CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-484

MICROBIOLOGY REVIEW(S)

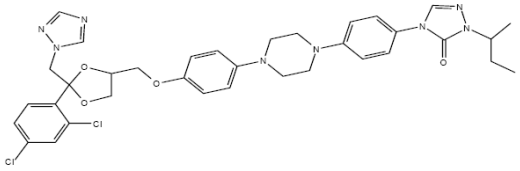
Date Received by CDER: 31 March 2009
Date Assigned: 14 April 2009
Date Review Completed: 29 October 2009
Reviewer: Kerry Snow

APPLICANT

Stiefel Laboratories, Inc
20 T.W. Alexander Drive
PO Box 14910
Research Triangle Park, NC 27709

DRUG PRODUCT NAME

Established name: Itraconazole
Proprietary name: Hyphanox
Chemical name: (±)-cis-4-[4-[4-[4[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolane-4- yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-^{3}H-1,2,4-triazol-3-one
Molecular formula: $C_{35}H_{38}Cl_2N_8O_4$
Molecular weight: 705.64
Chemical structure:



PROPOSED INDICATION

Oral treatment of onychomycosis of the toenail [redacted] (b) (4)

PROPOSED DOSAGE FORM, STRENGTH, ROUTE OF ADMINISTRATION AND DURATION OF TREATMENT

Dosage form: tablet
Route of administration: oral
Strength: 200 mg
Dosage: 200 mg (1 tablet) once daily for 12 consecutive weeks

DISPENSED

Rx

RELATED DOCUMENTS

NDA 20-083 Sporanox Oral Capsules, NDA 20-657 Sporanox Oral Solution

REMARKS

Itraconazole for the treatment of onychomycosis is currently approved under NDA 20-083 (Sporonox 100 mg capsules), NDA 20-657 (Sporonox oral solution), and NDA 20-966 (Sporonox injection). The Applicant has retained rights of reference to NDA 20-083 and 20-657, and to the Barrier Therapeutics Drug Master File #10725 for the itraconazole drug substance. The approved dosing regimen for the treatment of onychomycosis (toenails (b) (4) is 200 mg (b) (4) once daily for 12 weeks. The Applicant contends that a single 200 mg film-coated tablet would improve compliance, compared to the suggested regimen of two 100-mg tablets. Melt extrusion technology has been employed, in the development of the proposed 200 mg tablet, to purportedly reduce variability of absorption.

CONCLUSIONS

The Applicant has submitted sufficient data, collected from one Phase 3 clinical trial, to demonstrate comparable efficacy (non-inferiority) of itraconazole tablets (one 200 mg tablet delivered once daily for 12 weeks) to itraconazole capsules (two 100 mg capsules delivered once daily for 12 weeks), and superiority to placebo.

The majority of isolates, identified as fungal pathogens in subjects diagnosed with onychomycosis of the large toenail, were identified as *Trichophtyon rubrum* (1005 of 1057 isolates recovered at the Baseline Visit, ITT data set). Forty-four isolates of *T. mentagrophytes* were recovered, and 8 isolates of *Epidermophyton floccosum* were recovered. Microbiological success rates (negative KOH and fungal culture at the End of Study Visit) were comparable between the two active arms, in subjects infected by either species of the *Trichophyton* genus, but insufficient data was available to evaluate comparative efficacy in cases of infection by *E. floccosum*.

No notable decreased susceptibility of dermatophytes to itraconazole was observed during the study.

From a clinical microbiology perspective, the Application is approvable, provided the following changes are included in the proposed label:

2 pages of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

INTRODUCTION

Onychomycosis is a common fungal infection, most frequently caused by two genera of filamentous fungi (*Trichophyton* sp and *Epidermophyton* sp). *Candida* species are occasionally associated with nail infections in patients with chronic mucocutaneous candidiasis [Gorbach 2004]. Other filamentous fungi (non-dermatophytes) are isolated in rare instances, as the etiologic agents of nail disease [Murray 2003]. There are three types of true dermatophyte infection: 1) distal subungual onychomycosis, 2) proximal subungual onychomycosis, and 3) superficial white onychomycosis. Distal subungal onychomycosis (fungal infection originating from the distal portion of the nail and/or nail bed) is the most commonly diagnosed form of the disease.

Onychomycosis is diagnosed by physical examination, in combination with laboratory findings. Recent guidelines suggest that microscopic examination and culture of subungual debris increase the sensitivity and specificity of diagnosis, and that laboratory results are particularly important when systemic therapy is considered [Drake 1996].

Up to 25% of patients with onychomycosis can be categorized as poor responders or non-responders to topical and/or systemic treatment [Scher 2003]. Although most dermatophyte infections are restricted to the keratinized tissues that are derived from the skin (skin, hair, and nails), significant morbidity is associated with the infection, spread to surrounding tissues is frequent [Szepietowski 2006], and rare invasive disease (deep dermatophyte infection) may occur. Currently available topical therapy is usually inadequate for the successful treatment of nail infections. Oral treatment options for onychomycosis include griseofulvin, terbinafine, itraconazole, and fluconazole [Mandell 2005]. Systemic antifungal therapy, however, is associated with a variety of adverse effects (e.g. hepatotoxicity, congestive heart failure) and the extended time of treatment presents a compliance problem for some patients. Recent evidence suggests a 25 to 30% relapse rate for onychomycosis of the toenail, when treated with either oral terbinafine or oral itraconazole [de Berker 2009].

Itraconazole is active against most species of pathogenic fungi, including the dimorphic pathogens, *Candida* species, *Cryptococcus* species, and the primary agents of dermatomycoses (*Trichophyton* species, *Epidermophyton floccosum*, and *Microsporum* species). Oral itraconazole is poorly absorbed, but absorption is more predictable in solution form (as opposed to capsules). Itraconazole is highly protein bound (approximately 99%) and has an extended half-life in patients with hepatic dysfunction.

MECHANISM OF ACTION

The azole-based antimycotic agents appear to target the fungal heme proteins that cocatalyze 14α-demethylase, a P450 enzyme necessary for the conversion of lanosterol to ergosterol [Ghannoum 1999]. The inhibition of 14α-demethylase results in the depletion of the ergosterols that are required for the maintenance of fungal cell wall integrity, and in the

buildup of ergosterol precursors. Evidence suggests that this depletion results in increased cell permeability, with leakage of cell contents. Azoles may affect mammalian cholesterol biosynthesis, but this has only been demonstrated at very high dosages [Balkis 2002].

No new data have been submitted in this Application, regarding the mechanism of action of itraconazole.

ANTIMICROBIAL SPECTRUM OF ACTIVITY

Itraconazole has in vitro activity against a wide variety of pathogenic fungi, including the dimorphic pathogens (*Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Coccidiodes immitis*), most yeast (variable activity against *C. glabrata* and *C. krusei*), most *Aspergillus* species, and the principle agents of dermatomycoses (*Trichophyton* species, *Microsporum* species, and *Epidermophtyon floccosum*). Itraconazole is not active, in vitro, against *Fusarium* species, the zygomycetes, and *Scopulariopsis* species (a rare cause of onychomycosis).

The Applicant has assembled a reference list of studies from the literature, describing the in vitro activity of itraconazole against fungal pathogens commonly associated with onychomycosis (Table 1). Reported itraconazole activity, as summarized in this table, varies widely, with ranges of 0.07 – 128 mcg/ml against *C. albicans*, 0.0078 – 8 mcg/ml against *E. floccosum*, 0.063 – 64 mcg/ml against *Trichophyton* species, and 0.015 – 2 mcg/ml against *Microsporum* species. In the most recent of these studies [da Silva Barros 2007, Esteban 2005, Fernandez-Torres 2000, Gupta 2005, Singh 2007], researchers employed methods based on those described in the Clinical and Laboratory Standards Institute (CLSI) document M38-A ("Reference Method for Broth Dilution Antifungal Testing of Filamentous Fungi; Approved Standard"), including quality control procedures specified in that document. In these studies, the MIC_{90} of itraconazole against all relevant genera (*Microsporum* species, *Trichophyton* species, and *E. floccosum*) was ≤ 1 mcg/ml, with the upper range extending to > 8 mcg/ml against certain isolates of *T. rubrum* and *E. floccosum*.

Although in vitro studies indicate poor activity of itraconazole against Scopulariopsis brevicaulis, an uncommon cause of onychomycosis [Aquilar 1999], recent investigations have demonstrated clinical efficacy in "some cases of toe onychomycosis" [Gupta 2001].

No new data have been submitted in this Application, regarding the in vitro antifungal activity of itraconazole.

Table 1: In vitro primary pharmacology studies performed with itraconazole

Test System	Minimum Inhibitory Concentration Range (ug/ml)	Reference
Candida spp. *E. floccosum* *Microsporum* spp. *Trichophyton* spp.	0.063-128 0.063 0.063-0.25 0.063-64	Espinel-Ingroff (1984)
T. rubrum	0.01-2	Fernandez-Torres (2000)
E. floccosum *T. mentagrophytes* *T. rubrum*	0.01-8 0.01-2 0.01-8	Fernandez-Torres (2001)
E. Floccosum *M. audouinii* *M. canis* *M. cookei* *M. ferrugineum* *M. fulvum* *M. gallinae* *M. gypseum* *M. nanum* *M. praecox* *M. racemosum* *T. ajelloi* *T. balcaneum* *T. concentricum* *T. erinacei* *T. interdigitale* *T. phaseoliforme* *T. schoenleinii* *T. simii* *T. tonsurans* *T. verrucosum* *T. violaceum*	0.01-8 0.01-0.125 0.01-4 0.03 0.03-0.125 0.125 0.125 0.01-0.25 0.03 0.12 0.25 0.03-0.06 0.03-0.06 0.01 0.03-0.5 0.01-0.5 0.5 0.01-0.5 0.06-0.25 0.06-0.25 0.01 0.01-0.5	Fernandez-Torres (2001)
E. floccosum *M. canis* *M. gypseum* *T. mentagrophytes* *T. rubrum* *T. tonsurans*	0.0078-0.5 0.01-2 0.5-2 0.125-1 0.03-1 0.0078-1	Esteban (2005)
T. rubrum *T. mentagrophytes* *T. tonsurans* *Microsporum spp.* *E. floccosum*	0.015->8 0.015-0.25 0.015-0.5 0.015-0.5 0.015-8	Gupta (2005)

Table 1: In vitro primary pharmacology studies performed with itraconazole (cont'd)

Test System	Minimum Inhibitory Concentration Range (ug/ml)	Reference
T. rubrum	0.015-0.25	da Silva Barros (2007)
T. mentagrophytes	0.015-0.25	
T. rubrum	0.25-2	Singh (2007)
T. mentagrophytes	0.5	
T. tonsurans	0.25-1	
T. violaceum	1.0	
M. canis	0.03-1	
E. flocossum	0.06-0.25	
M. audouini	0.01-0.1	Van Cutsem (1987)
M. canis	0.01-0.1	
M. gypseum	0.01-0.1	
M. ferrugineum	0.01-0.1	
T. mentagrophytes	0.001-10	Van Cutsem (1987)
T. rubrum	0.001-0.1	
T. concentricum	0.01-0.1	
T. equinum	0.01	
T. schoeleini	0.01-0.1	
T. verucosum	0.01-1	
T. violaceum	0.01-0.1	
T. yaoundei	0.001	
T. soudanese	0.1	
T. ajelloi	0.01	
T. megnini	0.01	
T. tonsurans	0.1-10	
E. floccosum	0.001-0.1	Van Cutsem (1987)
C. albicans	0.001-100	Van Cutsem (1987)
C. stellatoidea	0.001–1	
C. tropicalis	0.001–1	
C. parapsilosis	0.01–10	
C. guilliermondii	0.1–1	
C. pseudotropicalis	0.01–0.1	
C. krusei	0.001–100	
C. parakrusei	0.01–0.1	
C. norvegensis	0.1	
C. lusitaniae	0.01–0.1	
C. brumptii	0.1	
C. lipolytica	0.1	
C. macedoniensis	0.1	
C. zeylanoides	0.1–1	
C. utilis	0.1	
C. ravautii	0.1	
C. pulcherrima	0.1	
C. mesenterica	0.1	

Table 1: In vitro primary pharmacology studies performed with itraconazole (cont'd)

Test System	Minimum Inhibitory Concentration Range (ug/ml)		Reference
	EUCAST	CLSI M27-A2	Espinel-Ingroff (2005)
C. albicans	0.008-1	0.01-16	
C. dubliniensis	0.008-0.06	0.008-0.25	
C. glabrata	0.008-4	0.01-16	
C. guilliermondii	0.008-16	0.03-16	
C. krusei	0.008-0.5	0.12-1	
C. lusitaniae	0.008-0.25	0.01-0.5	
C. parapsilosis	0.008-0.25	0.03-0.5	
C. tropicalis	0.008-16	0.06-16	
C. albicans	≤ 0.03-16		Tortorano (2005)
Scopulariopsis spp.	> 16		Aguilar (1999)
Scopulariopsis brevicaulis	≥ 100		Van Cutsem (1987)

CLSI: The Clinical and Laboratory Standards Institute (formerly the National Committee for Clinical Laboratory Standards [NCCLS])
EUCAST: European Committee on Antibiotic Susceptibility Testing
Source: This submission; Module 2.6.2

RESISTANCE STUDIES

Resistance to azoles may occur by a variety of mechanisms, including target modification (expression of low-affinity 14α-demethylases), overexpression of targets, alteration of membrane permeability to the azoles, and active efflux of the antifungal [Balkis 2002]. The correlation of clinical failures with increased MICs or the identification of a particular resistance genotype, however, is unclear and may be misleading. Treatment failure in cases of tinea pedis (and other dermatomycoses) is common, and is particularly problematic in cases of *T. rubrum* infection [Kwon-Chung 1992].

Fungal resistance to the azoles has been principally studied in yeasts (*Candida albicans*, primarily). Recent studies have demonstrated increasing resistance to triazole antifungals in species of filamentous fungi [Snelders 2008], including the development of resistance in the course of treatment [Bellete 2009]. Active efflux of itraconazole has been demonstrated in isolates of *T. rubrum* [Cervelatti 2006]. Recent investigations suggest that most itraconazole-resistant fungi demonstrate cross-resistance to other triazole antifungals, including voriconazole and posaconazole [Howard 2009].

Fungal arthroconidia, which purportedly represent the infectious form of most dermatophytes, may be inherently more resistant to specific antifungals (including itraconazole) than microconidial forms of the same species [Coelho 2008]. Susceptibility testing, as recommended in CLSI M38-A, is routinely performed with microconidial (or macroconidial) preparations [CLSI 2008].

No new data from in vitro studies have been submitted in this Application, regarding the development of resistance of dermatophytes to itraconazole.

ANTIMICROBIAL INTERACTION STUDIES

The Applicant has provided information culled from the recent literature to describe the pharmacodynamic interactions of itraconazole and other antifungals. The results of the listed studies are described as "highly variable." Only one of the studies was devoted to the antifungal interaction of itraconazole against dermatophytes [Ozawa 2005], in which itraconazole was found to be synergistic with tacrolimus against isolates of *T. mentagrophytes*. Other investigations demonstrated synergy of itraconazole with caspofungin, anidulafungin, nifedipine, and amiodarone against *Aspergillus* species. Antagonism was demonstrated, in both in vitro and in vivo experiments, between itraconazole and amphotericin B against isolates of *Aspergillus* species.

No new data from studies of antifungal interactions have been submitted in this Application.

EFFECT OF MISCELLANEOUS FACTORS ON ACTIVITY

PROTEIN BINDING

Itraconazole is highly bound by plasma proteins, with albumin being the major binging protein. In a study by the Applicant (Janssen Study Report N49687), plasma protein binding in humans was 99.82%, and was independent of drug concentration (0.1 to 0.5 mcg/ml). The results of this study are summarized in Table 2.

Table 2: Plasma protein binding

		Test Article: Itraconazole	
		Study Report: N 49687	
Testing Method: Equilibrium dialysis			
Parameter	**Rat**	**Dog**	**Human**
Plasma Protein Binding (%)	99.73	99.79	99.82
Plasma Free Fraction (%)	0.27	0.21	0.18
Blood/Plasma Ratio	0.68	0.61	0.58
Distribution (%) in Blood to:			
Plasma water	0.23	0.18	0.17
Plasma proteins	84.4	83.5	94.9
Blood Cells	15.4	16.4	5.0
Binding to Blood Cells (%)	90.6	90.6	95.2
Additional Information: The plasma protein binding was independent of drug concentration in the range of 0.1 - 0.5 ug/mL. The plasma protein binding was independent of pH in the range of 6.7 - 8.1. Albumin was the main binding protein for itraconazole in human plasma.			

ANIMAL AND HUMAN STUDIES

ANIMAL MODELS OF INFECTION

The Applicant has included information, selected from the scientific literature, describing the in vivo efficacy of itraconazole in animal models of dermatophyte infection.

In one study, published in 1987 [Van Cutsem 1987], albino guinea pigs were infected with *Microsporum canis* or *Trichophyton mentagrophytes* on the abraded back, and were treated orally or topically, at the time of infection or on Day 3 of infection. Oral comparators included ketoconazole and griseofulvin, and the topical comparator was ketoconazole. In this study, oral itraconazole at 1.25 mg/kg given once daily for 14 days, starting on Day 1 of infection, was superior to griseofulvin or ketoconazole dosed at 10 mg/kg once daily for the same time period. Efficacy of oral treatments, given at Day 3 of infection, was comparable between the three antifungals. Topical itraconazole treatment, begun on Day 3 of infection, was efficacious, with the majority of animals (38 of 42) noted as cured (culture negative) when treated with 0.25 mg/kg for 12 days.

In the same study, investigators studied the efficacy of oral itraconazole and ketoconazole at clearing lesions associated with disseminated trichophytosis in guinea pigs. In this investigation, itraconazole cure was more rapid than that of ketoconazole, and was more effective at lower doses. The effects of parental treatment, in cases of disseminated trichophytosis, were similar to those described for oral treatment.

In a second study, published in 1993 [Borgers 1993], investigators infected guinea pigs with either T. mentagrophytes or M. canis, and treated the animals with either topical bifonazole or oral itraconazole for 14 consecutive days. The researchers concluded that both treatments produced similar results in the stratum corneum of infected animals, but that oral itraconazole was more effective in clearing fungal infection of the hair shafts.

In a third study [Mieth 1994], utilizing a Hair Root Invasion Test (HIT) and Auricular Skin Temperature Test (STT) as quantitative methods for the determination of antifungal effects in the acute phase of dermatophyte infection, investigators demonstrated that oral terbinafine was more efficacious than either oral itraconazole or oral fluconazole in the treatment of infection by *T. mentagrophytes* or *T. rubrum*.

In a fourth cited study [Moriello 1995], investigators treated cats that had been infected by topical application of *M. canis*, with oral itraconazole or griseofulvin. Cats were treated 3 weeks after infection, and dosing continued for 100 days or until mycologic cure (three consecutive negative cultures, collected weekly). Mycologic cure was more rapid in cats treated with itraconazole (all cats culture-negative at 56 days), compared to those treated with griseofulvin (all cats culture-negative at 70 days).

No data from recent investigations of the in vivo antifungal of itraconazole against dermatophytes have been submitted in this Application.

HUMAN PHARMACOLOGIC STUDIES

Itraconazole is metabolized in the liver, with hydroxy-itraconazole as the primary metabolite (present at approximately twice the blood concentration of unchanged itraconazole). The in vitro antifungal activity of hydroxy-itraconazole is approximately equal to that of itraconazole [Debruyne 2001]. Itraconazole and its metabolites are primarily excreted in the feces (54%) and urine (35%).

The development program for Hyphanox included 5 Phase 1 studies (2 PK studies, 2 bioequivalence studies, and 1 bioavailability study). The Phase 1 studies are summarized in Table 3.

Table 3: Summary of Phase 1 Studies Conducted to Evaluate the Itraconazole 200-mg Tablet

Protocol No. (Location)	Objective	Study Design	Subject Population (Plan/Actual)	# Sites	Study Drug Group(s) = # Subjects	Dosing Regimen/ Duration	Study Period
BT300-BEL-002 (module 5, section 5.3.1.2)	To determine the bioequivalence of 1 itraconazole 200-mg tablet relative to 2 itraconazole 100-mg capsules taken in a single dose after a standard meal	Phase 1, open-label, randomized, 2-way crossover, single-center, oral dose study	Healthy subjects, 18 to 55 years of age (inclusive) (56/56[a])	1 (Belgium)	itraconazole 200-mg tablet = 56 itraconazole 100-mg capsules = 56	Single administration of 1 tablet or 2 capsules after a standard breakfast; 14-day washout period between study drugs; subjects followed for 4 days after each dosing	November 12, 2003-February 24, 2004
BT300-BEL-004 (module 5, section 5.3.3.1)	To assess the pharmacokinetics of itraconazole and hydroxy-itraconazole after a single dose of 2 itraconazole 200-mg tablets following a high-calorie, high-fat meal	Phase 1, open-label, single-center, single-arm, oral dose, descriptive study	Healthy female subjects, 18 to 65 years of age (inclusive) (16/16)	1 (Belgium)	itraconazole 200-mg tablets = 16	Single administration of 2 tablets after a high-calorie, high-fat breakfast; subjects followed for 5 days after dosing	January 14, 2005-February 19, 2005
BT0300BEL005 (module 5, section 5.3.1.2)	To determine the bioequivalence of 1 itraconazole 200-mg tablet relative to 2 itraconazole 100-mg capsules taken in a single dose after a high-calorie, high-fat meal	Phase 1, open-label, randomized, 2-way crossover, single-center, oral dose study	Healthy subjects, 18 to 55 years of age (inclusive) (56/56)	1 (Belgium)	itraconazole 200-mg tablet = 56 itraconazole 100-mg capsules = 56	Single administration of 1 tablet or 2 capsules after a high-calorie, high-fat breakfast; 14-day washout period between study drugs; subjects followed for 5 days after each dosing	March 1, 2005-April 25, 2005

BT0300BEL006 (module 5, section 5.3.1.2)	To assess the effect of food on the bioavailability of itraconazole 200-mg tablets and to compare the bioavailability (fasting) of itraconazole 200-mg tablets and itraconazole 100-mg capsules	Phase 1, open-label, randomized, 3-way crossover, oral dose, single-center study	Healthy subjects, 18 to 55 years of age (inclusive) (18/18)	1 (Belgium)	itraconazole 200-mg tablet (fasting) = 18 itraconazole 200-mg tablet (fed) = 18 itraconazole 100-mg capsules (fasting) = 18	Single administration of 1 tablet or 2 capsules under fasting conditions and of 1 tablet after a high-calorie, high-fat breakfast; 14-day washout period between study drugs; subjects followed for 5 days after each dosing	February 25, 2005-April 20, 2005
BT0300-108-USA (module 5, section 5.3.3.1)	To document the steady-state pharmacokinetics and safety of itraconazole 200-mg tablets when administered once daily for 14 days	Phase 1, open label, single-arm, oral dose, single-center study	Healthy subjects, 18 to 55 years of age (inclusive) (16/16)	1 (US)	itraconazole 200-mg tablet = 16	Administration of 1 tablet, QD after a standard breakfast for 14 days; subjects followed for 14 days after dosing period	May 20, 2008-July 7, 2008

The Phase 1 clinical trials failed to demonstrate bioequivalence of a single 200-mg itraconazole tablet and two 100-mg Sporonox (itraconazole) capsules. Data from these studies suggested that the 200-mg tablet had lower bioavailability than the two 100-mg capsules, and that this difference was exaggerated, depending on the type of breakfast given to subjects, prior to dosing (30% lower bioavailability in the 200-mg tablet arm, following a high-fat, high-calorie breakfast). In addition to the study-specific variability described above, the Phase 1 studies demonstrated notable subject-specific variability. In study BT300-BEL-002, for example, the mean AUC_{∞} (n=56) was 3.87 h·mcg/mL, with an SD of 1.85 h·mcg/mL (range: 1.06 – 8.58 3.87 h·mcg/mL), and C_{max} ranged from 83.1 ng/mL to 706 ng/ml (mean = 306 ng/ml, SD = 146 ng/ml).

Table 4: Mean (STD) pharmacokinetic parameters of itraconazole after 2 weeks of administration of 200 mg itraconazole once daily with a standard breakfast

Formulation	**N**	**C_{max}** (ng/mL)	**T_{max}** (h)	**AUC_{0-24}** (µg·h/mL)	**$t_{1/2}$** (h)
Itraconazole 200-mg film-coated tablet	7F and 7M[a]	741 (304)	3.9 (1.2)	10.18 (4.64)	37.5 (10.9)
Itraconazole 100-mg capsule	5 M[b]	1070 (499)	4.4 (2.1)	15.40 (6.88)	36.5 (4.3)
Itraconazole 100-mg capsule	5 F[c]	986 (151)	3.8 (1.1)	12.14 (2.94)	43.0 (14.9)

Studies have demonstrated that Sporonox (oral itraconazole, 200 mg) is present in the distal nail at one month after initiation of treatment (16 ng/g in toenails), and that concentrations rise during therapy (mean value = 197 ng/g in toenails) [Matthieu 1991]. Other investigators [Willemson 1992] have demonstrated itraconazole concentrations (during the 6 months, following 3 months of 200 mg/day dosing) of 730 ± 160 ng/g in toenails, with concentrations of the antifungal exceeding the MIC of the principle nail pathogens (*Trichophyton* species, *Microsporum* species, *E. floccosum*, and *C. albicans*). The

Applicant has provided no data, in this submission, regarding the pharmacokinetics/pharmacodynamics of itraconazole 100-mg tablets in nail tissue.

CLINICAL TRIAL

The Applicant has presented data from one Phase 3 clinical trial, designed to demonstrate the efficacy and safety of one itraconazole 200-mg film-coated tablet, compared to two 100-mg itraconazole capsules and placebo, in the treatment of onychomycosis of the toenail (summarized in Table 5). The study (BT0300-302-INT) was a multi-center, randomized, evaluator-blinded, parallel group, active-controlled trial. The study period was from 20 July 2006 through 2 October 2008. There were 1,381 subjects enrolled at 67 study centers (51 in the US, 8 in Canada, 4 in Latin America, and 4 in South Africa). Of the enrolled subjects, 593 were randomized to the itraconazole 200-mg arm, 590 to the itraconazole 100-mg (x 2) arm, and 198 to the placebo arm.

Table 5: Summary of Phase 3 Study Conducted to Evaluate the Itraconazole 200-mg Tablet

Protocol No. (Location)	Objective	Study Design	Subject Population (Plan/Actual)	# Sites	Study Drug Group(s) = # Subjects	Dosing Regimen/ Duration	Study Period
BT0300-302-INT (module 5, section 5.3.5.1)	To evaluate the safety and efficacy of itraconazole 200-mg tablets, itraconazole 100-mg capsules, and placebo tablets in the treatment of onychomycosis of the toenail	Phase 3, multi-center, 3-arm, randomized, evaluator-blind, active controlled, parallel group study	Subjects 16 to 75 years of age (inclusive) with onychomycosis (1,288/1,381)	47 (US) 6 (Canada) 4 (Latin America) 1 (South Africa)	itraconazole 200-mg tablet = 593 (582 evaluated for safety) itraconazole 100-mg capsules) = 590 (581 evaluated for safety) placebo tablet = 198 (191 evaluated for safety)	1 tablet or 2 capsules taken once daily after breakfast for 12 weeks; subjects followed for 40 weeks after dosing period	July 20, 2006- October 2, 2008

Table 6: Enrollment of Subjects by Country and Study Drug Group

	Itraconazole Tablets (N=593)	Itraconazole Capsules (N=590)	Placebo Tablets (N=198)	Total (N=1381)
US	527 (88.9%)	523 (88.6%)	176 (88.9%)	1226 (88.8%)
Latin America	31 (5.2%)	35 (5.9%)	11 (5.6%)	77 (5.6%)
Ecuador	6 (1.0%)	8 (1.4%)	3 (1.5%)	17 (1.2%)
Panama	9 (1.5%)	9 (1.5%)	3 (1.5%)	21 (1.5%)
Honduras	9 (1.5%)	9 (1.5%)	3 (1.5%)	21 (1.5%)
Dominican Republic	7 (1.2%)	9 (1.5%)	2 (1.0%)	18 (1.3%)
Canada	23 (3.9%)	21 (3.6%)	8 (4.0%)	52 (3.8%)
South Africa	12 (2.0%)	11 (1.9%)	3 (1.5%)	26 (1.9%)

Source: This submission, Clinical Study Report, Section 10 1

Subjects eligible for the trial were 16 to 75 years of age, with a diagnosis of onychomycosis of onychomycosis of at least one great toenail. Study drug was self-administered. There were eight scheduled study visits over a one-year period (12-week dosing evaluation and 40-week follow-up). KOH examinations and mycological cultures were performed at weeks 0, 12, 26, 39, and 52.

Table 7: Summary of subject baseline characteristics (ITT)

	Itraconazole Tablets (N=593)	Itraconazole Capsules (N=590)	Placebo Tablets (N=198)	Total (N=1381)	P-Value
IGA					
Clinical Cure	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.468[a]
Clinical Improvement	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Mild	25 (4.2%)	29 (4.9%)	5 (2.5%)	59 (4.3%)	
Moderate	332 (56.0%)	338 (57.3%)	114 (57.6%)	784 (56.8%)	
Severe	236 (39.8%)	223 (37.8%)	79 (39.9%)	538 (39.0%)	
Percent Nail Involvement					
0%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.520[a]
>0% to ≤25%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
>25% to ≤50%	240 (40.5%)	251 (42.5%)	87 (43.9%)	578 (41.9%)	
>50% to ≤75%	352 (59.4%)	339 (57.5%)	111 (56.1%)	802 (58.1%)	
>75% to ≤100%	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	
Length of Unaffected Target Toenail (mm)					
N	593	590	198	1381	0.620[b]
Mean	5.0	4.8	4.9	4.9	
STD	2.32	2.28	2.18	2.28	
Median	5.0	4.0	5.0	4.0	
Min. to Max.	2 to 13	1 to 15	2 to 11	1 to 15	

[a] P-value from a Cochran-Mantel-Haenszel test, stratified by analysis center.
[b] P-value from a two-way analysis of variance with factors of treatment group and analysis center.
Source: This submission, Module 2.7.3, Table 5

Clinical assessment at baseline was graded, based on "Investigator's Global Assessment" criteria (Table 8).

Table 8: Scale for the Investigator's Global Assessment

Score	Definition	Complete Description
0	Clinical Cure	No evidence of onychomycosis in target nail. Normal nail unit without subungual hyperkeratosis or onycholysis.
1	Clinical Improvement	Minimal evidence of onychomycosis in target nail. ≤10% dystrophy and/or discoloration with minimal subungual hyperkeratosis and/or onycholysis.
2	Mild	Target nail involvement ≤25% dystrophy and/or onycholysis.
3	Moderate	Target toenail involvement ≤50% dystrophy and/or discoloration with clear evidence of subungual hyperkeratosis and/or onycholysis.
4	Severe	Target nail involvement >50% dystrophy and/or discoloration with marked evidence of subungual hyperkeratosis and/or onycholysis.

Source: This submission, Clinical Study Report, Section 9.5.1.1.3

The primary efficacy endpoint for the study was complete cure (clinical cure and mycological cure) at week 52 (end of study). The secondary efficacy endpoint was clinical improvement at 52 weeks. Clinical and mycological outcomes were defined as:

- Clinical Cure: an IGA of 0 (clinical cure);
- Mycological Cure: a negative KOH examination and a negative culture for dermatophytes of the target toenail;
- Complete Cure: both a clinical cure and a mycological cure;
- Clinical Improvement: a mycological cure and an IGA score less than or equal to 1 (clinical improvement).

Two efficacy analysis populations were defined. The Intent to Treat (ITT) population included all randomized subjects. The Per Protocol (PP) population included all subject randomized to receive study drug, who completed week 52 without protocol violations.

The majority of enrolled subjects were seen by investigators in the U.S. (88.9%). Table 9 summarizes the geographic location of study subjects. No subjects were excluded from the ITT analysis set, but 236 subjects were excluded from the PP analysis set (91 (15.3%) from the itraconazole tablet arm, 102 (17.3%) from the itraconazole capsule arm, and 43 (21.7%) from the placebo arm), principally for missing visits at week 12 and/or week 52. Baseline demographics between the study arms were generally well balanced.

Table 9: Enrollment of subjects by country and study drug group

	Itraconazole Tablets (N=593)	Itraconazole Capsules (N=590)	Placebo Tablets (N=198)	Total (N=1381)
US	527 (88.9%)	523 (88.6%)	176 (88.9%)	1226 (88.8%)
Latin America	31 (5.2%)	35 (5.9%)	11 (5.6%)	77 (5.6%)
Ecuador	6 (1.0%)	8 (1.4%)	3 (1.5%)	17 (1.2%)
Panama	9 (1.5%)	9 (1.5%)	3 (1.5%)	21 (1.5%)
Honduras	9 (1.5%)	9 (1.5%)	3 (1.5%)	21 (1.5%)
Dominican Republic	7 (1.2%)	9 (1.5%)	2 (1.0%)	18 (1.3%)
Canada	23 (3.9%)	21 (3.6%)	8 (4.0%)	52 (3.8%)
South Africa	12 (2.0%)	11 (1.9%)	3 (1.5%)	26 (1.9%)

Source: This submission, Clinical Study Report, Section 9.5.1.1.3

Keratinaceous nail debris from beneath the nail plate (from trimmed nails) was collected at the investigational site and examined microscopically (at the local site), using potassium hydroxide (KOH) to dissolve non-fungal material. If the KOH examination was "positive" (presence of fungal elements noted), additional material was collected for fungal culture (performed by the central laboratory), and the subject was enrolled in the study. Subjects with KOH-negative specimens were permitted to have a second specimen collected, if they had clinical signs of onychomycosis and a positive Dermatophyte Test Medium (DTM) result (pH change, due to fungal growth on the selective medium). Subjects with KOH-negative results (from either collection) were excluded from the trial. Specimens for

microscopic examination and culture were collected at screening and weeks 12, 26, 39, and 52.

Specimens were shipped in Dermapak containers (provided by the Applicant) to the Mycology Consultant Lab (San Antonio, TX) for culture and identification of pathogens. Mycology Consultant Lab shipped recovered isolates to the Fungus Testing Laboratory (San Antonio, TX) for susceptibility testing. Specimens shipped inappropriately, delayed by more than 96 hours post collection, of insufficient quantity, improperly identified, or containing material other than skin or nail were rejected by the central laboratory. The Applicant has provided the laboratory procedure manual, including quality control procedures, in the microbiology report included in the NDA.

Specimens were plated on Sabouraud Dextrose Agar with chloramphenicol and cycloheximide, incubated at 30^{o}C, and held for up to 28 days. Cultures not growing at 28 days were resulted as "Negative Culture." Susceptibility testing was performed using broth microdilution techniques, according to procedures approved by CLSI [CLSI 2008], using itraconazole only. Susceptibility test results were read at 72 and 96 hours (tabulated and reported separately). Quality control was performed on each day of testing.

No pharmacokinetic determinations (including determination of nail concentrations of itraconazole) were conducted in the Phase 3 trial.

The outcomes of the Phase 3 trial are summarized in Table 10. Itraconazole delivered as one 200-mg tablet QD was determined to be non-inferior to itraconazole delivered as two 100-mg capsules QD, and superior to QD dosing of 1 placebo tablet, when administered for 12 weeks. The difference in primary efficacy success rates, observed at week 52 (End of Study Visit) for the active dosing groups were 0.56% for the ITT population and 092% for the PP population (lower limit of 97.5% CI: -4.3% [ITT], -4.7% [PP]).

Table 10: Summary of key study outcomes: proportions of subjects by dosing group with complete cure, clinical improvement, and mycological cure (ITT)

	Itraconazole Tablets	Itraconazole Capsules	Placebo Tablets
Complete Cure[a]	22.3%	21.7%	1.0%
Clinical Improvement[b]	33.7%	29.3%	2.0%
Mycological Cure[c]	44%	37%	6%

[a] Evaluated at week 52 and defined as consisting of both Clinical Cure (no evidence of onychomycosis in the target toenail and normal nail unit without subungual hyperkeratosis or onycholysis) and Mycological Cure (negative KOH and negative culture outcomes); 1 itraconazole 200-mg tablet is non-inferior to 2 itraconazole 100-mg capsules (lower limit of the 95% CI = -4.3%) and is superior to placebo tablets ($p<0.001$).

[b] Evaluated at week 52 and defined as no evidence or minimal evidence of onychomycosis in the target toenail (≤10% dystrophy and/or discoloration with minimal subungual hyperkeratosis and/or onycholysis) and Mycological Cure ; 1 itraconazole 200-mg tablet is non-inferior to 2 itraconazole 100-mg capsules (lower limit of the 95% CI = -1.1%) and is superior to placebo tablets ($p<0.001$).

[c] Evaluated at week 52; statistical comparisons between dosing groups were not performed.

Source: This submission, Module 2.7.3, Table 3

By-visit observations are summarized in Tables 11 (itraconazole tablets) and 12 (itraconazole capsules). The mycological cure rate for itraconazole tablets at the Week 52 visit was 44%, compared to 37% for itraconazole capsules. Fungal cultures, collected at the Week 52 visit, were negative for 60% of the subjects treated with itraconazole tablets, compared to 55% for subjects treated with itraconazole capsules.

Table 11: Summary of IGA and mycology by visit (ITT), Itraconazole Tablets (N = 593)

Itraconazole Tablets (N=593)	Baseline	Week 4	Week 8	Week 12	Week 26	Week 39	Week 52
IGA							
Clinical Cure	0 (0%)	0 (0%)	0 (0%)	4 (1%)	45 (8%)	120 (20%)	151 (25%)
Clinical Improvement	0 (0%)	5 (1%)	18 (3%)	48 (8%)	168 (28%)	162 (27%)	133 (22%)
Mild	25 (4%)	58 (10%)	77 (13%)	140 (24%)	179 (30%)	131 (22%)	97 (16%)
Moderate	332 (56%)	314 (53%)	323 (54%)	283 (48%)	154 (26%)	119 (20%)	142 (24%)
Severe	236 (40%)	216 (36%)	175 (30%)	118 (20%)	47 (8%)	61 (10%)	70 (12%)
Clinical Cure/Improvement	0 (0%)	5 (1%)	18 (3%)	52 (9%)	213 (36%)	282 (48%)	284 (48%)
Mild/Moderate	357 (60%)	372 (63%)	400 (67%)	423 (71%)	333 (56%)	250 (42%)	239 (40%)
Severe	236 (40%)	216 (36%)	175 (30%)	118 (20%)	47 (8%)	61 (10%)	70 (12%)
KOH Result							
Positive	593 (100%)			412 (69%)	294 (50%)	266 (45%)	285 (48%)
Negative	0 (0%)			181 (31%)	299 (50%)	327 (55%)	308 (52%)
Fungal Culture Result							
Positive	593 (100%)			352 (59%)	233 (39%)	227 (38%)	236 (40%)
Negative	0 (0%)			241 (41%)	360 (61%)	366 (62%)	357 (60%)
Mycologic Cure[a]							
Success				110 (19%)	231 (39%)	258 (44%)	258 (44%)
Failure				483 (81%)	362 (61%)	335 (56%)	335 (56%)
Complete Cure (Primary Endpoint at Wk 52)[b]							
Success				2 (<1%)	31 (5%)	88 (15%)	132 (22%)
Failure				591 (100%)	562 (95%)	505 (85%)	461 (78%)
Clinical Improvement (Secondary Endpoint at Wk 52)[c]							
Success				20 (3%)	128 (22%)	183 (31%)	200 (34%)
Failure				573 (97%)	465 (78%)	410 (69%)	393 (66%)

[a] Mycologic cure is defined as a negative KOH and a negative fungal culture.
[b] Complete Cure is defined as IGA = 'Clinical Cure' and mycologic cure.
[c] Clinical Improvement is defined as IGA = 'Clinical Cure' or 'Clinical Improvement' and mycologic cure.

Source: This submission; Clinical Study Report (BT0300-302-INT), Table 14.2.1.1

Table 12: Summary of IGA and mycology by visit (ITT), Itraconazole Capsules (N = 590)

Itraconazole Capsules (N=590)	Baseline	Week 4	Week 8	Week 12	Week 26	Week 39	Week 52
IGA							
Clinical Cure	0 (0%)	0 (0%)	0 (0%)	0 (0%)	47 (8%)	115 (19%)	166 (28%)
Clinical Improvement	0 (0%)	0 (0%)	8 (1%)	43 (7%)	157 (27%)	140 (24%)	97 (16%)
Mild	29 (5%)	59 (10%)	84 (14%)	125 (21%)	177 (30%)	148 (25%)	115 (19%)
Moderate	338 (57%)	307 (52%)	309 (52%)	282 (48%)	151 (26%)	137 (23%)	145 (25%)
Severe	223 (38%)	224 (38%)	189 (32%)	140 (24%)	58 (10%)	50 (8%)	67 (11%)
Clinical Cure/Improvement	0 (0%)	0 (0%)	8 (1%)	43 (7%)	204 (35%)	255 (43%)	263 (45%)
Mild/Moderate	367 (62%)	366 (62%)	393 (67%)	407 (69%)	328 (56%)	285 (48%)	260 (44%)
Severe	223 (38%)	224 (38%)	189 (32%)	140 (24%)	58 (10%)	50 (8%)	67 (11%)
KOH Result							
Positive	590 (100%)			405 (69%)	275 (47%)	281 (48%)	295 (50%)
Negative	0 (0%)			185 (31%)	315 (53%)	309 (52%)	295 (50%)
Fungal Culture Result							
Positive	590 (100%)			343 (58%)	242 (41%)	260 (44%)	265 (45%)
Negative	0 (0%)			247 (42%)	348 (59%)	330 (56%)	325 (55%)
Mycologic Cure[a]							
Success				107 (18%)	228 (39%)	226 (38%)	218 (37%)
Failure				483 (82%)	362 (61%)	364 (62%)	372 (63%)
Complete Cure (Primary Endpoint at Wk 52)[b]							
Success				0 (0%)	36 (6%)	84 (14%)	128 (22%)
Failure				590 (100%)	554 (94%)	506 (86%)	462 (78%)
Clinical Improvement (Secondary Endpoint at Wk 52)[c]							
Success				11 (2%)	118 (20%)	155 (26%)	173 (29%)
Failure				579 (98%)	472 (80%)	435 (74%)	417 (71%)

[a] Mycologic cure is defined as a negative KOH and a negative fungal culture.
[b] Complete Cure is defined as IGA = 'Clinical Cure' and mycologic cure.
[c] Clinical Improvement is defined as IGA = 'Clinical Cure' or 'Clinical Improvement' and mycologic cure.
Source: This submission; Clinical Study Report (BT0300-302-INT), Table 14.2.1.1

The predominant pathogen, analyzed in the ITT population (and PP population) was *T. rubrum*, with a total of 1005 isolates tested by the central facility (435 from the itraconazole tablet arm, 423 from the itraconazole capsule arm, and 147 from the placebo arm). A total of 44 isolates of *T. mentagrophytes* were analyzed in the ITT population (19 from the itraconazole tablet arm, 20 from the itraconazole capsule arm, and 5 from the placebo arm). Eight isolates of *E. floccosum* were cultured from subjects in the ITT population (3 from each of the active treatment arms and 2 from the placebo arm). With one exception, the upper range of MIC results for itraconazole (interpreted at the 96-hour reading) against isolates of *T. rubrum* was 1 mcg/ml (the MIC of one isolate, collected from a subject in the itraconazole capsule arm, was ≥ 8 mcg/ml). The upper ranges for isolates of *T. mentagrophytes* and *E. floccosum* were 0.125 mcg/ml and 0.25 mcg/ml, respectively. No other fungi were isolated and tested from subjects enrolled in the trial.

Against isolates of *T. rubrum* and *T. mentagrophytes*, treatment with itraconazole tablets and capsules resulted in similar efficacy (Tables 13 and 14). Against isolates of *E. floccosum*, treatment with itraconazole capsules resulted in a notably higher percentage of complete cure (66.7% compared to 20% observed for treatment with itraconazole tablets), but the numbers of isolates were too few to interpret meaningfully.

Table 13: Summary of complete cure at Visit 8 (Week 52) by subgroup (ITT)

Baseline Dermatophyte	*T. rubrum*			*T. mentagrophytes*		
	Itraconazole Tablets (N=561)	Itraconazole Capsules (N=564)	Placebo Tablets (N=188)	Itraconazole Tablets (N=27)	Itraconazole Capsules (N=23)	Placebo Tablets (N=7)
Complete Cure[a]						
Success	129 (23.0%)	124 (22.0%)	2 (1.1%)	2 (7.4%)	2 (8.7%)	0 (0.0%)
Failure	432 (77.0%)	440 (78.0%)	186 (98.9%)	25 (92.6%)	21 (91.3%)	7 (100.0%)

	E. floccosum		
	Itraconazole Tablets (N=5)	Itraconazole Capsules (N=3)	Placebo Tablets (N=3)
Complete Cure[a]			
Success	1 (20.0%)	2 (66.7%)	0 (0.0%)
Failure	4 (80.0%)	1 (33.3%)	3 (100.0%)

[a] Complete Cure at Visit 8 (Week 52) defined as both Clinical Cure and Mycologic Cure. Clinical Cure is defined as an IGA score for the target toenail of 0. Mycologic cure is defined as a negative KOH and negative dermatophyte culture for any dermatophyte.

Source: This submission; Clinical Study Report [BT0300-302-INT], Table 14.2.9.1

Table 14: Summary of complete cure at Visit 8 (Week 52) by subgroup (PP)

Baseline Dermatophyte	*T. rubrum*			*T. mentagrophytes*		
	Itraconazole Tablets (N=474)	Itraconazole Capsules (N=467)	Placebo Tablets (N=149)	Itraconazole Tablets (N=23)	Itraconazole Capsules (N=18)	Placebo Tablets (N=5)
Complete Cure[a]						
Success	123 (25.9%)	114 (24.4%)	2 (1.3%)	2 (8.7%)	2 (11.1%)	0 (0.0%)
Failure	351 (74.1%)	353 (75.6%)	147 (98.7%)	21 (91.3%)	16 (88.9%)	5 (100.0%)

	E. floccosum		
	Itraconazole Tablets (N=5)	Itraconazole Capsules (N=3)	Placebo Tablets (N=1)
Complete Cure[a]			
Success	1 (20.0%)	2 (66.7%)	0 (0.0%)
Failure	4 (80.0%)	1 (33.3%)	1 (100.0%)

[a] Complete Cure at Visit 8 (Week 52) defined as both Clinical Cure and Mycologic Cure. Clinical Cure is defined as an IGA score for the target toenail of 0. Mycologic cure is defined as a negative KOH and negative dermatophyte culture for any dermatophyte.

Source: This submission; Clinical Study Report [BT0300-302-INT], Table 14.2.9.2

No resistant breakpoints have been defined for itraconazole against filamentous fungi (including dermatophytes). The itraconazole resistant breakpoint against isolates of *Candida albicans* is ≥ 1 mcg/ml [CLSI M27-S3 2008]. Three isolates of *T. rubrum*, recovered at the Baseline Visit in this trial, had MIC values of 1 mcg/ml or greater, including one isolate in the itraconazole tablet arm (MIC = 1 mcg/ml), one isolate in the itraconazole capsule arm (MIC ≥ 8 mcg/ml), and one isolate in the placebo arm (MIC = 1 mcg/ml). None of the three subjects from which these isolates were recovered at the screening visit, were dermatophyte culture-positive at the Week 12 Visit. Two, including the subjects in the placebo and capsule arms, were KOH-positive (microbiological failures), and were also listed as clinical failures, with IGA scored as "moderate". The third subject, included in the table arm, was listed as a clinical success at Week 12 Visit, and was KOH and culture negative (microbiological success).

All other isolates collected at the Baseline Visit exhibited MIC values < 1 mcg/ml and, with one exception, no significant shifts were noted in MIC values in those isolates (i.e. increase in MIC values from < 1 mcg/ml to ≥ 1 mcg/ml). The one exception, regarding notable MIC shift, occurred in isolates collected from Subject 12028. Trichophyton rubrum isolates from this subject (itraconazole table arm) had MIC values of 0.25 mcg/ml at screening, and 1.0 mcg/ml at Week 12. Subsequent visits, however, produced isolates with MIC values of 0.06 mcg/ ml (Week 26), 0.125 mcg/ml (Week 39), and 0.5 mcg/ml (Week 52).

At the Week 52 visit, all collected dermatophyte isolates had MIC values < 1 mcg/ml. No increase in itraconazole resistance was noted during therapy.

Four subjects met the criteria, used by the central laboratory, for defining new dermatophyte infections, contracted during the course of the clinical trial. These criteria were based on a positive KOH and fungal culture following at least one visit that had been deemed a complete clinical and microbiological success. Details of the four subjects are summarized in Table 15. Isolates recovered at the Week 52 visit, from subjects previously listed as clinical and microbiological successes, were not tested for susceptibility to itraconazole (but were listed as clinical and microbiological failures, at this visit). No MIC values for isolates recovered from these subjects exceeded 1 mcg/ml.

Table 15: New dermatophyte infections diagnosed during Phase 3 clinical trial

Treatment Group	Subject number	Treatment success visit	New infection visit	MIC values (72 hours/96/hours)
Itraconazole tablets	45016	Week 39	Week 52	≤ 0.015/0.06 through Week 26; No values for Week 52
Itraconazole tablets	66015	Week 39	Week 52	0.03/0.125 through Week 12; No values for Week 52
Itraconazole tablets	81004	Week 26	Week 39	0.125/0.125 at Screening; 0.125/0.25 at Week 39
Itraconazole tablets	83010	Week 26	Week 52	0.25/0.25 at Screening; No values after Screening

Source: Study report bt0300-302-int-mic-report, page 2

CONCLUSIONS

See above.

APPLICANT'S PROPOSED SUBSECTION OF THE PACKAGE INSERT (PORTIONS PERTAINING TO CLINICAL MICROBIOLGY)

(b) (4)

AGENCY'S PROPOSED SUBSECTION OF THE PACKAGE INSERT (PORTIONS PERTAINING TO CLINICAL MICROBIOLGY)

(b) (4)

[redacted]

(b) (4)

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F. Marsik, Ph.D.
MicroTL/HFD-520

1 Nov 09 FIN FJM

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22484	ORIG-1	STIEFEL LABORATORIES INC	HYPHANOX 200MG FILM-COATED TABLETS

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/s/

KERRY SNOW
11/02/2009

FREDERIC J MARSIK
11/02/2009

Clinical Microbiology: 45-Day Meeting Checklist NDA - Fileability
NDA 22-484: Hyphanox for oral treatment of onychomycosis of the toenail
Reviewer: Kerry Snow Date Review completed: 29 April 2009

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

No.	Item	Yes	No	Comments
1	Is the clinical microbiology information (preclinical/nonclinical and clinical) described in different sections of the NDA organized in a manner to allow substantive review to begin?	✓		Preclinical microbiology information is principally provided through reference to NDAs for Sporonox Capsule (NDA 20-083) and Sporonox Oral Solution (NDA 20-657) (oral itraconazole 100 mg)
2	Is the clinical microbiology information (preclinical/nonclinical and clinical) described in different sections of the NDA indexed, paginated, and/or linked in a manner to allow substantive review to begin?	✓		
3	Is the clinical microbiology information (preclinical/nonclinical and clinical) in different sections of the NDA legible so that substantive review can begin?	✓		
4	On its face, has the applicant submitted *in vitro* 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?	✓		See comment No.1
5	Has the applicant submitted draft provisional breakpoint and interpretive criteria, along with quality control (QC) parameters, if applicable, in a manner consistent with contemporary standards, which attempt to correlate criteria with clinical results of NDA studies, and in a manner to allow substantive review to begin?			n/a
6	Has the applicant submitted any required animal model studies necessary for approvability of the product based on the submitted draft labeling?	✓		
7	Has the applicant submitted all special/critical studies/data requested by the Division during pre-submission discussions?	✓		

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8	Has the applicant submitted the clinical microbiology datasets in a format which intends to correlate baseline pathogen with clinical and microbiologic outcomes exhibited by relevant pathogens isolated from test of cure or end of treatment?	✓		
9	Has the applicant submitted a clinical microbiology dataset in a format which intents to determine resistance development by correlating changes in the phenotype (such as *in vitro* susceptibility) and/or genotype (such as mutations) of the baseline relevant pathogen with clinical and microbiologic outcome as exhibited by relevant pathogens isolated from test of cure or end of treatment?	✓		
10	Has the applicant used standardized methods or if non-standardized methods were used has the applicant included full 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?	✓		
11	Is the clinical microbiology draft labeling consistent with 21 CFR Parts 201, 314, 601 and current Divisional policy.	✓		
12	FROM A CLINICAL MICROBIOLOGY PERSPECTIVE, IS THIS NDA FILEABLE? **IF NO, GIVE REASONS BELOW.**	✓		

Any Additional Clinical Microbiology Comments:
No additional comments.

Name
Reviewing Clinical Microbiologist **MicroTL/HFD-520**
1 May 09 FIN FJM

Kerry Snow

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/s/

Kerry Snow
5/1/2009 10:18:47 AM
MICROBIOLOGIST

Frederic Marsik
5/1/2009 10:36:55 AM
MICROBIOLOGIST