CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-484

MEDICAL REVIEW(S)

Addendum to Original Medical Officer's Review of NDA 22-484

DOC TYPE: NDA 22-484

Sponsor: Stiefel Laboratories, Inc.

Drug: Itraconazole
Route of Administration: Oral
Dosage Form: 200mg tablet
Active Ingredient(s): Itraconazole
Pharmacologic Category: Azole antifungal agent
Proposed Indication: Onychomycosis of toenail
Drug Development Phase: 3

Review completion date: April 28, 2010

Medical Officer: Snezana Trajkovic, M.D.
Team Leader: David Kettl, M.D.
Project Manager: Nichelle Rashid, RPM

Background:

Medical officer review of the original submission for NDA 22-484 was completed on March 29, 2010, and recommended approval of this application for onychomycosis of the toenail. This addendum provides additional information in regards to labeling.

The original medical officer review includes the "Table 25: Summary of Treatment Phase Adverse Events by System Organ Class and Preferred Term". This table contains a summary of adverse events during the treatment phase of the Phase 3 trial. Adverse events were reported by System Organ Class and Preferred Term. The preferred term categories were further refined during the labeling process and consensus was reached regarding reporting for these categories. This review provides recommendations for final labeling.

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

(b) (4)

The final recommended label also includes additional information not addressed in the review dated 3/29/2010.
The review team concluded that the list of drugs that has a drug interaction potential with itraconazole was incomplete, and following the Agency's request, the sponsor submitted additional drug interaction information which was based on an extensive literature search. The review team recommended that methadone and felodipine be added to the contraindication section and to the boxed warning.

Information to support the labeling includes the finding that "Itraconazole increased Cmax of felodipine ~8-fold, AUC(0-32) and AUC(0-inf)] about 6-fold, and the elimination half-life 2-fold. The decreases in blood pressure and the increases in heart rate were significantly greater during the itraconazole phase than during the placebo phase. However, the correlation between the PK changes of felodipine and the Cmax or AUC of itraconazole was not statistically significant."

In addition, it was recommended that all contraindicated drugs be included in the boxed warning for Tradename itraconazole, and recommended the same to DSPTP for the Sporanox prescribing information.

120 Day Safety Update Report

The sponsor submitted a 120 day safety update report, stating that there is no new safety information as the product is not yet marketed and there are no ongoing trials.

This reviewer continues to recommend approval of this NDA application with final labeling as agreed by the sponsor.

Snezana Trajkovic, M.D.
Medical Officer
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/

SNEZANA TRAJKOVIC
04/28/2010

DAVID L KETTL
04/28/2010
Concur with approval recommendation

CLINICAL REVIEW

Application Type	NDA 505(b)(1)
Application Number(s)	22-484
Priority or Standard	Standard
Submit Date(s)	March 31, 2009
Received Date(s)	March 31, 2009
PDUFA Goal Date	April 30, 2010
Reviewer Name(s)	Snezana Trajkovic
Review Completion Date	March 26, 2010
Established Name	Itraconazole
(Proposed) Trade Name	Tradename
Therapeutic Class	Azole Antifungal
Applicant	Stiefel Laboratories, Inc.
Formulation(s)	Tablet 200mg
Dosing Regimen	Once daily
Indication(s)	Oral treatment of onychomycosis of the toenail
Intended Population(s)	18 years of age and older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The applicant submitted a 505 (b) (1) New Drug Application for Tradename-itraconazole 200mg tablets indicated for treatment of onychomycosis of the toenail. The applicant's product is a new formulation of already approved drug product itraconazole, currently marketed as Sporanox. Sporanox is currently available in an oral 100mg capsule and solution for both, intravenous and oral administration and is indicated for treatment of severe fungal infections as well as onychomycosis of the toenail and fingernail.

One Phase 3 (BT0300-302-INT) randomized, multi-center, parallel group, placebo-controlled, evaluator-blinded trial was conducted to establish the noninferiority of once daily Tradename-itraconazole 200mg tablet compared to once daily treatment of two 100mg itraconazole capsules (Sporanox) and to demonstrate superiority to placebo when administered for 12 weeks in the treatment of onychomycosis of the toenail. In this Phase 3 trial, Tradename-itraconazole 200mg tablet successfully demonstrated noninferiority to Sporanox and superiority over placebo for treatment of onychomycosis of toenail.

Safety data included 1516 subjects from 6 trials conducted under the clinical development program. The incidence of adverse events related to both itraconazole formulations tested (200mg tablet and 100mg capsule) was comparable to incidence of adverse events of currently marketed Sporanox and other approved triazole antifungal agents.

The applicant has adequately demonstrated that Tradename-itraconazole 200mg tablet is safe and effective for the treatment of onychomycosis of toenail in patients 18 years and older.

From a clinical perspective, it is recommended that the application be approved.

1.2 Risk Benefit Assessment

The safety and efficacy of the Tradename- itraconazole 200mg tablet was demonstrated in one Phase 3 trial (BT0300-302-INT), two Phase 1, bioequivalency trials (BT0300-BEL-002 and BT0300-BEL-005), one Phase 1 bioavailability trial (BT0300-BEL-006) and two Phase 2 PK trials (BT0300-BEL-004 and BT0300-108-USA).

The Phase 3 Trial was a randomized, multi-center, parallel group, placebo-controlled, evaluator-blinded study designed to evaluate the safety and efficacy of once daily (QD) administration of one Tradename- itraconazole 200mg tablet in comparison to once daily administration of two

itraconazole 100mg capsules and once daily administration of one placebo tablet in the treatment of onychomycosis of the great toenail, as this was selected for efficacy evaluation. The trial was conducted in 1354 patients, ages 16 to 75 years with a laboratory confirmed diagnosis of onychomycosis of the toenail.

The adverse event (AE) profile reported in these studies was similar to the adverse event profile of the comparator drug, Sporanox.

The primary efficacy endpoint was a Complete Cure at week 52. Complete Cure was defined as both a Clinical Cure and a Mycological Cure. A Clinical Cure was considered an IGA score of 0 for the target toenail, and a Mycological Cure included both a negative KOH examination and a negative culture for dermatophytes of the target toenail.

Tradename- itraconazole 200mg tablet product was tested for non-inferiority relative to the results obtained for the itraconazole 100mg capsule group and for superiority relative to the results obtained in the placebo tablet group.

The results demonstrated a clinically meaningful and statistically significant number of subjects with Complete Cure of onychomycosis of great toenail. The data showed that Tradename-itraconazole 200mg tablet was non-inferior to the approved itraconazole 100mg capsule (Sporanox) and superior to the placebo.

The safety profile of Tradename- itraconazole 200mg tablets was comparable to safety profile of approved Sporanox. There were no deaths during the development of the Tradename-itraconazole 200mg tablet. With the exception of one Serious Adverse Event (cholelithiasis) all other Serious Adverse Events were deemed by this reviewer not to be related to the study drug. Adverse events observed during the Phase 1 and Phase 3 trials were mild to moderate in severity.

Itraconazole 100mg capsule is currently approved as Sporanox for treatment of onychomycosis as well as severe fungal infections in the adult population.

The clinical development program for the Tradename- itraconazole 200mg tablet did not include patients younger than 16 years of age in any of the clinical studies. Considering that the prevalence of onychomycosis among children 17 years old or younger in North America is 0.44% and worldwide is from 0% to 2.6% [9], this reviewer agrees that the sponsor's request for the waiver in the pediatric population should be granted.

Since only two subjects under the age of 18 participated in Phase 3 trial this reviewer recommends restriction of the age indication for this new product to adults 18 years of age and older.

The Pediatric Review Committee considered this application on 10/28/2009. The PeRC recommendation concurred with the Division recommendations to restrict this product to adult use in patients 18 years of age and older and a waiver for patients under 18 years of age was granted.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Tradename-itraconazole 200mg tablet is a new formulation of an approved drug product containing itraconazole, currently marketed under the name Sporanox, approved by the Agency on September 11, 1992. Sporanox prescribing information includes a boxed warning for congestive heart failure, negative inotropic effect, and drug interactions. The proposed boxed warning is similar to the boxed warning of Sporanox. Clinical review of 6 clinical trials submitted in support of NDA revealed that there were a few events where negative inotropic effects of the drug could not be excluded but there were no unexpected myocardial ischemia, infarcts or stroke reports.

This reviewer concurs that the boxed warning is appropriate upon approval of Tradename-itraconazole 200mg tablet, and that there should be no additional risk management activities recommended at this time. Discussions with DSPTP to develop consistent labeling for the two products are ongoing as of the date of this review. There is no new postmarketing safety information for Sporanox, as well as there were no new safety signals identified during the development program of Tradename-itraconazole that would warrant REMS at the present time.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarketing requirements or commitments are recommended for this application.

2 Introduction and Regulatory Background

2.1 Product Information

Itraconazole is a synthetic triazole antifungal agent. Tradename-itraconazole 200mg tablet is a new formulation of an approved drug product containing itraconazole, currently marketed under the name Sporanox. Tradename-itraconazole 200mg tablet is not bioequivalent to Sporanox 100mg capsule. The current Agency approved itraconazole products are:

1. **Sporanox 100mg capsules** (NDA 20083, approved on 9/11/92), is indicated for treatment of blastomycosis (pulmonary and extrapulmonary), histoplasmosis (including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis) and, aspergillosis (pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy) in immunocompromised, and non-immunocompromised patients. Additionally, Sporanox is indicated for treatment of onychomycosis of the toenail, with or without fingernail involvement, due to dermatophytes (tinea unguium), and onychomycosis of the fingernail due to dermatophytes (tinea unguium) in non-immunocompromised patients.

Dosing regimen for treatment of toenail onychomycosis is 200mg (two 100mg capsules) once daily for 12 consecutive weeks.

Dosing regimen for treatment of fingernail onychomycosis is 2 treatment pulses, each consisting of 200mg (2 100mg capsules) b.i.d (400mg/day) for 1 week. The pulses are separated by a 3-week period without Sporanox therapy.

2. **Sporanox oral solution** (NDA 20657, approved 2/21/97) is indicated for empiric therapy of febrile neutropenic patients with suspected fungal infections and for the treatment of oropharyngeal and esophageal candidiasis.

3. **Sporanox injectable solution** (NDA 20966, approved 3/30/99) is indicated for empiric therapy of febrile neutropenic patients with suspected fungal infections. Sporanox injection is also indicated for the treatment of the following fungal infections in immunocompromised and non-immunocompromised patients: Blastomycosis (pulmonary and extrapulmonary), histoplasmosis (including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis) and aspergillosis (pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy).

4. **Itraconazole 100mg capsule** generic (ANDA 76104, approved on 5/28/04).

The proposed indication for Tradename-itraconazole 200mg tablet is treatment of patients with onychomycosis of the toenail.

The sponsor has conducted 2 bioequivalence trials (BT300-BEL-002; BT0300BEL05) and 2 bioavailability trials (BT0300BEL006; BT0300-BEL-004) that demonstrated that Tradename-itraconazole 200mg tablet was not bioequivalent to two itraconazole 100mg capsules. Therefore, the sponsor was requested to demonstrate safety and efficacy of the new itraconazole 200mg tablet formulation in the treatment of onychomycosis of the toenal

The sponsor proposed the trade name “Hyphanox”, but this proposed name has not been approved following review by OSE/DMEPA.

2.2 Tables of Currently Available Treatments for Proposed Indications

Onychomycosis is a condition that affects approximately 3% of population in developed countries. Onychomycosis is caused by 3 main classes of fungi: dermatophytes, yeast and nondermatophyte molds. Two major pathogens are responsible for 90% of onychomycosis cases. Trichophyton rubrum accounts for 70% and Trichophyton mentagrophytes accounts for 20% of all cases. Yeast and nondermatophyte molds account for 8% and 2% of onychomycosis cases respectively. [5, 17, 16]

There are three types of true dermatophyte infection: distal subungual onychomycosis, proximal subungual onychomycosis and superficial white onychomycosis.

Onychomycosis is diagnosed by physical examination, in combination with laboratory findings. Microscopic examination and culture of subungual debris increase the sensitivity and specificity of diagnosis, and laboratory results are particularly important when systemic therapy is considered.

Pharmaceutical therapeutic options include topical antifungal agents and oral systemic agents.

Currently available topical agents are used for limited cases of mild to moderate onychomycosis [17].

Systemic antifungal agents generally show higher efficacy rate than topical agents, but have potential to cause serious adverse events.

The only topical agent currently approved for treatment of onychomycosis is Ciclopirox 8% Nail Lacquer.

Ciclopirox 8% Nail Lacquer is a topical solution that has complete cure rate of approximately 5.5% to 8.8% (as per product label). The most common adverse events reported were periungual erythema and erythema of the proximal nail fold.

Systemic therapy approved for onychomycosis includes griseofulvin, itraconazole and terbinafine.

Griseofulvin is fungistatic with in vitro activity against various species of Microsporum, Epidermophyton and Trichophyton. Reported clinical cure rate is between 3% and 38% (per current literature). The most common adverse reactions include: hypersensitivity type skin rashes, urticaria, angioedema, and rarely reported proteinuria and leucopenia.

The newer generation of oral antifungal agents (itraconazole and terbinafine) has largely replaced older therapies in the treatment of onychomycosis in clinical practice. They have been reported to offer shorter treatment regiments, higher cure rates, and fewer adverse events. [19]

Terbinafine hydrochloride is a synthetic allylamine antifungal compound. It has been approved for treatment of onychomycosis of toenail and fingernail. Reported clinical cure rate is approximately 38% (as per product label). [6]

Cases of liver failure, Stevens-Johnson syndrome and Toxic Epidermal Necrolysis, exacerbation of Systemic Lupus Erythematosus, changes in the ocular lens and retina have been reported with the use of terbinafine.

Itraconazole is a synthetic triazole antifungal agent. Itraconazole 100mg capsules have been approved for treatment of toenail and fingernail onychomycosis. Analysis of 3 double-blind, placebo-controlled trials using 200mg of itraconazole once daily for 12 weeks showed 14% mycologic and clinical cure rate, and 35% of overall success (mycologic cure and minimal nail involvement) as per product label.[20]

Adverse events including hepatotoxicity and liver failure, ventricular disfuction, congestive heart failure and pulmonary edema have been reported in patients taking itraconazole. Peripheral

neuropathy, and transient or permanent hearing loss have been reported in patients receiving treatment with itraconazole.

Itraconazole and its major metabolite, hydroxyitraconazole, are inhibitors of CYP3A4. Therefore, interactions with dugs dependent on CYP3A4 metabolism may occur.

Life-threatening cardiac dysrhythmias and/or sudden death have occurred in patients using cisapride, pimozide, levacetylmethadol, methadone, and quinidine concomitantly with itraconazole.

Summary of approved medications for treatment of toenail onychomycosis is presented in Table1.

Table 1: Approved Medications for Treatment of Toenail Onychomycosis

Medication (Drug class)	Dosage form	Dosing Regimen	Success Rates	Anti-fungal Activity
Topical Agents				
Ciclopirox (hydroxypyridone) NDA 21022 (12/17/1999)	Nail lacquer 8%	Applied to nails daily for 48 weeks	Complete Cure: 5.5% -8.8%	Dermatophytes
Systemic Agents				
Griseofulvin (Spiro-benzo[b] furan) NDA 50475 (4/16/1975)	500-1000mg tablet/capsule	Daily until infection clears (up to 12 months)	Clinical Cure: 3%-38%	Dermatophytes
Itraconazole (Triazole) NDA 20083 (9/11/1992)	100mg capsule	2 capsules once daily for 12 weeks	Complete Cure: 14%	Dermatophytes, yeasts, other fungi
Terbinafine Hydrochloride (Allylamine) NDA 20539 (5/10/1996)	250mg tablets	1 tablet once daily for 12 weeks	Complete Cure:38%	Dermatophytes

Source: sponsor and Agency information

2.3 Availability of Proposed Active Ingredient in the United States

Itraconazole is currently a marketed drug product under the name Sporanox 100mg capsule (NDA 20083, approved 9/11/92), Sporanox oral solution (NDA 20657, approved 2/21/97) and Sporanox injectable solution (NDA 20966, approved 3/30/99), and generic itraconazole 100mg capsule (ANDA 76104, approved 5/28/04)

2.4 Important Safety Issues with Consideration to Related Drugs

Itraconazole belongs to a class of synthetic triazole antifungal agents. The triazoles available for clinical use include fluconazole, itraconazole, voriconazole and posaconazole.

Itraconazole and fluconazole represent the first generation of systemic triazoles. As a class, triazoles act predominantly by inhibiting cytochrome P450 (CYP)-dependent conversion of lanosterol to ergosterol, the main sterol in the cell membrane of most fungi, resulting in inhibition of cell growth and replication. Both drugs have quite different pharmacokinetic properties. Whereas fluconazole has nearly complete oral bioavailability, circulates in plasma mostly as free drug, undergoes only negligible hepatic metabolism, and is excreted predominantly through the kidneys in unchanged form, itraconazole, a poorly water-soluble compound, is not as well absorbed by the gastrointestinal tract, has high protein binding and extensive hepatic metabolism, and is excreted in inactive form through the liver and kidneys.

Triazoles are generally well tolerated, but they have significant potential for drug-drug interactions through interference with the hepatic CYP3A4 metabolic pathway and potential for hepatic toxicity, including liver failure and death.

Life threatening cardiac dysrhythmias including QT prolongation, torsades de pointes, ventricular tachycardia, cardiac arrest and sudden death were reported when cisapride, pimozide, levomethadil, methadone, or quinidine were used concomitantly with itraconazole and other CYP3A4 inhibitors.

When Itraconazole was administered intravenously to dogs and healthy volunteers, negative inotropic effects were noted.

Transient or permanent hearing loss has been reported in patients receiving treatment with Itraconazole.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Discussion of the regulatory activity of the sponsor's drug development program

Pre-IND Meeting: October 25, 2004

- The design of the proposed protocol synopses for the pharmacokinetic studies as outlined in the briefing package appeared appropriate to support the clinical program for the use of itraconazole 200mg film-coated tablet in the same dermatological indications and dosing regimens as approved for Sporanox 100mg capsules.

- The sponsor's plan to pursue the approval for a new dosage form, itraconazole 200mg tablet, [redacted] (b) (4) was discussed.

- The Available data demonstrated that the two dosage forms (200g tablet and Sporanox two 100mg capsules) were not bioequivalent. The new 200mg tablet was outside of BE range.

- The sponsor was requested to characterize the pharmacokinetics of itraconazole tablets following the 400mg dose as per its new proposed dosing regimen (once a day) compared to the approved twice daily dosing regimen for the Sporanox 100mg capsules.

End of Phase 2 Meeting: December 8, 2005

At that time the sponsor intended to study itraconazole tablets for the treatment of [redacted] (b) (4) In addition the following points were discussed during the meeting:

- It was recommended that the sponsor conducts one three-arm study comparing the efficacy of sponsor's itraconazole product to Sporanox (at the labeled dose) for the indication studied, and to placebo. Tradename itraconazole should be superior to placebo and noninferior to Sporanox. If Tradename itraconazole is not bioequivalent to Sporanox, the Agency needs relative safety and efficacy information for Hyphanox vs. the currently marketed itraconazole product.

- Agency recommended that Mycology Cure should be assessed at a time when no

itraconazole is expected to remain in the nail, at least 4 weeks after the completion of treatment. Where Mycology Cure is defined as a negative KOH and a negative culture for any dermatophyte, then the definition of Complete Cure seems appropriate; however, changes to the definition of Mycology Cure should not be limited to a negative culture for the dermatophyte isolated at baseline.

- It would seem appropriate to request a waiver from pediatric studies in subjects younger than (b) (4) years of age.

Special Protocol Assessment (SPA): March 7, 2006

The design of the Phase 3 pivotal trial was the subject of the Special Protocol Assessment (SPA) submitted on March 7, 2006 (received on March 8, 2006).

The proposed development plan was a departure from the previously discussed development plan at the End of Phase 2 Meeting. Previously submitted studies, Serial #000 and #002, proposed dosing of Tradename itraconazole at (b) (4) for treatment of onychomycosis (b) (4) (b) (4) New protocol proposed investigation of a single dose, 200mg itraconazole tablet once daily for treatment of toenail onychomycosis.

Special Protocol Assessment (SPA): May 31, 2006

The design of the Phase 3 pivotal trial was the subject of the Special Protocol Assessment (SPA) submitted on May 31, 2006 (received June 1, 2006). The sponsor submitted changes based on the initial SPA review. The Agency generally concurred with the proposed protocol changes.

A Type A meeting was held on July 24, 2006 to discuss the Agency's feedback on the study design.

Guidance Meeting: July 24, 2006

1. The Agency was in agreement with sponsor's proposed primary endpoint, which is the difference in percentage of patients achieving both clinical cure (an IGA of 0 with no evidence of onychomycosis in target nail - normal nail unit without subungual hyperkeratosis or onycholysis) and mycologic cure (negative KOH and negative culture for dermatophytes of the target toenail).

2. The Agency did not agree with the sponsor's choice and definition of the secondary endpoints:

- The use of clinical IGA "almost clear" criterion that would truly reflect an "almost clear" endpoint and, when combined with mycological cure, could be acceptable as a secondary endpoint.

- The sponsor included a secondary endpoint that described the number of toenails (b) (4) [redacted] The secondary endpoints for toenail onychomycosis and any evidence of success would not be used for labeling or marketing.

3. It appeared that the AUC was higher for Tradename itraconazole compared to Sporanox therefore, more safety information may be needed. The sponsor agreed to submit additional summary information.

Pre-NDA meeting scheduled for February 4, 2009.

The sponsor cancelled pre-NDA meeting on February 2, 2009 following receipt of the draft comments.

<u>Summary of Major Areas of Agreements and Disagreements with the sponsor</u>
(From The Guidance Meeting July 24, 2006)

- The Agency was in agreement with sponsor's proposed primary endpoint, which is the proportion of subjects in each dosing group with Complete Cure at Visit 8 (Week 52), the primary evaluation visit. In this study, Complete Cure was defined as both a Clinical Cure and a Mycological Cure. A Clinical Cure was considered an IGA score of 0 for the target toenail, and that a Mycological Cure must have included both a negative KOH examination and a negative culture for dermatophytes of the target toenail.
- The Agency did not agree with the sponsor's choice and definition of the secondary endpoints. Agency recommended to the sponsor to use clinical IGA "almost clear" criterion that would truly reflect an "almost clear" endpoint and, when combined with mycological cure, could be acceptable as a secondary endpoint.
- The sponsor agreed that secondary endpoints for toenail onychomycosis and any evidence of success would not be used for labeling or marketing

The sponsor has conducted the Phase 3 trial in accordance with the protocol that was agreed upon by the sponsor and FDA.

3 Ethics and Good Clinical Practice

3.1 Quality and Integrity

Following sites were selected for DSI inspection:

- Site 15: Steven Kempers, M.D.

  Reason: At this site there were subjects for whom the study drug dispensation information was temporarily available to blinded personnel. Therefore, there was the possibility that the blind was broken for a set of subjects.

- Site 38: Raza Aly, PhD

  Reason: This site was selected based on number of enrolled subjects, and number of treatment responders.

DSI Report of Inspection of Site 15 (Steven Kempers, M.D.)

At this site, 140 subjects were screened, 72 were enrolled, and four dropped out. At this site, 72 subject records were audited with respect to informed consent and the primary efficacy endpoint. Inspection revealed that there was a potential unblinding issue in that drug accountability information was recorded on blinded source documents that had the potential to unblind the study (i.e., whether subjects were taking 100mg capsules or 200mg tablets or placebo). There was no indication that any of the investigators at the site were actually unblinded as the result of the inclusion of this information. Blinding does not appear to have been compromised.

The recommendation by DSI investigator was that noted deviations would not appear to have a significant impact on data integrity, and the data appear acceptable in support of the respective application.

DSI Report of Inspection of the Site 38 (Raza Aly, PhD)

At this site, 107 subjects were screened, 49 were enrolled, 41 completed the study, and eight dropped out. All 107 subject records were audited with respect to informed consent. Of the 49 enrolled subjects, the records of 25 subjects were reviewed with respect to inclusion/exclusion criteria, medical histories, baseline status, randomization, primary and secondary efficacy endpoints, concomitant medications, clinical evaluations, safety assessments, adverse events,

protocol deviations, subject withdrawals and terminations, and source document information and line listings as compared with corresponding CRFs.

The recommendation by DSI investigator was that noted deviations would not appear to have a significant impact on data integrity, and the data appear acceptable in support of the respective application.

Clinical reviewer's comments: The issue of unblinding did not appear to affect study results or conclusions. As discussed below, Agency's analysis of efficacy data excluding the involved sites did not change the efficacy conclusions.

To insure that potential unblinding issues did not affect efficacy determinations, the sensitivity analysis discarding the data from the seven sites where the blind was potentially broken was performed. Efficacy results and analysis procedures were the same as those used in the primary analysis. Exclusion of all subjects from these sites resulted in the exclusion of a total of 301 subjects. Despite the removal of 301 subjects from the total number of enrolled subjects in this analysis, efficacy was demonstrated for the non-inferiority objective comparing Tradename-itraconazole 200mg tablets to itraconazole 100mg capsules for the ITT and PP populations as well as the superiority objective for comparing the itraconazole 200mg tablets to placebo tablets. Please refer for full discussion in Section 6.1.4.

3.2 Compliance with Good Clinical Practices Submission

The protocol and Informed Consent Forms were reviewed by the Investigational Review Board (IRB) associated with the trial sites or by consulting central IRB, and approved prior to trial initiation. Per clinical trial reports, subjects signed informed consent form prior to enrollment into the trial.

The sponsor stated that this study was designed, monitored, and conducted in accordance with Good Clinical Practice (GCP) requirements and the ethical principles.

3.3 Financial Disclosures

The sponsor certified (Form 3453) that they had not entered into any financial arrangement with any of the clinical investigators.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

CMC data have been extensively reviewed by the Drug Product and Drug Substance Reviewer, Christopher Hough, Ph.D.

The Office of Compliance did not issue their recommendation regarding manufacturing site acceptability until January, 2010, following closure of the initial CMC recommendation in their review:

"The Sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA also has provided sufficient stability information for the drug product to assure strength, purity, and quality of the drug product during the expiration dating period. However, all issues involving labels and final recommendation from the Office of Compliance concerning establishment acceptability have not been resolved as of the date of this review. Therefore, this NDA will not be recommended for approval until these issues are resolved."

Subsequent inspection of manufacturing facilities was determined by the Office of Compliance to be acceptable, and there are no outstanding CMC issues.

4.2 Clinical Microbiology

Clinical Microbiology Consultation Conclusion:

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

From a clinical microbiology perspective, the Application is approvable, provided the recommended changes are included in the proposed label."

Clinical reviewer's comments: This reviewer agrees with conclusions of microbiology reviewer, and concurs that (b) (4) *should not be included in the prescribing information.*

4.3 Preclinical Pharmacology/Toxicology

No new non-clinical trials of the active pharmaceutical ingredient were conducted in the support of this NDA. The sponsor of Tradename-itraconazole 200mg tablet (Stiefel Laboratories, Inc.) has a Right of Reference for clinical and non-clinical data from the sponsor of Sporanox (Johnson & Johnson). The non-clinical safety profile of the proposed tablet formulation is based on studies conducted to support the safety of Sporanox 100mg capsule (NDA 20-083 approved in 1992) and Sporanox solution (NDA 20-657 approved in 1997).

All preclinical pharmacology/toxicology itraconazole studies were conducted with Sporanox, none with formulations reviewed in this NDA. Therefore, except for a few cardiovascular studies conducted in late 1990s, no additional preclinical studies were specifically conducted to evaluate the drug effect(s) on other vital organ functions.

The non-clinical reviewer recommended approval of this NDA.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Itraconazole belongs to the first generation of systemic triazoles. As a class, triazoles act predominantly by inhibiting cytochrome P450 (CYP)-dependent conversion of lanosterol to ergosterol, the main sterol in the cell membrane of most fungi, resulting in inhibition of cell growth and replication.

4.4.2 Pharmacodynamics

"No information is provided in this submission on the metabolism of itraconazole following administration of 200mg tablets. However, it is found in the Clinical Pharmacology section of the Sporanox label that itraconazole is metabolized predominantly by CYP3A4, resulting in the formation of several metabolites including hydroxy-itraconazole, the major and bioactive metabolite. Fecal excretion of the parent drug was 3-18% of the dose and renal excretion of the parent drug is less than 0.03% of the dose. About 40% of the dose is excreted as inactive metabolites in the urine. No single excreted metabolite represents more than 5% of a dose. "

The labeling for Tradename-itraconazole will mirror that of Sporanox for this section.

4.4.3 Pharmacokinetics

The Clinical Pharmacology Reviewer's Conclusions:

"A Tradename-itraconazole 200mg tablet and two 100mg Sporanox capsules are non bioequivalent based on the results from BT300-BEL-002, BT0300BEL005, and BT0300BEL006 studies. Total exposure of itraconazole was about 15% higher with the itraconazole 200mg film-coated tablet than with the itraconazole 100mg capsules, when dosing occurred in the fasted state and after a standard breakfast. When dosing occurred after a high-fat, high-calorie breakfast, however, the itraconazole 200mg film-coated tablet had a 30% lower bioavailability. Below are a table, summarizing the mean and 90% CI of Cmax, AUC and Tmax from all three studies, and this reviewer's conclusions:

- The effects of food on the comparative BA of Tradename-itraconazole vs. Sporanox are not unidirectional and depend on the composition of the meal.

- Under a high-fat high-calorie meal condition, the exposure of Tradename-itraconazole was 30 % lower than that for Sporanox. As such, safety related to the systemic exposure to itraconazole is not of a particular issue under this condition, while it may raise a question regarding its potential impact on the efficacy. To note, however, is that there is high inter-subject variability in the exposure with coefficient of variations (CV) for AUC in the range of 56-66 %, which may be accounted by the itraconazole intrinsic property of low solubility. Furthermore, in reality it is unlikely that patients will have high-fat high-calorie breakfast everyday for 12 weeks, leading to a consistent reduction in the systemic concentrations of itraconazole. Rather, it is anticipated that the mean plasma concentrations of Tradename-itraconazole will fluctuate around the mean plasma concentrations expected from Sporanox, depending on the composition of a daily meal. Therefore it is the reviewer's opinion that the differences in the exposure between Tradename itraconazole and Sporanox under this specific high-fat high-calorie meal condition will not have significant clinical impact.

- Under a standard meal condition, Cmax of Tradename-itraconazole was equivalent to that of Sporanox, while the exposure was ~15 % higher than Sporanox. However, the CVs of AUC for Tradename-itraconazole and Sporanox observed in this study are large, ranging 44 % – 48 %, and the 15 % difference is unlikely to have clinical significance.

- Under a fasting condition, the exposure of Tradename-itraconazole was higher (15 %) than Sporanox. Additionally, AUC following Tradename itraconazole administration under fasting status was still lower than those observed for both Sporanox and

Tradename-itraconazole tablet under fed conditions, and therefore no safety issues are expected.

- While the exposure of Hyphanox did not meet the bioequivalent criteria compared to Sporanox, the slight differences described above are unlikely to have clinical significance due to inherent high inter-subject variability."

Clinical reviewer's comment: It was noted that there is difference of exposure of Tradename-itraconazole in comparison to Sporanox depending on meal conditions.

Under fasting conditions the exposure to Tradename-itraconazole was 15% higher than Sporanox although the AUC was still lower than those observed for both Tradename-itraconazole and Sporanox under fed conditions.

When dosing occurred under high-fat, high-calorie meal Tradename-itraconazole had 30% lower bioavailability in comparison to Sporanox. Therefore no safety issues are anticipated.

Under fed conditions (standard meal) the exposure of Tradename-itraconazole was 15% higher than Sporanox. However the coefficient of variations for AUC was in range of up to 43-66% and, therefore the difference of 15% could be due inter-subject variability.

The accumulation ratio of Tradename-itraconazole tablet at a steady state is comparable to that of Sporanox (~10), suggesting no greater increase of itraconazole or hydroxy-itraconazole following 12 week treatment period. The steady state level of Tradename-itraconazole was reached by day 10 and PK parameters obtained at day 14 reflect the drug's disposition pattern at a steady state.

In addition Tradename-itraconazole tablet had 14.7% higher exposure than Sporanox, as measure by AUC 0-∞ (geometric mean), and 90% CI was 103.7-126.8, showing a deviation of 1.8% from the BE limit.

In the Phase 3 trial no new safety signals were observed during the dosing period or during the follow-up period. Adverse events in Tradename-itraconazole group were similar to those in Sporanox treatment group.

On the basis of the discussion above it is not anticipated that 15% increased exposure of Tradename-itraconazole will have clinical safety implications.

The variability of exposures related to meal conditions is addressed by the labeling requirement to take Tradename-itraconazole with a full meal. Labeling is adequate to address the clinical pharmacology issues related to absorption variability.

Drug Interactions

Itraconazole has significant potential for drug-drug interactions through interference with the hepatic CYP3A4 metabolic pathway. Drug-drug interaction potential of itraconazole was addressed in the Sporanox label and Tradename-itraconazole proposed label.

During the review of the sponsor's proposed label, the review team recognized that the list of drugs that has drug interaction potential with itraconazole was incomplete, and not all of the contraindicated drugs were listed in the boxed warning. Following the Agency's request, the sponsor submitted additional drug interaction information which was based on an extensive literature search.

The following recommendation for label changes based on the review of the submitted literature articles are summarized in the Table 2 below.

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Since the information on some of the drugs listed above is not adequate to warrant labeling changes at this time or the drugs are not marketed in United States only the following drugs are included into the Tradename-itraconazole label: Efavirenz, Meloxicam, Maraviroc, Aripiprazole, Felodipine, Methadone, Rapaglinide.

Reviewer's Comments:

This reviewer recommends that all of the contraindicated drugs for itraconazole be included in the boxed warning. Methadone is the only new product to be added from the information submitted in this application. The other products (Cisapride, Midazolam, Nosoldipine, Pimozide, Quinidine, Dofetilide, Triazolam, Levacetylmethadol, Ergot alkaloids (Dihydroergotamine, Ergometrine, Ergotamine and Methylergometrine) were previously known to be contraindicated but have not yet been added to the existing boxed warning for Sporanox.

Division of Dermatology and Dental Products has had discussions regarding drug interaction labeling with Division of Special Pathogens and Transplant Products,, which regulates the labeling for Sporanox, since the indication for onychomycosis was submitted and approved as a Type 6 NDA and the Sporanox labeling has since reverted to DSPTP. A supplement request to the Sporanox sponsor is anticipated from DSPTP once the action for Tradename-itraconazole occurs. The goal will be to have consistent labeling between the two related products.

5 Sources of Clinical Data

Sources of clinical data include one Phase 3 trial enrolling 1,354 subjects (BT0300-302-INT), two Phase 1, bioequivalency trials (BT0300-BEL-002 and BT0300-BEL-005) enrolling 112 subjects, one Phase 1 bioavailability trial (BT0300-BEL-006) enrolling 18 subjects and two Phase 2 PK trials (BT0300-BEL-004 and BT0300-108-USA) enrolling 32 subjects. Four of the 5 Phase 1 studies were open-label, single-center studies intended to evaluate the itraconazole 200mg tablet in healthy, adult volunteers. Summary of Clinical Trials is displayed in Table 2:

Table 3: Description of Clinical Trials

Study Identifier; Type of Study	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
BT300-BEL-002; Phase 1, Bioequivalence (11/12/03-2/24/04)	To determine the bioequivalence of 1 itraconazole 200mg tablet relative to 2 itraconazole 100mg capsules taken in a single dose after a standard meal	Open-label, active controlled, randomized, 2-way crossover, single-center	Itraconazole 200mg tablet and itraconazole 100mg capsule; 1 tablet or 2 capsules after a standard breakfast; Oral dose	56	Healthy subjects, 18 to 55 years of age (inclusive)	Single administration of each study drug separated by a 14-day washout period with subjects followed for 4 days after each dosing
BT0300BEL005; Phase 1, Bioequivalence (3/1/05-4/25/05)	To determine the bioequivalence of 1 itraconazole 200mg tablet relative to 2 itraconazole 100mg capsules taken in a single dose after a high-calorie, high-fat meal	Open-label, active controlled, randomized, 2-way crossover, single-center	Itraconazole 200mg tablet and itraconazole 100mg capsule; 1 tablet or 2 capsules after a high-calorie, high-fat breakfast; Oral dose	56	Healthy subjects, 18 to 55 years of age (inclusive)	Single administration of each study drug separated by a 14-day washout period with subjects followed for 5 days after each dosing

Table 3: Description of Clinical Trials (Continued)

Study Identifier; Type of Study	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
BT0300BEL006; Phase 1, Bioavailability (2/25/05-4/20/05)	To assess the effect of food on the bioavailability of itraconazole 200mg tablets and to compare the bioavailability (fasting) of itraconazole 200mg tablets and itraconazole 100mg capsule	Open-label, active controlled, randomized, 3-way crossover, single-center	Itraconazole 200mg tablet and itraconazole 100mg capsule; 1 tablet (fasting), 1 tablet (fed: high-calorie, high-fat breakfast), or 2 capsules (fasting);	18	Healthy subjects, 18 to 55 years of age (inclusive)	Single administration of each study drug separated by a 14-day washout period with subjects followed for 5 days after each dosing
BT300-BEL-004; Phase 1, PK (1/14/05-2/19/05)	To assess the pharmacokinetics of itraconazole and hydroxyl-itraconazole after a single dose of 2 itraconazole 200mg tablets following a high-calorie, high-fat meal	Open-label, single-arm, single-center	Itraconazole 200mg tablet; 2 tablets after a high-calorie, high-fat breakfast; Oral dose	16	Healthy female subjects, 18 to 65 years of age (inclusive)	Single administration of study drug with subjects followed for 5 days after dosing

Table 3: Description of Clinical Trials (Continued)

Study Identifier; Type of Study	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
BT0300-108-USA; Phase 1, Steady-State PK (5/20/08-7/7/08)	To document the steady state pharmacokinetics and safety of itraconazole 200mg tablets when administered once daily for 14 days	Open label, single-arm, single-center	Itraconazole 200mg tablet; 1 tablet QD after a standard breakfast; Oral dose	16	Healthy subjects, 18 to 55 years of age (inclusive)	14 days of study drug administration with subjects followed for 14 days after dosing
BT0300-302-INT; Phase 3, Safety and Efficacy (7/20/06-10/2/08)	To evaluate the safety and efficacy of itraconazole 200mg tablets, itraconazole 100mg capsules, and placebo tablets in the treatment of onychomycosis of the toenail	Multi-center, 3-arm, randomized, evaluator-blind, active- and placebo-controlled, parallel group	Itraconazole 200mg tablet or itraconazole 100mg capsule or placebo tablet; 1 tablet or 2 capsules QD after breakfast; Oral dose	1,381	Subjects 16 to 75 years of age (inclusive) with onychomycosis	12 weeks of study drug administration with subjects followed for 40 weeks after dosing

Source: sponsor's submission, Tabular Listing of Al Clinical Studies Section 5.2

5.2 Review Strategy

The review of efficacy is based primarily of the single Phase 3 trial, BT0300-302-INT. This was multi-center, randomized, parallel group, evaluator-blind, placebo-controlled trial in 1381 subjects, 16 to 75 years of age.

The review of safety was based on one pivotal clinical trial that enrolled 1,354 subjects (BT0300-302-INT), two Phase 1, bioequivalency trials (BT0300-BEL-002 and BT0300-BEL-005) enrolling 112 subjects, one Phase 1 bioavailability trial (BT0300-BEL-006) enrolling 18 subjects and two Phase 1 PK trials (BT0300-BEL-004 and BT0300-108-USA) enrolling 32 subjects.
Review of 5 Phase 1 trials was deferred to Clinical Pharmacology; however, adverse event data were included in the safety analysis.
The sponsor of Tradename-itraconazole 200mg tablet (Stiefel Laboratories, Inc.) has a Right of Reference for clinical and non-clinical data from the sponsor of Sporanox (Johnson & Johnson). The non-clinical safety profile of the proposed 200mg tablet formulation is based on studies conducted to support the safety of Sporanox 100mg capsule (NDA 20-083 approved in 1992) and Sporanox solution (NDA 20-657 approved in 1997).

5.3 Discussion of Individual Studies/Clinical Trials

Trial BT0300-302-INT

Title

A phase III Randomized, Evaluator-Blind, Parallel Group Study of the Safety and Efficacy of Itraconazole Tablets, Itraconazole Capsules and Placebo in the Treatment of Onychomycosis of the Toenail.

Trial objective

Study was designed to evaluate the non-inferiority of one Tradename-itraconazole 200mg tablet given once daily to two itraconazole 100mg capsules given once daily and the superiority of itraconazole tablets to placebo in treatment of onychomycosis of the great toenail.

Trial design

BT0300-302-INT was a randomized, multi-center, parallel group, placebo-controlled, evaluator-blinded trial designed to evaluate the safety and efficacy of once daily (QD) administration of one Tradename-itraconazole 200mg tablet in comparison to two itraconazole 100mg capsules (Sporanox) and one placebo tablet in the treatment of onychomycosis of the great toenail. The study was designed to include 1,288 subjects who were 16 to 75 years of age (inclusive), of either sex, and had clinical diagnosis of distal and /or lateral subungual onychomycosis affecting at least one great toenail. Eligible subjects were randomized 3:3:1 to administer one Tradename-itraconazole 200mg tablet, two itraconazole 100mg capsules, or one placebo tablet after breakfast, QD for 12 weeks. The study consisted of 8 visits, which comprised the 12 week dosing period as well as a 40-week follow-up period.

Patient population

Subjects 16 to 75 years of age, of either sex, with clinical diagnosis of distal and/or lateral subungual onychomycosis affecting at least one great toenail were included into the trial.

Inclusion Criteria:

For inclusion into the trial, subjects were required to fulfill all of the following criteria:

1. The subject completed an appropriately administered informed consent process which included signing the IEC/IRB approved informed consent form;
2. The subject was willing and able to take the study drug, comply with clinical trial instructions, and commit to all the follow-up visits for the duration of the clinical trial;

3. The subject was in good general health and free of any disease state or physical condition which, in the investigator's opinion, might have impaired evaluation of onychomycosis of the toenail or might have exposed the subject to unacceptable risk by study participation;
4. If the subject was a woman of childbearing potential she must have had a negative urine pregnancy test and must have agreed to use an effective form of birth control (stabilized on oral contraceptives for at least 3 months or using implanted, transdermal or injected contraceptive hormones, intra-uterine device, vaginal ring, cervical cap, condom and spermicidal agent or diaphragm and spermicidal agent) during study drug administration and for 60 days following the last dose of study drug;
5. The subject had a clinical diagnosis of distal and/or lateral subungual onychomycosis affecting at least 1 great toenail;
6. The subject had onychomycosis on the more severe great toenail (target toenail) involving >25% – 75% of the entire nail unit.
7. The length of unaffected part of the target toenail (clear toenail) was ≥2 mm measured from the proximal nail fold to the onychomycotic border;
8. The subject had direct microscopic examination with KOH that was positive for the hyphae associated with dermatophytes on the target toenail;
9. The subject was between 16-75 years old, inclusive, and of either sex.

Exclusion Criteria:

The following constituted the exclusion criteria for the trial:

1. Subject had a history of sensitivity to any of the ingredients in the study drugs;
2. Subject was currently participating in, or had within the prior 24 weeks participated in an investigational trial involving systemic treatment for onychomycosis of the fingernail or toenail;
3. Subject was currently participating in, or had within the prior 30 days participated in an investigational trial;
4. Subjects with onychomycosis of the target toenail caused by molds, and/or *Candida spp*. without the presence of a dermatophyte;
5. Subjects with white superficial onychomycosis or significant dystrophy of the target toenail that, in the opinion of the investigator, would have impaired evaluation of the onychomycosis;
6. Subjects with total dystrophic onychomycosis or proximal subungual onychomycosis of the target toenail;
7. Subjects with mycotic spikes or exclusively lateral groove involvement of the target toenail;
8. Subjects with zero nail growth of the target toenail as demonstrated by no nail growth over the preceding 12 months;
9. Subjects with very thick target toenails >3 mm;
10. Subjects with peripheral vascular circulation significantly impaired as demonstrated by absent pedal pulses;
11. Subjects who were nursing;
12. Subjects with a history of hypersensitivity to azoles;

13. Subjects with a history of congestive heart failure (CHF) or ECG signs indicative of conditions that suggest CHF such as:

    - Right ventricular hypertrophy, left ventricular hypertrophy with ST-T wave changes;
    - Low wave voltage;
    - Dilated cardiomyopathy;
    - Atrial strain;
    - Q-waves and left bundle branch block in subjects with ischemic disease;

14. Subjects who were being treated with:

    - CYP3A4 metabolized substrates that could have prolonged the QT-interval, (e.g., terfenadine, astemizole, cisapride, levacetylmethadol [levomethadyl], misolastine, pimozide, quinidine, dofetilide, sertindole);
    - Oral triazolam, oral midazolam;
    - CYP3A4 metabolized HMG-CoA reductase inhibitors (eg, lovastatin, simvastatin, atorvastatin, cerivastatin);
    - Calcium channel blockers (eg, dihydropyridines and verapamil);
    - Potent enzyme inducers of CYP3A4, (eg, phenytoin, phenobarbital, carbamazepine, isoniazid, rifampin, rifabutin);
    - Ergot alkaloids (eg, dihydroergotamine, ergometrine, ergotamine, and methylergometrine);
    - Potent enzyme inhibitors of CYP3A4 (eg, erythromycin and clarithromycin);
    - Warfarin, buspirone, coumarin-like drugs, benzodiazepines, oral hypoglycemics, protease inhibitors or reverse transcriptase inhibitors, digoxin, ciclostazol, eletriptan and halofantrine;

15. Subjects who had cancer or history of cancer, except non-melanoma skin cancer;
16. Subject was immunocompromised (infected with Human Immunodeficiency Virus);
17. Subjects with active lichen planus, psoriasis, or a history of either;
18. Subjects with a history of liver toxicity to other drugs;
19. Subjects who were using systemic immunosuppressants (e.g., cyclosporine, tacrolimus, methotrexate, 6-mercaptopurine);
20. Subjects with clinically significant abnormal screening laboratory test values;
21. Subjects who were ethanol or drug abusers or had a prior history of ethanol or drug abuse;
22. Subject had used systemic antifungals within 12 weeks prior to screening;
23. Subject had used systemic steroids [except occasional, non-routine (less than 4 times per week] use of inhaled corticosteroids] within 30 days prior to screening;
24. Subject had used topical antifungal nail lacquers on any toenail within 30 days prior to screening;
25. Subject had used any other topical onychomycosis treatment on any toenail within 2 weeks prior to screening;

26. Subject had used any nail polish, nail polish remover, or acrylic nails on the target toenail within 1 day prior to screening.

Study Visits and Procedures

Qualified subjects who met the inclusion/exclusion criteria were enrolled into the study.

The study consisted of 12 week dosing period and 40 week follow -up period. Specifically, the visits included a screening visit (up to week -9), randomization visit (week 0), 3 dosing period visits (weeks 4, 8 and 12), 2 post-dosing period follow-up visits (weeks 26 and 39) and an exit visit (week 52).

Overall study plan and study visit schedule is presented in Table 4.

Table 4: Overall Study Plan

Visit	1	2	3	4	5	6	7	8
Study week	-9	0	4	8	12	26	39	52
Screening [a]								
Dosing Evaluation Period [b]								
Follow-up Period [c]								

Source: sponsor's submission, Figure 1; Section 5.3.5.1.3.

a: Up to 9 weeks in duration
b: 12 weeks in duration
c: 40 weeks in duration

At week 0, the inclusion/exclusion criteria were reviewed, and subjects were randomized (3:3:1) to study drug and were dispensed (respectively) itraconazole tablets, itraconazole capsules, or placebo tablets. Subjects were instructed to self-administer 1 Tradename-itraconazole 200mg tablet, 2 itraconazole 100mg capsules, or 1 placebo tablet QD for 12 weeks at approximately the same time every morning after a full meal. Dosing began the day after the week 0 visit and ended on the day prior to the week 12 visit.

Table 5: Evaluation and Study Visit Schedule

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Study Week	**-9 [a]**	**0**	**4**	**8**	**12**	**26**	**39**	**52**
Informed Consent/Assent [b]	X							
Medical History	X							
Percent Nail Involvement of Target Toenail	X	X	X	X	X	X	X	X
Length of Unaffected Part or Area of Target Toenail	X	X	X	X	X	X	X	X
IGA		X	X	X	X	X	X	X
Number of Toenails and Fingernails with Onychomycosis Involvement		X			X			X
Signs and Symptoms of Tinea Pedis		X	X	X	X	X	X	X
KOH Examination	X				X	X	X	X
DTM Culture of Target Toenail (optional based on initial KOH outcome)	X							
Mycologic Culture (Central Lab)	X				X	X	X	X
Urine Pregnancy Test [c]	X	X			X			X
Clinical Laboratory Sampling	X		X	X	X			X
ECG	X	X	X	X	X			
Audiology		X			X			X
Randomize Subject		X						
Dispense Study Drug		X	X	X				
Study Drug Intake		←	—	—	→			
Collect Study Drug			X	X	X			
Photography (at Selected Sites)	X	X	X	X	X	X	X	X
Record Concomitant Therapies	X	X	X	X	X	X	X	X
Record Adverse Events [d]	X [d]	X	X	X	X	X	X	X

Source: Sponsor's submission, Table 5; Section 5.3.5.1.3.

a: Screening may have taken up to 9 weeks; **b**: Written informed consent/assent was obtained prior to conducting any study-related procedures; **c**: For female subjects of childbearing potential; test had a minimum sensitivity of 25 mIU β-human chorionic gonadotropin /mL urine; **d**: Non-serious AEs were collected for all randomized subjects

beginning at week 0. Serious AEs, if observed or reported, were collected for all subjects beginning immediately following informed consent at screening.

At Visit 1 (Screening) the investigator would identify a target toenail and record its location in the eCRF. The target toenail is the great toenail with the more severe involvement of onychomycosis. At all visits the target toenail was trimmed back to the hyponychium before performing the clinical evaluations. After completing the clinical evaluations additional trimming of the target toenail proximal to the hyponychium was used to collect optimal KOH/mycological samples.

Over the course of the study at each site, the same investigator/evaluator would perform examinations on the same individual subject. At all post-screening study visits (beginning with week 0), the percent nail involvement of the target toenail was scored, the length of the unaffected part of the target toenail was measured, and an Investigator's Global Assessment (IGA) of the overall disease severity was conducted. Photographs of the target toenail also were re-obtained from subjects at the sites selected for participation at week 0.

In addition to the post-screening procedures already described, the number of toenails and fingernails with onychomycosis involvement were counted at randomization (week 0), at the end of the dosing period (week 12), and at the end of the study (week 52). KOH examinations also were conducted and mycological cultures were obtained at the last dosing period study visit and at each follow-up visit (at weeks 12, 26, 39, and 52).

Percent nail involvement

The target toenail was evaluated for the proportion of the nail with evidence of onychomycosis, taking into consideration the extent of onycholysis and hyperkeratosis affecting the entire nail unit. After trimming the nail back to the hyponychium, the Target Toenail was viewed from all relevant angles (top down and edge on), and the one integer recorded that best describes the Percent Nail Involvement according to the scale shown in Table 6.

Table 6: Scale for the Evaluation of the Percent Nail Involvement

Score	Description
0	0% nail involvement
1	>0% to ≤ 25% nail involvement
2	>25% to ≤ 50% nail involvement
3	>50% to ≤ 75% nail involvement
4	>75% to ≤ 100% nail involvement

Source: sponsor's submission, Table 6; Section 5.3.5.1.3.

At Visit 1 the subject must have a Percent Nail Involvement score of 2 or 3 (25-75%) in order to be enrolled in the study.

At Visit 2 the subject must have a Percent Nail Involvement score or 2 or 3 (25-75%) in order to be randomized to study medication.

The IGA consisted of an assessment of the overall severity of onychomycosis for the target toenail. This assessment took into consideration onycholysis, hyperkeratosis, and percent nail involvement.

Table 7: Investigator's Global Assessment Scale

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 nail 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: sponsor's submission, Table 7; Section 5.3.5.1.3.

Length of Unaffected Part of the Target Toenail

At every study visit or if the subject prematurely withdraws from the study, the investigator would measure the length of the unaffected part of the nail on the target toenail. To perform these measures the investigator would use a scalpel (or equivalent instrument) to make a superficial notch at the midline of the normal nail plate of the target toenail adjacent to the onychomycotic border at Visit 1. The investigator would measure the length of the unaffected part of the nail on the target toenail in millimeters (mm) from this notch to the proximal nail fold. The investigator could deepen the notch and/or use ink, marker or other means to improve the visibility of the notch.

If the onychomycosis progressed proximal to the notch at subsequent visits the investigator would make a new notch to indicate the new onychomycotic border. This process would be repeated anytime the disease progressed proximal to the previous notch used for measuring the length of the unaffected part of the target toenail. If a new notch was required in response to disease progression this information was noted on the appropriate eCRF page.

At Visit 1 the Length of Unaffected Part of the Target Toenail should be ≥2mm for the subject to be enrolled in the study.
At Visit 2 the Length of Unaffected Part of the Target Toenail should be ≥2mm for the subject to be randomized to study medication.

Safety monitoring

Clinical laboratory specimens (blood and urine for chemistry, hematology, and urinalysis) were collected at screening, weeks 4, 8, 12, and 52. ECGs were obtained at screening and throughout the dosing period at weeks 0, 4, 8, and 12. Female subjects of childbearing potential underwent repeat urine pregnancy tests at weeks 0, 12, and 52. Audiology tests were performed 3 times during the study: at randomization (week 0); at the end of the dosing period (week 12); and at exit (week 52).

Concomitant Medication:

Subjects were prohibited from using any concomitant medication listed in the exclusion criteria during the entire clinical trial with the exception of those medications listed in exclusion criterion #14. Those particular medications were prohibited beginning at week 0 and continuing through 3 weeks after the last dose of study drug.

During the dosing evaluation period (weeks 0 through 12), subjects who were taking acid secretion suppressors (H_2 antagonists, proton pump inhibitors) were required to administer the assigned study drug along with a cola beverage. Subjects who were taking acid neutralizing medicines (aluminum hydroxide) were required to take those medicines at least 2 hours after ingestion of the study drug.

Subjects were prohibited from applying acrylic nails to the target toenail at all times during the trial. While subjects were allowed to use nail polish/lacquer and nail polish remover, the subjects were instructed to remove nail polish/lacquer from the target toenail at least 1 day prior to any study visit.

Randomization

Subjects enrolled in the study were randomized in a 3:3:1 ratio to receive Tradename-itraconazole 200mg tablets, itraconazole 100mg capsules, or placebo tablets respectively. The randomization schedule was stratified by investigational site, and utilized a block size of 7. Within each site, Subject Boxes, corresponding to the randomization scheme, were assigned to

eligible subjects in ascending numerical order at the week 0 visit; assignment began with the lowest Subject Box number available. Designated staff members at each site who did not otherwise participate in the study or evaluate the subjects dispensed the study drug and thus were unblinded. In all other respects, access to the randomization schedule (the study drug identification codes) was kept restricted until after the database was locked and the study was unblinded.

Blinding

Because the appearance of the active drugs could not be masked, and the number of tablets administered was different from the number of capsules administered, absolute blinding could not be accomplished. Tradename-itraconazole 200mg tablet and the placebo tablet matched one another in appearance and dosing regimen. Designated individual at each site who was not involved with the evaluation of the subjects dispensed, collected, and accounted for all study drugs. Further, the subjects were instructed not to discuss the appearance of their assigned study drug or its associated dosing regimen with the site personnel. Efficacy was based on assessments performed by the blinded investigator/evaluator.

Discontinuation from the study

In this study, subjects could have withdrawn or been withdrawn for any of the following reasons:

- Noncompliance;
- Protocol Violation;
- Consent Withdrawal;
- Lack of Efficacy;
- Lost to Follow-Up;
- Administrative Decision;
- Investigator Discretion;
- Other;

Additionally, the investigator/evaluator may have directed the subject to reduce the frequency, or discontinue the dosing of the study drug if any significant drug intolerance was observed or if symptoms of a concomitant illness (sore throat, gastrointestinal upset) temporarily interfered with the subject's ability to take the study drug. If the subject could not return to QD dosing within 7 days of reducing the dosing frequency or stopping study drug usage, he/she must have been discontinued from the study. (Reasons for all investigator-directed dose modifications were reported as adverse events). Further, subjects must have discontinued study drug and been withdrawn from the trial if:

- The subject had a serum alkaline phosphatase (ALP) level greater than or equal to 2 times the laboratory upper limit of normal;

- The subject has a serum alanine aminotransferase (ALT) (serum glutamate pyruvate transaminase [SGPT]) level greater than or equal to 2 times the laboratory upper limit of normal;
- The subject has a serum aspartate aminotransferase (AST) (serum glutamate oxaloacetic transaminase [SGOT]) level greater than or equal to 2 times the laboratory upper limit of normal accompanied by ALP or bilirubin levels greater than the laboratory upper limit of normal;
- The subject developed signs or symptoms of CHF (shortness of breath, unusual swelling of the feet, ankles or legs, sudden weight gain, unusual fatigue, coughing up white or pink phlegm, or unusually rapid heartbeat);
- The subject developed signs or symptoms of liver dysfunction (loss of appetite, nausea or vomiting, jaundice, dark colored urine, or pale stool);
- The subject developed a severe allergic reaction to the study drug;
- The subject experienced an auditory abnormality that, in the investigator's opinion, may have been attributable to the study drug;
- The subject experienced neuropathy which, in the investigator's opinion, may have been attributable to the study drug;
- The subject had a clinically significant, abnormal ECG finding.

Efficacy and Endpoint Measures

Primary Efficacy Endpoint

The primary efficacy endpoint was the proportion of subjects in each dosing group with Complete Cure at Visit 8 (Week 52), the primary evaluation visit. In this study, Complete Cure was defined as both a Clinical Cure and a Mycological Cure. A Clinical Cure was considered an IGA score of 0 for the target toenail, and that a Mycological Cure must have included both a negative KOH examination and a negative culture for dermatophytes of the target toenail.

Secondary Efficacy Endpoint

The secondary efficacy endpoint was the proportion of subjects in each dosing group with Clinical Improvement at Visit 8 (Week 52). In this study, Clinical Improvement was defined as both a Mycological Cure and an IGA score for the target toenail of ≤1.

The primary and secondary endpoints were tested for both non-inferiority and superiority. Specifically, the results observed in the Tradename-itraconazole 200mg tablet group were tested for non-inferiority relative to the results obtained in the itraconazole 100mg capsule group. Further, the results observed in the Tradename-itraconazole 200mg tablet group were tested for superiority relative to the results obtained in the placebo tablet group.

Other Endpoints and Exploratory Parameters

- Percent nail involvement of the target toenail was evaluated at all study visits and was reported based on a visual approximation using a scale that ranged from 0 (0%) to 4 (>75% to ≤100%) in whole unit intervals.
- Total number of toenails and fingernails affected with onychomycosis at weeks 0, 12, and 52.
- Signs and symptoms of tinea pedis as recorded at all post-screening study visits (weeks 0, 4, 8, 12, 26, 39, and 52). Evaluations of tinea pedis included type (assessed as interdigital, plantar dyshidrotic, or plantar chronic erythemato-squamous), as well as scaling, erythema, and pruritis (each scored independently using a scale that ranged in whole unit intervals from 0 (none) to 3 (severe).

Photography

At 6 selected study sites, high-resolution, standardized color photographs of the target toenail were taken at all study visits. The photographs were taken both before and after the target toenail was trimmed and notched.
The process for obtaining the photographs required the toenail to be in the same position for each image. Fixed lighting and shading, a standardized background, the same camera-subject distance, and the identical camera settings were used to ensure consistency across sites and images. The color photographs documented the gross morphological changes in the condition of each subject's nail over time with exposure to the study drug.

Protocol Deviations

Protocol deviations significant enough to exclude a subject from either the per protocol (PP) or Safety analysis sets included no documentation of study drug use, no post-baseline evaluations, violations of the entry criteria, missed visits, non-compliance or use of prohibited concomitant medications, and off-schedule visits.

6 Review of efficacy

Efficacy Summary

One Phase 3 trial was conducted to establish the noninferiority of 12 week treatment of onychomycosis of toenail with once daily itraconazole 200mg tablet to once daily treatment of two itraconazole 100mg capsules (Sporanox) and to demonstrate superiority to placebo. In this

Phase 3 trial, Tradename-itraconazole 200mg tablet demonstrated noninferiority to Sporanox and superiority over placebo tor treatment of onychomycosis of toenail.

6.1 Indication

The proposed indication for Tradename-itraconazole tablet is for the treatment of onychomycosis of the toenail

6.1.1 Methods

The primary data used to support the application were from the single Phase 3 trial, BT0300-302-INT. Trial BT0300-302-INT was a randomized, multi-center, placebo-controlled, evaluator blinded, parallel group trial designed to evaluate the safety and efficacy of Tradename-itraconazole 200mg tablets relative to itraconazole 100mg capsules and placebo tablets in the treatment of onychomycosis of the great toenail. Discussion of primary, secondary and exploratory endpoints are presented in section 6.1.4 and 6.1.5.

At Visit 1 (Screening) the investigator would identify a target toenail and record its location in the e-CRF. The target toenail is the great toenail with the more severe involvement of onychomycosis. At all visits the target toenail was trimmed back to the hyponychium before performing the clinical evaluations. After completing the clinical evaluations additional trimming of the target toenail proximal to the hyponychium was used to collect optimal KOH/mycological samples.

Over the course of the trial at each site, the same investigator/evaluator would perform examinations on the same individual subject. At all post-screening trial visits (beginning with week 0), the percent nail involvement of the target toenail was scored, the length of the unaffected part of the target toenail was measured, and an Investigator's Global Assessment (IGA) of the overall disease severity was conducted. Photographs of the target toenail also were re-obtained from subjects at the sites selected for participation at week 0.

In addition to the post-screening procedures already described, the number of toenails and fingernails with onychomycosis involvement were counted at randomization (week 0), at the end of the dosing period (week 12), and at the end of the study (week 52). KOH examinations also were conducted and mycological cultures were obtained at the last dosing period study visit and at each follow-up visit (at weeks 12, 26, 39, and 52). For the IGA and Percent Nail Involvement scale please refer to section 5.3.

6.1.2 Demographics

In this study, 1381 subjects were randomized to study drug; 593 subjects in the Tradename-itraconazole 200mg tablet group, 590 subjects in the itraconazole 100mg capsule group, and 198

subjects in the placebo tablet group. Of these subjects, 1226 (88.8%) were enrolled at 47 sites in the US, 77 (5.6%) were enrolled at 4 sites in Latin America, 53 (3.8%) were enrolled at 6 sites in Canada, and 26 (1.9%) were enrolled at 1 site in South Africa.

1169 (84.6%) of subjects completed the study, of which 517 (87.2%) in Tradename-itraconazole 200mg group, 469 (84.1%) in itraconazole 100mg capsule group and 156 (78.8%) in placebo tablet group.

The majority of subjects were male (74.9%), Caucasian (86.5%) and enrolled in the United States (88.8%). For the tabulations by race, the applicant's study report and reviewer analysis differ slightly. In the study report, subjects with multiple races listed are counted in multiple race categories whereas the review only counts such subjects once; these are listed under the category of "Other". Results of the baseline comparisons for age, gender, ethnicity and race are provided in Table 8.

Table 8: Subjects Demographic Characteristics

	Itraconazole Tablet (N=593)	**Itraconazole Capsule (N=590)**	**Placebo Tablet (N=198)**
Age (years)			
N	593	590	198
Mean	47.1	47.0	49.2
STD	11.86	12.67	11.2
Median	48.0	47.0	49.0
Min. to Max.	17 to 75	19 to 75	17 to 75
Gender			
Male	441 (74.4%)	440 (74.6%)	153 (77.3%)
Female	152 (25.6%)	150 (25.4%)	45 (22.7%)
Ethnicity			
Hispanic/Latino	103 (17.4%)	112 (19.0%)	32 (16.2%)
Not Hispanic/Latino	490 (82.6%)	478 (81.0%)	166 (83.8%)
Race			
American Indian/ Alaska Native	5 (1%)	5 (1%)	3 (2.0%)
Asian	5 (1%)	4(0.7%)	2 (1.0%)
Black/African American	48 (8.1%)	48 (8.1%)	18 (9.1%)
Native Hawaiian/Other Pacific Islander	0 (0.0%)	1 (0.2%)	0 (0.0%)
White	512 (86.3%)	493 (83.6%)	169 (85.4%)
Other	25 (4.2%)	41 (6.9%)	7 (3.5%)

Source: Statistical reviewer

The population of subjects enrolled in this study was consistent, in terms of age and gender, with the population affected by onychomycosis.

In terms of race (Whites: Tradename-itraconazole 86.3%; Itraconazole capsule 83.6% and Placebo 85.4%) and ethnicity (Non Hispanic/Latino: Tradename-itraconazole 82.6%; Itraconazole capsule 81% and Placebo 83.8%) there is no significant difference in numbers between treatment subgroups. However, most of the trial subjects were white (86.3%). As per current scientific literature, race and ethnicity do not play a role in prevalence, severity or treatment outcome in patients with onychomycosis.

In the age group 16 to 18 years the sponsor included one subject in itraconazole tablet group, no subjects in itraconazole capsule group and one subject in placebo group. Therefore, any conclusions about safety and efficacy of the Tradename- itraconazole 200mg tablet in this age group cannot be made due to lack of adequate number of subjects. See additional discussion below in section 7.6.3.

Baseline Prognostic Factors

Three baseline prognostic factors with the potential to impact efficacy conclusions were explored that might vary between subjects: type of fungi, investigator global assessment, and percent nail involvement. The baseline distribution of these three prognostic factors is similar across treatment arms. A majority of randomized subjects in the intend to treat (ITT) group had a baseline IGA score that equated to moderate (56.8% of the subjects) and a percent nail involvement score of 3 (i.e., an involvement of greater than 50% to less than or equal to 75%) in 58.1% of the subjects. No statistically significant differences among dosing groups were observed in the baseline characteristics of IGA score, percent nail involvement or type of fungal infection of the target toenail.

The summary of subject's baseline characteristics is presented in Table 9.

Table 9: Summary of Subject Baseline Characteristics (ITT)

	Itraconazole Tablet (N=593)	Itraconazole Capsule (N=590)	Placebo Tablet (N=198)	P-Value
IGA				
Clinical Cure	0	0	0	0.652
Clinical Improvement	0	0	0	
Mild	25 (4.2%)	29 (4.9%)	5 (2.5%)	
Moderate	332 (56.0%)	338 (57.3%)	114 (57.6%)	
Severe	236 (39.8%)	223 (37.8%)	79 (39.9%)	
Percent Nail Involvement				
0%	0	0	0	0.696
>0% to ≤ 25%	0	0	0	
>25% to ≤50%	240 (40.5%)	251 (42.5%)	87 (43.9%)	
>50% to ≤75%	352 (59.4%)	339 (57.5%)	111 (56.1%)	
>75% to ≤100%	1 (0.2%)	0	0	
Fungi				0.654
E. Floccosum	5 (1%)	3 (1%)	3 (2%)	
T. Mentagrophytes	27 (5%)	23 (4%)	7 (4%)	
T. Rubrum	561 (95%)	564 (96%)	188 (95%)	

Source: Agency Statistical reviewer's analysis using ADCU.XPT.

6.1.3 Subject Disposition

In the trial BT0300-302-INT, a total of 1381 subjects were enrolled from 58 centers located in 7 countries (Canada, Dominican Republic, Ecuador, Honduras, Panama, United States, and South Africa). Of the 1381 subjects enrolled, 593 subjects were randomized to Tradename-itraconazole 200mg tablet group, 590 subjects in the itraconazole 100mg capsule group, and 198 subjects in the placebo tablet group.

Of all enrolled subjects, 1,169 (84.6%) completed the trial and this included 517 of the 593 (87.2%) subjects in the Tradename-itraconazole 200mg tablet group, 496 out of 590 (84.1%) subjects in the itraconazole 100mg capsule group, and 156 out of 198 (78.8%) subjects in the placebo tablet group. The most frequently reported reasons for study discontinuation were:

- *Lost to follow-up*: 27 (4.6%) for Tradename-itraconazole 200mg tablet group, 34 (5.8%) for itraconazole 100mg capsule group, and 14 (7.1%) for placebo tablet group.

- *Adverse Events:* 21 (3.5%) for Tradename-itraconazole 200mg tablet group, 31 (5.3%) for itraconazole 100mg capsule group, and 8 (4%) for placebo tablet group.

- *Consent Withdrawal:* 14 (2.4%) for Tradename-itraconazole 200mg tablet group, 14 (2.4%) for itraconazole capsule group, and 10 (5.1%) for placebo tablet group.

- *Other:* 11 (1.9%) for Tradename-itraconazole 200mg tablet group, 8 (1.4%) for itraconazole 100mg capsule group, and 3 (1.5%) for placebo table group. The most frequent reason for subject discontinuation in this group includes the following: subject moved out of area and subject took exclusionary medication.

The summary of subject completion and discontinuations is presented in Table 10.
Detailed discussion about discontinuation due to adverse events is presented in section 7.3.4

Table 10: Summary of Subjects Completion/Discontinuation

	Itraconazole Tablets (N=593)	Itraconazole Capsules (N=590)	Placebo Tablets (N=198)	Total (N=1381)
Number of Subjects Randomized	593	590	198	1381
Number of Subjects Who Completed the Study	517 (87.2%)	496 (84.1%)	156 (78.8%)	1169 (84.6%)
Number of Subjects Who Discontinued the Study	76 (12.8%)	94 (15.9%)	42 (21.2%)	212 (15.4%)
Reasons for Discontinuation				
Non-Compliance	1 (0.2%)	2 (0.3%)	1 (0.5%)	4 (0.3%)
Protocol Violation	2 (0.3%)	3 (0.5%)	2 (1.0%)	7 (0.5%)
Consent Withdrawn	14 (2.4%)	14 (2.4%)	10 (5.1%)	38 (2.8%)
Lack of Efficacy	0 (0.0%)	0 (0.0%)	3 (1.5%)	3 (0.2%)
Lost to Follow-up	27 (4.6%)	34 (5.8%)	14 (7.1%)	75 (5.4%)
Administrative Decision	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.1%)
Investigator Discretion	0 (0.0%)	2 (0.3%)	0 (0.0%)	2 (0.1%)
Adverse Event	21 (3.5%)	31 (5.3%)	8 (4.0%)	60 (4.3%)
Other	11 (1.9%)	8 (1.4%)	3 (1.5%)	22 (1.6%)

Source: Sponsor's Submission, Table 14.0.4 Section 5.3.3.1.3

6.1.4 Analysis of Primary Endpoint

Statistical Methodology

General

The primary efficacy endpoint was Complete Cure rate at Visit 8 (week 52) the primary evaluation visit. In this study, Complete Cure was defined as both a Clinical Cure and a Mycological Cure. A Clinical Cure was considered an IGA score of 0 for the target toenail, and that a Mycological Cure must have included both a negative KOH examination and a negative culture for dermatophytes of the target toenail.

The primary analyses of the primary efficacy variable, Complete Cure (Clinical Cure and Mycological Cure) at Visit 8 (Week 52), includes non-inferiority testing comparing the efficacy of Tradename-itraconazole tablets to itraconazole capsules and superiority testing of Tradename-itraconazole tablets to placebo tablets for the intent-to-treat (ITT) and per-protocol populations (PP).
Non-inferiority testing used the one-sided 97.5% confidence interval approach with a non-inferiority margin of -10% (Summaries of statistical results for the non-inferiority comparison include a two-sided 95% confidence interval so as to also include an upper confidence bound). Two-sided hypothesis testing is conducted for the superiority analyses using a significance level of 0.05.

Reviewer comment: These statistical aspects of efficacy were in accordance with Agency recommendations made following review of the Special Protocol Assessment (7/14/06).

Additionally, the proportion of subjects with Clinical Improvement, secondary efficacy variable, at Visit 8 (Week 52) is analyzed for non-inferiority and superiority.

No adjustments of p-values for multiple comparisons are made. No interim analyses were conducted. SAS software was used for all of the sponsor's data analyses and tabulations provided in the study report. The reviewer's analysis is performed using the R Software.

Population

Two efficacy analysis populations were identified and included intend-to-treat (ITT) and per protocol (PP). The ITT analysis population included all subjects who were randomized to and received study drug. The PP analysis population included a subset of the ITT subjects who completed week 52 without noteworthy protocol violations (i.e., without subject or investigator activities that possibly could have interfered either with the administration of the study drug or with the precise evaluation of efficacy). A subject was included in the per-protocol analyses if all of the following criteria were met:

- A subject who met the inclusion/exclusion criteria;
- The subject has not taken or applied any interfering concomitant medications;

- The subject has completed Visit 5 and Visit 8;
- The subject has completed Visit 8 within the visit window of ±14 days;
- The subject has not missed more than one interim visit during the treatment period or more than one interim visit during the no treatment follow-up period; and
- The subject has been compliant with the dosing regimen (i.e., subject must have taken 80% to 120% of the expected doses). Dosing compliance for subjects who prematurely discontinued from the treatment phase of the study due to treatment failure or adverse events were based on the number of days the subjects participated in the treatment phase of the study,

In the primary and secondary analyses, both the ITT and PP analysis populations were evaluated.

Missing Data

The Last Observation Carried Forward (LOCF) method is used as the primary imputation approach for subjects who prematurely discontinue from the study and have missing data at Visit 8 (Week 52). Additionally, sensitivity analyses investigating the impact of the LOCF method of data imputation are performed using the following approach.

- Subjects with a missing Visit 8 (Week 52) evaluation will have “failure" imputed for their missing Visit 8 evaluation.
- Subjects with a missing Visit 8 (Week 52) evaluation will have “success" imputed for their missing Visit 8 evaluation.

Sensitivity analysis is presented in Table 15 and Table16.

Testing Procedures

The protocol states that the non-inferiority analyses will be restricted to the active treatment groups with the intent-to-treat population as the primary population. The superiority analysis is restricted to the itraconazole 200mg tablets and placebo tablets treatment groups and is performed on the ITT and PP populations.

Reviewer’s Comment: In the SPA review the Division stated that both the ITT and PP population should be considered primary for a non-inferiority comparison which is consistent with ICH E9. In addition, the Division stated that for a superiority comparison, it considers the ITT population as primary with the PP as supportive. These definitions of primary and supportive analysis populations will be used in this review of efficacy.

Superiority Methodology

Primary tests of superiority are conducted for the proportion of subjects with Complete Cure at Visit 8 which is analyzed with a Cochran-Mantel-Haenszel test, stratified by analysis center. Superiority will be established if $p < 0.05$.

Non-Inferiority Methodology

The test for demonstrating the non-inferiority of the proportion of subjects with Complete Cure is based on the Complete Cure rate at Visit 8 (Week 52) with a non-inferiority margin of -10%, and will be established if the lower limit of the one-sided 97.5% confidence interval for the difference between Complete Cure rates (Tradename-itraconazole tablets minus itraconazole capsules) is greater than -10%. The statistical analysis method uses Wald's confidence interval with Yates' continuity correction.

Primary Analysis Results

Based upon the definitions of the primary endpoint and analysis populations, both efficacy objectives met the pre-specified statistical criteria (Table 11). The treatment effects (δ= Tradename-itraconazole Tablets - comparator) for each population were:

Non-Inferiority: 0.6% (ITT) and 0.9% (PP)
Superiority: 21.3% (ITT) and 23.8% (PP)

In regard to the number of subjects (ITT) with Complete Cure at week 52 (end of study), 132 (22.3%), 128 (21.7%), and 2 (1.0%) subjects were successes in the Tradename-itraconazole 200mg tablet, itraconazole 100mg capsule, and placebo tablet dosing groups, respectively.

Within the PP analysis set, the number of subjects with Complete Cure at week 52 was 126 (25.1%), 118 (24.2%), and 2 (1.3%) for the Tradename-itraconazole 200mg tablet, itraconazole 100mg capsule, and placebo tablet dosing groups, respectively.

Superiority of Tradename-itraconazole 200mg tablets to placebo tablets was clearly significant in both populations ($p < 0.0001$). The non-inferiority comparison of Tradename-itraconazole 200mg tablets to itraconazole 100mg capsules demonstrated that the lower bound of the one-sided 97.5% confidence interval was above the prespecified margin of -10%.

The lower limit of the 97.5% CI in the observed difference between proportions of subjects by active study drug with Complete Cure at week 52 was -4.3% in the ITT analysis set and -4.7% in the PP analysis set. Because these limits were greater than the pre-specified margin of -10%, the

primary analysis demonstrated that Tradename-itraconazole 200mg tablets are non-inferior to itraconazole 100mg capsules.

The results of the primary efficacy analysis are presented in Table 11.

Table 11: Complete Cure Results (Primary Analysis)

	Itraconazole Tablet 200mg	Itraconazole Capsule 100mg	Placebo Tablet
ITT Population Sample Size Success (%) Statistical Comparison	 593 132 (22.3%) -	 590 128 (21.7%) (-4.3%, 5.5%)†	 198 2 (1.0%) p< 0.0001*
PP Population Sample Size Success (%) Statistical Comparison	 502 126 (25.1%) -	 488 118 (24.2%) (-4.7%, 6.5%)†	 155 2 (1.3%) p<0.0001*

Source: Study Report Table 17. Results reproduced using ADCU.XPT.
† Two-sided 95% Confidence interval (CI) for the difference in Complete Cure rates (Tablets minus Capsules) was computed using Walds confidence interval with Yates continuity correction.
* P-Value from a Cochran-Mantel-Haenszel test stratified by analysis center. Study Report Table 17. Results reproduced using ADCU.XPT. The superiority analysis was restricted to the Tradename-itraconazole and placebo dosing groups.

The primary endpoint is essentially a composite endpoint, consisting of two components: Clinical Cure and Mycological Cure. Each of these components is analyzed in the two sections that follow to examine the efficacy of each component.

Clinical Cure: The protocol definition of Clinical Cure is a week 52 IGA score of 0 for the target toenail. Based on this component of the primary endpoint, both the non-inferiority and superiority comparisons reached the statistical success criteria identified for the primary endpoint (Table 12). Note that for this component of the primary endpoint, the Sporanox 100 mg capsule formulation had a slightly improved response rate than the Tradename-itraconazole 200 mg tablet formulation.

Table 12: Clinical Cure Results

	Itraconazole Tablet 200mg	Itraconazole Capsule 100mg	Placebo Tablet
ITT Population Sample Size Success (%) Statistical Comparison	593 151 (25.5%) -	590 166 (28.1%) (-7.9%, 2.5%)†	198 6 (3.0%) p< 0.0001*
PP Population Sample Size Success (%) Statistical Comparison	502 142 (25.1%) -	488 151 (24.2%) (-8.5%, 3.2%)†	155 5 (3.2%) p<0.0001*

Source: Study Report Tables 14.2.17.1 and 14.2.17.2 with Agency statistical reviewer analysis using ADCU.XPT to derive statistical tests.
† Two-sided 95% Confidence interval (CI) for the difference in Clinical Cure rates (Tablets minus Capsules) was computed using Wald's confidence interval with Yates' continuity correction.
* p-Value from a Cochran-Mantel-Haenszel test stratified by analysis center. The superiority analysis was restricted to the Tradename-itraconazole and placebo dosing groups.

Mycological Cure: The protocol definition of Mycological Cure is a negative potassium hydroxide microscopic examination (KOH) and a negative culture for dermatophytes of the target toenail at week 52. Based on this component of the primary endpoint, both the non-inferiority and superiority comparisons reached the statistical success criteria identified for the primary end point (Table 13). Note that for this component of the primary endpoint, Tradename-itraconazole 200mg tablet was superior to both placebo tablets and itraconazole 100mg capsule. Overall response rates were higher for Mycological Cure rates than Clinical Cure rates.

Table 13: Mycological Cure Results (continued)

	Itraconazole Tablet 200mg	Itraconazole Capsule 100mg	Placebo Tablet
ITT Population Sample Size Success (%) Statistical Comparison	 593 258 (43.5%) -	 590 218 (36.9%) (0.8%, 12.3%)†	 198 11 (5.6%) p< 0.0001*
PP Population Sample Size Success (%) Statistical Comparison	 502 233 (46.4%) -	 488 194 (39.8%) (-0.3%, 13.0%)†	 155 11 (7.1%) p<0.0001*

Source: Statistical reviewer analysis using ADCU.XPT.
† Two-sided 95% Confidence interval (CI) for the difference in Mycological Cure rates (Tablets minus Capsules) was computed using Walds confidence interval with Yates continuity correction.
*p-Value from a Cochran-Mantel-Haenszel test stratified by analysis center. The superiority analysis was restricted to the Tradename-itraconazole and placebo dosing groups.

Sensitivity Analysis to Address the Blinding Issues

In the study report, the sponsor stated that the blind may have been broken in several sites. In the 74 day letter the Division requested the sponsor provide additional information on the nature of the unblinding. The sponsor responded, stating that study coordinators who dispensed study product, received returned study product, and were responsible for product accountability inadvertently recorded the number of units dispensed which would have the potential to break the blind as the Tradename tablets are 200mg and the capsules 100mg (i.e. twice as many capsules were dispensed as tablets). The sponsor claims that the investigators at the seven sites where this occurred did not notice this information to actually break the blind with the exception of one investigator (Dr. Matheson) who enrolled a single subject.

To insure that potential unblinding issues did not affect efficacy determinations, the following sensitivity analysis discards the data from the seven sites where the blind was potentially broken. Efficacy results and analysis procedures are the same as those used in the primary analysis. Note that the exclusion of all subjects from these sites results in the exclusion of a total of 301 subjects which is larger than the total number of subjects the sponsor reports as potentially being unblinded, 93 subjects (i.e. of the 301 subjects enrolled at these 7 sites, only 93 are claimed by the sponsor to have the potential of being unblinded).

Despite the removal of 301 subjects from the total number of enrolled subjects in this analysis, efficacy was again demonstrated for the non-inferiority objective comparing Tradename-itraconazole 200mg tablets to itraconazole 100mg capsules for the ITT and PP population as well as the superiority objective for comparing the itraconazole 200mg tablets to placebo tablets (Table 14). Also note the Complete Cure rates for Tradename-itraconazole 200mg tablets are lower in this analysis in comparison to the primary analysis whereas those of itraconazole 100mg capsules remain roughly the same.

Table 14: Complete Cure Results (Blinding Issue Analysis)

	Itraconazole Tablet 200mg	Itraconazole Capsule 100mg	Placebo Tablet
ITT Population			
Sample Size	464	460	156
Success (%)	91 (19.6%)	98 (21.3%)	1 (0.6%)
Statistical Comparison	-	(-7.1%%, 3.7%)†	p< 0.0001*
PP Population			
Sample Size	397	383	155
Success (%)	87 (21.9%)	91 (23.8%)	1 (0.8%)
Statistical Comparison	-	(-8.0%, 4.3%)†	p<0.0001*

Source: Statistical reviewer analysis using ADCU.XPT

† Two-sided 95% Confidence interval (CI) for the difference in Complete Cure rates (Tablets minus Capsules) was computed using Walds confidence interval with Yates continuity correction.

* P-Value from a Cochran-Mantel-Haenszel test stratified by analysis center. The superiority analysis was restricted to the Tradename-itraconazole and placebo dosing groups.

Missing Data Sensitivity Analysis

The protocol defined primary method of data imputation was last observation carried forward (LOCF). To assess the impact of missing data, two sensitivity analyses were protocol specified for the primary endpoint of complete cure: (1) impute all missing as successes (2) impute all missing as failures. Recall that the percentage of subjects with missing data is highest in the placebo tablet group (21.2%) followed by the itraconazole 100mg capsule group (15.9%) and finally the Tradename-itraconazole 200mg tablet group (12.8%); please refer to Table 9. Efficacy results using these alternate imputation strategies are presented below for both the ITT and PP populations.

Missing Data Imputed as Failures:

Imputation of the Week 52 missing data as failures resulted in consistent efficacy conclusions as using LOCF which is reported in the primary analysis (Table 15). This conclusion is expected as nearly all subjects with missing Week 52 data are Complete Cure failures at the time of drop out.

Table 15: Complete Cure Results (Sensitivity Analysis: Missing = Failure)

	Itraconazole Tablet 200mg	Itraconazole Capsule 100mg	Placebo Tablet
ITT Population			
Sample Size	593	590	198
Success (%)	127 (21.4%)	125 (21.2%)	2 (1.0%)
Statistical Comparison	-	(-4.6%%, 5.1%)†	P< 0.0001*
PP Population			
Sample Size	502	488	155
Success (%)	122 (24.3%)	118 (24.2%)	2 (1.3%)
Statistical Comparison	-	(-5.4%, 5.7%)†	P<0.0001*

Source: Study Report Table 22; results reproduced using ADCU.XPT

† Two-sided 95% Confidence interval (CI) for the difference in Complete Cure rates (Tablets minus Capsules) was computed using Walds confidence interval with Yates continuity correction.

* P-Value from a Cochran-Mantel-Haenszel test stratified by analysis center.

Missing Data Imputed as Successes:

Consistent with the imputation of missing data using LOCF as well as imputing all missing as complete cure failures, results when imputing the missing data as successes also reaches pre-specified statistical criteria (Table 16). As such, the alternate methods of data imputation provide evidence of the superiority of itraconazole tablets to placebo tablets and non-inferiority of Tradename-itraconazole tablets to itraconazole capsules.

Table 16: Complete Cure Results (Sensitivity Analysis: Missing = Success)

	Itraconazole Tablet 200mg	Itraconazole Capsule 100mg	Placebo Tablet
ITT Population Sample Size Success (%) Statistical Comparison	 593 208 (35.1%) -	 590 219 (37.1%) (-7.7%%, 3.6%)†	 198 42 (21.2%) P< 0.0001*
PP Population Sample Size Success (%) Statistical Comparison	 502 146 (37.1%) -	 488 143 (29.3%) (-6.1%, 5.6%)†	 155 7 (4.5%) P<0.0001*

Source: Study Report Table 22; results reproduced using ADCU.XPT

† Two-sided 95% Confidence interval (CI) for the difference in Complete Cure rates (Tablets minus Capsules) was computed using Wald's confidence interval with Yates' continuity correction.

* P-Value from a Cochran-Mantel-Haenszel test stratified by analysis center.

Clinical reviewer conclusion: This reviewer agrees with the statistical reviewer's conclusion that method of imputation did not have an impact on efficacy results. Efficacy endpoints were successfully demonstrated regardless of the imputation method for missing data.

6.1.5 Analysis of Secondary Endpoint

A single secondary endpoint was included in the protocol, Clinical Improvement. Clinical Improvement is similar to the primary endpoint except that the component of the endpoint related to the IGA score now allows scores of 1 or 0 to be a success (primary endpoint included only subjects with an IGA score of 0); in addition, subjects must have a Mycological Cure to be determined a success for this endpoint as well. Statistical evaluation of this endpoint met the pre-specified statistical criteria (Table 17).

Table 17: Clinical Improvement Results (Secondary Endpoint Analysis)

	Itraconazole Tablet 200mg	Itraconazole Capsule 100mg	Placebo Tablet
ITT Population Sample Size Success (%) Statistical Comparison	 593 200 (33.7%) -	 590 173 (29.3%) (-1.1%%, 9.9%)†	 198 4 (2.0%) P< 0.0001*
PP Population Sample Size Success (%) Statistical Comparison	 502 186 (37.1%) -	 488 158 (32.4%) (-1.5%, 10.8%)†	 155 4 (2.6%) P<0.0001*

Source: Study Report Table 18; results reproduced using ADCU.XPT

† Two-sided 95% Confidence interval (CI) for the difference in Complete Cure rates (Tablets minus Capsules) was computed using Wald's confidence interval with Yates' continuity correction.

* P-Value from a Cochran-Mantel-Haenszel test stratified by analysis center.

Clinical reviewer comment: (b) (4)

Conclusions and Recommendations

A single Phase 3 trial was conducted demonstrating Tradename-itraconazole 200mg tablets are non-inferior to itraconazole 100mg capsules and superior to placebo tablets for the treatment of toenail onychomycosis. The primary efficacy parameter is the Complete Cure rate defined as both Clinical Cure and Mycological Cure at Visit 8 (Week 52). In this trial, Tradename-itraconazole 200mg tablets were found to be superior to placebo tablets ($p < 0.05$) and non-inferior to itraconazole capsules (NI margin < -10%).

The sponsor reported that during the trial the trial blind may have been broken as personnel responsible for dispensing the medication wrote down the number of pills dispensed on the CRF (the capsules are double the number of tablets). Agency analysis, removing these sites, still resulted in successfully meeting pre-specified statistical criteria. Several other sensitivity analyses provided consistent efficacy results with the primary analysis. The totality of the evidence supports: Tradename-itraconazole 200mg tablets are superior to placebo tablets, and itraconazole 200mg tablets are non-inferior to itraconazole 100mg capsules when using a NI margin of -10%.

Additional efficacy information

The sponsor has submitted color photographs taken at 6 selected study sites. The photographs were taken at all study visits and before and after the target toenail was trimmed and notched.

Reviewer's comments: Review of the submitted photographs and the corresponding individual efficacy response data revealed no inconsistencies.

6.1.6 Other Endpoints

The following additional exploratory endpoints and parameters were evaluated:

(b) (4)

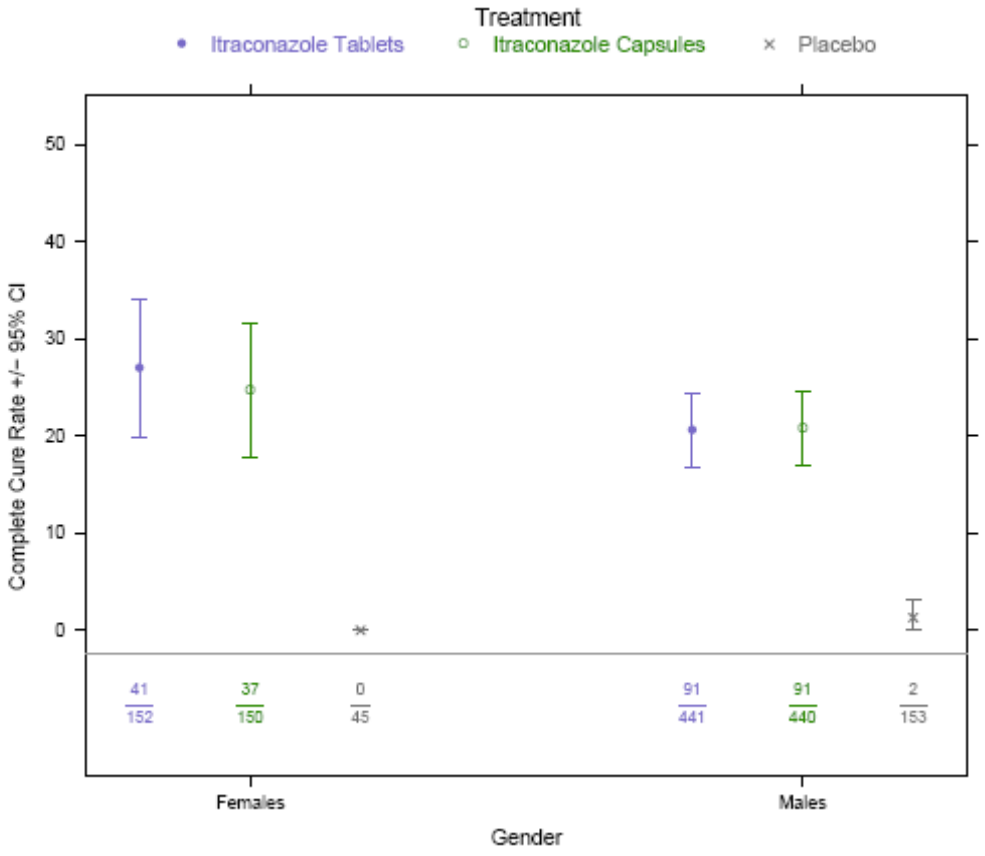
Clinical reviewer comment: Since labeling claims were not made on exploratory endpoints, these were not reviewed. This reviewer recommends that marketing claims based on these exploratory endpoints not be allowed.

6.1.7 Subpopulations

Gender

Figure 1 depicts Complete Cure rates according to gender along with unadjusted 95% confidence intervals. Complete Cure rates for Tradename-itraconazole 200mg tablets and itraconazole 100mg capsules were similar within each gender and these corresponding treatment effects were similar for both males and females. Note that no confidence interval is presented for the female subjects treated with placebo tablets as none of these subjects were defined as Complete Cure by Week 52.

Figure 1: Efficacy Results According to Gender



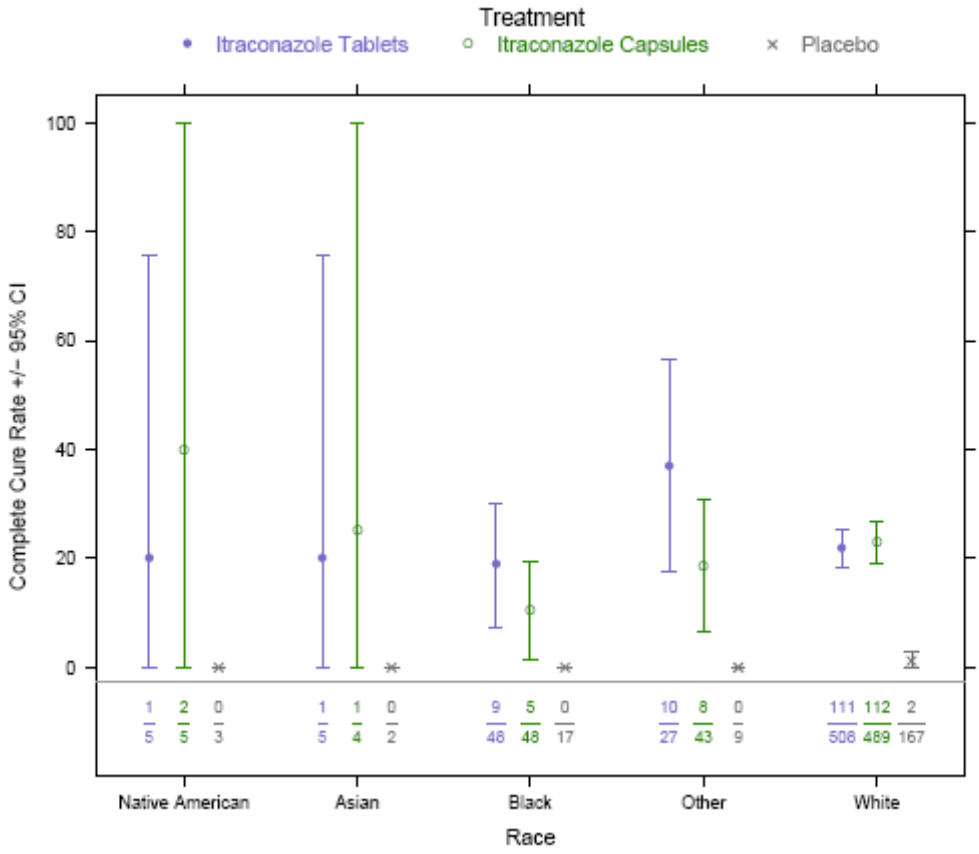
Source: Statistical Review

Reviewer's comments: Other than minor variations the success rate was not affected by gender.

Race

A small fraction of subjects were enrolled with races listed other than White. Figure 2 depicts the mean Complete Cure rates along with unadjusted 95% confidence intervals by race for each treatment group. As two subjects treated with placebo tablets had a week 52 cure rate, note that the confidence interval is not presented for Native American, Asian, Black, and Other racial subgroups. Overall, the comparison of Tradename-itraconazole 200mg tablets to itraconazole 100mg capsules is similar within each race. In addition, the treatment effects are quite similar across the racial subgroups though comparisons are subject to large amounts of variability due to the limited sample sizes.

Figure 2: Efficacy Results According to Race

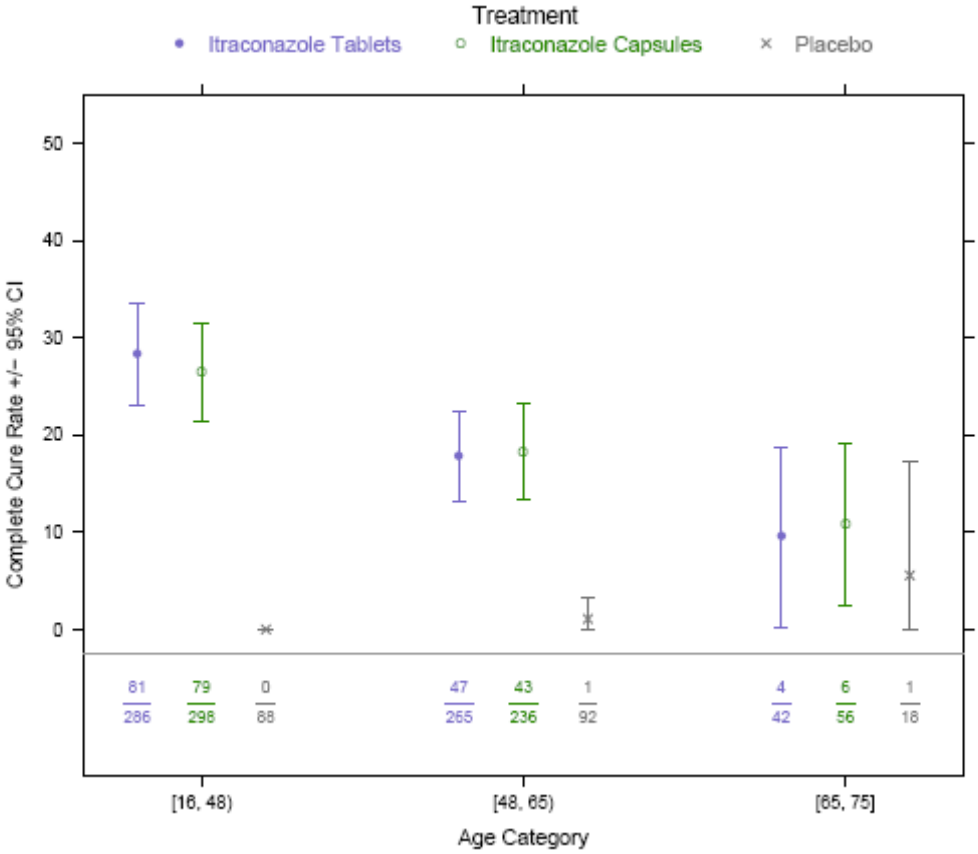


Source: Statistical Review

Age

Three categories of age were created as the following: [16; 48), [48; 65), and [65; 75]. The cut points for age were decided based on the median age of subjects enrolled, 48 and the arbitrary definition of the elderly population, 65 used in FDA guidance. Complete Cure rates and unadjusted 95% confidence intervals are presented in Figure 3 for each of the three age groups. A general trend is that efficacy rates tended to decrease with age for both Tradename-itraconazole 200mg tablets and itraconazole 100mg capsules though treatment responses within a given age group were similar for the two treatments. A total of 2 subjects randomized to placebo tablets were defined as a Complete Cure at Week 52. Thus, point estimates and the corresponding confidence intervals for this treatment group are inconclusive.

Figure 3: Efficacy Results According to Age



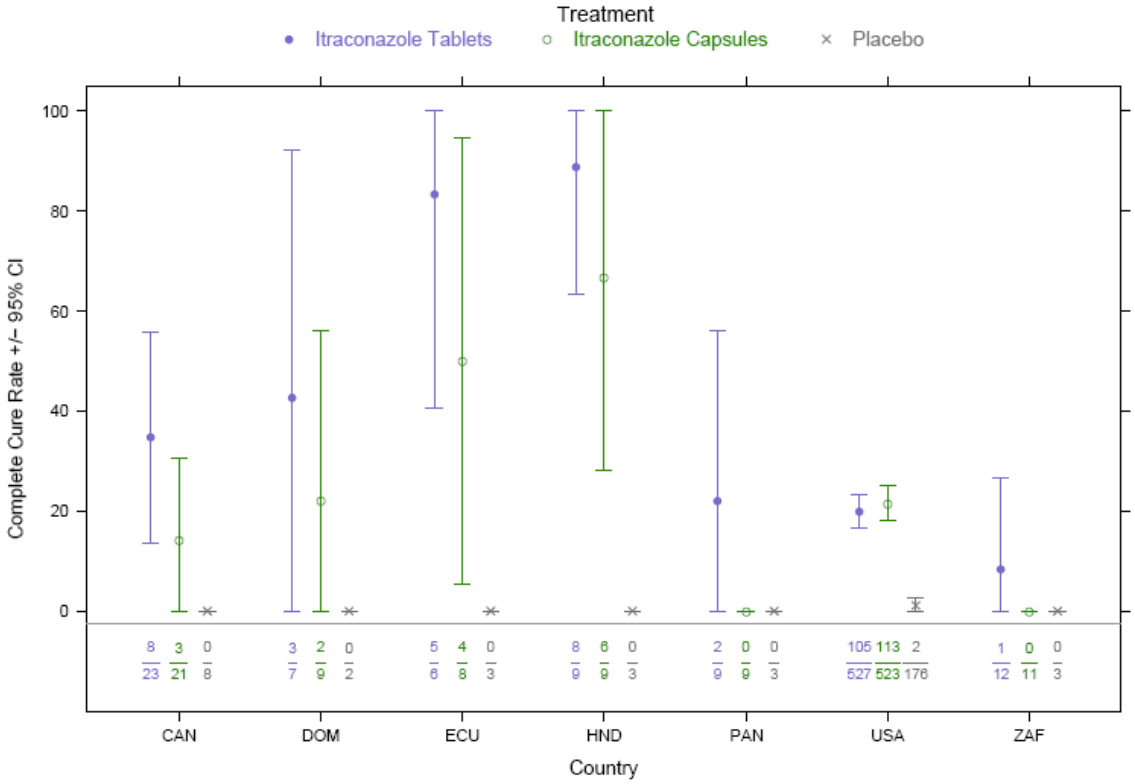
Source: Statistical Review

Reviewer's comments:
Age appeared to have a role in successful outcomes: while the active dosing groups were similar to one another within age subgroups, there was a difference between subgroups that favored younger subjects.

<u>Efficacy by Country</u>

Study BT0300-302-INT was conducted in 7 countries: Canada, Dominican Republic, Ecuador, Honduras, Panama, United States, and South Africa. The majority of subjects were enrolled in the United States (88.8%). Figure 4 depicts the Complete Cure rates along with unadjusted 95% confidence intervals for each treatment group for each country. With limited data for non-U.S. sites, it is difficult to draw any conclusions for these countries. Overall, the Complete Cure rates were similar between Tradename-itraconazole 200mg tablets and itraconazole 100mg capsules for each country.

Figure 4: Efficacy Results According to Country

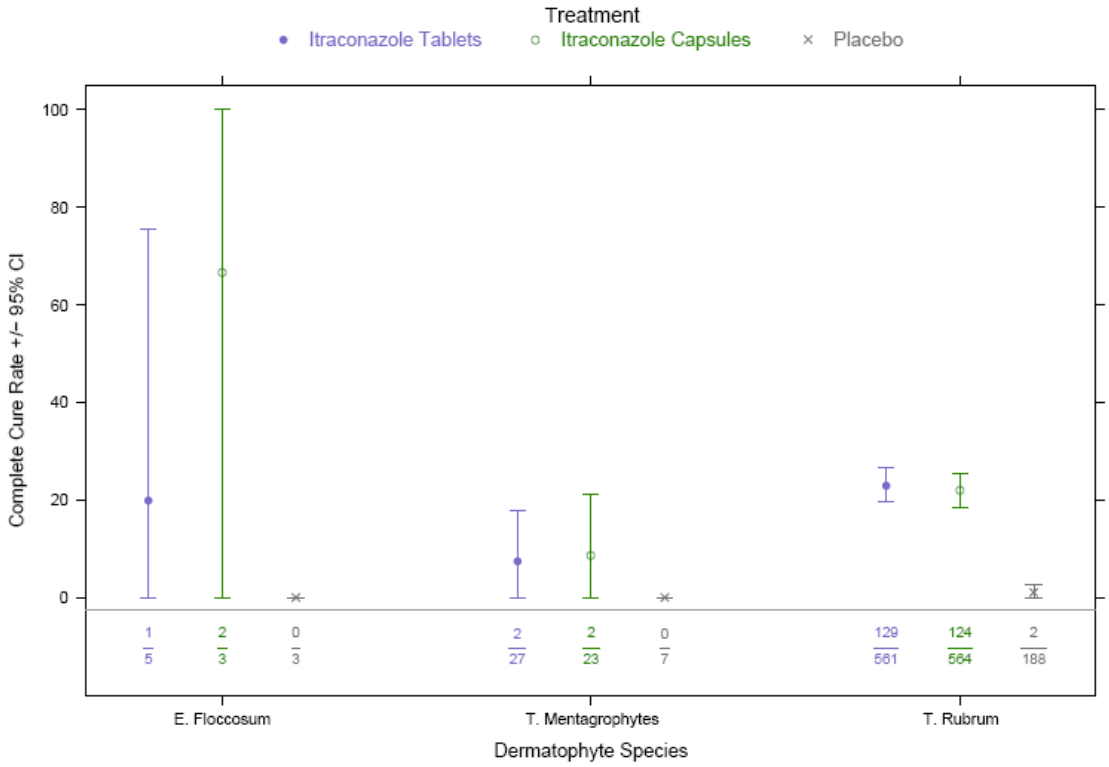


Source: Statistical Review

Efficacy by Dermatophyte Species

Three different dermatophyte species were included at baseline: Epidermophyton Floccosum, Trichophyton Mentagrophytes, and Trichophyton Rubrum. The majority of subjects were infected with T. Rubrum (95.1%). Figure 5 depicts Complete Cure rates for each of these species. With a limited number of subjects infected with dermatophytes other than T. Rubrum, BT0300-302-INT does not provide much information about effectiveness in these species. Consequently, the efficacy results are similar to those presented in the primary analysis.

Figure 5: Efficacy Results According to Dermatophyte Species



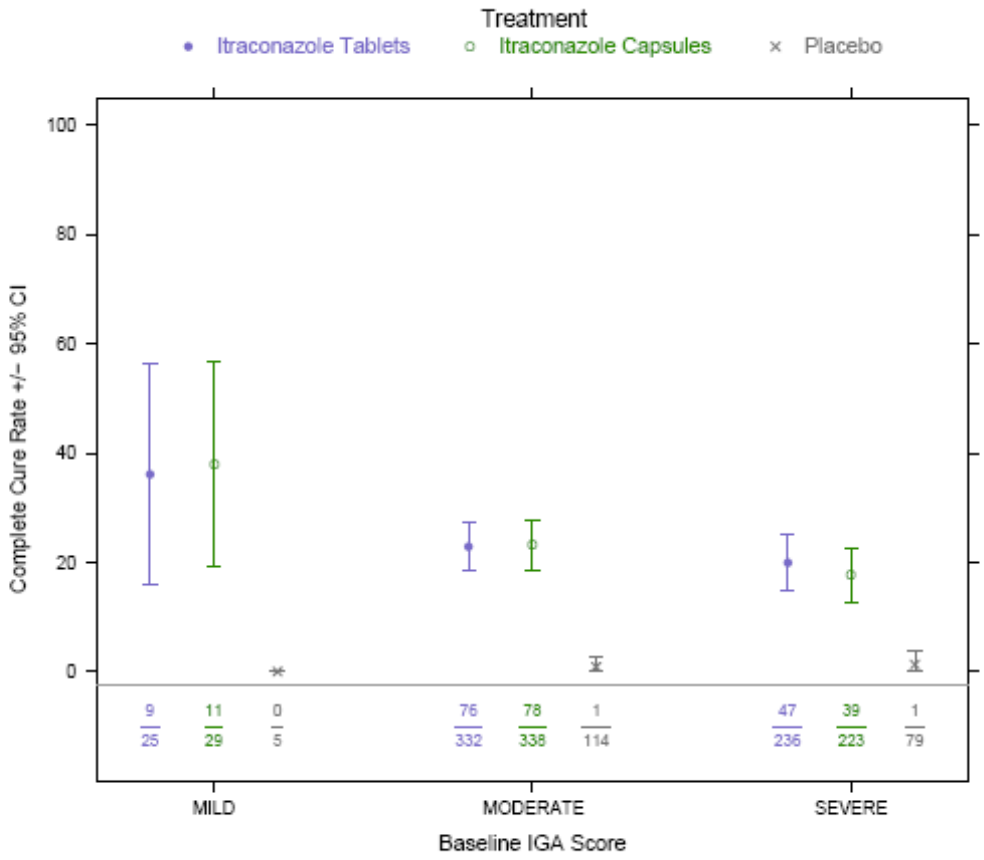
Source: Statistical Review

Efficacy by Baseline IGA Score

At baseline subjects enrolled with an IGA score of mild, moderate, and severe; Table 9 contains the distribution of the IGA scores for subjects at baseline. Overall, the majority of subjects enrolled with a baseline IGA score of Moderate (56.8%). The following post hoc analysis presents the efficacy rate based on the baseline IGA score.

Figure 6 depicts the efficacy results as well as tabular information for Complete Cure rates by the baseline IGA score. While a small fraction of subjects enrolled with baseline IGA scores of "Mild", the overall trend for each of the two active treatment group results in a decreased Complete Cure rate for higher IGA scores. However, there is little difference between those with Moderate and Severe IGA scores. In all IGA baseline score subgroups, there is similar Complete Cure rate for Tradename-itraconazole 200mg tablet and itraconazole 100mg capsule which are both clearly superior to placebo tablets.

Figure 6: Efficacy Results by Baseline IGA Score



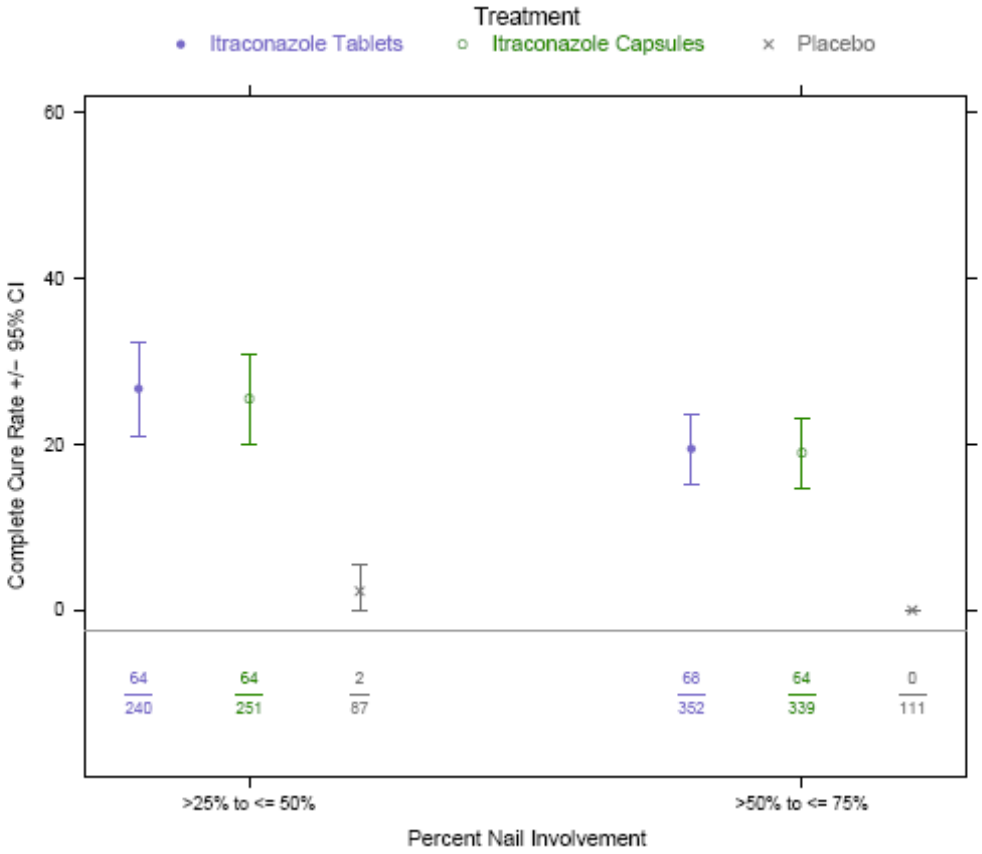
Source: Statistical Review

Efficacy by Nail Involvement

For the assessment of percent nail involvement, the target toenail was divided into five categories: 0% involvement; >0% to ≤ 25%; > 25% to ≤ 50%; > 50% to ≤ 75%, and > 75% to ≤100%. At baseline all but one subject enrolled with a baseline percent nail involvement of > 25% to ≤ 50% or > 50% to ≤ 75%. For this analysis, the one subject who enrolled with a baseline percent nail involvement greater than 75% was excluded - this subject was a treatment failure.

Figure 7 depicts the efficacy results as well as tabular information for Complete Cure rates by the baseline percent nail involvement. Overall, the trend shows that both Tradename-itraconazole 200mg tablets and itraconazole 100mg capsules are less effective in cases where the nail involvement is greater. However, within a given level of the nail involvement, the two itraconazole treatments have similar Complete Cure rates.

Figure 7: Efficacy Results by Baseline Nail Involvement



Source: Statistical Review

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The applicant stated that the goal of their development plan for the Tradename-itraconazole 200mg tablet was to provide a product with a similar efficacy profile to Sporanox, but with the purported advantage of a simpler dosing regimen. The pivotal Phase 3 study was designed to demonstrate the non-inferiority of the same daily dose of itraconazole in the new tablet formulation to that of the existing capsule formulation and superiority to placebo.

The results of the statistical analyses of the clinical data demonstrate that once daily dosing with one Tradename-itraconazole 200mg tablet is non-inferior to once daily dosing with two itraconazole 100mg capsules and is superior to once daily dosing with one placebo tablet in the treatment of toenail onychomycosis when administered for 12 weeks and evaluated at 52 weeks.

Based on the efficacy results obtained in the Phase 3 trial, a dosing regimen of one 200mg itraconazole tablet taken once daily for 12 weeks after a full meal is recommended for approval.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The persistence of efficacy and tolerance effects was not evaluated during the conduct of the Phase 3 trial. Recurrence or recrudescence were not evaluated.

7 Review of Safety

Safety Summary

Safety data included 6 trials conducted under the Tradename-itraconazole 200mg tablet clinical development program ((BT0300-302-INT; BT0300-BEL-002; BT0300-BEL-005; BT0300-BEL-006; BT0300-BEL-004 and BT0300-108-USA). The incidence of adverse events related to both itraconazole formulations tested (200mg tablet and 100mg capsule) was comparable to incidence of adverse events of marketed Sporanox and other triazole antifungal agents reported in literature.

There were no deaths. There was one serious adverse event (cholelithiasis) that was considered by this review to be related to the Tradename-itraconazole 200mg tablet. All other serous adverse events were not related to the study drug. The adverse event profiles for the treatment phase of the trial for the two itraconazole formulations were quite similar. No new safety signals or concerns were noted.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data from 6 studies sponsored by the applicant were submitted in the application. The safety of 200mg Tradename-itraconazole tablet for treatment of onychomycosis of toenail was evaluated in one pivotal clinical trial enrolling 1,354 subjects (BT0300-302-INT), two Phase 1, bioequivalency trials (BT0300-BEL-002 and BT0300-BEL-005) enrolling 112 subjects, one Phase 1 bioavailability trial (BT0300-BEL-006) enrolling 18 subjects and two Phase 1 PK trials (enrolling 32 subjects). Four of the 5 Phase 1 studies were open-label, single-center studies intended to evaluate the Tradename-itraconazole 200mg tablet in healthy, adult volunteers. Safety evaluation data were reported separately for each study.
Summary of trials used for evaluation of safety is presented in Table 18.

Table 18: Studies Providing Safety Information

Study Number	Study Design And Type of Control	Number of Subjects	Test Product(s); Dosage Regimen;
BT0300-BEL 002	Phase 1, open label, randomized, 2 way crossover, single-center, oral dose	Itraconazole 200mg tablet N = 56 Itraconazole 100mg capsule N = 56	Single administration of 1 tablet or 2 capsule after a standard breakfast;
BT300-BEL-004	Phase 1 open label, single center, single-arm, oral dose,	Itraconazole 200mg tablets N = 16	Single administration of 2 tablets after a high-calorie, high-fat breakfast
BT0300BEL 005	Phase 1, open label, randomized, 2-way crossover, single-center, oral dose	Itraconazole 200mg tablet N = 56 Itraconazole 100mg capsule N = 56	Single administration of 1 tablet of 2 capsule after a high-calorie, high-fat breakfast
BT0300BEL 006	Phase 1, open-label, randomized, 3-way crossover, oral dose, single-center	Itraconazole200mg tablet (fasting) N = 18 Itraconazole 200mg tablet (fed) N = 18 Itraconazole 100mg capsule(fasting) N = 18	Single administration of 1 tablet of 2 capsule under fasting conditions and of 1 tablet after a high-calorie, high-fat breakfast
BT0300-108-USA	Phase 1,open label, single-arm ,oral dose, single-center	Itraconazole 200mg tablet N = 16	Administration of 1 tablet, QD after a standard breakfast for 14 days
BT0300-302-INT	Phase 3, multi-center, 3 arm, randomized, evaluator blind, active and placebo-controlled, parallel group	Itraconazole 200mg tablet N = 582 Itraconazole 100mg capsule N = 581 Placebo tablet N = 191	1 tablet of 2 capsules taken once daily after breakfast for 12 weeks

Source: Compiled from the sponsor's submission, Table1, Section 5.2

7.1.2 Categorization of Adverse Events

Adverse events were classified by body system and preferred term using the Medical Directory of Regulatory Affairs (MedDRA) classification, and summarized by incidence, severity, and causality to the study drug.

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

Safety data from all 6 submitted studies were evaluated separately. The study designs were too different to allow pooling of data across studies, thus each study was analyzed separately.

7.2 Adequacy of Safety Assessments

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

Across all 6 studies, 1516 subjects were enrolled and evaluated for safety. Of these subjects, 744 were exposed to the Tradename-itraconazole 200mg tablet, 711 subjects were exposed to the itraconazole 100mg capsule, and 191 subjects were exposed to the placebo.

The summary of subjects exposed to study drug across all 6 trials is presented in Table 19.

Table 19: Summary of Subjects Exposure to Study Drug

Study	Itraconazole 200mg Tablet	Itraconazole 100mg Capsule	Placebo Tablet	Total number of subjects by Study	Itraconazole Any form
Phase 1					
BT300-BEL-002	56	56	--	56	56
BT300-BEL-004	16	--	--	16	16
BT300BEL005	56	56	--	56	56
BT300BEL006	18	18	--	18	18
BT300-108-USA	16	--	--	16	16
Phase 3					
BT300-302-INT	582	581	191	1354	1163
Total by Study Drug	744	711	191	1516	1325

Source: Sponsor's submission, Table 3; Section 2.7.4

In the Phase 3 study BT0300- 302-INT at week 0, subjects were randomized (3:3:1) to study drug, and were dispensed Tradename-itraconazole tablets, itraconazole capsules, or placebo tablets respectively. Subjects were instructed to self-administer 1 Tradename-itraconazole 200mg tablet, 2 itraconazole 100mg capsules, or 1 placebo tablet QD for 12 weeks. Dosing began the day after the week 0 visit and ended on the day prior to the week 12 visit.

The mean (STD) number of doses administered within the Tradename-itraconazole 200mg tablet, itraconazole 100mg capsule, and placebo tablet dosing groups, respectively, was 79.5 (14.82), 76.7 (17.23), and 77.6 (16.30). In general, the largest proportion of subjects in each dosing group ingested between 68 and 100 doses of the assigned study drug. Approximately 95% or more of the subjects in each dosing group remained on the study drug for more than 6 weeks; more than 90% of the subjects remained on the study drug for more than 10 weeks.

A complete summary of subject exposure to study drug by dosing group is presented in Table 20.

Table 20: Extent of Exposure in Phase 3 Trial (BT0300-302-INT)

	Itraconazole Tablets	Itraconazole Capsules	Placebo Tablets
Number of Subjects	582	581	191
Number of Doses			
N	580	578	190
Mean	79.5	76.7	77.6
STD	14.82	17.23	16.30
Min. to Max.	1 to 126	2 to 105	6 to 98
Number of Doses			
>100	5 (0.9%)	2 (0.3%)	0 (0.0%)
68 to 100	525 (90.5%)	503 (87.0%)	169(88.9%)
50 to 67	22 (3.8%)	31 (5.4%)	10 (5.3%)
30 to 49	9 (1.6%)	13 (2.2%)	4 (2.1%)
10 to 29	11 (1.9%)	17 (2.9%)	4 (2.1%)
<10	8 (1.4%)	12 (2.1%)	3 (1.6%)
Weeks on Study Drug			
>0	572 (100.0%)	568 (100.0%)	186 (100.0%)
>2	563 (98.4%)	554 (97.5%)	181 (97.3%)
>4	557 (97.4%)	547 (96.3%)	179 (96.2%)
>6	552 (96.5%)	539 (94.9%)	176 (94.6%)
>8	550 (96.2%)	532 (93.7%)	173 (93.0%)
>10	543 (94.9%)	523 (92.1%)	172 (92.5%)
>12	211 (36.9%)	193 (34.0%)	51 (27.4%)

Source: Sponsor's submission, Table 25; Section 5.3.5.1.3.

There is adequate exposure with the drug in terms of overall number of patients. Of all subjects exposed to the drug, 1107 were male and 436 were female. Although the majority of exposed subjects were male, the number of exposed female subjects was adequate to allow safety evaluation in this population.
Age distribution included adult population (16 to 75 years of age). Pediatric population was excluded from this trial.
As per trial protocol, study drug was supposed to be taken once daily, however it was noted that some subjects took study drug more/less frequently. No adverse events related to overexposure were reported, therefore no influence on safety evaluation are expected.
The overexposure as well as underexposure were roughly balanced across treatment arms and are not expected to influence the efficacy results.

Dose and duration of the exposure were adequate for evaluation of safety. Appropriate laboratory testing and clinical evaluations were carried out in exposed patients to allow adequate safety evaluations. Noted cases of overexposure and underexposure were evenly distributed across the treatment arms and not expected to influence the efficacy results.

Demographics of Target Population

Subject's demographic characteristics across all clinical trials and for Phase 3 trial BT302-INT are presented in Table 21 and Table 8 Section 6.1.2.

Table 21: Subjects Demographic Characteristics Across All Clinical Trials

	BT0300-302-INT (N=1354)	BT0300 BEL006 (N=18)	BT300-BEL-004 (N=16)	BT0300-108-USA (N=16)	BT300-BEL-002 (N=56)	BT0300 BEL005 (N=56)
Age						
Mean	47.5	40.3	35.8	36.3	38.4	38.4
Range	16 to 75	26 to 53	19 to 58	23 to 53	21 to 55	19 to 55
Gender						
Female	336	9	16	8	28	28
Male	1018	9	0	8	28	28
Race						
American Indian/ Alaska Native	18					
Asian	11			2		
Black/African American	106			2		
Native Hawaiian Pacific Islander	1					
White	1155	18	16	12		56
Other	73					

Source: Compiled for the sponsor's submission, Table 4 and Table 7, Section 2.7.4

The demographics were consistent across treatment groups. However, the majority of subjects were male (more than 74% per treatment arm) and Caucasian (more then 84% per treatment arm), and Non Hispanic (more then 81% per treatment arm).

7.2.2 Explorations for Dose Response

No dose response evaluations were conducted during the development of itraconazole 200mg tablet. Sporanox is indicated for treatment of onychomycosis with dose of 100mg two capsule one daily. The sponsor developed Tradename-itraconazole 200mg tablet that is intended to have similar safety and efficacy profile as Sporanox but with more convenient once daily dosing. Therefore, no additional dose response evaluations were done.

7.2.4 Routine Clinical Testing

The following safety evaluations were conducted during the trial: clinical laboratory testing (blood for chemistry, hematology, and urinalysis) were collected at screening, weeks 4, 8, 12, and 52. ECGs were obtained at screening and throughout the dosing period at weeks 0, 4, 8, and 12. Female subjects of childbearing potential underwent repeat urine pregnancy tests at weeks 0, 12, and 52. Audiology tests were performed 3 times during the study: at randomization (week 0); at the end of the dosing period (week 12); and at exit (week 52). Physical examinations and vital signs were not preformed during the conducts of the Phase 3 study. In each of the Phase 1 studies, physical examinations, vital signs and ECGs were obtained at entry and exit.

Clinical reviewer's comments:
Methods, tests used, frequency of testing, and evaluations over time were adequate for evaluation of safety of the drug product and were in line with Agency recommendations.

7.2.5 Metabolic, Clearance, and Interaction Workup

Two pharmacokinetic studies, two bioequivalence and one bioavailability study were conducted during the development of the Tradename-itraconazole tablet. Please refer to Clinical Pharmacology review for detailed information on these trials.

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

Itraconazole is currently marketed drug product under the name Sporanox. It is available in 3 formulations: Sporanox capsules (NDA 20083, 9/11/92, Sporanox oral solution (NDA 20657, 2/21/97) and Sporanox solution for injection (NDA 20966, 3/30/99).

Itraconazole and fluconazole represent the first generation of systemic triazoles. As a class, triazoles act predominantly by inhibiting cytochrome P450 (CYP)-dependent conversion of lanosterol to ergosterol, the main sterol in the cell membrane of most fungi, resulting in inhibition of cell growth and replication.

Triazoles have significant potential for drug-drug interactions through interference with the hepatic CYP3A4 metabolic pathway and potential for hepatic toxicity, including liver failure and death.

Life threatening cardiac dysrhythmias including QT prolongation, torsades de pointes, ventricular tachycardia, cardiac arrest and sudden death have been reported when cisapride, pimozide, levomethadil of quinidine were administered concomitantly with Itraconazole and other CYP3A4 inhibitors.

When Sporanox was administered intravenously to dogs and healthy human volunteers, negative inotropic effects were seen.

Transient or permanent hearing loss has been reported in patients receiving treatment with itraconazole.

Tradename-itraconazole 200mg tablet product was evaluated specifically for adverse events that are considered common for the drug class: hepatotoxicity, cardiotoxicity and ototoxicity.

Clinical reviewer's comments:

Applicant has used adequate methodology to detect specific adverse events that may be expected in the drug belonging to triazole antifungal class.

The analysis of safety results revealed that reported adverse events in itraconazole tablet group were similar to adverse events reported for itraconazole capsule group and consistent with expected adverse events for the drug class. No additional unexpected adverse events have been reported.

7.3 Major Safety Results

The evaluation of safety was conducted on all subjects who were randomized to study drug, had documented use of at least 1 dose of the assigned drug, and presented for at least 1 post-baseline assessment. This included 1,354 subjects, 582 of whom were randomized to the Tradename-itraconazole 200mg tablet group, 581 of whom were randomized to the itraconazole 100mg capsule group, and 191 of whom were randomized to the placebo tablet group. The safety analysis is based on an evaluation of the extent of exposure to study drug, adverse events, and other safety related parameters including 12-lead ECG findings, auditory outcomes, clinical laboratory analyses (chemistry, hematology, and urinalysis), and the outcomes of urine pregnancy tests.

7.3.1 Deaths

No deaths were reported during clinical development of Tradename-itraconazole 200mg tablet.

7.3.2 Nonfatal Serious Adverse Events

There were no serious AEs reported in any of the Phase 1 studies. No dose ranging studies were conducted in support of this NDA. Please refer to the Table 2 for list of all trials.

During the Phase 3 trial, 25 subjects reported 29 serious adverse events, 13 (2.2%) in Tradename-itraconazole 200mg tablet group, 13 (2.2%) in itraconazole 100mg capsule group, and 3 (1.5%) in the placebo group.

During the dosing period of Phase 3 trial, 6 subjects (two in each dosing group) reported serious adverse events.
One case of cholelithiasis (Subject #24090 in Tradename-itraconazole 200mg group) was considered related to the study drug by the sponsor.

Following are serious adverse events that occurred during the dosing period:

Tradename-Itraconazole 200mg tablet

- Subject #24090 experienced cholelithiasis, which was considered related to dosing with the Tradename-itraconazole 200mg tablet. This serious event did not result in subject discontinuation from the trial.

- Subject # 13017 was diagnosed with prostate cancer, which was considered not related to the Tradename-itraconazole 200mg tablet. This adverse event did not result in subject discontinuation from the trial.

Itraconazole 100mg capsule

- Subject #26060 developed inferior myocardial infarction. The subject subsequently developed congestive heart failure. This adverse event led to discontinuation from the trial.

- Subject # 5574 experienced neck pain. This serious adverse event did not result in subject discontinuation from the trial.

Placebo

- Subject # 63009 was diagnosed with diverticulitis. This adverse event did not lead to discontinuation from the trial.

- Subject #69073 experienced pancreatitis. This adverse event led to discontinuation from the trial.

Remaining 23 serious adverse events occurred well after the dosing period and were not considered to be related to the study drug.

Three serious adverse events reported in the itraconazole 100mg capsule group (myocardial infarction, cerebrovascular accident, and glioblastoma multiforme) did lead to subject discontinuation. Of these, one adverse event was reported during the dosing period and other two were reported during the follow-up period. All other subjects completed the trial. Summary of serious adverse events are displayed in Table 22.

Table 22: Summary of Serious Adverse Events Study BT0300-302-INT

Subject No.	Dosing Group	Adverse Event	Subject Disposition
13017	Itraconazole 200mg tablet	Prostate cancer	Completed
15133	Itraconazole 200mg tablet	Gastric ulcer hemorrhage	Completed
15140	Itraconazole 200mg tablet	Prostate cancer	Completed
16008	Itraconazole 200mg tablet	Thyroid gland cancer	Completed
16130	Itraconazole 200mg tablet	Uterine cancer	Completed
16197	Itraconazole 200mg tablet	Laryngeal cancer	Completed
19028	Itraconazole 100mg capsule	Jaw fracture	Completed
19074	Placebo tablet	Lung malignant neoplasm	Completed
21003	Itraconazole 100mg capsule	Appendicitis	Completed
24090	Itraconazole 200mg tablet	Cholelithiasis	Completed
26003	Itraconazole 200mg tablet	Angina unstable	Completed
26060	Itraconazole 100mg capsule	Myocardial infarction, Cardiac failure congestive, Pleural effusion Anemia	**Discontinued**

Table 22: Summary of Serious Adverse Events Study BT0300-302-INT (continued)

40132	Itraconazole 200mg tablet	Coronary artery disease	Completed
46010	Itraconazole 100mg capsule	Cholelithiasis	Completed
49011	Itraconazole 200mg tablet	Non-small cell lung cancer, Brain cancer metastatic	Completed
53070	Itraconazole 200mg tablet	Myocardial infarction	Completed
55074	Itraconazole 100mg capsule	Neck pain	Completed
63009	Placebo tablet	Diverticulitis	Completed
66051	Itraconazole 100mg capsule	Calculus uretheric	Completed
67075	Itraconazole 100mg capsule	Cerebrovascular Accident	**Discontinued**
68110	Itraconazole 200mg tablet	Carotid artery aneurysm	Completed
69073	Placebo tablet	Pancreatitis	Completed
69103	Itraconazole 200mg tablet	Appendicitis	Completed
70019	Itraconazole 100mg capsule	Myocardial infarction	Completed
90101	Itraconazole 100mg capsule	Glioblastoma multiforme	**Discontinued**

Source: Sponsor's submission, Table 22; Section 2.7.4

There were reports of serious adverse events of cardiovascular and cerebrovascular disease in both Tradename-itraconazole 200mg tablet and itraconazole 100mg capsule groups. These adverse events were not unusual in number or unexpected.

Concerns about cardiac and cerebrovascular adverse events associated with Sporanox would apply to Tradename-itraconazole irrespective of their incidence in the Tradename-itraconazole clinical development program since subjects with risk factors for cardiovascular events were excluded from the trial. This reviewer recommends that similar contra-indications and warnings for cardiac and concomitant medications administration that cause QT prolongation are included in the Tradename-itraconazole PI. Sporanox labeling addresses these adverse events in warning and contra-indications section.

7.3.3 Dropouts and/or Discontinuations

In the study BT0300-302-INT, 1,381 subjects were randomized to study drug; this included 593 subjects in the Tradename-itraconazole 200-mg tablet group, 590 subjects in the itraconazole 100-mg capsule group, and 198 subjects in the placebo tablet group. Of all enrolled subjects, 1,169 (84.6%) completed the study and this included 517 (87.2%) subjects in the Tradename-itraconazole 200-mg tablet group, 496 (84.1%) subjects in the itraconazole 100-mg capsule group, and 156 (78.8%) subjects in the placebo tablet group.
The most frequently reported reasons for study discontinuation were:

- *Lost to follow-up:* 27 (4.6%) for Tradename-itraconazole 200mg tablet group, 34 (5.8%) for itraconazole 100mg capsule group, and 14 (7.1%) for placebo tablet group.
- *Adverse Events:* 21 (3.5%) for Tradename-itraconazole 200mg tablet group, 31 (5.3%) for itraconazole 100mg capsule group, and 8 (4%) for placebo tablet group.

- *Consent Withdrawal:* 14 (2.4%) for Tradename-itraconazole 200mg tablet group, 14 (2.4%) for itraconazole capsule group, and 10 (5.1%) for placebo tablet group.

- *Other:* 11 (1.9%) for Tradename-itraconazole 200mg tablet group, 8 (1.4%) for itraconazole 100mg capsule group, and 3(1.5%) for placebo table group. The most frequent reason for subject discontinuation in this group includes the following: subject moved out of area and subject took exclusionary medication.

Further discussion about subject's discontinuation due to adverse events is presented in section 7.3.4. Summary of subject's completion and discontinuation are presented in Table 23.

Table 23: Summary of Subjects Completion/Discontinuation

	Itraconazole Tablets (N=593)	Itraconazole Capsules (N=590)	Placebo Tablets (N=198)	Total (N=1381)
Number of Subjects Randomized	593	590	198	1381
Number of Subjects Who Completed the Study	517 (87.2%)	496 (84.1%)	156 (78.8%)	1169 (84.6%)
Number of Subjects Who Discontinued the Study	76 (12.8%)	94 (15.9%)	42 (21.2%)	212 (15.4%)
Reasons for Discontinuation				
Non-Compliance	1 (0.2%)	2 (0.3%)	1 (0.5%)	4 (0.3%)
Protocol Violation	2 (0.3%)	3 (0.5%)	2 (1.0%)	7 (0.5%)
Consent Withdrawn	14 (2.4%)	14 (2.4%)	10 (5.1%)	38 (2.8%)
Lack of Efficacy	0 (0.0%)	0 (0.0%)	3 (1.5%)	3 (0.2%)
Lost to Follow-up	27 (4.6%)	34 (5.8%)	14 (7.1%)	75 (5.4%)
Administrative Decision	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.1%)
Investigator Discretion	0 (0.0%)	2 (0.3%)	0 (0.0%)	2 (0.1%)
Adverse Event	21 (3.5%)	31 (5.3%)	8 (4.0%)	60 (4.3%)
Other	11 (1.9%)	8 (1.4%)	3 (1.5%)	22 (1.6%)

Source: sponsor's submission, Table 14.0.4; Section 5.3.5.1.3

7.3.4 Significant Adverse Event

Adverse Events that Led to Discontinuation of Study Drug

Across all 6 studies, 1516 subjects were enrolled and evaluated for safety. Of these subjects, 744 were exposed to the Tradename-itraconazole 200mg tablet, 711 subjects were exposed to the itraconazole 100mg capsule, and 191 subjects were exposed to the placebo.

In the Phase 3 study, 60 subjects experienced adverse events that led to discontinuation of study medication. Of those, 23 subjects were in Tradename-itraconazole 200mg tablet group, 29 subjects were in 100mg itraconazole capsule group, and 8 subjects in the placebo tablet group.

The most frequent reported adverse events that led to discontinuation from the Tradename itraconazole 200mg tablet group were as follow: hepatic enzyme increased in 7 (1.2%) subjects; skin rash and urticaria in 3 (0.5%) of subjects; and dizziness in 3 (0.5%) subjects.
In the itraconazole 100mg capsule group the most frequently reported adverse events that led to discontinuation of subjects were as follow: skin rash and urticaria in 6 (1.0%) subjects, hepatic enzyme increased in 6 (1.0%) subjects; dyspnea and respiratory tract congestion in 4 (0.7%) subjects; and abdominal pain and nausea in 4 (0.7%) subjects.

Two subjects in Tradename-itraconazole 200mg tablet and 100mg capsule group respectively were discontinued from the trial due to electrocardiogram QT prolongation. These adverse events were considered related to the study drug in all 4 subjects. They were reported during the dosing period. All four cases were asymptomatic and required no therapy. One of the cases did not resolve while other three resolved upon discontinuation of the study drug.

No more than 1 subject discontinued from the placebo tablet group for any specific event.

Additionally, 19 subjects (8 in the Tradename-itraconazole 200mg tablet, 9 in the itraconazole 100mg capsule, and 2 in the placebo tablet groups) discontinued the study drug temporarily due to AEs. Summary of most frequent adverse events that led to discontinuation of study drug is presented in Table 24.

Table 24: Most Frequent Adverse Events that Resulted in Discontinuation of Study Medication

System Organ Class Preferred Term	**Itraconazole 200mg tablet N=582**	**Itraconazole 100mg capsule N=581**	**Placebo tablet N=191**
CARDIAC DISORDERS Coronary artery disease Myocardial infarction Palpitations Tachycardia	**0 (0.0%)**	**4 (0.7%)** 1 (0.2%) 1 (0.2%) 1 (0.2%) 1 (0.2%)	**0 (0.0%)**
EAR AND LABYRINTH DISORDERS Tinnitus	**1 (0.2%)** 1 (0.2%)	**1 (0.2%)** 1 (0.2%)	**0 (0.0%)**
GASTROINTESTINAL DISORDERS Abdominal pain [d] Nausea	**3 (0.5%)** 0 (0.0%) 0 (0.0%)	**4 (0.7%)** 2 (0.3%) 2 (0.3%)	**1 (0.5%)** 0 (0.0%) 0 (0.0%)

Table 24: Most Frequent Adverse Events that Resulted in Discontinuation of Study Medication (continued)

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITONS Fatigue Oedema peripheral Chest pain	**2 (0.3%)** 1 (0.2%) 1 (0.2%) 0 (0.0%)	**3 (0.5%)** 1 (0.2%) 1 (0.2%) 1 (0.2%)	**0 (0.0%)**
IMMUNE SYSTEM DISORDERS Drug hypersensitivity	**1 (0.2%)** 1 (0.2%)	**0 (0.0%)**	**0 (0.0%)**
INVESTIGATIONS Hepatic enzymes increased [a] Electrocardiogram abnormal [b]	**10 (1.7%)** 7 (1.2%) 2 (0.3%)	**9 (1.5%)** 6 (1.0%) 2 (0.3%)	**1 (0.5%)** 0 (0.0%) 0 (0.0%)
METABOLISM AND NUTRITON DISOREDS Dehydration Hyperkalemia	**1 (0.2%)** 1 (0.2%) 0 (0.0%)	**1 (0.2%)** 0 (0.0%) 1 (0.2%)	**0 (0.0%)**
MUSCULOSCELETAL AND CONNECTIVE TISSUE DISORDERS Arthralgia Muscle spasm Myalgia	**1 (0.2%)** 0 (0.0%) 1 (0.2%) 0 (0.0%)	**1 (0.2%)** 0 (0.0%) 0 (0.0%) 1 (0.2%)	**2 (1.0%)** 1 (1.0%) 0 (0.0%) 1 (0.5%)
NERVOUS SYSTEM DISORDERS Dizziness Headache	**3 (0.5%)** 3 (0.5%) 0 (0.0%)	**3 (0.5%)** 0 (0.0%) 2 (0.3%)	**1 (0.5%)** 0(0.0%) 1 (0.5%)
RESPIRATORY, THORACIC AND MEDIASTINAL DOSORDERS Dyspnea Respiratory Tract Congestion	**0 (0.0%)**	**3 (0.5%)** 3 (0.5%) 1 (0.2%)	**1 (0.5%)** 0 (0.0%) 0 (0.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS Rash [c] Urticaria	**3 (0.5%)** 2 (0.3%) 1 (0.2%)	**8 (1.4%)** 3 (0.5%) 3 (0.5%)	**2 (1.0%)** 0 (0.0%) 0 (0.0%)

Source: Sponsor's submission, Table 14.3.1.2; Section 5.3.5.1.3
Counts reflect numbers of subjects reporting one of more adverse events classified for MedDRA system organ classes and preferred terms. At each level of summarization subjects are only counted once.
a, b, c, d -Please see Appendix 1.

Review of the adverse events that led to discontinuation of study drug revealed that the most frequent adverse events were elevation of hepatic enzymes and skin rash. These adverse events were not unusual or unexpected.

There were four cases of QT prolongation that were related to the study drug (2 in Tradename-itraconazole 200mg tablet group and 2 in itraconazole 100mg capsule group), resulted in subject discontinuation, All cases the QT prolongation were mild and non-serious.

No new safety signals were revealed during the conduct of this trial. Labeling is adequate to inform prescribers of the possible cardiac adverse events, and the adverse event profile, in the opinion of this reviewer, was not worse than the experience from Sporanox. Labeling which is similar to Sporanox is recommended for Tradename-itraconazole.

Treatment Phase Adverse Events Occurring in ≥1% of Subjects

In this trial, 829 subjects (61%) reported 1 or more adverse events. Of those, 341 (41%) were in Tradename-itraconazole 200mg tablet group, 373 (44%) in itraconazole 100mg capsule group, and 115 (13%) in placebo group.

The respective proportions of subjects in the Tradename-itraconazole 200mg tablet, itraconazole 100mg capsule, and placebo tablet dosing groups who reported at least 1 adverse event (regardless of severity, seriousness, or relationship to the study drug) were 59% (341/582), 64% (373/581), and 60% (115/191).

During the dosing period the most frequently reported adverse events were in the system organ classes of:

- **Gastrointestinal disorders** (reported by 6.2%, 7.7% and 8.8% of the subjects in Tradename-itraconazole 200mg tablet, itraconazole 100mg capsule and placebo dosing groups respectively). Of those the most frequently reported adverse events were abdominal pain (1.9%, 1.9% and 1.0% of subjects across dosing groups), diarrhea (1.7%, 1.4% and 3.1% across dosing groups) and nausea (1.7%, 1.4% and 1.6% across dosing groups)

- **Infections and infestations** (reported by 12.0%, 12.6% and 14.7% of the subjects in Tradename-itraconazole 200mg tablet, itraconazole 100mg capsule and placebo dosing groups respectively). Of those the most frequently reported adverse events were upper respiratory tract infections (6.0%, 6.3% and 7.3% across dosing groups)

- **Investigations/laboratory evaluations** (reported by 9.6%, 7.9% and 6.8% of the subjects in Tradename-itraconazole 200mg tablet, itraconazole 100mg capsule and placebo dosing groups respectively). Of those the most frequently reported adverse event was hepatic enzymes increased (3.6%, 2.9% and 0.0% across dosing groups).
- **Musculoskeletal and connective tissue disorders** (reported by 5.0%, 6.2% and 6.8% of the subjects in Tradename-itraconazole 200mg tablet, itraconazole 100mg capsule and placebo dosing groups respectively). Of those the most frequently reported adverse event was back pain (1.2%, 1.7% and 2.1% across dosing groups).

Summary of Treatment Phase adverse events by System Organ Class and Preferred Term is presented in Table 25.

Table 25: Summary of Treatment Phase Adverse Events by System Organ Class and Preferred Term

System Organ Class Preferred Term	**Itraconazole 200mg tablet (N = 582)**	**Itraconazole 100mg capsule (N = 581)**	**Placebo (N=191)**
CARDIAC DISORDERS	**8 (1.4%)**	**15 (2.6%)**	**1 (0.5%)**
Arrhythmia [g]	8 (1.4%)	9 (1.5%)	1 (0.5%)
EAR AND LABYRINTH DISORDERS	**28 (4.8%)**	**28 (4.8%)**	**9 (4.7%)**
Hypoacusis	19 (3.3%)	16 (2.8%)	6 (3.1%)
GASTROINTESTINAL DISORDERS	**36 (6.2%)**	**51 (8.8%)**	**17 (8.9%)**
Abdominal pain [a]	11 (1.9%)	11 (1.9%)	2 (1.0%)
Diarrhea	10 (1.7%)	8 (1.4%)	6 (3.1%)
Nausea	10 (1.7%)	8 (1.4%)	3 (1.6%)
GENERAL DISORDERS OF ADMINISTRATION SITE CONDITIONS	**16 (2.7%)**	**18 (3.1%)**	**9 (4.7%)**
Fatigue [b]	11 (1.9%)	6 (1.0%)	5 (2.6%)
INFECTIONS AND INFESTATIONS	**70 (12%)**	**73 (12.6%)**	**28 (14.7%)**
Upper respiratory tract infection [c]	35 (6.0%)	37 (6.3%)	14 (7.3%)
Bacteriuria	8 (1.4%)	7 (1.2%)	3 (1.6%)
Urinary tract infection	6 (1.0%)	9 (1.5%)	1 (0.5%)

Table 25: Summary of Treatment Phase Adverse Events by System Organ Class and Preferred Term (continued)

INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**21 (3.6%)**	**21 (3.6%)**	**5 (2.6%)**
INVESTIGATIONS Hepatic enzymes increased [d] Electrocardiogram abnormal [e]	**56 (9.6%)** 21 (3.6%) 8 (1.4%)	**46 (7.9%)** 17 (2.9%) 13 (2.2%)	**13 (6.8%)** 0 (0.0%) 3 (1.6%)
MUSCULOSCELETAL AND CONNECTIVE TISSUE DISORDERS Back pain	**29 (5.0%)** 7 (1.2%)	**36 (6.2%)** 10 (1.7%)	**13 (6.8%)** 4 (2.1%)
NERVOUS SYSTEM DISORDERS Headache Dizziness	**26 (4.5%)** 13 (2.2%) 7 (1.2%)	**27 (4.6%)** 16 (2.8%) 3 (0.5%)	**6 (3.1%)** 3 (1.6%) 0 (0.0%)
RENAL AND URINARY DISORDERS	**8 (1.4%)**	**6 (1.0%)**	**1 (0.5%)**
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS Cough Pharyngolagyngeal pain	**25 (4.3%)** 7 (1.2%) 6 (1.0%)	**27 (4.6%)** 3 (0.5%) 5 (0.9%)	**4 (2.1%)** 0 (0.0%) 1 (0.5%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS Rash [f] Urticaria	**19 (3.3%)** 4 (0.7%) 1 (0.2%)	**28 (4.8%)** 9 (1.5%) 3 (0.5%)	**7 (3.7%)** 0 (0.0%) 0 (0.0%)

Source: sponsor's submission, Table 14.3.1.3.1; Section 5.3.5.1.3
Counts reflect numbers of subjects reporting one of more adverse events classified for MedDRA system organ classes and preferred terms. At each level of summarization subjects are only counted once.
a, b, c, d, e, f, g: Please see Appendix 2

Review of adverse event occurring in frequency of ≥1% during the dosing period revealed that most frequent adverse events were upper respiratory tract infections, elevation of hepatic enzymes and abdominal pain. These adverse events were not unusual or unexpected. No new safety signals were revealed. These will be captured in product labeling. Labeling negotiations are ongoing as of the closure of this review.

During the follow-up period the most frequently reported adverse events were in the system organ classes of:

- **Infections and infestations** (reported by 17%, 17.5% and 10.1% of the subjects in Tradename-itraconazole 200mg tablet, itraconazole 100mg capsule and placebo dosing groups respectively). Of those the most frequently reported adverse event was nasopharyngitis (3.7%, 5.8% and 2.4% across dosing groups)

- **Ear and labyrinth disorders** (reported by 3.9%, 7.4% and 6.0% of the subjects in Tradename-itraconazole 200mg tablet, itraconazole 100mg capsule and placebo dosing groups respectively). Of those the most frequently reported adverse event was hypoacusis (3.6%, 7.0% and 4.8% across dosing groups)

- **Injury, poisoning, and procedural complications** (reported by 4.1%, 6.4% and 6% of the subjects in Tradename-itraconazole 200mg tablet, itraconazole 100mg capsule and placebo dosing groups respectively).

- **Musculoskeletal and connective tissue disorders** (reported by 5.8%, 3.7% and 3.6% of the subjects in Tradename-itraconazole 200mg tablet, itraconazole 100mg capsule and placebo dosing groups respectively). Of those the most frequently reported adverse events were pain in extremity (1.5 %, 0.2% and 0.6% across dosing groups) and back pain (1.3%, 1% and 1.2% across dosing groups).

A summary of adverse events that occurred during the follow-up period is presented in Table 26.

Table 26: Summary of Follow-up Phase Adverse Events by System Organ Class and Preferred Term

System Organ Class Preferred Term	**Itraconazole 200mg tablet (N = 535)**	**Itraconazole 100mg capsule (N = 515)**	**Placebo (N=168)**
CARDIAC DISORDERS	**3 (0.6%)**	**3 (0.6%)**	**1 (0.6%)**
Angina unstable	1 (0.2%)	0 (0.0%)	0 (0.0%)
Myocardial infarction	1 (0.2%)	0 (0.0%)	0 (0.0%)
Cardiac failure, congestive	0 (0.0%)	1 (0.2%)	0 (0.0%)
EAR AND LABYRINTH DISORDERS	**21 (3.9%)**	**38 (7.4%)**	**10 (6.0%)**
Hypoacusis	19 (3.6%)	36 (7.0%)	8 (4.8%)

Table 26: Summary of Follow-up Phase Adverse Events by System Organ Class and Preferred Term (continued)

GASTROINTESTINAL DISORDERS Abdominal pain [c]	**13 (2.4%)** 0 (0.0%)	**11 (2.1%)** 2 (0.4%)	**1 (0.6%)** 1 (0.6%)
GENERAL DISORDERS OF ADMINISTRATION SITE CONDITION	**11 (2.1%)**	**5 (1.0%)**	**0 (0.0%)**
INFECTIONS AND INFESTATIONS Nasopharyngitis [a]	**91 (17%)** 20 (3.7%)	**90 (17.5%)** 30 (5.8%)	**17 (10.1%)** 4 (2.4%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**22 (4.1%)**	**33 (6.4%)**	**10 (6.0%)**
INVESTIGATIONS Hepatic enzymes increased [b]	**14 (2.6%)** 7 (1.3%)	**8 (1.6%)** 1 (0.2%)	**7 (4.2%)** 0 (0.0%)
MUSCULOSCELETAL AND CONNECTIVE TISSUE DISORDERS Back pain Pain in extremity	**31 (5.8%)** 7 (1.3%) 8 (1.5%)	**19 (3.7%)** 5 (1.0%) 1 (0.2%)	**6 (3.6%)** 2 (1.2%) 1 (0.6%)
NERVOUS SYSTEM DISORDERS Headache	**8 (1.5%)** 5 (0.9%)	**17 (3.3%)** 5 (1.0%)	**2 (1.2%)** 2 (1.2%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL. CYSTS AND POLYPS)	**9 (1.7%)**	**7 (1.4%)**	**1 (0.6%)**
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS Cough	**5 (0.9%)** 3 (0.6%)	**16 (3.1%)** 6 (1.2%)	**5 (3.0%)** 1 (0.6%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	**6 (1.1%)**	**6 (1.2%)**	**0 (0.0%)**
SKIN AND SUBCUTANEOUS TISSUE DISORDERS Ingrowing nail	**16 (3.0%)** 10 (1.9%)	**23 (4.5%)** 8 (1.6%)	**3 (1.8%)** 0 (0.0%)

Source: sponsor's submission, Table 14.3.1.3.2.
Counts reflect numbers of subjects reporting one of more adverse events classified for MedDRA system organ classes and preferred terms. At each level of summarization subjects are only counted once.
a, b, c: Please see Appendix 3

Adverse events that were reported during the follow-up period were less likely to be drug related considering that the half life of the Tradename-itraconazole 200mg tablet, after repeated dosing, is approximately 36 hours.

Additional Studies Used for Safety Evaluation

Safety reports of Phase 1 trials

Study BT300-BEL-002

A total of 56 healthy subjects received single dose of Tradename-itraconazole 200mg tablet or 2 itraconazole 100mg capsules in 2-way crossover trial with 14 day wash-out period. 56 subjects received the study drug and were included in safety analysis.

During the conduct of the Bioequivalence study BT300-BEL-002 there were no deaths or serious adverse events.

In Tradename-itraconazole 200mg group, twenty nine subjects (53%) experienced 44 adverse events (46%).

The most frequently reported adverse events were: headache in 12 subjects, fatigue and nausea in 2 subjects respectively. These adverse events were considered possibly related to the study drug and were of mild to moderate intensity.

There were two adverse events that required discontinuation of the study drug:

- Subject No. 19 discontinued because he had to take prohibited medication for flu-like symptoms. This adverse event was mild in intensity.
- Subjects No. 51 discontinued because he needed to take antibiotics to treat pharyngitis that was moderate in intensity.
- In itraconazole 100mg capsule group, thirty subjects (57%) experienced a total of 43 (45%) adverse events (45%). The most frequent adverse event was headache (11 subjects), nausea, diarrhea and loose stool in 3 subjects respectively. These adverse events were mild to moderate in severity.

Overall the most frequent adverse event was headache with 30 events (31.6%) reported in 24 subjects (42.9%).

Reviewer's comments: The most frequent adverse event reported during the conduct of this trial was headache. No labeling recommendations are recommended based on this trial experience.

tudy BT0300BEL006

This was a three-way cross-over trial of single dose of one 200mg Tradename-itraconazole tablet or two itraconazole 100mg capsule with 14 day wash-out period in 18 healthy volunteers.
18 subjects received the study medication and were included in the safety analysis.

There were no deaths or serious adverse events reported and there were no adverse events that required discontinuation of the study drug.

Twelve subjects experienced 22 adverse events.

In the fasting Tradename-itraconazole 200mg group there were 5 adverse events and they were all mild.

In the fed state Tradename-itraconazole 200mg group there were 11 adverse events. Except for one event of moderate headache all other events were mild in severity. Four events (abdominal pain, dyspepsia and stomach discomfort) were possibly related to the study drug.

In the itraconazole 100mg group there were 5 adverse events. One subjects experienced two adverse events (nasopharyngitis and headache) that was moderate in severity. All other adverse events were of mild intensity.

The most frequent adverse event was nasopharyngitis reported in 4 subjects (22%). Other events were reported in maximum of 2 subjects (11%).

One pregnancy was reported after intake of the 2 itraconazole 100mg capsules. The pregnancy resulted in the birth of healthy newborn twins.

Reviewer's comments: The most frequent adverse event reported during the conduct of this trial was nasopharyngitis. No labeling changes are recommended based on this trial.

BT300-BEL-005

This was two-way cross-over, single oral dose study of Tradename-itraconazole 200mg tablet or 2 itraconazole 100mg capsules in 56 healthy volunteers.

All 56 subjects received the study medication and were included in the safety analysis.

There were no deaths or serious AEs reported.

In this trial 41 subjects reported 76 adverse events. The most frequent adverse events were headache (11 subjects, 20%), application site reaction (9 subjects, 16%) and fatigue (6 subjects, 11%). One subject reported moderate migraine. All other adverse events were mild in severity.

One event of abdominal discomfort was considered related to the study drug (itraconazole 100mg capsule).

The most frequent adverse event reported during the conduct of this trial was headache. No labeling changes are recommended based on this trial.

BT300-108-USA

This was trial of daily dose of Tradename-itraconazole 200mg tablets for 14 consecutive days in 16 healthy volunteers.

All 16 subjects received the study drug and were included in the safety analysis. No subject discontinued study drug due to an adverse events.

No deaths or serious or severe adverse events were reported.

Five subjects (31.3%) reported 14 adverse events. Most adverse events were reported by one subject. Two subjects reported headache and two subjects reported anorexia. All adverse events were considered mild in severity. Except for one case of joint swelling that was considered unrelated, all other AEs were considered possibly related to study drug.

The most frequent adverse events reported during the conduct of this trial were headache and anorexia. No labeling changes are recommended based on this trial.

BT300-BEL-004

This trial was a single administration of 2 Tradename-itraconazole 200mg tablets in 16 healthy female volunteers.

All 16 subjects who received the study drug were included in the safety analysis.
There were no deaths or serious adverse events and no subject discontinued this trial prematurely due to and adverse events.

Eight subjects reported 10 adverse events. All adverse events were mild in severity. Thee adverse events reported by 2 subjects (abdominal pain, diarrhea and nausea) were considered possibly related to the study drug. Headache was reported in 2 subjects and was the only adverse event reported in more than one subject.

The most frequent adverse events reported during the conduct of this trial were headache, abdominal pain and diarrhea. In the opinion of this reviewer, all of these adverse events were possibly related to the study drug. No labeling changes are recommended based on this trial.

Conclusion: In the conduct of Phase 1 trial no new safety signals were revealed. No labeling changes are recommended based on these early phase trials.

7.3.5 Submission Specific Primary Safety Concerns

The most serious safety concerns with itraconazole are potential for hepatotoxicity, cardiotoxicity and drug-drug interaction. Please see section 2.4.

7.4.1 Common Adverse Events

7.4.2 Laboratory Findings

During the conduct of 5 Phase 1 trials, none of the observed laboratory abnormalities were considered clinically relevant and were not reported as adverse events.

The following laboratory evaluations were conducted during the Phase 3 trial: Clinical laboratory testing (blood and urine for chemistry, hematology, and urinalysis) were collected at screening, weeks 4, 8, 12, and 52. ECGs were obtained at screening and throughout the dosing period at weeks 0, 4, 8, and 12. Female subjects of childbearing potential underwent repeat urine pregnancy tests at weeks 0, 12, and 52. Audiology tests were performed 3 times during the study: at randomization (week 0); at the end of the dosing period (week 12); and at exit (week 52).

Clinical laboratory evaluations results out of range of normal were reported as adverse events and were considered related to the study drugs.

The most frequently reported laboratory abnormalities, during the treatment phase of the trial, were elevation of hepatic enzymes: 21 (3.6%) subjects in Tradename-itraconazole 200mg tablet group, and 17 (2.9%) subjects in itraconazole 100mg capsule group. Next most frequent laboratory abnormality reported was abnormal electrocardiogram: 8 (1.4%) subjects in Tradename-itraconazole 200mg tablet group and 13 (2.2%) subjects in itraconazole 100mg capsule group and 3 (1.6%) subjects in placebo group).

The most frequently reported laboratory abnormality, during the follow-up phase, was elevation of hepatic enzymes: 7 (1.3%) subjects in Tradename-itraconazole 200mg tablet group and 1 (0.2%) in itraconazole 100mg capsule group.

During the conduct of the Phase 3 trial, 18 subjects were discontinued due to abnormal laboratory evaluations: 9 subjects in Tradename-itraconazole 200mg tablet group, 9 subjects in itraconazole capsule 100mg group. The reasons for discontinuation were as follow:

1. Elevation of hepatic enzymes in 14 subjects: 7 (1.2%) subjects in Tradename-itraconazole 200mg tablet group and 6 (1.0%) subjects in itraconazole 100mg capsule group. No subjects in placebo group had abnormal hepatic enzymes.

2. Abnormal electrocardiogram in 4 subjects: 2 (0.3%) subjects in Tradename-itraconazole 200mg tablet and 2 (0.3%) subjects in the 100mg capsule group.

3. Hyperkalemia in one subject (0.2%) who received itraconazole 100mg capsule.

Subjects who were discontinued due elevation of hepatic enzymes had the following laboratory results:

- AST/ALT elevation >10x the ULN in 2 subjects [one subject (0.2%) from Tradename-itraconazole 200mg tablet group and one from (0.2%) itraconazole 100mg capsule group][a].

- AST/ALT elevation >5x the ULN in 3 (0.5%) subjects from Tradename-itraconazole 200mg tablet group and 2 (0.3%) subject from itraconazole 100mg capsule group.

- AST/ALT elevation >3x the ULN in 3 (0.5%)subjects in Tradename-itraconazole 200mg tablet group and 3(0.5%) subjects in itraconazole 100mg capsule group.

Of all subjects with elevated hepatic enzymes one subject (from itraconazole capsule 100mg group) had elevation of total bilirubin of >1.5x ULN.

Alkaline phosphatase [b] elevation of >1.5x ULN was reported in 2 subjects, both in Tradename-itraconazole 200mg tablet group.

ECG evaluations are discussed in section 7.4.4.
Audiology evaluations are discussed in section 7.4.3.1

a: Reference range: AST (11-37U/L); ALT (8-43U/L)
b: Reference range: Alkaline phosphatase (36-118U/L)

Laboratory evaluation during the conduct of the Phase 3 trial has revealed that the most frequent abnormality was elevation of liver function tests. There were no significant differences in frequency of elevation of liver function tests between Tradename- itraconazole 200mg tablet group and itraconazole 100mg capsule group.

This laboratory abnormality was not unexpected given the post marketing experience of Sporanox. Elevation of liver function tests in patients treated with itraconazole has been well

documented during the development program of Sporanox, during the postmarketing experience, and in literature. There were no significant differences in frequency of elevation of liver function tests between Tradename-itraconazole 200mg tablet and itraconazole capsule. No new safety signals in laboratory evaluations were observed.

7.4.3 Vital Signs

In each of the 5 Phase 1 trials, physical examination and vital sign assessments were obtained at entry and exit. In the Phase 3 trial, there were no physical examinations or vital sign collection. For all 5 Phase 1 trials, there were minor fluctuations in blood pressure that was deemed to be not clinically relevant. Overall, no significant changes in vital signs were observed between trial entry and exit.

7.4.3.1 Auditory Examinations

Auditory examinations were conducted during the Phase 3 trial at weeks 0, 12 and 52.

Conclusions of the ENT reviewer are presented as follow:

"The presented audiology results (focusing on frequencies from 500 to 8000 Hz) do not seem to be very different among the three subject groups (itraconazole 200-mg tablet, itraconazole 100-mg capsule, placebo tablet). These results, however, might not reflect the actual impact of ototoxicity on hearing acuity. The sponsor only reports "clinically significant changes" as defined by the protocol. Also, the sponsor did not provide a way to verify the recorded air- and bone-conduction thresholds (e.g., by comparing these thresholds to speech recognition thresholds). It is thus not possible to verify the audiology data in study report.

The sponsor's audiology testing was not designed in a way that permits assessment of the impact of drug ototoxicity on hearing acuity. Therefore it not possible to assess, based on the data presented in the study report, if loss in hearing acuity is a safety concern for Tradename-itraconazole 200-mg tablet."

This clinical reviewer agrees with the ENT reviewer's conclusion. Sponsor's proposed labeling regarding Tradename-itraconazole on hearing acuity (which stated that (b) (4) *were noted in this phase 3 trial)has not been substantiated and only the general precautions which are similar to the Sporanox prescribing information should be included in the Tradename-itraconazole label.*

7.4.4 Electrocardiograms (ECGs) and Cardiac Safety Findings

Electrocardiograms and Cardiac Safety reports were evaluated by DCRP reviewer. The findings are reported as fallow:

"Review of Narratives for Serious Adverse Events and Adverse Events.

There were no deaths across all studies. In Study BT0300-302-INT, 25 subjects reported SAEs and 60 subjects discontinued due to AEs across all dosing groups. Narratives for cardiac SAEs and discontinuations due to cardiac AEs in the CSR and CRFs for BT0300-302-INT were reviewed. They are summarized as follows:

200 mg tablet dosing group:

- Subject 26003 was a 62 yr old white male, who had an AE of unstable angina resulting in hospitalization and stent placement 242 days after the start of the dosing period.

- Subject 40132 was a 59 yr old white male who was diagnosed with CAD 223 days after the start of the dosing period which resulted in hospitalization with medication. Subject 53070 was a 41 yr old white male experienced an MI 152 days after the start of the dosing period. The event resulted in hospitalization.

- Subject 68110, a 56 yr old white male with hypertension and hyperlipidemia, was discontinued due to a left carotid artery aneurysm 221 days after the start of the dosing period.

100 mg Capsule dosing group

- Subject 26060 was a 61 yr old white male with ongoing medical conditions of hypercholesterolemia and depression. He developed an inferior MI 22 days after the start of the dosing period and congestive heart failure/left pleural effusion 63 days after the start of the dosing period. These events resulted in hospitalization, medication and discontinuation from the study after the MI.

- Subject 67075, a 46 yr old white male was discontinued due to a CVA 168 days after the start of the dosing period.

- Subject 70019, a 49 yr old white female discontinued due to myocardial ischemia 306 days after the start of the dosing period.

- Subject 64050, a 66 yr old White male with no known CAD reported an AE of CAD which resulted in discontinuation from the study 20 days after the start of the dosing period.

Cardiology Reviewer's Comments:

- *Possible relationship to study drug cannot be excluded for Subjects 26060 and 64050.*

- *Possible negative inotropic effect/myotoxicity cannot be excluded in the following subjects:*

  Subject 46022, a 40 yr old black female, with history of hypertension assigned to the 100mg capsule group was discontinued for the AEs of "chest pain, hyperhidrosis and dyspnea" 34 and 50 days after the start of the dosing period. The event was considered unrelated to study drug. LVEF assessments are not reported.

  Subject 17038, a 29 yr old black female assigned to the 100mg capsule group was discontinued 30 days after the start of the dosing period for an AE of "swelling (hands & ankles)". Her only other concomitant medication was Tylenol. The event was considered related to study drug. Again, possibility of angioedema vs. CHF cannot be excluded and insufficient information is available.

  Subject 56039, a 37 yr old white female assigned to the 200mg tablet group was discontinued due to an AE of "bilateral foot and ankle edema" 19 days after the start of the dosing period. Her only concomitant medication was ortho-tri-cyclen. The event was considered related to study drug.

  Subject 27034, a 54 yr old white male assigned to the 100mg capsule group with no history of CAD/risk factors was discontinued since he developed AEs of "tachycardia and dyspnea", 1 day after the start of the dosing period. ECG assessment on the day of the event is unavailable.

  Subject 90021, a 43 yr old white male assigned to the 100mg capsule group was discontinued due to an AE of "palpitation" 2 days after the start of the dosing period. The event was considered unrelated to study drug. ECG report is unavailable.

- *Data from the Hyphanox phase 3 study are limited due to the following issues*

  a. There were no LVEF or troponin assessments.

  b. Since patients with history or risk factors for CHF and patients taking calcium channel blockers or medications that could prolong the QT interval were excluded, AEs similar to those reported post-marketing and in the literature with Sporanox are unexpected.

c. While there were a few events where negative inotropic effects due to study drug cannot be excluded, there was nothing unusual or unexpected in the narratives for myocardial ischemia or infarct and CVA reported.

- *Concerns about cardiac adverse events (i.e. significant ventricular arrhythmias and negative inotropy) associated with Sporanox would apply to Hyphanox irrespective of their incidence in the Hyphanox clinical development program since subjects with risk factors for CHF were excluded. Although there is some reassurance that the cases of CHF occurred post-marketing more frequently in the pulse therapy (400mg/day) group, we recommend that similar contra-indications and warnings for CHF and concomitant medications that cause QT prolongation are included in the Hyphanox PI.*

- *Our comments are based on the predications of bioequivalence as proposed by the sponsor. We assume that although there are 15% higher exposures reported with the itraconazole tablet after a standard meal, there would be no clinically meaningful difference in AE profile."*

Clinical reviewer's comments: During the conduct of Phase 3 trial there were cardiovascular adverse events reported in the Tradename-itraconazole where the relationship to study drug could not be excluded. However, the nature and number of adverse events were similar to adverse events reported for Sporanox and the profile forTradename-itraconazole is not expected to be substantially different. The proposed labeling for Tradename-itraconazole, which is similar to that for Sporanox, addresses these adverse events in warnings and contra-indications section.

7.4.5 Special Safety Studies/Clinical Trials

No additional special safety trials were conducted during the development of itraconazole tablet.

7.4.6 Immunogenicity

Not applicable, as the drug is not a therapeutic protein.

7.5 Other Safety Explorations

No other safety explorations were performed. No non-clinical studies of the active pharmaceutical ingredients were conducted in support of this NDA.

7.5.1 Dose Dependency for Adverse Events

During the conduct of the Phase 3 study safety and efficacy of 200mg tablet of itraconazole was evaluated. No additional dose dependent safety explorations were conducted.

7.5.2 Time Dependency for Adverse Events

Adverse Events and laboratory evaluations were reported during the dosing and the follow-up periods. No additional time dependant safety explorations were conducted.

7.5.3 Drug-Demographic Interactions

Onychomycosis is most prevalent in older individuals, and while there are no racial differences in susceptibility, males are three times more likely to be affected than females.

Phase 1 trials included only healthy volunteers. In general, subjects were younger, with mean age in mid- to upper-thirties. Studies either had a balance of male and females subjects or enrolled females subjects exclusively.

In the Phase 3 trial the demographics were consistent across treatment groups. However, the majority of subjects were male (more than 74% per treatment arm). The mean age of study subjects was 47.4 years and range was 16 to 75 years.

All age groups, with the exception of pediatric population, were included during the development of Tradename-itraconazole 200mg tablet. There were 2 subjects under the age of 18 that participated in this trial. One 16 year old subject was in itraconazole 200mg group and the one 17 year old subject was in the placebo tablet group.

Age appeared to have a role in successful outcomes: A general trend is that efficacy rates tended to decrease with age for both itraconazole tablets and itraconazole capsules though treatment responses within a given age group were similar for the two treatments.

The majority of subjects in the trial were Caucasian (more then 84% per treatment arm).
The comparison of Tradename-itraconazole tablets to itraconazole capsules is similar within each race. In addition, the treatment effects are quite similar across the racial subgroups though comparisons are subject to large amounts of variability due to substantial differences in the number of subjects included in each subgroup. Therefore, no meaningful conclusions could be drawn.

Phase 3 trial was conducted in 7 countries: Canada, Dominican Republic, Ecuador, Honduras, Panama, United States, and South Africa. The majority of subjects were enrolled in the United States (88.8%).

With limited data for non-U.S. sites, it is difficult to draw any conclusions for these countries. Overall, the Complete Cure rates were similar between Tradename-itraconazole tablets and itraconazole capsules for each country.

7.5.4 Drug-Disease Interactions

No additional drug dependent effects on the disease course of onychomycosis were evaluated during the development of the Tradename-itraconazole 200mg tablet.

7.5.5 Drug-Drug Interactions

The applicant did not conduct drug-drug interaction assessments in the clinical trials during product development.

It is recognized that itraconazole and its major metabolite (hydroxy-itraconazole) are inhibitors of CYP3A4 and thus itraconazole-containing products may decrease the elimination of medicinal products that are metabolized by CYP3A4. Further, drugs that induce CYP3A4 may decrease the plasma concentrations of itraconazole-containing therapies, while drugs that inhibit CYP3A4 may increase the plasma concentrations of itraconazole-containing therapies. Use of drugs known to interact with itraconazole was prohibited during the Phase 3 trial.

The sponsor's proposed labeling is based on labeling of approved itraconazole product, Sporanox. The sponsor has a right of reference to the Sporanox NDA 20083 (itraconazole capsule) and NDA 20657 (itraconazole solution). Sporanox labeling revision was done on March 3, 2009.
Considering that the Tradename-itraconazole is a new formulation of Sporanox, and the Tradename-itraconazole did not have reports of all adverse event experiences listed in the Sporanox labeling, it is reasonable that these adverse events are included in labeling of Tradename-itraconazole.

The sponsor provided literature reports of additional drug-drug interactions with itraconazole that are not currently listed in the Sporanox labeling or proposed labeling for Tradename-itraconazole. For the review of these reports, and labeling recommendations please see Section 4.4.3.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Controlled trials were not of sufficient duration to permit assessment of carcinogenicity.

7.6.2 Human Reproduction and Pregnancy Data

The protocol for each of the clinical trials excluded the participation of pregnant female subjects, therefore no specific reproduction or pregnancy information was obtained on the use of Tradename-itraconazole 200mg tablets. One subject in study BT0300BEL006 and 1 subject in study BT0300-302-INT became pregnant during the trials. In the case of the subject from study BT0300BEL006, the pregnancy resulted in the birth of healthy newborn twins. In case of the subject from study BT0300-302-INT, the pregnancy resulted in a healthy newborn. No study-related or dosing-related adverse experiences were reported by either of the women.
Nursing females were not included in the trials.

Itraconazole 100mg capsules are listed as Pregnancy Category C in the current approved labeling. This reviewer recommends that similar language to that label be included in the Tradename label.

7.6.3 Pediatrics and Assessment of Effects on Growth

No children under the age of 16 were included in the trial therefore; no specific pediatric assessment or effects on growth were obtained.

There were 2 subjects under the age of 18 that participated in Phase 3 trial. One 16 year old subject was in itraconazole 200mg group and the one 17 year old subject was in the placebo tablet group. Therefore, no meaningful conclusions about safety of efficacy could be drawn in this population. [4,6,7,8,9,10,11,12,13,14,15,20]

(b) (4)

Since the number of subjects less than 18 years of age was insufficient to conclude anything regarding pediatric safety or efficacy, this reviewer recommends a waiver for all pediatric subjects and restriction of the age indication for this new product to adults 18 years of age and older.

The Pediatric Review Committee considered this application on 10/28/2009. The PeRC recommendation concurred with the Division recommendations to restrict this product to adult use in patients 18 years of age and older. A waiver for patients under 18 years of age was granted.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Itraconazole is non-addictive and no information regarding drug abuse was obtained in the clinical studies. In the Phase 3 study, during which subjects administered the study drug QD at home for 12 weeks, no reports of drug abuse were obtained.

No withdrawal effects were observed in the Phase 3 study following daily administration of Tradename-itraconazole 200mg tablets for 12 weeks. Neither withdrawal nor rebound effects are expected following exposure to itraconazole.

No information regarding overdose was obtained in the clinical studies since all subjects either administered the study drug at the investigational site (Phase 1 studies) or completed the study without evidence of significant non-compliance or adverse events suggestive of overdose (Phase 3 trial).

7.7 Additional Submissions / Safety Issues

No additional safety issues have been indentified.

8 Postmarket Experience

Itraconazole 200mg tablet is not a marketed product therefore there is no postmarketing experience available. However, postmarketing data for the Sporanox-itraconazole 100mg capsule used in the treatment of onychomycosis is available within its original NDA 20-083 along with all subsequent, associated safety reports and published literature. The safety profile observed during the development of the Tradename-itraconazole 200mg tablet is consistent with that of the Sporanox itraconazole 100mg capsule, and product labeling is adequate to communicate risks to patients and prescribers.

9 Appendices

Appendix 1:

a: The following preferred terms were also included: Hepatic enzymes increased, Hepatic enzymes abnormal, Transaminases increased, Alanine aminotransferase increased Aspartate aminotransferase increased.

b: The following preferred terms were also included: Electrocardiogram QT prolonged

c: The following preferred terms were also included: Rash erythematous, Rash macular, Rash papular, Drug eruption.

d: The following preferred terms were also included: Abdominal discomfort

Appendix 2:

a: The following preferred terms were also included: Abdominal discomfort, Abdominal distention, Abdominal pain lower, Abdominal pain upper, Epigastric discomfort.

b: The following preferred terms were also included: Malaise.

c: The following preferred terms were also included: Nasopharyngitis, Pharyngitis, Rhinitis, Sinusitis, Tonsillitis.

d: The following preferred terms were also included: Hepatic enzymes abnormal, Liver function test abnormal, Transaminases increased, Alanine aminotransferase increased, Aspartate aminotransferase increased.

e: The following preferred terms were also included: Electrocardiogram QT corrected interval prolonged, Electrocardiogram QT prolonged, Electrocardiogram T wave abnormal, Electrocardiogram T wave inversion.

f: The following preferred terms were also included: Rash erythematous, Rash macular, Rash papular, Rash pruritic.

g: The following preferred terms were also included: Atrial bigeminy, Atrial fibrillation, Bundle branch block, palpitations, Sinus bradicardia, and Sinus tachycardia.

Appendix 3:

a: The following preferred terms were also included: Pharyngitis, Pharyngitis streptococcal.

b: The following preferred terms were also included: Alanine aminotransferase increased, Aspartate aminotransferase increased.

c: The following preferred terms were also included: Abdominal discomfort, Abdominal distension, Abdominal pain upper.

Appendix 4:

a: The following preferred terms were also included: Abdominal discomfort, Abdominal distension, Abdominal pain upper, Epigastric discomfort.

b: The following preferred terms were also included: Alanine aminotransferase increased, Aspartate aminotransferase increased, Hepatic enzymes abnormal, Liver function test

abnormal.
c: The following preferred terms were also included: Bundle branch block, Palpitations, Sinus bradicardia, Tachycardia.

Appendix 5:

a: The following preferred terms were also included: Abdominal discomfort, Abdominal distension, Abdominal pain upper, Epigastric discomfort, Stomach discomfort.

b: The following preferred terms were also included:, Liver function test abnormal, Hepatic enzymes increased, Transaminases increased, Alanine aminotransferase increased, Aspartate aminotransferase increased.

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9.2 Labeling Recommendations

Sponsor's proposed label is based on the existing Sporanox label. Changes to the proposed label supplied by applicant were based on evaluation of clinical studies for the NDA, DMEPA, and DDMAC reviews. A Patient Package Insert (PPI) has been included and reviewed by the Division.

Final labeling is pending negotiations with the sponsor.

9.3 Advisory Committee Meeting

No Advisory Committee was convened for this application.

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/

SNEZANA TRAJKOVIC
03/29/2010

DAVID L KETTL
03/29/2010
Concur with approval recommendation. See CDTL review.

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: August 11, 2009

From: Suchitra Balakrishnan, MD, Ph.D.

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Nichelle Rashid
Regulatory Project Manager
Division of Dermatology and Dental Products

Subject: DCRP consult to evaluate cardiac safety findings in NDA 22-484

This memo responds to your consult to us dated March 31, 2009 to evaluate the cardiac adverse events and ECG findings observed in clinical trials of Hyphanox, an antifungal developed by Stiefel Laboratories, Inc. The consult appears to have been prompted by the boxed warning for congestive heart failure and negative inotropic effects in the current package insert (PI) for Sporanox.

The following materials were reviewed

- Your consult dated March 31 2009.
- Summary of Clinical Safety for Hyphanox *(eCTD 2.7.4)* contained in NDA 22484
- The PI for Sporanox (itraconazole) approved on March 5, 2009
- Article in Lancet, Volume 357, June 2, 2001 by Syed R Ahmad, Sarah J Singer, Brad G Leissa
- Clinical Study Report (CSR) for BT300-302-INT

BACKGROUND

Sporanox (itraconazole 100-mg capsules) was approved in the USA in 1992 for treatment of systemic fungal infections and onychomycosis of the toenail and fingernail. The recommended dose of Sporanox for treatment of toenail onychomycosis is two 100-mg capsules daily for 12

weeks. Stiefel Laboratories has submitted a NDA for HYPHANOX™ (200-mg itraconazole tablet to be taken once daily) for the same indication.

Sporanox has a boxed warning for congestive heart failure and negative inotropy. Dose related negative inotropic effects were noted when itraconazole was administered intravenously to anesthetized dogs. In a healthy volunteer study, transient, asymptomatic decreases in left ventricular ejection fraction were observed using gated SPECT imaging; these resolved before the next infusion, 12 hours later. There are also reports of congestive heart failure in post-marketing experienced more frequently with the 400 mg/day dose administered with pulse therapy for onychomycosis (200 mg bid for 1 week followed by a three week drug -free period and a second one week course of 200 mg bid).

In 2001 Ahmad *et al* from the Office of Post-marketing Risk Assessment and the Division of Special Pathogens and Immunological Products in CDER published an article in the *Lancet* reviewing 58 reports of congestive heart failure received between 1992 and 2001 for itraconazole. A similar search in AERS did not identify any cases of congestive heart failure in association with the other azole antifungal drugs ruling out the possibility of a class effect. The authors reported that a causal relationship with itraconazole was difficult to prove since most patients who died were very sick and were taking many medications. 43 patients were reported to have risk factors or diseases which might confound an association between the use of itraconazole and development of congestive heart failure. However they describe two representative cases in the article in patients on pulse therapy for onychomycosis. A 60 yr old man with no known risk factors for CHF or concomitant medications developed acute pulmonary edema with itraconazole. His symptoms disappeared with de-challenge and recurred on re-challenge. Similarly, a 59 yr old man developed new onset congestive heart failure with resolution of symptoms on de-challenge. On the basis of their review, the labeling of itraconazole was revised and itraconazole was contraindicated for the treatment of onychomycosis in patients with evidence of ventricular dysfunction with re-assessment of risk vs. benefits for the treatment of systemic fungal infections.

In addition to congestive heart failure, since itraconazole is a strong CYP3A4 inhibitor, drug interactions between Sporanox and drugs associated with QT prolongation and pro-arrhythmia, resulting in serious cardiovascular events are also included in the boxed warning.

Sporanox PI

Due to the issues described above, the Sporanox PI has the following statements regarding Cardiac Safety Issues: under boxed warning:

> "Congestive Heart Failure
> SPORANOX® (itraconazole) Capsules should not be administered for the treatment of onychomycosis in patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF. If signs or symptoms of congestive heart failure occur during administration of SPORANOX® Capsules, discontinue administration. When itraconazole was administered intravenously to dogs and healthy human volunteers, negative inotropic effects were seen.

> "Drug Interactions: Co-administration of cisapride, pimozide, quinidine, dofetilide, or levacetylmethadol (levomethadyl) with SPORANOX® (itraconazole) Capsules, Injection or Oral Solution is contraindicated SPORANOX®, a potent cytochrome P450 3A4 isoenzyme system (CYP3A4) inhibitor, may increase plasma concentrations of drugs metabolized by this pathway. Serious cardiovascular events, including QT prolongation, torsades de pointes, ventricular tachycardia, cardiac arrest, and/or sudden death have occurred in patients using cisapride, pimozide, levacetylmethadol (levomethadyl), or quinidine, concomitantly with SPORANOX® and/or other CYP3A4 inhibitors."

Sporanox is contra-indicated for the treatment of onychomycosis in patients with evidence of ventricular dysfunction or a history of CHF. Careful review of risk versus benefits is advised in patients with risk factors such as cardiac ischemic or valvular disease, COPD, renal failure and other edematous disorders. Caution is also advised when administering calcium channel blockers due to possible additive negative inotropic effects and metabolic inhibition by itraconazole.

Reviewer's Comments: On review of the PI, peripheral edema (4%) and hypertension (3%) were reported in the clinical trials for systemic fungal infections in immunocompromised patients. 2% of patients in the toenail onychomycosis trials temporarily or permanently discontinued treatment due to the AE of HTN but not CHF. On review of a PubMed search there are reports of congestive heart failure in the literature associated with itraconazole.

A PubMed literature search for QT prolongation associated with itraconazole was also done. The reports in the literature are also drug-drug interactions, since itraconazole is a strong CYP 3A4 inhibitor. There were no reports of QT prolongation or significant ventricular arrhythmias/sudden death with itraconazole alone.

<u>Hyphanox Clinical Program</u>

The applicant conducted five Phase 1 studies (two PK, two bioequivalence, and one bioavailability) and one Phase 3 study (safety and efficacy). Across all six studies, 1,516 subjects were enrolled and evaluated for safety. Of these subjects, 744 were administered Hyphanox, 711 subjects were administered Sporanox, and 191 subjects were administered placebo.

The sponsor reports that overall, the tablet formulation does not meet the criteria for bioequivalence with the capsules, Total exposure, area under the curve (AUC), of itraconazole was about 15% higher with the itraconazole 200-mg film-coated tablet than with two itraconazole 100-mg capsules when dosing occurred under the fasted state and after a standard breakfast. Peak plasma concentrations were similar under those two conditions. However, following a high-fat, high-calorie breakfast, the itraconazole 200-mg film-coated tablet had a 30% lower bioavailability than two itraconazole 100-mg capsules. Under these conditions, the 200-mg film-coated tablet had a 20% lower peak plasma concentration than two itraconazole 100-mg capsules. The itraconazole 200-mg film-coated tablet will be recommended to be taken with a full meal (a standard breakfast) to maximize absorption, the same as the recommendation in itraconazole 100-mg capsule labeling.

The phase 3 study (BT0300-302-INT) was a randomized, multi-center, parallel group, active- and placebo-controlled, evaluator-blinded trial designed to evaluate the safety and efficacy of QD administration of one Hyphanox (itraconazole 200-mg tablet) relative to two SPORANOX® (itraconazole 100-mg capsules) and one placebo tablet in the treatment of onychomycosis of the great toenail. 1381 male and female subjects, 16-75 yers of age who had clinical diagnoses of distal and/or lateral subungual onychomycosis that affected at least 1 great toenail were randomized 3:3:1 to administer one of three study drugs: the itraconazole 200-mg tablet; two itraconazole 100-mg capsules; or a placebo tablet.

Subjects were excluded for the following:

- Subjects with a history of congestive heart failure (CHF) or ECG signs indicative of conditions that suggest CHF such as:
    - Right ventricular hypertrophy, left ventricular hypertrophy with ST-T wave changes;
    - Low wave voltage;
    - Dilated cardiomyopathy;
    - Atrial strain;
    - Q-waves and left bundle branch block in subjects with ischemic disease;
- Subjects who were being treated with:
    - CYP3A4 metabolized substrates that could have prolonged the QT-interval, (e.g., terfenadine, astemizole, cisapride, levacetylmethadol [levomethadyl], misolastine, pimozide, quinidine, dofetilide, sertindole);
    - Oral triazolam, oral midazolam;
    - CYP3A4 metabolized HMG-CoA reductase inhibitors (e.g., lovastatin, simvastatin, atorvastatin, cerivastatin);
    - Calcium channel blockers (eg, dihydropyridines and verapamil);
    - Potent enzyme inducers of CYP3A4, (eg, phenytoin, phenobarbital, carbamazepine, isoniazid, rifampin, rifabutin);
    - Ergot alkaloids (eg, dihydroergotamine, ergometrine, ergotamine, and methylergometrine);
    - Potent enzyme inhibitors of CYP3A4 (eg, erythromycin and clarithromycin);
    - Warfarin, buspirone, coumarin-like drugs, benzodiazepines, oral hypoglycemics, protease inhibitors or reverse transcriptase inhibitors, digoxin, ciclostazol, eletriptan and halofantrine;

Reviewer's Comments: No LVEF or troponin assessments were done.

The study consisted of a 12-week dosing evaluation period and a 40-week follow-up period, including a screening visit, a randomization visit (week 0), three dosing period visits (weeks 4, 8, and 12), two post-dosing period follow-up visits (weeks 26 and 39), and an exit visit (week 52).

<u>Sponsor's Data and Analysis of Cardiac Safety</u>
Source: Summary of Clinical Safety

> "During the dosing period of the study, within the system organ class of cardiac disorders, 1 subject in the itraconazole 100-mg capsule group experienced a myocardial infarction; the event was serious, unrelated to the study drug, and resulted in subject

discontinuation. During the follow-up period, also within the system organ class of cardiac disorders, serious AEs of angina unstable, coronary artery disease, and myocardial infarction were reported by subjects in the itraconazole 200-mg tablet group and serious AEs of cardiac failure congestive and myocardial ischemia were reported by subjects in the itraconazole 100-mg capsule group. None of these events was related to the study drug and none led to subject discontinuation. No other serious AEs related to cardiac disorders were reported and no serious AEs related to ECG findings were observed.

"Over the course of the study, cardiac disorders that resulted in subject discontinuation included coronary artery disease, myocardial infarction, palpitations, and tachycardia. Each of these events was reported by just 1 subject in the itraconazole 100-mg capsule group and, with the exception of myocardial infarction, none was serious. Within the system organ class of investigations, 4 subjects reported events that led to discontinuation. Specifically, 1 subject in the itraconazole 200-mg tablet group discontinued due to electrocardiogram abnormal, and 1 subject in the itraconazole 200-mg tablet group and 2 subjects in the itraconazole 100-mg capsule group discontinued due to electrocardiogram QT prolonged. In fact, the event of electrocardiogram abnormal also concerned a QTc prolongation. In all four cases, the observed absolute QTc values were of no significant clinical concern. Specifically, 2 subjects (54046 and 52128) had bradycardia accompanied by an uncorrected QT interval slightly exceeding 500 ms. In both cases, the QTcB and QTcF values were <450 ms and QTc was not increased relative to baseline. In the third subject (22057), the QTcB and QTcF values were 461 ms and the increase in QTc versus baseline was <60 ms. The fourth subject (58024) had QTcB and QTcF values of 463 ms and 441 ms, respectively. The increase versus baseline exceeded 60 ms."

Reviewer's Comments: See review of narratives for SAEs and AEs below. No QTcB or QTcF values exceeding 480 ms were observed in any subject during the dosing period. Clinically significant QT prolongation is not expected in this trial since patients with concomitant medications that could cause QT prolongation were excluded. Similarly, since patients with history or risk factors for CHF and patients taking calcium channel blockers were excluded, AEs similar to those reported post-marketing and in the literature with Sporanox are unexpected.

<u>Review of Narratives for SAEs and AEs</u>

There were no deaths across all studies. In Study BT0300-302-INT, 25 subjects reported SAEs and 60 subjects discontinued due to AEs across all dosing groups. Narratives for cardiac SAEs and discontinuations due to cardiac AEs in the CSR and CRFs for BT0300-302-INT were reviewed. They are summarized as follows:

<u>200 mg tablet dosing group:</u>

- Subject 26003 was a 62 yr old white male, who had an AE of unstable angina resulting in hospitalization and stent placement 242 days after the start of the dosing period.
- Subject 40132 was a 59 yr old white male who was diagnosed with CAD 223 days after the start of the dosing period which resulted in hospitalization with medication.

- Subject 53070 was a 41 yr old white male experienced an MI 152 days after the start of the dosing period. The event resulted in hospitalization.
- Subject 68110, a 56 yr old white male with hypertension and hyperlipidemia, was discontinued due to a left carotid artery aneurysm 221 days after the start of the dosing period.

<u>100 mg Capsule dosing group</u>

- Subject 26060 was a 61 yr old white male with ongoing medical conditions of hypercholesteremia and depression. He developed an inferior MI 22 days after the start of the dosing period and congestive heart failure/left pleural effusion 63 days after the start of the dosing period. These events resulted in hospitalization, medication and discontinuation from the study after the MI.
- Subject 67075, a 46 yr old white male was discontinued due to a CVA 168 days after the start of the dosing period.
- Subject 70019, a 49 yr old white female discontinued due to myocardial ischemia 306 days after the start of the dosing period.
- Subject 64050, a 66 yr old White male with no known CAD reported an AE of CAD which resulted in discontinuation from the study 20 days after the start of the dosing period.

<u>Reviewer's Comments</u>

- *Possible relationship to study drug cannot be excluded for Subjects 26060 and 64050.*
- *Possible negative inotropic effect/myotoxicity cannot be excluded in the following subjects:*
    - *Subject 46022, a 40 yr old black female, with history of hypertension assigned to the 100-mg capsule group was discontinued for the AEs of "chest pain, hyperhidrosis and dyspnoea" 34 and 50 days after the start of the dosing period. The event was considered unrelated to study drug. LVEF assessments are not reported.*
    - *Subject 17038, a 29 yr old black female assigned to the 100-mg capsule group was discontinued 30 days after the start of the dosing period for an AE of "swelling (hands & ankles)". Her only other concomitant medication was Tylenol. The event was considered related to study drug. Again, possibility of angioedema vs. CHF cannot be excluded and insufficient information is available.*
    - *Subject 56039, a 37 yr old white female assigned to the 200-mg tablet group was discontinued due to an AE of "bilateral foot and ankle edema" 19 days after the start of the dosing period. Her only concomitant medication was ortho-tricyclen. The event was considered related to study drug.*
    - *Subject 27034, a 54 yr old white male assigned to the 100-mg capsule group with no history of CAD/risk factors was discontinued since he developed AEs of "tachycardia and dyspnoea", 1 day after the start of the dosing period. ECG assessment on the day of the event is unavailable.*
    - *Subject 90021, a 43 yr old white male assigned to the 100-mg capsule group was discontinued due to an AE of "palpitation" 2 days after the start of the dosing period. The event was considered unrelated to study drug. ECG report is unavailable.*

Reviewer's Assessments for Sporanox:

An MGPS datamining analysis of the AERS database for the broad high level terms (HLT's) of cardiomyopathies, heart failure signs and symptoms, heart failures NEC, left ventricular failures, right ventricular failures, ventricular arrhythmias and cardiac arrest was performed. The signal scores (EBGM and EB05 values) for TdP and cardiac failure were just greater than 2 indicating possible higher incidence than the background rate in the general population. On review of the narratives for TdP they were predominantly due to higher exposures to other drugs associated with QT prolongation in the presence of itraconazole. Of the 85 cases of cardiac failure, 15 of these were reported after 2001. On review of these narratives, there was significant confounding due to co-morbidities and concomitant medications (including calcium channel blockers) but relationship to study drug could not be excluded. Information was incomplete in some of these reports. However, these data by themselves alone do not indicate causal association and perhaps the division can consult the Office of Surveillance and Epidemiology regarding this issue.

Configuration: CBAERS BestRep (S) **Run :** Generic (S) **Run ID:** 930
Dimension: 2 **Selection Criteria:** Generic name(Itraconazole) + PT(HLT=...) **Where:** EBGM > 2.0
3 rows Sorted by Generic name, EBGM desc

Generic name	PT	HLT	N	EBGM	EB05	EB95
Itraconazole	Torsade de pointes	Ventricular arrhythmias and cardiac arrest	29	3.66	2.68	4.91
Itraconazole	Cardiac failure	Heart failures NEC	85	2.65	2.21	3.15
Itraconazole	Cardiac failure acute	Heart failures NEC	4	2.47	1.08	5.04

ID:	930
Type:	MGPS
Name:	Generic (S)
Description:	Generic; Suspect drugs only; Minimum count=1; Standard strata (Age, FDA Year, Gender); includes PRR and ROR; includes hierarchy information
Project:	CBAERS Standard Runs
Configuration:	CBAERS BestRep (S)
Configuration Description:	CBAERS data; best representative cases; suspect drugs only; with duplicate removal
As Of Date:	07/17/2009 00:00:00
Item Variables:	Generic name, PT
Stratification Variables:	Standard strata
Highest Dimension:	2
Minimum Count:	1
Calculate PRR:	Yes
Calculate ROR:	Yes
Base Counts on Cases:	Yes
Use "All Drugs" Comparator:	No
Apply Yates Correction:	Yes
Stratify PRR and ROR:	No
Fill in Hierarchy Values:	Yes
Exclude Single Itemtypes:	Yes
Fit Separate Distributions:	Yes
Save Intermediate Files:	No
Created By:	Empirica Signal Administrator
Created On:	07/24/2009 06:56:33 EDT
User:	Suchitra Balakrishnan
Source Database:	Source Data: CBAERS data from Extract provided by CBER as of 07/17/2009 00:00:00 loaded on 2009-07-23 10:10:13.0

Dimension: 2 **Selection Criteria:** Generic name(Itraconazole) + PT(HLT=Cardiomyopathies, Heart failure signs and symptoms, Heart failures NEC, Left ventricular failures, Right ventricular failures, Ventricular arrhythmias and cardiac arrest) **Where:** EBGM > 2.0

SELECT * FROM OutputData_930 WHERE (DIM=2 AND EBGM>2.0 AND ((P1='D' AND ITEM1 IN ('Itraconazole') AND P2='E' AND H1ITEM2 IN ('Cardiomyopathies','Heart failure signs and symptoms','Heart failures NEC','Left ventricular failures','Right ventricular failures','Ventricular arrhythmias and cardiac arrest')))) ORDER BY ITEM1,EBGM desc

These data do not, by themselves, demonstrate causal associations; they may serve as a signal for further investigation.

DCRP Comments for DDDP

1. Data from the Hyphanox phase 3 study are limited due to the following issues
    a. There were no LVEF or troponin assessments.

b. Since patients with history or risk factors for CHF and patients taking calcium channel blockers or medications that could prolong the QT interval were excluded, AEs similar to those reported post-marketing and in the literature with Sporanox are unexpected.
c. While there were a few events where negative inotropic effects due to study drug cannot be excluded, there was nothing unusual or unexpected in the narratives for myocardial ischemia or infarct and CVA reported.

2. Concerns about cardiac AEs (i.e. significant ventricular arrhythmias and negative inotropy) associated with Sporanox would apply to Hyphanox irrespective of their incidence in the Hyphanox clinical development program since subjects with risk factors for CHF were excluded. Although there is some reassurance that the cases of CHF occurred post-marketing more frequently in the pulse therapy (400 mg/day) group, we recommend that similar contra-indications and warnings for CHF and concomitant medications that cause QT prolongation (this list needs to be updated-refer to www.azcert.org) are included in the Hyphanox PI.

3. We did not review information regarding bioequivalence between two itraconazole 100-mg capsules and 200-mg tablets. Our comments are based on the predications of bioequivalence as proposed by the sponsor. We assume that that although there are 15% higher exposures reported with the itraconazole tablet after a standard meal, there would be no clinically meaningful difference in AE profile.

Thank you for requesting our input into the development of this product under this NDA We welcome more discussion with you now and in the future.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22484	ORIG 1		HYPHANOX 200MG FILM-COATED TABLETS

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/s/

SUCHITRA M BALAKRISHNAN
08/11/2009

NORMAN L STOCKBRIDGE
08/11/2009

DDDP CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA
NDA 22-484 Hyphanox for Onychomycosis of toenail
(Related IND 69,847)

	Yes	No	N/A	Comment
FORMAT/ORGANIZATION/LEGIBILITY				
1. Identify the general format that has been used for this application, e.g. electronic CTD.	Electronic eCTD			
2. On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	Yes			
3. Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	Yes			
4. For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	Yes			
5. Are all documents submitted in English, or are English translations provided when necessary?	Yes			
6. On its face, is the clinical section of the application legible so that substantive review can begin?	Yes			
LABELING				
7. Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56[1] and 201.57, current divisional and Center policies, and the design of the development package?	Yes			
SUMMARIES				
8. Has the applicant submitted all the required discipline summaries (*i.e*, Module 2 summaries)?	Yes			
9. Has the applicant submitted the integrated summary of safety (ISS)?	Yes			
10. Has the applicant submitted the integrated summary of efficacy (ISE)?	Yes			
11. Has the applicant submitted a benefit-risk analysis for the product?	Yes			
12. Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	505 (b)(1) Sponsor confirmed that the NDA will be filed as a 505(b)(1) application and Barrier has the right to cross reference all of Janssen's data submitted to NDA 20-803, Sporanox Capsules.			
DOSE				
13. If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			No	No dose ranging studies were done. Dose is the same as for currently approved itraconazole product- Sporanox (200mg once daily)
EFFICACY				
14. On its face, do there appear to be the requisite number of				One 3 arm study designed to

[1] http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html

adequate and well controlled studies in the application? Pivotal Study #1 BT0300-302-INT Indication: onychomycosis of toenail Pivotal Study #2 Indication:	Yes			show non-inferiority to itraconazole capsules and superiority to placebo SPA Review 5/06
15. Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	Yes			Unblinding issues will be a review issue
16. Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	Yes			The primary efficacy endpoint was the proportion of subjects in each dosing group with Complete Cure at week 52 as requested by Agency 7/06 Tcon: Sponsor stated that toenails are the primary site of indication sought (b) (4) [redacted] any evidence of success will not be used for labeling or marketing. It was further understood that if proposed labeling would so be impacted, this would have to be revisited with further discussion.
17. Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		No		There were 4 sites in Latin America 77 (Ecuador: 17; Panama:21; Honduras: 21; Dominican Republic:18) One site in South Africa: 26; and 6 sites in Canada: 52
SAFETY				
18. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	Yes			
19. Has the applicant submitted adequate information to assess the arrythmogenic potential of the product (*e.g.*, QT interval studies, if needed?	Yes			
20. Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product?	Yes			

OTHER STUDIES				
21. Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?	Yes			
22. For an Rx-to-OTC switch application, are the necessary special OTC studies included (*e.g.*, labeling comprehension)?			NA	
PEDIATRIC USE				
23. Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	Yes			
ABUSE LIABILITY				
24. If relevant, has the applicant submitted information to assess the abuse liability of the product?			NA	
FOREIGN STUDIES				
25. Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			No	
DATASETS				
26. Has the applicant submitted datasets in a format to allow reasonable review of the patient data?		No		See Biostat comments
27. Has the applicant submitted datasets in the format agreed to previously by the Division?				
28. Are all datasets for pivotal efficacy studies available and complete for all indications requested?				
29. Are all datasets to support the critical safety analyses available and complete?				
30. For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints?				
CASE REPORT FORMS				
31. Has the applicant submitted all required Case Report forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	Yes			
32. Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			NA	
FINANCIAL DISCLOSURE				
33. Has the applicant submitted the required Financial Disclosure information for study investigators?	Yes			
GOOD CLINICAL PRACTICE				
34. Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	Yes			
CONCLUSION				
35. From a clinical perspective, is this application fileable? If “no”, please state why it is not?	Yes			

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

Snezana Trajkovic, MD

Reviewing Medical Officer

David Kettl, MD

Clinical Team Leader

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

/s/

Snezana Trajkovic
6/3/2009 03:54:34 PM
MEDICAL OFFICER

David Kettl
6/3/2009 04:26:55 PM
MEDICAL OFFICER