazole, TBF= terbinafine; BFZ = Bifonazole; NC = No change (1/2MIC – 2MIC); SDA = Sabouraud Dextrose Agar; SDB = Sabouraud Dextrose Broth; YMA = Bact-yeast morphology agar (YMA); CA = Casitone Agar

<sup>a</sup> SDA at pH 7, an inoculum of  $1 \times 10^6$  conidia/mL, no serum or urea added, incubated at 27°C for 7 days

Source: Study Report E7<sup>(14)</sup>

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**2.6.2. Candida species**

The effect of various testing conditions was determined using the microbroth dilution method against *C. albicans* IFO 0579 strain. Yeast cells were inoculated to standard media containing a series of two-fold dilution of luliconazole, lanconazole or terbinafine at 0.00031 – 64 µg/mL or bifonazole at 0.005 – 82 µg/mL. The MICs was determined as the minimum drug concentration to lower the OD at 20% or lower (IC<sub>80</sub>) than the value of the positive control. To evaluate the effect of culture medium, organisms were grown SDA, SDB, RPMI 1640, and synthetic amino acid media fungal (SAAMF). To evaluate the effects of medium pH, CA media was adjusted to a pH between 5 and 9. To evaluate the effects of inoculum size, plates were inoculated from fungal suspensions ranging from 1 x 10<sup>3</sup> cells/mL to 1 x 10<sup>8</sup> cells/mL. To evaluate the effects of serum, CA media was supplemented with human serum (Type AB, Cosmobio) at 10% or 20% (v/v). To evaluate the effect of addition of urea, CA media was supplemented with 1.25% to 5% urea (Katayama Chemical). It is important to note that the sponsor stated that the standard conditions included Casitone Agar at pH 7, no serum or urea added, using an inoculum of 1 x 10<sup>3</sup> cells/mL and incubated at 27°C for 7 days. However, these conditions were not met, since the MICs changed as the testing conditions were experimentally changed (Table 17). The results show that:

- The MICs for test drugs were influenced by the type of media used. Luliconazole MICs with SDA and SDB were higher than other media and were 32-fold and 16-fold higher than CA (standard media). In contrast, the MICs with RPMI 1640 and SAAMF showed the lowest MICs and were 4-fold and 8-fold lower than CA.
- The effect of pH to luliconazole MIC against *C. albicans* strain showed no change at pHs that ranged from pH6 to pH8, however, were 2-fold higher or lower at pH 5 and pH9, respectively.
- Luliconazole MICs increased as the amount of fungi inoculated increased. When the inoculum concentration increased from 1 x 10<sup>3</sup> to 1 x 10<sup>8</sup> cells/mL, luliconazole MICs were increased by 256-fold or greater. Similar effects were observed for lanconazole and bifonazole. The inoculum effect on the MIC of terbinafine was unknown because MIC values with the amount equal to 1 x 10<sup>4</sup> cells/mL or higher could not be determined.
- The MICs of luliconazole increased 16-fold when evaluated in the presence of 10% or 20% serum relative to standard conditions (no serum). Lanconazole and bifonazole MICs were increase 8-fold or higher; in contrast, the effect of serum on terbinafine MICs was unknown because MIC values could not be determined.
- The luliconazole MICs decreased as the concentration of urea increased. Similar trends were observed with lanconazole and bifonazole.

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Table 17: Effect of culture conditions on MIC values of luliconazole and comparators against *C. albicans* IFO 0579 strain.

Factors	<i>C. albicans</i> IFO 0579			
	NND-502	LCZ	TBF	BFZ
Culture Media				
CA	0.5	1	32	2
SDA	16	32	64	4
SDB	8	16	32	4
RPMI 1640	0.13	0.13	>64	4
SAAMF	0.063	0.063	8	4
pH7	2	4	>64	8
pH 5	4	8	64	16
pH 6	2	4	>64	8
pH 8	2	4	>64	4
pH 9	1	2	>64	8
Inoculum size				
10 <sup>3</sup>	0.25	0.5	32	2
10 <sup>4</sup>	0.5	2	>64	4
10 <sup>5</sup>	1	4	>64	4
10 <sup>6</sup>	4	8	>64	8
10 <sup>7</sup>	16	16	>64	8
10 <sup>8</sup>	>64	>64	>64	>64
Addition of serum				
0	2	4	>64	8
10%	32	32	>64	>64
20%	32	32	>64	>64
Addition of urea				
0	2	4	>64	8
1.25%	1	2	64	8
2.5%	0.5	0.5	16	4
5%	0.25	0.5	1	2

NND-502=luliconazole; CA = Casitone agar; SDA = Sabouraud dextrose agar; SDB = Sabouraud dextrose broth; SAAMF = Synthetic amino acid media, fungal;

Source: Study Report# E8<sup>(15)</sup>

### 2.7. Susceptibility Test Methods

No interpretive criteria were provided for potential pathogens. No information was provided regarding proposed susceptibility testing and/or quality control parameters.

### 2.8. Antimicrobial interactions and fixed combination studies

The *in vitro* activity of luliconazole analogues and metabolites were evaluated against *Trichophyton* and *Candida* strains. Luliconazole two analogues (b) (4) and (b) (4) and one of its major metabolites (M-10) were tested against four strains of *T. mentagrophytes*, four strains of *T. rubrum*, six strains of *C. albicans* and five strains of *C. glabrata*. Each drug was diluted in DMSO were added to the medium at 1% and 100 µL of the medium were dispensed to each well of 96-well flat bottled microplates. After adding 100 µL of the fungal inoculum to each well, the cultures were incubated at 27°C. Cultures containing 100 µL of medium without antifungal agents and 100 µL of the fungal organism was used as positive control. Cultures containing 200 µL of medium not

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containing the fungal inoculum were used as negative control. Each experiment was conducted in duplicate. The cultures were incubated up to seven days and visual observation was made each day the second day. The endpoint of the observation was determined by the confirming red color of the positive control. Difference spectrum of optical density at 570 – 595 nm was measured using a microplate reader. The minimum inhibitory concentration was determined defined as the concentration of the antifungal agent which shows 20% or less of the value of the positive control. The MIC value against *Trichophyton* strains were 15 – 250 time higher ( (b) (4) ) and 120 – 1000 times higher ( (b) (4) ) than luliconazole; whereas the M10 metabolite were > 16 µg/mL (Table 18). The MIC value against *Candida* strains which were 4-500 times higher ( (b) (4) ) and 8 – 1000 times higher ( (b) (4) ) than luliconazole whereas the M10 metabolite was > 16 µg/mL. Overall, the antifungal activity of conformational analogues ( (b) (4) ) was extremely weaker than luliconazole and clear antifungal activity was not shown for the metabolite (M10) at the MICs tested.

Table 18: Activity of luliconazole, its analogues ( (b) (4) ) and metabolites (M10) against antifungal strains.

<i>Trichophyton mentagrophytes</i> (n=4)				
Strain	MIC(µg/mL)			
	NND-502	Z-502	S-E-502	M-10
ATCC 18748	0.0020	0.060	1.0	>16
TIMM 1189	0.0010	0.030	0.50	>16
TIMM 2789	0.0020	0.060	0.50	>16
IFO 5810	0.0020	0.060	1.0	>16
Geometric mean	0.0017	0.050	0.71	>16
<i>T. rubrum</i> (n=4)				
Strain	MIC(µg/mL)			
	NND-502	Z-502	S-E-502	M-10
TIMM 1822	0.00050	0.016	0.13	>16
TIMM 1830	0.00024	0.016	0.060	>16
IFO 5467	0.00050	0.060	0.13	>16
IFO 6204	0.00024	0.0080	0.060	>16
Geometric mean	0.00035	0.019	0.088	>16
<i>C. albicans</i> (n=5)				
Strain	MIC(µg/mL)			
	NND-502	Z-502	S-E-502	M-10
TIMM 2640	0.060	1.0	2.0	>16
IFO 0197	0.030	2.0	4.0	>16
IFO 0579	0.060	2.0	2.0	>16
IFO 0588	0.13	4.0	4.0	>16
IFO 1270	0.25	2.0	2.0	>16
IFO 1386	0.060	2.0	2.0	>16
Geometric mean	0.077	2.0	2.5	>16
<i>C. glabrata</i> (n=5)				
Strain	MIC(µg/mL)			
	NND-502	Z-502	S-E-502	M-10
TIMM 1064	0.030	4.0	4.0	>16
TIMM 1070	0.030	2.0	8.0	>16
TIMM 2831	≤ 0.0080	1.0	1.0	>16
TIMM 2882	≤ 0.0080	0.50	0.50	>16
TIMM 3171	≤ 0.0080	0.50	1.0	>16
Geometric mean	0.014 <sup>1)</sup>	1.1	1.7	>16

<sup>1)</sup>: MIC value of ≤ 0.008 was estimated to be 0.008 µg/mL for geometric mean calculation  
<sup>2)</sup>: not calculated

NND-502=luliconazole; (b) (4) = analogues of luliconazole; M-10 = metabolite of luliconazole

Source: Study Report# E-32<sup>(16)</sup>

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**Reviewer's Comments:**

*Clinical and laboratory isolates were evaluated for their susceptibility to luliconazole and other comparators. Clinical isolates were collected mostly from hospitals geographically distributed throughout Japan. There were no isolates tested that were evaluated in the United States. Guidelines for susceptibility testing of filamentous fungi have been established (CLSI M38P and M38-A); however, these methods were not employed by the applicant. For dermatophytes, the methods used in susceptibility testing were either the macrobroth or microbroth dilution methods. The applicant noted that it was difficult to determine the endpoint by visual judgment of turbidity using the macrobroth dilution method for slow-growing fungi such as dermatophytes. The microbroth dilution method was performed using a colorimetric redox indicator, Alamar Blue to determine the minimum inhibitory concentration endpoint. Luliconazole MIC values varied depending on the method and strains used, the reasons for these differences in the MICs are unclear. Using the microbroth dilution method, luliconazole MICs against *T. rubrum*, *T. mentagrophytes* and *E. floccosum* were  $\leq 0.002$   $\mu\text{g/mL}$ , which was similar to lanoconazole but lower than terbinafine or bifonazole. Luliconazole was active against dematiaceous fungi, hyaline hyphomycetes, yeast and *Malassezia* spp; however, was less effective against zygomycetes. The antifungal activity of conformational analogues (b) (4) was extremely weaker than luliconazole and clear antifungal activity was not shown for the metabolite (M10) at the MICs tested.*

*The determination of the minimum fungicidal concentrations (MCC) activity of luliconazole varied by method used, however, overall fungicidal activity was shown against *T. rubrum* and *T. mentagrophytes*. Using the microbroth dilution method, organisms were inhibited at or above 2x the MIC. Morphological changes in the germinating hyphae of *T. rubrum* were observed with luliconazole at concentrations low as 0.004 ng/mL.*

*The effects of culture conditions on the in vitro activity of luliconazole against dermatophytes were evaluated using the agar dilution method. There were no studies that evaluated the effects of culture conditions on the in vitro activity of luliconazole using the macrobroth or microbroth dilution method. The agar dilution studies showed consistent or little effect on the in vitro activity of luliconazole when testing conditions were varied (i.e., culture media, pH, inoculum size or addition of urea) against the dermatophytes tested. However, addition of serum affected the activity of luliconazole by increasing the MICs. No information was provided regarding QC parameters for susceptibility testing. No proposed interpretive criteria were provided for potential pathogens.*

*No information was provided on the development of resistance to luliconazole against dermatophytes or other fungal organisms.*

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### 3. ANIMAL MODELS OF INFECTION

The activity of luliconazole and comparators were evaluated in guinea pig models of tinea infection.

#### 3.1. Tinea pedis

For tinea pedis animal models of infection, the plantar hind feet of male Hartley guinea pigs were cleaned and the skin surface lightly abraded. Sterile adhesive bandages soaked with 0.1 mL of *T. mentagrophytes* strain TIMM2789 in physiological saline with 0.1% Tween 80 was applied to these areas under occlusive dressing for 7 days. The animals were reared for another 10 days to fully develop infection. Animals were allocated to treatment groups based on the gross signs of scaling at the infected site. Each drug (0.1 mL of solution, cream or vehicle) was applied topically to each plantar for once daily treatment for either 3, 4 or 7 days. The drugs tested were luliconazole (0.25%, 0.5% or 1%), lanoconazole 1%, terbinafine 1% or bifonazole 1% which were compared to untreated or vehicle base controls. At study termination, animals were sacrificed and the plantar skin tissue excised and cut into 20 small blocks. The blocks were incubated at 27°C for 14 days in SDA plates. Visual colony formation on the plates was assessed. A skin block yielding fungal growth was regarded as positive. The percentage of fungal positive feet for each group was calculated as a culture positive rate and compared to untreated control and vehicle base control. A tabulation of the *in vivo* studies conducted with luliconazole solution, luliconazole cream and comparators is presented in Table 19. The results showed that:

- Dermal application of the luliconazole cream 0.25%, 0.5% or 1% once daily for 3 days markedly reduced infection intensity, decreased lesion scores and growth of fungal organisms. Skin samples were culture negative in animals treated with luliconazole cream 0.5% and 1.0%. A three day application of luliconazole cream 1% was more effective than lanoconazole cream (ASTAT®), Terbinafine cream 1% (LAMISIL®) or Bifonazole cream 1% (MYOSPOR®).
- Similarly, dermal application of 0.25%, 0.5% and 1.0% of luliconazole solution of PEG300) for three to seven days markedly decreased infection intensity and growth of fungal organisms. Skin samples were fungal culture negative after 3 days of treatment with 1.0% or at seven days after treatment with 0.5%.
- The effectiveness of luliconazole solution 1% was similar to luliconazole cream in this model

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Table 19: Therapeutic effect of luliconazole and comparators in the guinea pig tinea pedis model

Model	Dosing Schedule	Mycological therapeutic effect (Culture Positive)	Reference
Luliconazole Cream	Dose study <ul style="list-style-type: none"> <li>0.25%, 0.5%, 1% for 3 days</li> <li>Comparison with existing drugs (1%)</li> </ul>	Luliconazole: 1% (0) = 0.5% (0) > 0.25% (10)  1% Concentration: Luliconazole (0)= LCZ(0) > TBF(10) > BFZ(100)	<a href="#">Study Report E-12<sup>(18)</sup></a>
	Treatment Period <ul style="list-style-type: none"> <li>2 days v. 2 days (comparator)</li> <li>2 days v. 4 days comparator</li> </ul>	1% Concentration: Luliconazole 2 days (30) > LCZ 2 days (70) > TBF 2 days (70)  1% Concentration: Luliconazole 2 days (30) > LCZ 4 days (40) > TBF 4 days (50) > BFZ 4 days (100)	<a href="#">Study Report E-13<sup>(19)</sup></a>
Luliconazole Solution	Dose study <ul style="list-style-type: none"> <li>0.25%, 0.5%, 1% for 3 days</li> <li>Comparison with existing drugs (1%)</li> </ul> Treatment period <ul style="list-style-type: none"> <li>3 days v. 3 days (comparator)</li> <li>7 days v. 7 days (comparator)</li> </ul>	Luliconazole 1% (0) > 0.5% (20) > 0.25% (70)  0.25% concentration: Luliconazole (70) > LCZ (90) = TBF (90) 0.5% concentration: Luliconazole (20) > TBF (50) > LCZ (60) 1% concentration : Luliconazole (00) > LCZ (30) = TBF (30)  3 Day Application at 0.5% Concentration: Luliconazole (30) > TBF (50) > LCZ (70) 7 Day Application at 0.5% Concentration: Luliconazole (0) > TBF (10) > LCZ (20)	<a href="#">Study Report E-11<sup>(17)</sup></a>
Luliconazole cream and solution	Dose study <ul style="list-style-type: none"> <li>1% cream or solution for 2 days</li> <li>Comparison with existing drugs (1%)</li> </ul>	Luliconazole 1% cream (10) = Luliconazole 1% solution (10)  Luliconazole 1% cream (10) = Luliconazole 1% solution (10) > LCZ (30) > TBF (100) = BFZ (100)	<a href="#">Study Report E-16<sup>(20)</sup></a>

NOTE: a>b means had "a" superior mycological therapeutic activity to "b" in infection models; a=b means that "a" had similar mycological therapeutic activity as "b" in infection models; BFZ = bifinoazole (MYOSPOR®); LCZ = lanoconazole (ASTAT®) TBF = terbinafine (LAMISIL®)

### 3.2. Tinea corporis

For tinea corporis animal models of infection, the dorsal skin areas of male Hartley guinea pigs were shaved and the upper horny layer of the skin removed with adhesive tape. Application of a single 0.05 mL inoculum of the *T. mentagrophytes* TIMM 1189 strain in physiological saline with 0.1% Tween 80 was applied to two areas (2 cm in diameter) under non-occlusive conditions. The animals were reared for 10 days to fully develop the infection. Groups of animals were allocated to treatment groups based on the gross signs of lesions at the affected sites. Each drug (0.2 mL of solution, cream or vehicle) was applied topically to each site once daily for 4, 7 or 8 consecutive days. The drugs tested were luliconazole (0.25%, 0.5% or 1%), lanoconazole 1%, terbinafine 1% or bifonazole 1% which were compared to untreated or vehicle base controls. The animals were followed for additional 5 days of observation. At study termination, animals were sacrificed and the skin sites were excised and cut into small blocks. The blocks were cultured on SDA plates at 27°C for 14 days. Visual colony formation on the plates was

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assessed. A skin block yielding fungal growth was regarded as positive. The percentage of fungal positive skin sites for each group was calculated as a culture positive rate and compared to untreated control and vehicle base control. A tabulation of the *in vivo* studies conducted with either luliconazole solution and/or cream is presented in Table 20. The results showed that:

- Dermal application of luliconazole cream 0.25%, 0.5% or 1.0% once daily for 7 days markedly reduced lesion scores and growth of fungal organisms. Skin samples were cultured negative from animals treated with luliconazole cream 1%. An eight day application of luliconazole cream 1% was comparable to lanoconazole cream 1% but more effective than terbinafine cream 1% or bifonazole cream 1%.
- The effectiveness of luliconazole solution 1% was similar to luliconazole cream 1% in this model.

Table 20: Therapeutic effect of luliconazole and comparators in the guinea pig tinea corporis model

Model	Dosing Schedule	Mycological therapeutic effect (Culture Positive)	Reference
Luliconazole Cream	Dose study • 0.25%, 0.5%, 1% for 7 days • Comparison with existing drugs (1%)	Luliconazole: 1% (10) > 0.25% (30) > 0.5% (40)  1% Concentration: Luliconazole (10) > LCZ(40) > TBF (90) > BFZ(100)	<a href="#">Study Report E-14<sup>(21)</sup></a>
	Treatment period • 4 days v. 4 days (comparator) • 8 days v. 8 days comparator	4 Days Tx : Luliconazole 1% (20) > TBF (70) > LCZ (100)  8 Day Tx: Luliconazole 1% (0)= LCZ (0) > TBF (60) > BFZ (100)	<a href="#">Study Report E-15<sup>(22)</sup></a>
Luliconazole cream and solution	Dose study • 1% cream or solution for 6 days • Comparison with existing drugs (1%)	Luliconazole 1% cream (20) > Luliconazole 1% solution (30)  Luliconazole 1% cream (20) > Luliconazole 1% solution (30) > TBF (40) > LCZ (60) > BFZ (100)	<a href="#">Study Report E-17<sup>(23)</sup></a>

NOTE: a>b means had "a" superior mycological therapeutic activity to "b" in infection models; a=b means that "a" had similar mycological therapeutic activity as "b" in infection models; BFZ = bifonazole (MYOSPOR®); LCZ = lanoconazole (ASTAT®) TBF = terbinafine (LAMISIL®)

### 3.3. Cutaneous candidiasis

For animal models of cutaneous candidiasis infections, the dorsal skin areas of male Hartley guinea pigs were shagged and a single 0.1 mL inoculum of *C. albicans* TIMM 2640 strain in Yeast Carbon base broth was applied to two areas on the skin (2 cm in diameter) under non-occlusive conditions. The animals were reared for 5 days to fully develop the infection. Animals were rendered neutropenic by administering prednisolone acetate (30 mg/kg/day s.c.) two days before inoculation, the day of inoculation and two and four days after inoculation. Each drug (0.2 mL) was topically applied to each site once daily for 3 days and animals were followed for 5 days of observation. The drugs tested were luliconazole cream (0.25%, 0.5%, or 1%), lanoconazole cream 1%, terbinafine cream 1% or bifonazole cream 1% which were compared to untreated or

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vehicle base controls. At study termination, the animals were sacrificed and the skin sites were excised, homogenized and cultured on agar plates at 37°C for 2 days. The CFU/site was calculated. A tabulation of the *in vivo* studies conducted with either luliconazole solution and/or cream is presented in Table 21. The results showed that dermal application of luliconazole cream 0.5% or 1.0% once daily for 3 days reduced number of colonies by 80 -96% relative to untreated control. Luliconazole cream 1% were superior to lanoconazole cream 1%, bifonazole cream 1% and terbinafine cream 1%.

Table 21: Therapeutic effect of luliconazole and comparators in the guinea pig cutaneous candidiasis model

Model	Dosing Schedule	Mycological therapeutic effect (Culture Positive)	Reference
Luliconazole Cream	Dose study • 0.25%, 0.5%, 1% for 3 days • Comparison with existing drugs (1%)	Luliconazole: 1% (4) > 0.25% (7) > 0.5% (20)  1% Concentration: Luliconazole (9) > LCZ(21) > TBF (42) > BFZ (67)	<a href="#">Study Report E-18<sup>(24)</sup></a>

NOTE: a>b means had "a" superior mycological therapeutic activity to "b" in infection models; a=b means that "a" had similar mycological therapeutic activity as "b" in infection models; BFZ = bifonazole (MYOSPOR®); LCZ = lanoconazole (ASTAT®) TBF = terbinafine (LAMISIL®)

**Reviewer's Comments:**

*In guinea pig models of tinea infection, dermal application of luliconazole cream 1% for either four or eight days showed decrease in infection intensity, decreased lesion scores and no growth of microorganisms. Therapeutic efficacy of luliconazole cream 1% was similar to lanoconazole cream; however, was more effective than terbinafine cream 1% or bifonazole cream 1%. The luliconazole 1% solution showed similar results to the luliconazole cream 1%.*

**4. PHARMACOKINETICS/PHARMACODYNAMICS**

**4.1. *In vitro* pharmacodynamics**

*In vitro* binding (absorption) studies of luliconazole to keratin, a key fibrous structural protein of hair, skin and nails at 25 and 100 µg/g showed that the adsorption rate of luliconazole was 94 -95% compared to 99% with terbinafine at similar concentrations. The extraction (desorption) of luliconazole from keratin was 9.3 – 9.6% or about 2.2 to 4.7 higher than terbinafine.

**4.2. *In vivo* pharmacodynamics**

In an *in vivo* study, the concentration of luliconazole in the plantar skin from guinea pigs following topical (dermal) application of luliconazole cream 1% once daily for five days was 85.6 µg/g which was 3 times higher than terbinafine cream 1%. Extraction of luliconazole from these skin areas approached 84% of the residual amounts applied which was 19% for terbinafine.

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In another study, the concentration of luliconazole in the plantar skin from guinea pigs following a single dermal application of luliconazole cream 1% was 56.4 µg/g, which was 1.6 fold higher than a similar dose of terbinafine cream 1%. At 15 days, the amount of luliconazole retained in the plantar skin decreased by 0.55 µg/g.

A single application of luliconazole 1% cream for 14 or 21 days prior to inoculation with *T. mentagrophytes* significantly reduced the infection rate and intensity in plantar skin from guinea pigs, indicating that luliconazole may be bioavailable in the stratum corneum for several weeks. The infection prevention by luliconazole cream 1% was shown to be greater than terbinafine cream 1% in a guinea pig tinea pedis model.

#### 4.3. Human pharmacodynamics

Systemic exposure to luliconazole was low as evaluated in two phase 1 studies at doses up to 10 times the proposed clinical dose. There was no accumulation, steady state was achieved and small increases in  $C_{max}$  and  $AUC_{0-24}$  were seen from Day 1 to Day 15. The maximum mean values on Day 15 for  $C_{max}$  (7.358 ng/mL) and  $AUC_{0-24}$  (121.74 ng\*hr/mL) were insignificant relative to that observed for the marketed orally administered imidazole drugs such as ketoconazole (multiple dose  $AUC$  10450 ng\*h/mL) and itraconazole (multiple dose  $C_{max}$  = 3500 ng/mL; multiple dose  $AUC$  = 39000 ng\*h/mL), representing approximately 0.21 relative to itraconazole multiple dose  $C_{max}$ .

Plasma luliconazole concentrations were approximately 10-fold higher in subjects with tinea cruris relative to those with tinea pedis, though still orders of magnitude less than those observed for the marketed, orally administered imidazole drugs such as ketoconazole.

## 5. CLINICAL TRIALS

### 5.1. Tinea pedis

The clinical development program supporting the efficacy of luliconazole cream 1% in the treatment of tinea pedis included two pivotal phase 3 studies (MP-1000-02 and MP-1000-03) and one phase 2 dose-finding study (TP-0801), conducted in men and women at least 12 years of age and older. A summary of the study designs are presented in Table 22. For the purposes of this review, efficacy analyses will be based on the results of the two pivotal Phase 3 studies (MP-1000-02 and MP-1000-03).

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Table 22: Summary of Study Designs for Tinea Pedis Infection.

Phase	Protocol No. Geographic Region	Study Design	Target Daily Dosage (Duration)	Total# of Subjects
3	MP-1000-02 12 investigational sites 11 in United States 1 in Puerto Rico	Randomized, double-blind, parallel group, vehicle-controlled.  Adult subjects at least 12 years or older with a clinical diagnosis of tinea pedis on one or both feet characterized by at least moderate erythema, moderate scaling and mild pruritus	Luliconazole cream 1% (Product 33525) applied once daily  Vehicle cream (placebo) applied once daily  14-day treatment period	321 subjects (randomized) 159 Luliconazole 162 Vehicle cream  209 subjects (MITT) 106 Luliconazole 103 Vehicle cream
3	MP-1000-03 14 investigational sites 12 in United States 2 in Central America	Randomized, double-blind, parallel group, vehicle-controlled.  Adult subjects at least 12 years or older with a clinical diagnosis of tinea pedis on one or both feet characterized by at least moderate erythema, moderate scaling and mild pruritus	Luliconazole cream 1% (Product 33525) applied once daily  Vehicle cream (placebo) applied once daily  14-day treatment period	322 subjects (randomized) 159 Luliconazole 162 Vehicle cream  214 subjects (MITT) 107 Luliconazole 107 Vehicle cream
2	TP-0801 5 investigational sites (all in U.S.)	Multi-center, randomized, double-blind, duration-ranging, parallel group study	Luliconazole cream 1% (Product 33525) Applied once daily  Vehicle cream (placebo) applied once daily  14-day or 28-day treatment	123 subjects (randomized) 50 Luliconazole (14 days) 49 Luliconazole (28 days) 24 Vehicle cream (28 days)  96 subjects (MITT) 41 Luliconazole (14 days) 35 Luliconazole (28 days) 20 Vehicle cream (28 days)

**5.1.1. Study Design**

The two studies (MP-1000-02 and MP-1000-03) were similar in design with respect to the visit schedule, subject population, length of therapy, efficacy endpoints and statistical considerations. The differences between the two studies included the fact that MP-1000-02 was conducted at different investigational sites by different investigators than MP-1000-03. Clinical sites were geographically diverse to provide a broad spectrum of demographic groups. MP-1000-02 enrolled 321 subjects from 12 different U.S sites and MP-1000-03 enrolled 322 adult subjects from 14 investigational sites including 12 sites in the U.S. and 2 in Central America.

In both studies, each subject at baseline had clinical diagnosis of interdigital tinea pedis characterized by clinical evidence of tinea infection (at least moderate erythema,

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moderate scaling and mild pruritus) based on signs and symptoms. In addition, subjects had to have a mycological diagnosis of interdigital tinea pedis by detecting fungal hyphae by microscopy (potassium hydroxide [KOH] wet mount) as well as a confirmed dermatophyte present based on culture results performed at a central mycology laboratory.

Subjects were randomized in a 1:1 allocation ratio to receive Luliconazole Cream 1% (n=159) or vehicle (n=162). All subjects received the trial drug to which they were randomized pending results of the baseline dermatophyte culture. Subjects applied a thin layer of the study drug (Luliconazole 1% cream or vehicle) once daily for 14 days to affected area plus an approximate ½ inch margin surrounding the healthy skin of the affected area. Subjects were asked to apply the study drug to all interdigital areas.

Subjects were evaluated at baseline, end of treatment and at follow-up visits (7, 14 and 28 days after end of treatment) (Figure 7). For mycological assessments, samples were taken by scraping the area of the foot with the most extensive scaling or a representative site of overall severity.

Figure 7: Study Design for Tinea pedis (MP-1000-02 and MP-1000-03)

<b>SCREENING (Day -1 to 0)</b>	<b>TREATMENT (1 through 14 days)</b>	<b>EARLY FOLLOW-UP (7 and 14 days after end-of- treatment)</b>	<b>END OF STUDY (28 days after end- of-treatment)</b>
Diagnosis of tinea pedis was established based on: <ul style="list-style-type: none"> <li>• Clinical signs and symptoms of infection (erythema, scaling and pruritus)</li> <li>• Mycological confirmation (positive KOH and culture results for dermatophytes)</li> </ul> Randomization to study drug therapy within each investigational center	Luliconazole cream 1% or vehicle cream (placebo) once daily for 14 days	Subject returned to study center for assessment of mycological and clinical response and safety	Subject returned to study center for assessment of microbiological and clinical response and safety

**5.1.2. Measures of Efficacy**

The two phase 3 clinical studies used identical measures of efficacy and at similar assessment time points. Table 23 shows the number and percentages of subjects in each population for studies MP-1000-02 and MP-1000-03. For the purposes of this review, efficacy analyses were based on the Modified Intent-to-Treat (MITT) population with missing data imputed using the Last Observation Carried Forward (LOCF). The MITT population was defined as all subjects who were randomized to study drug, dispensed medication and had positive baseline KOH and dermatophyte cultures for which the primary efficacy endpoint was available.

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Table 23: Summary of subjects with tinea pedis in study MP-1000-02 and MP-1000-03

Subject Populations	Luliconazole Cream 1%	Vehicle Cream	Total
<b>MP-1000-02</b>			
<i>Total Randomized</i>	159	162	321
Safety	152	153	305
MITT	106	103	209
Per Protocol	88	80	168
<b>MP-1000-03</b>			
<i>Total Randomized</i>	160	162	322
Safety	153	153	306
MITT	107	107	214
Per Protocol	66	60	126

MITT = subjects randomized, dispensed medication and positive baseline KOH and fungal culture results  
 PP = subset of the MITT population who had completed the EOT and three weeks post-treatment evaluations without any noteworthy study protocol violations.

The protocol specified primary efficacy endpoint was the proportion of subjects achieving “complete clearance” at day 42. “Complete clearance” was defined as the combination of a “clinical cure” (absence of the erythema, scaling and pruritus or a grade 0 for each) and “mycological cure” (negative KOH examination and dermatophyte culture). As shown in Table 24, at day 42, complete clearance of interdigital tinea pedis was experienced overall by 20.2% (43/213) of the Luliconazole 1% Cream treated subjects compared with 2.4% (5/210) in the vehicle treated arm. Similar results were noted for the secondary outcomes examining the parameters of “effective treatment”, “clinical cure” and “mycological cure”. The overall proportion of subjects with a mycological cure (defined as negative KOH and dermatophyte culture) was significantly higher among the Luliconazole 1% cream treated subjects (58.7%) compared to vehicle treated subjects (22.4%).

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Table 24: Complete Clearance, effective treatment, mycological cure and clinical cure for interdigital type tinea pedis (MITT population)

Assessments	Luliconazole Cream 1% [n/N (%)]	Vehicle Cream [n/N (%)]	P-value <sup>a</sup>
<b>MP-1000-02</b>			
Complete Clearance at Day 42* <sup>b</sup>	28/106 (26.4)	2/103 (1.9)	<0.001
Effective Treatment at Day 42 <sup>c</sup>	50/106 (47.2)	10/103 (9.7)	<0.001
Clinical Cure at Day 42 <sup>d</sup>	31/106 (29.3)	8/103 (7.8)	<0.001
Mycological Cure at Day 42 <sup>d</sup>	65/106 (61.3)	18/103 (17.5)	<0.001
Complete Clearance at Day 28	15/106 (14.1)	2/103 (1.9)	0.001
<b>MP-1000-03</b>			
Complete Clearance at Day 42* <sup>e</sup>	15/107 (14.0)	3/107 (2.8)	0.002
Effective Treatment at Day 42	35/107 (32.7)	16/107 (14.9)	0.002
Clinical Cure at Day 42	16/107 (15.0)	4/107 (3.7)	<0.001
Mycological Cure at Day 42	60/107 (56.1)	29/107 (27.1)	<0.001
Complete Clearance at Day 28	10/107 (9.3)	4/107 (3.7)	0.001

\*Primary Efficacy Outcome interdigital type tinea pedis at Day 42

<sup>a</sup>P-value for difference between treatment groups from a CMH general association

<sup>b</sup>Complete clearance = erythema, scaling and pruritus grades of 0 in addition negative KOH and negative fungal culture

<sup>c</sup>Clinical cure = Severity scores of 0 (none) for erythema, scaling and pruritus

<sup>d</sup>Mycological cure = negative KOH and negative fungal culture

<sup>e</sup>Effective treatment = Negative KOH and fungal culture and severity scores of 0 (none) and 1 (mild) for erythema and scaling and 0 (none) for pruritus

Note: Last observation carried forward (LOCF) was used to impute missing data prior to analysis

## 5.2. Tinea cruris

The clinical development program supporting the efficacy and safety of Luliconazole cream 1% in the treatment of tinea cruris included one phase 3 study (MP-1000-01) in male and female subjects at least 12 years or older. Study MP-1000-01 was a multi-center, randomized, double-blind, parallel group, vehicle-controlled study conducted at 27 investigational sites (Table 25).

Table 25: Summary of Study Design for Tinea cruris infection.

Phase	Protocol No. Geographic Region	Study Design	Target Daily Dosage (Duration)	Total# of Subjects
3	MP-1000-01  27 investigational sites 23 in U.S. 1 in Puerto Rico 3 in Central America	Multi-center, randomized, double- blind, parallel group, vehicle-controlled study	Luliconazole cream 1% (Produce 33525) Applied once daily  Vehicle cream (placebo) applied once daily  7-day treatment	480 subjects (randomized) 318 Luliconazole 162 Vehicle cream  371 subjects (MITT) 165 Luliconazole 106 Vehicle cream

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**5.2.1. Study Design**

The study for tinea cruris (MP-1000-01) was similar in design to tinea pedis studies (MP-1000-02 and MP-1000-03). Eligible subjects were patients with clinical diagnosis of tinea cruris characterized by clinical evidence of tinea infection (at least moderate erythema, mild scaling and mild pruritis) based on signs and symptoms. In addition, subjects had to have detected fungal hyphae by microscopy based on a positive KOH result followed by confirmed dermatophyte present based on culture result performed at a central mycology laboratory. Subjects who subsequently showed a negative baseline culture for a dermatophyte at the central mycology laboratory were categorized as “delayed exclusions” and were excluded from the efficacy analyses.

Subjects were randomized in a 2:1 allocation ratio to receive Luliconazole Cream 1% (n=146) or vehicle placebo (n=73). All subjects applied study medication to affected areas (groin, thighs and abdomen) once daily for 7 days and approximately 2.5 cm (1 inch) of surrounding clinically healthy skin. Subjects were evaluated at baseline, end of treatment and at follow-up visits (7, 14 and 28 days after end of treatment; Figure 8).

Figure 8: Study Design for Tinea cruris (MP-1000-01)

<b>SCREENING (Day -1 to 0)</b>	<b>TREATMENT (1 through 7 days)</b>	<b>EARLY FOLLOW-UP (7 days after end- of-treatment)</b>	<b>END OF STUDY (14 days after end- of-treatment)</b>
Diagnosis of tinea cruris was established based on: <ul style="list-style-type: none"> <li>• Clinical signs and symptoms of infection (erythema, scaling and pruritus)</li> <li>• Mycological confirmation (positive KOH and culture results for dermatophytes)</li> </ul> Randomization to study drug therapy within each investigational center	Luliconazole cream 1% or vehicle cream (placebo) once daily for 7 days	Subject returned to study center for assessment of mycological and clinical response and safety	Subject returned to study center for assessment of microbiological and clinical response and safety

**5.2.3. Measures of Efficacy**

The primary efficacy analysis was based on the MITT population with missing data imputed using the LOCF method (Table 26). A total of 256 subjects included in the MITT population were randomized Luliconazole Cream 1% (n=165) or vehicle Cream group (n=91). All eligible subjects had positive baseline fungal cultures.

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Table 26: Summary of subjects with tinea cruris in study MP-1000-01

Subject Populations	Luliconazole Cream 1%	Vehicle Cream	Total
<b>MP-1000-02</b>			
<i>Total Randomized</i>	318	165	483
Safety	311	160	471
MITT	165	91	256
Per Protocol	134	68	201

MITT = subjects randomized, dispensed medication and positive baseline KOH and fungal culture results  
 PP = subset of the MITT population who had completed the EOT and three weeks post-treatment evaluations without any noteworthy study protocol violations.

For tinea cruris, the primary endpoint was defined the same as for tinea pedis but was evaluated at a different time point on day 28. As shown in Table 27, 17.6% (29/165) of the subjects in the Luliconazole cream 1% group achieved “complete clearance” compared to 4.4% (4/91) of the subjects in the vehicle cream group. All secondary endpoint analyses showed statistical significance examining the parameters for “effective treatment”, “clinical cure” and “mycological cure” at Day 28. The differences based on “effective treatment” at Day 21 and Day 14 were also statistically significant. Though a greater proportion of subjects in the Luliconazole Cream 1% group achieved “effective treatment” compared to subjects in the vehicle cream at Day 7; however, the difference was not statistically significant.

Table 27: Complete Clearance, effective treatment, mycological cure and clinical cure for tinea cruris (MITT population)

Assessments	Luliconazole Cream 1% [n/N (%)]	Vehicle Cream [n/N (%)]	P-value <sup>a</sup>
<b>MP-1000-01</b>			
Complete Clearance at Day 28 <sup>*b</sup>	29/165 (17.6)	4/91 (4.4)	0.001
Effective Treatment at Day 28 <sup>c</sup>	62/165 (37.6)	15/91 (16.5)	0.0003
Clinical Cure at Day 28 <sup>d</sup>	40/165 (24.2)	6/91 (6.6)	0.0003
Mycological Cure at Day 28 <sup>d</sup>	111/165 (67.3)	34/91 (37.4)	<0.0001
Effective Treatment at Day 21	56/165 (33.9)	9/91 (9.9)	<0.0001
Effective Treatment at Day 14	41/165 (24.9)	9/91 (9.9)	0.003
Effective Treatment at Day 7	23/165 (13.9)	4/91 (4.4)	0.01

<sup>\*</sup>Primary Efficacy Outcome interdigital type tinea pedis at Day 28

<sup>a</sup>P-value for difference between treatment groups from a CMH general association

<sup>b</sup>Complete clearance = erythema, scaling and pruritus grades of 0 in addition negative KOH and negative fungal culture

<sup>c</sup>Clinical cure = Severity scores of 0 (none) for erythema, scaling and pruritis

<sup>d</sup>Mycological cure = negative KOH and negative fungal culture

<sup>e</sup>Effective treatment = Negative KOH and fungal culture and severity scores of 0 (none) and 1 (mild) for erythema and scaling and 0 (none) for pruritis

Note: Last observation carried forward (LOCF) was used to impute missing data prior to analysis

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**5.3. Microbiological Response**

**5.3.1. Mycological Response by Infection Type**

The mycological response by patient at the Test-of-Cure are summarized in Table 28 for the MITT population as well as listed by KOH microscopic analysis and fungal culture results. The overall “mycological cure” were similar across treatment groups by infection type (Table 28). The mycological cure in the luliconazole cream 1% treated subjects with tinea cruris were 67.3%, and in the two studies that evaluated subjects with tinea pedis were 61.3% and 56.1%, respectively. It is important to note that a negative mycological response was less likely observed at the investigation sites (KOH results) compared with that observed at the central laboratory (fungal culture results). These differences may be due to the fact that investigators were not asked to assess the viability of the fungal organisms when performing KOH analysis. As such “mycological cure” (negative KOH and negative culture) is a very conservative analysis and may not reflect the activity of the drug observed.

Table 28: Mycological Response at End of Study by Infection Type (MITT)

Infection Type	By-patient Mycological Response	Luliconazole Cream 1%	Vehicle Cream
Tinea cruris (MP-1000-01)	N	165	91
	Mycological Cure	111 (67.3)	34 (37.4)
	KOH Negative	139 (84.2)	50 (55.0)
	Culture Negative	147 (89.1)	57 (62.6)
Tinea pedis (MP-1000-02)	N	106	103
	Mycological Cure	65 (61.3)	18 (17.5)
	KOH Negative	67 (63.2)	33 (32.0)
	Culture Negative	94 (88.7)	41 (39.8)
Tinea pedis (MP-1000-03)	N	107	107
	Mycological Cure	60 (56.1)	29 (27.1)
	KOH Negative	64 (59.8)	46 (43.0)
	Culture Negative	95 (88.8)	51 (47.7)

**5.3.2. Mycological response by pathogen**

Table 29 shows the mycological response rate by skin pathogens isolated in the evaluable population. The incidence of the fungal organisms was similar between the Luliconazole Cream 1% and Vehicle Cream groups. The most prevalent dermatophyte isolated at baseline was *T. rubrum* (78.9%). For Luliconazole Cream 1% treated subjects, the combined mycological cure rate against *T. rubrum* were 61.4% and 79.3% against *E. floccosum*. The overall mycological cure rate was variable in subjects with *T. mentagrophytes* as well with polymicrobial infections, though the number of subjects with these types of infections was small.

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Dermatology and Dental Consult

**NDA#: 204,153**  
**Luliconazole, 1% Cream**  
**Tinea Pharmaceuticals, Inc.**

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Table 29: Mycological Cure at Test-of-Cure by Baseline Pathogen (MITT Population)

Baseline Pathogen	Mycological Cure at Test-of-Cure	
	Luliconazole Cream 1% [n/N1 (%)]	Vehicle Cream [n/N1 (%)]
<b>Tinea pedis</b>		
<i>T. rubrum</i>	101/172 (58.7)	34/171 (19.9)
<i>T. mentagrophytes</i>	17/27 (63.0)	10/17 (58.8)
<i>E. floccosum</i>	5/9 (55.6)	2/15 (13.3)
<i>T. mentagrophytes</i> and <i>E. floccosum</i>	4/4 (100)	2/2 (100)
<i>T. rubrum</i> and <i>E. floccosum</i>	2/4 (50)	1/5 (20)
Other <sup>1</sup>	0/1 (0)	0/0 (0)
<b>Tinea cruris</b>		
<i>T. rubrum</i>	82/126 (65.1)	19/65 (29.2)
<i>T. mentagrophytes</i>	7/14 (50.0)	7/11 (63.6)
<i>E. floccosum</i>	18/20 (90.0)	6/12 (50.0)
<i>T. mentagrophytes</i> and <i>E. floccosum</i>	4/4 (100)	2/2 (100)
Other <sup>1</sup>	0/1 (0)	0/1 (0)
<b>Combined Indications</b>		
<i>T. rubrum</i>	183/298 (61.4)	53/236 (22.5)
<i>T. mentagrophytes</i>	24/41 (58.5)	17/28 (60.7)
<i>E. floccosum</i>	23/29 (79.3)	8/27 (29.6)
<i>T. mentagrophytes</i> and <i>E. floccosum</i>	4/4 (100)	2/2 (100)
<i>T. rubrum</i> and <i>E. floccosum</i>	2/4 (50)	1/5 (20)
Other <sup>1</sup>	0/2 (0)	0/1 (0)

Note: Test-of-Cure = for tinea cruris subjects were evaluated at Day 28 and for tinea pedis subjects were evaluated at Day 42; n = number of patients with mycological cure of the specified pathogen at Test-of-Cure; N1= number of patients with specified pathogen at baseline; Percentages were calculated as (n/N1) x 100

<sup>1</sup>Other = *Microsporum gypseum* in the Luliconazole Cream 1% group (one subject) and *Trichophyton tonsurans* in the Vehicle Cream group (one subject).

### 5.3.3. Antimicrobial Susceptibility

Antimicrobial susceptibility testing was performed before initiation of study drug and were repeated during the duration of therapy and again at the conclusion of therapy in patients in which isolates were cultured. Susceptibility testing was performed in accordance with the CLSI guidelines M38-A2 against clinical isolates obtained from subjects enrolled in the three phase 3 studies. Briefly, testing parameters included testing in RPMI-1640 media with L-glutamine and without bicarbonate, buffered with MOPS, an inoculum size of a  $1 - 5 \times 10^3$  and incubated at 35°C for 4 days. Final drug concentration ranges were 0.001 – 0.5 µg/mL for luliconazole, 0.003 – 16 µg/mL for itraconazole and 0.004 – 2 µg/mL for terbinafine. The minimum inhibitory concentration (MIC) was

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defined as the lowest concentration that resulted in 80% reduction in fungal growth as compared to drug-free control wells. The MICs were determined on day 4. Quality control was monitored by including *T. mentagrophytes* ATCC MYA-4439 on each day of testing. The luliconazole MIC values were  $\leq 0.001$   $\mu\text{g/mL}$  against all clinical isolates, similar to the data observed in the surveillance studies (Table 30). Overall, luliconazole MICs were 4 – 12 fold lower than itraconazole and terbinafine. There was no correlation of MIC and clinical and microbiological response. There was no increase in MICs in pre-treatment and post-treatment pairs from either of the trials.

Table 30: Activity of luliconazole and comparators against dermatophytes isolated in subjects enrolled in clinical trials

	Luliconazole			Terbinafine			Itraconazole		
	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	MIC <sub>50</sub>	MIC <sub>90</sub>	Range
<b>Tinea cruris (MP-1000-01)</b>									
<i>E. floccosum</i> (n=48)	0.001	0.001	0.001	0.03	0.03	0.004 – 0.06	0.03	0.06	0.03 – 0.5
<i>M. gypseum</i> (n=3)	--	--	0.001	--	--	0.03	--	--	0.125
<i>T. mentagrophytes</i> (n=42)	0.001	0.001	0.001	0.015	0.015	0.004 – 0.003	0.03	0.03	0.03 – 0.125
<i>T. rubrum</i> (n=338)	0.001	0.001	0.001	0.015	0.03	0.004 – 2	0.03	0.06	0.03 – 0.5
<i>T. tonsurans</i> (n=2)	--	--	0.001	--	--	0.008 – 0.015	--	--	0.03 – 0.06
<i>T. mentagrophytes</i> MYA-4439			0.001			0.008	--	--	0.06 – 0.25
<b>Tinea pedis (MP-1000-02)</b>									
<i>E. floccosum</i> (n=23)	0.001	0.001	0.001	0.015	0.03	0.008 – 2	0.03	0.03	0.03 – 0.25
<i>M. gypseum</i> (n=1)	--	--	0.001	--	--	0.03	--	--	0.125
<i>T. mentagrophytes</i> (n=18)	0.001	0.001	0.001	0.015	0.015	0.008 – 0.015	0.03	0.125	0.03 – 0.125
<i>T. rubrum</i> (n=331)	0.001	0.001	0.001	0.015	0.03	0.004 – 0.125	0.03	0.06	0.03 – 0.125
<i>T. mentagrophytes</i> MYA-4439			0.001			0.008	--	--	0.125 – 0.25
<b>Tinea pedis (MP-1000-03)</b>									
<i>E. floccosum</i> (n=28)	0.001	0.001	0.001	0.004	0.015	0.004 – 0.03	0.03	0.03	0.03 – 0.06
<i>M. gypseum</i> (n=2)	--	--	0.001	--	--	0.004	--	--	0.03
<i>T. mentagrophytes</i> (n=47)	0.001	0.001	0.001	0.004	0.008	0.004 – 0.015	0.03	0.03	0.03 – 0.25
<i>T. rubrum</i> (n=304)	0.001	0.001	0.001	0.008	0.015	0.004 – 0.25	0.03	0.06	0.03 – 0.5
<i>T. mentagrophytes</i> MYA-4439			0.001			0.008	--	--	0.125 – 0.25

**Reviewer's Comments:**

The applicant has conducted three pivotal phase 3 double-blind, placebo-controlled clinical studies to determine the efficacy and safety of luliconazole cream 1% for the treatment of tinea pedis and tinea cruris in subjects <sup>(b)</sup><sub>(4)</sub> years of age and older. In all three phase 3 efficacy studies, the primary endpoint was met which showed that a higher proportion of subjects in the luliconazole cream 1% arm had “complete clearance” compared to subjects in the vehicle cream group. Similar results were noted for the secondary outcomes examining the parameters of “effective treatment”, “clinical cure” and “mycological cure”. Mycological cure was defined as negative KOH result and fungal culture.

Luliconazole cream 1% was shown to be active against *T. rubrum* and *E. floccosum* in

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*clinical trials.*

(b) (4)

*No susceptibility testing interpretive criteria for luliconazole are recommended.*

**6. LABELING**

The applicant has provided the proposed labeling (only the microbiology subsection of the labeling is discussed below).

**6.1. Applicant's Proposed Labeling**

The labeling in the submission dated 12/11/2012 is as follows:

(b) (4)

***Reviewer's Comments:***

*The following changes to the proposed label are recommended:*

- The labeling should be consistent with the standard format for the Section 12.1 Mechanism of Action and Section 12.4 Microbiology section of the labeling. The applicant should use the standard language and headers as provided in the Physicians Labeling Rule 21 CFR Parts 201, 314 and 601 for the "Microbiology" portion of the labeling in section 12.4.*

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- *For the Mechanism of Action – the applicant has shown that luliconazole is in the azole antifungal class. Like other azoles, luliconazole inhibits ergosterol synthesis, a constituent of fungal cell membranes.* (b) (4)

- *Labels for anti-infective products should address the issue of microbial resistance. It is recommended that a Mechanism of Resistance subheading in Section 12.4 should be included with the following sentence, “To date, a mechanism of resistance to luliconazole has not been described.”*

- *In order for an organism to become part of the “first list” it should be based on pathogens evaluated during clinical studies. Based on the three pivotal clinical studies in subjects with tinea pedis and tinea cruris infections, luliconazole was shown to be active against *T. rubrum* and *E. floccosum*.* (b) (4)

*It is recommended that the list of organisms in the INDICATIONS AND USAGE section as well as MICROBIOLOGY section include only *T. rubrum* and *E. floccosum*.*

- *Based on the available information, no susceptibility testing interpretive criteria for luliconazole are recommended at this time*

**6.2. FDA’s Version of the Labeling**

**12.1 Mechanism of Action**

Luzu Cream is a topical antifungal drug [See Clinical Pharmacology (12.4)]

(b) (4)

**12.4 Microbiology**

(b) (4)

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(b) (4)

**Mechanism of action**

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

**Mechanism of Resistance**

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

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

*Trichophyton rubrum*

*Epidermophyton floccosum*

**7. RECOMMENDATIONS**

The application is approvable pending an accepted version of the labeling.

**8. REFERENCES**

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- (2) Koga H. Inhibition of ergosterol synthesis of Trichophyton with NND-502. **Study Report# E-27.** 2002.
- (3) Niwano Y. Kuzuhara N. In vitro antifungal activity of NND-502 against the Trichophyton. **Study Report# E-1.** 1995
- (4) Yamaguchi H., Uchida K., and Nishiyama Y. Development research for NND-502 investigation of antifungal spectrum for NND-502 against causal strains of superficial mycosis. **Study Report# E-5.** 2002
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- (13) Koga Y, Nanjo I, Matsuba K. Inhibitory effect of NND-502 against production of protease by *Trichophyton*. **Report# E-29.** 2002
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- (16) Koga H, Fujisaki N, Matsuba K and Tsuji Y. In vitro antifungal activity of conformational analogues and metabolites of NND-502. **Study Report# E-32.** 2002.
- (17) Niwano Y. Kuzuhara N. Therapeutic effects of NND-502 solution (PEG400) in the guinea pig tinea pedis model. **Study Report# E-11.** 1995
- (18) Niwano Y., Kuzuhara N., Goto Y. And Hirano S. Therapeutic effects of NND-502 Cream in the guinea pig tinea pedis model. **Study Report# E-12.** 1997.
- (19) Niwano Y., Kuzuhara N., Goto Y., Hirakawa S. Therapeutic effects of short-term application of 1% NND-502 cream in the guinea pig tinea pedis model. **Study Report #E-13.** 1997.
- (20) Matsui Y. Therapeutic effects of 1% NND-502 solution in the guinea pig tinea pedis model. **Study Report#E-16.** 2001.
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- (23) Koga H. Comparison of luliconazole solution and cream in the guinea pig tinea corporis model. **Study Report#E-17.**

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- (27) Mathisen A. A randomized, double-blind, vehicle-controlled study evaluating the efficacy and safety of Product 33525 in subjects with tinea pedis. **Study Report MP-1000-02.** 2012.
- (28) Mathisen A. A randomized, double-blind, vehicle-controlled study evaluating the efficacy and safety of Product 33525 in subjects with tinea pedis. **Study Report MP-1000-03.** 2012.
- (29) Fothergill AW. In vitro susceptibility testing of luliconazole, itraconazole and terbinafine against the dermatophytes obtained in a phase III clinical trial (MP-1000-01). **Study Report# Fothergill 2012** 2012
- (30) Fothergill AW. In vitro susceptibility testing of luliconazole, itraconazole and terbinafine against the dermatophytes obtained in a phase III clinical trial (MP-1000-02). **Study Report# Fothergill 2012a** 2012
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Simone M. Shurland, Ph.D.  
Clinical Microbiology Reviewer  
DAIP  
July 11, 2013

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Kerry Snow, M.S., M.T. (ASCP)  
Acting Microbiology Team Leader  
DAIP  
KGS 23 July 2013

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SIMONE SHURLAND  
07/23/2013

KERRY SNOW  
07/24/2013

## MICROBIOLOGY FILING CHECKLIST for Supplement Review

**NDA Number:**

NDA 204-153

**Applicant:**

Medicis Pharmaceutical Corp

**Stamp Date:**

12/11/2012

**Drug Name:**

Luliconazole Cream 1%

**NDA Type:**

Original-1

**Supplement Number:**

Original-1

On **initial** overview of the NDA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comments</b>
1	Is the microbiology information (preclinical/nonclinical and clinical) described in different sections of the NDA organized in a manner to allow substantive review to begin?	<b>X</b>		
2	Is the microbiology information (preclinical/nonclinical and clinical) indexed, paginated and/or linked in a manner to allow substantive review to begin?	<b>X</b>		
3	Is the microbiology information (preclinical/nonclinical and clinical) legible so that substantive review can begin?	<b>X</b>		
4	On its face, has the applicant <u>submitted</u> <i>in vitro</i> data in necessary quantity, using necessary clinical and non-clinical strains/isolates, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling?	<b>X</b>		
5	Has the applicant <u>submitted</u> any required animal model studies necessary for approvability of the product based on the submitted draft labeling?			N/A
6	Has the applicant <u>submitted</u> all special/critical studies/data requested by the Division during pre-submission discussions?	<b>X</b>		
7	Has the applicant <u>submitted</u> the clinical microbiology datasets in a format which intends to correlate baseline pathogen with clinical and microbiologic outcome?	<b>X</b>		
8	Has the applicant <u>submitted</u> draft/proposed interpretive criteria/breakpoint along with quality control (QC) parameters and interpretive criteria, if applicable, in a manner consistent with contemporary standards, which attempt to correlate criteria with clinical results of NDA/BLA studies, and in a manner to allow substantive review to begin?			N/A
9	Has the applicant <u>submitted</u> a clinical microbiology dataset in an appropriate/standardized format which intends to determine resistance development by correlating changes in the phenotype (such as <i>in vitro</i> susceptibility) and/or genotype (such as mutations) of the baseline pathogen with clinical and microbiologic outcome?			N/A

## MICROBIOLOGY FILING CHECKLIST for Supplement Review

	Content Parameter	Yes	No	Comments
10	Has the applicant used standardized or nonstandardized methods for measuring microbiologic outcome? If nonstandardized methods were used, has the applicant included complete details of the method, the name of the laboratory where actual testing was done and performance characteristics of the assay in the laboratory where the actual testing was done?	<b>X</b>		
11	Has the applicant <u>submitted</u> draft labeling consistent with current regulation, divisional and Center policy, and the design of the development package?	<b>X</b>		
12	Has the applicant <u>submitted</u> annotated microbiology draft labeling consistent with current divisional policy, and the design of the development package?	<b>X</b>		
13	Have all the study reports, published articles, and other references been included and cross-referenced in the annotated draft labeling or summary section of the submission?	<b>X</b>		
14	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		<b>X</b>	

**IS THE MICROBIOLOGY SECTION OF THE APPLICATION FILEABLE? X YES \_NO**

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

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

**No additional clinical microbiology comments**

Simone M. Shurland, Ph.D.

Reviewing Microbiologist

February 1, 2013

Date

Kerry Snow, MT(ASCP)

Acting Microbiology Team Leader

February 1, 2013

Date

Microbiology Filing Checklist for Supplement NDA

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/s/  
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SIMONE SHURLAND  
02/01/2013

KERRY SNOW  
02/01/2013