

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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STATISTICAL REVIEW(S)



US Department of Health and Human Services
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STATISTICAL REVIEW AND EVALUATION
NEW DRUG APPLICATION
CLINICAL STUDIES

NDA/Serial Number: 22-484/SN000
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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Itraconazole is approved for the treatment of onychomycosis in the U.S. and has been marketed since the mid-1990s using a once daily (QD) administration for 12 weeks of two 100-mg itraconazole capsules (Sporanox, Janssen Pharmaceutical Products, L.P., Titusville, NJ, U.S.). The sponsor has now developed a 200-mg itraconazole tablet that is intended to have similar safety and efficacy profiles to that of Sporanox when treating patients with toenail onychomycosis.

A single Phase 3 trials was conducted, Study 302, with the efficacy objective of demonstrating Itraconazole Tablets are non-inferior to Itraconazole 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 Study 302, Itraconazole 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). A conservative sensitivity analysis, removing these sites, still resulted in reaching the pre-specified statistical criteria. Several other sensitivity analyses provided consistent efficacy results with the primary analysis.

The adverse event profile of both doses of itraconazole were similar. AE rates were compared for the duration of the trial as well as during the treatment phase of the study - time on treatment plus 14 days following last dose of drug. Several serious adverse events were reported though no major differences were observed in the Itraconazole Tablets treatment arm over Itraconazole Capsules and Placebo Tablets. Note that the study was not powered to detect any safety issues.

1.2 Brief Overview of Clinical Studies

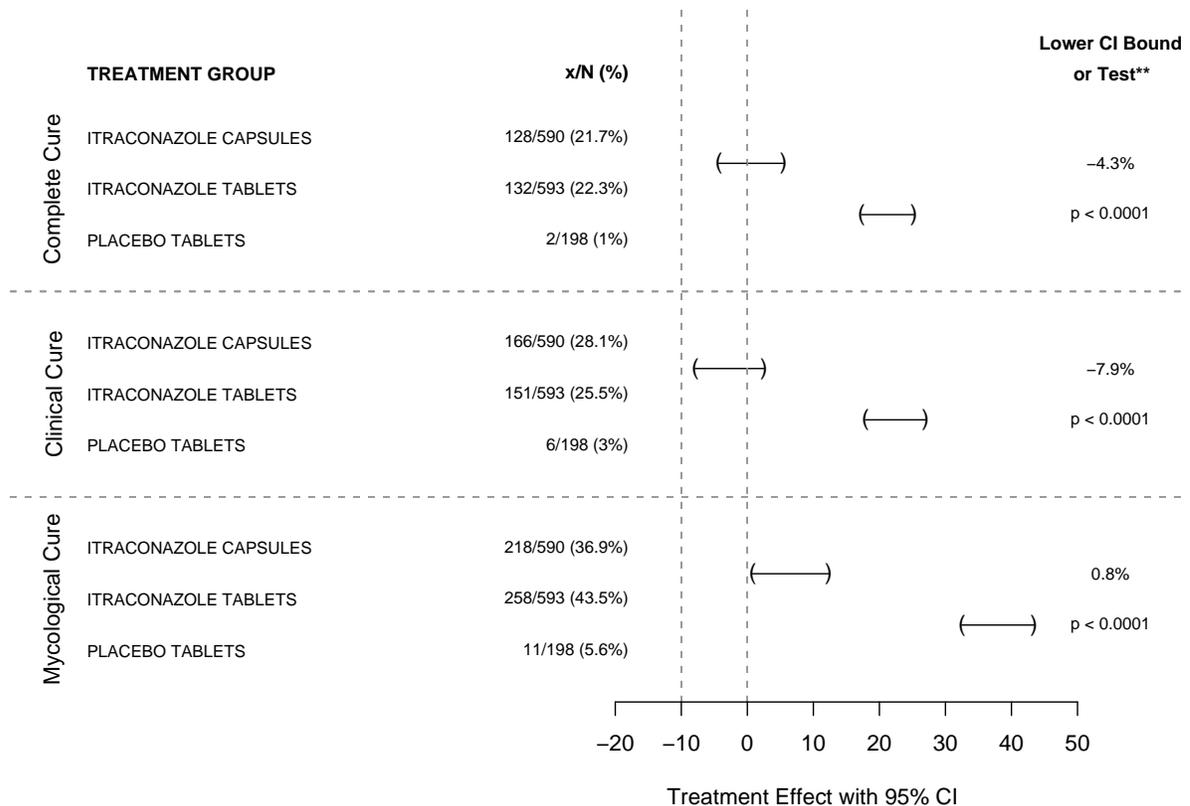
A single pivotal Phase 3 trial, Study 302, was completed to assess the safety and efficacy of Itraconazole Tablets. Study 302 assessed three treatments Itraconazole Tablets, Itraconazole Capsules, and Placebo Tablets with the objective of establishing the superiority of Itraconazole Tablets to Placebo Tablets and the non-inferiority of Itraconazole Tablets to Itraconazole Capsules (NI margin of -10%). The treatment duration was for 12 weeks with the primary time point for evaluating efficacy occurring at Week 52. A total of 1381 subjects were enrolled in the trial from 58 centers located in 7 countries (Canada, Dominican Republic, Ecuador, Honduras, Panama, United States, and South Africa). The primary efficacy endpoint was the Complete Cure rate which consisted of Clinical Cure (IGA = 0 for the target toenail) and Mycological Cure (negative KOH and negative culture for dermatophytes of the target toenail).

1.3 Statistical Issues and Findings

On 03/16/2006 (SN016) the sponsor submitted a revised protocol for Special Protocol Assessment to study itraconazole tablets in the treatment of *toenail* onychomycosis. The proposed treatment for this indication was 200 mg QD for 12 weeks which follows the labeled treatment duration of Sporanox for toenail onychomycosis. In the SPA review, the primary analysis methods were agreed upon with only a few minor statistical recommendations such as increasing the number of subjects enrolled per site and the definition of the primary analysis population for the non-inferiority comparison.

Efficacy assessment was based upon the Complete Cure rate which is defined as a Clinical Cure (IGA = 0 on the target toenail) and Mycological Cure (negative KOH and negative culture for dermatophytes of the target toenail). The primary timepoint for efficacy evaluation was at Week 52. The comparison of Itraconazole Tablets to Itraconazole Capsules and placebo each met the pre-specified efficacy objectives (Figure 1; results are depicted for the ITT population with missing data imputed using LOCF, results are consistent using the PP population).

Figure 1: Efficacy Result Summary



** Lower bound of a one-sided 97.5% CI and p-value from CMH test

The adverse event profile of both doses of itraconazole were similar. AE rates were compared for the duration of the trial as well as during the treatment phase of the study - time on treatment plus 14 days following last dose of drug. Several serious adverse events were reported though no major differences were observed in the Itraconazole Tablets treatment arm over Itraconazole Capsules and Placebo Tablets. Note that the study was not powered to detect any safety issues.

2 INTRODUCTION

Itraconazole was initially developed by Janssen Research Foundation (JRF) and approved as Sporanox (itraconazole 100-mg capsules) on September 11, 1992 and currently is marketed in the United States by Janssen Pharmaceuticals. The current indications for Sporanox include systemic fungal infections and onychomycosis of the toenail and fingernail. Sporanox requires QD administration of two 100-mg capsules for 12 weeks in the treatment of toenail onychomycosis.

Stiefel Laboratories is the sponsoring organizing submitting the NDA for a 200-mg itraconazole tablet (Proposed Trade Name: Hyphanox) to be taken as 1 **tablet** QD for 12 weeks. The NDA is submitted under 505(b)(2) of The Act where a right of reference is granted by Janssen to NDA 20-083 (Sporanox oral capsules) and NDA 20-657 (Sporanox oral solution).

2.1 Regulatory History

The sponsor had an End of Phase 2 meeting with the Agency on December 12, 2005. (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] At this time the Division recommended the sponsor also study toenail onychomycosis. In addition, the following comment was provided in regards to the phase 3 development of [Tradename].

“For the NDA submission, the Agency recommends that you conduct one three-arm study comparing the efficacy of your itraconazole product to Sporanox (at the labeled dose) for the indication studied, and to placebo. [Tradename] should be superior to placebo and non-inferior to Sporanox.”

On 03/16/2006 (SN016) the sponsor submitted a revised protocol for Special Protocol Assessment to study Itraconazole Tablets in the treatment of *toenail* onychomycosis. Treatment for this indication is 200 mg QD for 12 weeks which follows the labeled treatment duration of Sporanox for toenail onychomycosis. In the SPA review, the primary analysis methods were

agreed upon with only a few minor statistical recommendations such as increasing the number of subjects enrolled per site and the definition of the primary analysis population for the non-inferiority comparison.

2.2 Clinical Trial Overview

The clinical development program for itraconazole tablets includes five phase 1 studies (2 PK, 2 bioequivalence, and 1 bioavailability) and one phase 3 study (safety and efficacy). Of these six studies, the single phase 3 trial is the subject of the Biostatistics review.

The Phase 3 study, BT0300-302-INT (Study 302), was a randomized, multi-center, parallel group, placebo-controlled, evaluator-blinded trial designed to evaluate the safety and efficacy of QD administration of 1 itraconazole 200-mg tablet relative to 2 itraconazole 100-mg capsules and 1 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 diagnoses of distal and/or lateral subungual onychomycosis affecting at least 1 great toenail. Eligible subjects were randomized 3:3:1 to administer 1 itraconazole 200-mg tablet, 2 itraconazole 100-mg capsules, or 1 placebo tablet after breakfast, QD for 12 weeks. The study consisted of 8 visits, which comprised the 12-week dosing evaluation period as well as a 40-week follow-up period.

2.3 Data Sources

The sponsor submitted data sets which comply with CDISC standards; therefore data sets which follow the **Study Data Tabulation Model** (SDTM) are submitted as well as data which follow the **Analysis Data Model** (ADaM). The data sets used for the statistical review of Study BT0300-302-INT are located in the EDR at: `//CDSESUB1/EVSPROD/NDA022484/0000/m5/datasets/bt0300-302-int`.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The evaluation of efficacy is based upon Study BT0300-302-INT which is titled, “A Phase 3 Randomized, Evaluator-Blind, Parallel Group Study of the Safety and Efficacy of Itraconazole Tablets, Itraconazol Capsules and Placebo in the Treatment of Onychomycosis of the Toenail.”

3.1.1 Study Design

3.1.2 Endpoints

3.1.2.1 Primary Endpoint The primary efficacy parameter is the Complete Cure rate defined as both Clinical Cure and Mycological Cure at Visit 8 (Week 52) the primary evaluation visit. Clinical Cure is defined as an Investigator's Global Assessment (IGA) score for the target toenail of 0 (table 1). Mycological Cure is defined as a negative KOH and negative culture for dermatophytes of the target toenail. Those subjects with positive KOH and/or growth of dermatophytes of the target toenail are deemed a mycological failure.

Table 1: **Description of Investigator Global Assessment**

0 (Clinical Cure):	No evidence of onychomycosis in target nail. Normal nail unit without subungual hyperkeratosis or onycholysis
1 (Clinical Success):	Minimal evidence of onychomycosis in target nail. $\leq 10\%$ dystrophy and/or discoloration with minimal subungual hyperkeratosis and/or onycholysis
2 (Mild):	Target nail involvement. $\leq 25\%$ dystrophy and/or onycholysis
3 (Moderate):	Target toenail involvement. $\leq 50\%$ 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.

3.1.2.2 Secondary Endpoints A single secondary endpoint is listed, and defined as Clinical Improvement which consists of Mycological Cure and an IGA score for the target toenail of ≤ 1 . The time point for analysis is at Visit 8 (Week 52).

3.1.3 Patient Disposition and Baseline Characteristics

3.1.3.1 Patient Disposition A total of 1381 subjects were enrolled in the trial from 58 centers located in 7 countries (Canada, Dominican Republic, Ecuador, Honduras, Panama, United States, and South Africa). Of the 1381 subjects enrolled, 593 were randomized to Itraconazole Tablets, 590 randomized to Itraconazole Capsules, and 198 randomized to Placebo Tablets. 517 of the 593 subjects (87.2%) randomized to Itraconazole Tablets completed the trial, 496 out of 590 subjects (84.1%) randomized to Itraconazole Capsules completed the trial, and 156 out of 198 (78.8%) of subjects randomized to Placebo Tablets completed the trial (table 2). The top two reasons for dropout were adverse events and lost to follow-up for the two active treatment arms. The top two reasons for dropout for Placebo Tablets were loss to follow-up and consent withdrawn.

Table 2: **Summary of Subject Completion/Discontinuation**

	Itraconazole Tablets (<i>N</i> = 593)	Itraconazole Capsules (<i>N</i> = 590)	Placebo Tablets (<i>N</i> = 198)
Completed the Trial	517 (87.2)	496 (84.1)	156 (78.8)
Discontinued	76 (12.8)	94 (15.9)	42 (21.2)
Administrative Decision	0 (0.0)	0 (0.0)	1 (0.5)
Adverse Event	21 (3.5)	31 (5.3)	8 (4.0)
Consent Withdrawn	14 (2.4)	14 (2.4)	10 (5.1)
Investigator Discretion	0 (0.0)	2 (0.3)	0 (0.0)
Lack of Efficacy	0 (0.0)	0 (0.0)	3 (1.5)
Lost to Follow-up	27 (4.6)	34 (5.8)	14 (7.1)
Non-Compliance	1 (0.2)	2 (0.3)	1 (0.5)
Other	11 (1.9)	8 (1.4)	3 (1.5)
Protocol Violation	2 (0.3)	3 (0.5)	2 (1.0)

Source: Study Report Table 11; results reproduced by reviewer using ADSL.XPT

3.1.3.2 Baseline Demographic Factors The distribution of demographic factors by treatment group is similar across treatments (table 13 provided in the Appendix Section A.0.2). The majority of subjects enrolled were males (74.9%) and White (86.5%) enrolled in the United States (88.8%). For the tabulations by race, the 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.

3.1.3.3 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. Note that inclusion criteria required subjects have positive KOH and a positive culture for dermatophytes; thus these factors are not included in this summary. The baseline distribution of these three prognostic factors is similar across treatment arms (table 3). The majority of subjects were enrolled with the baseline *T. Rubrum* dermatophyte (95.1%), a baseline IGA score of Moderate (mean = 56.8%), and a nail involvement between 50% and 75% (58.1%). Analysis of efficacy for each of these prognostic factors is provided in Section 4.2.

Table 3: Baseline Prognostic Factors by Treatment

	Itraconazole Tablets (<i>N</i> = 593)	Itraconazole Capsules (<i>N</i> = 590)	Placebo Tablets (<i>N</i> = 198)	Test Statistic
Fungi				$\chi_4^2 = 2.45, P = 0.654$
<i>E. Floccosum</i>	1% (5)	1% (3)	2% (3)	
<i>T. Mentagrophytes</i>	5% (27)	4% (23)	4% (7)	
<i>T. Rubrum</i>	95% (561)	96% (564)	95% (188)	
IGA				$\chi_4^2 = 2.46, P = 0.652$
Mild	4% (25)	5% (29)	3% (5)	
Moderate	56% (332)	57% (338)	58% (114)	
Severe	40% (236)	38% (223)	40% (79)	
Percent Nail Involvement				$\chi_4^2 = 2.22, P = 0.696$
>25% to ≤50%	40% (240)	43% (251)	44% (87)	
>50% to ≤75%	59% (352)	57% (339)	56% (111)	
>75% to ≤100%	0% (1)	0% (0)	0% (0)	

Numbers after percents are frequencies. Test used: Pearson test.

Source: Reviewer's Analysis using ADCU.XPT.

3.1.4 Statistical Methodology

Details of the statistical methodology provided below are based upon the protocol. Any analysis details that deviate from the protocol are highlighted as such.

3.1.4.1 General 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 Itraconazole Tablets to Itraconazole Capsules and superiority testing of Itraconazole Tablets to Placebo Tablets for the intent-to-treat and per-protocol populations.

Non-inferiority testing uses 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.

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 are planned. SAS software was used for all of the sponsor's data analyses and tabulations provided in the study report. The reviewers analyses is performed using the R Software[1].

3.1.4.2 Populations The intent-to-treat population includes all subjects randomized and dispensed study medication. This is the primary analysis population for the superiority comparison. In conjunction with the PP population, this is also the analysis population used in the non-inferiority comparison.

The per-protocol population is a subset of the intent-to-treat population. Subjects are eligible for the per-protocol analysis if they complete Visit 8 (Week 52) without noteworthy study protocol violations (i.e., any subject or investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy). A subject is included in the per-protocol analyses if all of the following criteria are met:

- A subject who meets 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 discontinue from the treatment phase of the study due to treatment failure or adverse events will be based on the number of days the subjects participated in the treatment phase of the study,

3.1.4.3 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 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.

3.1.4.4 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 analyses is restricted to the Itraconazole Tablets and Placebo Tablets treatment groups and is performed on the ITT and PP populations.

Reviewer 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 statistical review of efficacy.

3.1.4.4.1 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 $p < 0.05$.

3.1.4.4.2 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 (itraconazole tablets minus itraconazole capsules) is greater than -10%. The statistical analysis method uses Wald's confidence interval with Yates' continuity correction.

3.1.5 Primary Analysis Results

The primary efficacy endpoint is the Complete Cure rate defined as both Clinical Cure and Mycological Cure at Visit 8 (Week 52). A Clinical Cure is defined as IGA score of 0 and a Mycological Cure is defined as a negative KOH test and negative dermatophyte culture. For the non-inferiority comparison, both the ITT and PP populations were considered primary; whereas the ITT population is considered primary for the superiority comparison, and the PP is considered supportive.

Based upon the definitions of the primary endpoint and analysis populations, both efficacy objectives met the pre-specified statistical criteria (table 4). The treatment effects ($\delta = \text{Itraconazole Tablets} - \text{comparator}$) for each population were:

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

Superiority : 21.3% (ITT) and 23.8% (PP)

Superiority of Itraconazole Tablets to Placebo Tablets was clearly significant in both populations ($p < 0.0001$). The non-inferiority comparison of Itraconazole Tablets to Itraconazole

Capsules demonstrated that the lower bound of the one-sided 97.5% confidence interval was above the pre-specified margin of -10%.

Table 4: **Complete Cure Results (Primary Analysis)**

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

[†] 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 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.

3.1.5.1 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 endpoint¹ (table 5). Note that for this component of the primary endpoint, the capsule formulation had a slightly improved response rate than the tablet formulation.

¹Note that the protocol did not include an analysis on this endpoint; this is based on reviewer analysis.

Table 5: **Clinical Cure Results**

	Itraconazole Tablets	Itraconazole Capsules	Placebo Tablets
ITT Population			
Sample Size	593	590	198
Success (%)	151 (25.5%)	166 (28.1%)	6 (3.0%)
Statistical Comparison	-	(-7.9%, 2.5%)	$p < 0.0001$
PP Population			
Sample Size	502	488	155
Success (%)	142 (28.3%)	151 (30.9%)	5 (3.2%)
Statistical Comparison	-	(-8.5%, 3.2%)	$p < 0.0001$

[†] Two-sided 95% Confidence interval (CI) for the difference in Clinical 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 Tables 14.2.17.1 and 14.2.17.2 with reviewer analysis using ADCU.XPT to derive statistical tests.

3.1.5.2 Mycological Cure : The protocol definition of Mycological Cure is a negative potassium hydroxide 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 endpoint² (table 6). Note that for this component of the primary endpoint, Itraconazole Tablets was *superior* to both Placebo Tablets and Itraconazole Capsules. Overall response rates were higher for Mycological Cure rates than Clinical Cure rates.

3.1.6 Sensitivity Analysis to Address the Blinding Issue

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 tablets are 200 mg and the capsules 100 mg (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.

²Note that the protocol did not include an analysis on this endpoint; this is based on reviewer analysis.

Table 6: **Mycological Cure Results**

	Itraconazole Tablets	Itraconazole Capsules	Placebo Tablets
ITT Population			
Sample Size	593	590	198
Success (%)	258 (43.5%)	218 (36.9%)	11 (5.6%)
Statistical Comparison	-	(0.8%, 12.3%)	$p < 0.0001$
PP Population			
Sample Size	502	488	155
Success (%)	233 (46.4%)	194 (39.8%)	11 (7.1%)
Statistical Comparison	-	(0.3%, 13.0%)	$p < 0.0001$

[†] 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.

Reviewer analysis using ADCU.XPT.

As a conservative analysis, 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, this sensitivity analysis met the non-inferiority objective comparing Itraconazole Tablets to Itraconazole Capsules for both the ITT and PP population as well as the superiority objective for comparing the Itraconazole Tablets to Placebo Tablets (table 7). Also note the the Complete Cure rates for Itraconazole Tablets are lower in this analysis in comparison to the primary analysis whereas those of Itraconazole Capsules remain roughly the same.

3.1.7 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 group (21.2%) followed by the itraconazole capsule group (15.9%) and finally the itraconazole

Table 7: Complete Cure Results (Blinding Issue Analysis)

	Itraconazole Tablets	Itraconazole Capsules	Placebo Tablets
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	123
Success (%)	87 (21.9%)	91 (23.8%)	1 (0.8%)
Statistical Comparison	-	(-8.0%, 4.3%) [†]	p < 0.0001*

[†] 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.

Reviewer Analysis using ADCU.XPT

tablet group (12.8%); refer to table 2. Efficacy results using these alternate imputation strategies is presented below for both the ITT and PP populations.

3.1.7.1 Missing 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 8). This conclusion is expected as nearly all subjects with missing Week 52 data are Complete Cure failures at the time of drop out.

3.1.7.2 Missing 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 8). As such, the alternate methods of data imputation provide evidence of the superiority of Itraconazole Tablets to Placebo Tablets and non-inferiority of Itraconazole Tablets to Itraconazole Capsules.

Table 8: Complete Cure Results (Sensitivity Analysis: Missing = Failure)

	Itraconazole Tablets	Itraconazole Capsules	Placebo Tablets
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*

[†] 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 22; results reproduced using ADCU.XPT

Table 9: Complete Cure Results (Sensitivity Analysis: Missing = Success)

	Itraconazole Tablets	Itraconazole Capsules	Placebo Tablets
ITT Population			
Sample Size	593	590	198
Success (%)	208 (35.1%)	219 (37.1%)	42 (21.2%)
Statistical Comparison	-	(-7.7%, 3.6%) [†]	p < 0.0001*
PP Population			
Sample Size	502	488	155
Success (%)	146 (29.1%)	143 (29.3%)	7 (4.5%)
Statistical Comparison	-	(-6.1%, 5.6%) [†]	p < 0.0001*

[†] 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 22; results reproduced using ADCU.XPT

3.1.8 Secondary Endpoint Results

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 10).

Table 10: **Clinical Improvement Results (Secondary Endpoint Analysis)**

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

[†] Two-sided 95% Confidence interval (CI) for the difference in Clinical Improvement 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 18; results reproduced using ADCU.XPT

3.2 Evaluation of Safety

The evaluation of safety is based upon the single Phase 3 Study, Study BT0300-302-INT. The evaluation of safety is conducted on the safety population which is protocol defined as 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 (i.e., post-week 0) assessment. Based on this definition of the safety population, 1354 subjects are included in the analysis of safety. Adverse events were recorded using the MedDRA dictionary version 9.0. Note that in all summaries for adverse events that occur multiple times within the same subject, the event is only counted once in the following tabular displays.

3.2.1 Adverse Events

3.2.1.1 General Summary A general listing of ALL AE's that occurred within the 52 weeks a subject was enrolled in the trial are presented in Table 11 which includes both the MedDRA preferred term (PT) as well as the system organ classification (SOC) when the preferred term is reported in at least 3% of subjects. Note that this tabulation of adverse events includes all events regardless of their reported relation to study drug which may have occurred at any time in the 52 week trial. Overall, this summary of adverse events does not reveal any major differences between the two active doses of itraconazole.

3.2.1.2 Events During Treatment Phase In this analysis only the adverse events which occurred during the treatment phase of the trial. The treatment phase of the trial is defined as the date the first dose is taken until 14 days after the last dose of study drug is taken. For the 1354 subjects included in the safety population, Table 12 contains the MedDRA PT's and SOC's for each of the treatment groups when a single AE occurs in at least 3% of subjects. Note that this summary includes all reported adverse events regardless of the reported relation to study drug. Consistent with the general summary, the adverse event profiles for the treatment phase of the study for the two active doses of itraconazole were quite similar.

Table 11: Adverse Events by System Organ Class and Preferred Term

	Itraconazole Tablets (N = 582)	Itraconazole Capsules (N = 581)	Placebo Tablets (N = 191)
Ear and labyrinth disorders			
Hypoacusis	35 (6.0)	47 (8.1)	12 (6.3)
Tinnitus	5 (0.9)	10 (1.7)	3 (1.6)
Gastrointestinal disorders			
Nausea	12 (2.1)	9 (1.5)	3 (1.6)
Diarrhoea	10 (1.7)	9 (1.5)	6 (3.1)
General disorders and administration site conditions			
Fatigue	9 (1.5)	7 (1.2)	5 (2.6)
Infections and infestations			
Nasopharyngitis	33 (5.7)	39 (6.7)	11 (5.8)
Influenza	14 (2.4)	14 (2.4)	4 (2.1)
Upper respiratory tract infection	14 (2.4)	28 (4.8)	9 (4.7)
Sinusitis	13 (2.2)	16 (2.8)	3 (1.6)
Urinary tract infection	10 (1.7)	12 (2.1)	2 (1.0)
Bacteriuria	9 (1.5)	8 (1.4)	3 (1.6)
Bronchitis	7 (1.2)	5 (0.9)	2 (1.0)
Tinea pedis	4 (0.7)	6 (1.0)	3 (1.6)
Injury, poisoning and procedural complications			
Muscle strain	8 (1.4)	6 (1.0)	2 (1.0)
Musculoskeletal and connective tissue disorders			
Back pain	13 (2.2)	14 (2.4)	5 (2.6)
Pain in extremity	12 (2.1)	6 (1.0)	2 (1.0)
Arthralgia	6 (1.0)	10 (1.7)	5 (2.6)
Myalgia	4 (0.7)	2 (0.3)	4 (2.1)
Nervous system disorders			
Headache	17 (2.9)	19 (3.3)	4 (2.1)
Respiratory, thoracic and mediastinal disorders			
Cough	10 (1.7)	9 (1.5)	1 (0.5)
Pharyngolaryngeal pain	6 (1.0)	9 (1.5)	2 (1.0)
Skin and subcutaneous tissue disorders			
Ingrowing nail	12 (2.1)	8 (1.4)	0 (0.0)
Vascular disorders			
Hypertension	10 (1.7)	6 (1.0)	5 (2.6)

Source: Reviewer's Analysis using ADAE.XPT

Table 12: Adverse Events by System Organ Class and Preferred Term (Events Reported During *Treatment Phase* of the Trial)

	Itraconazole Tablets (<i>N</i> = 582)	Itraconazole Capsules (<i>N</i> = 581)	Placebo Tablets (<i>N</i> = 191)
Ear and labyrinth disorders			
Hypoacusis	19 (3.3)	16 (2.8)	6 (3.1)
Gastrointestinal disorders			
Diarrhoea	10 (1.7)	8 (1.4)	6 (3.1)
Nausea	10 (1.7)	8 (1.4)	3 (1.6)
General disorders and administration site conditions			
Fatigue	9 (1.5)	6 (1.0)	5 (2.6)
Infections and infestations			
Nasopharyngitis	18 (3.1)	17 (2.9)	7 (3.7)
Bacteriuria	8 (1.4)	7 (1.2)	3 (1.6)
Sinusitis	6 (1.0)	9 (1.5)	2 (1.0)
Upper respiratory tract infection	6 (1.0)	11 (1.9)	5 (2.6)
Musculoskeletal and connective tissue disorders			
Back pain	7 (1.2)	10 (1.7)	4 (2.1)
Arthralgia	3 (0.5)	6 (1.0)	4 (2.1)
Nervous system disorders			
Headache	13 (2.2)	16 (2.8)	3 (1.6)

Source: Reviewer's Analysis using ADAE.XPT

3.2.2 Serious Adverse Events

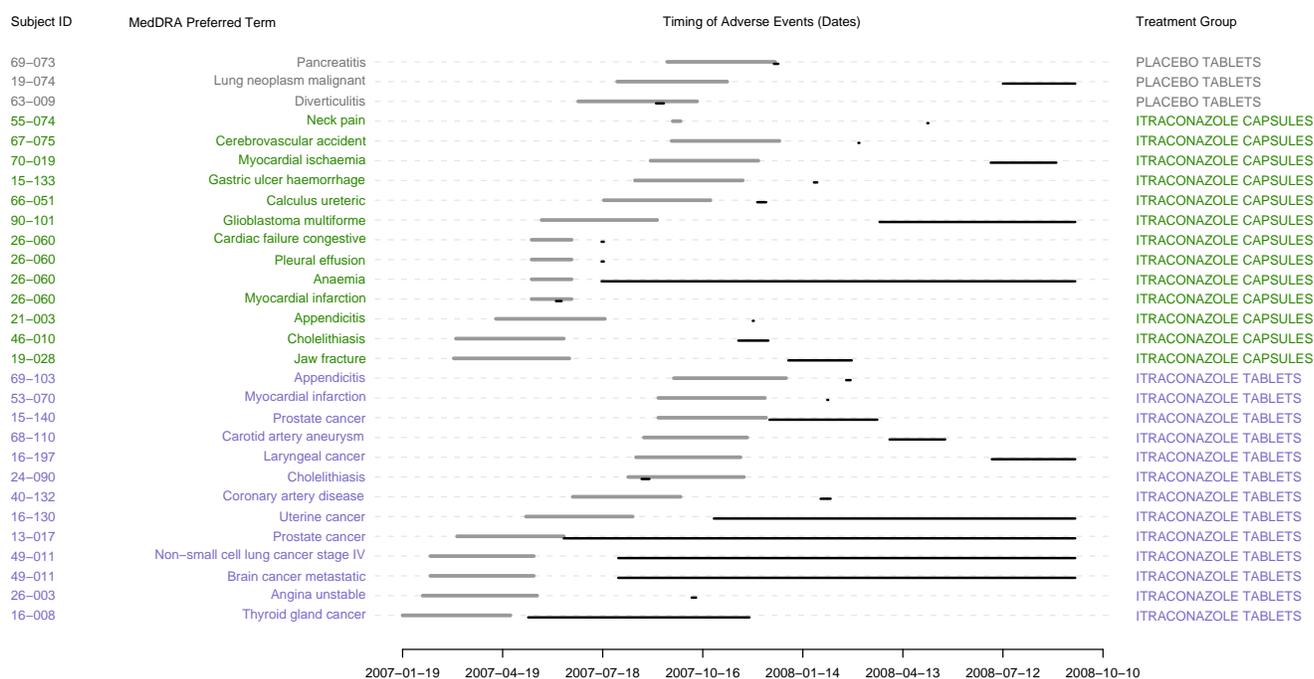
A serious AE was defined as any AE that resulted in death, a life-threatening event, required hospitalization or prolonged an existing hospitalization, caused a persistent or significant disability/incapacity, or resulted in a congenital anomaly or birth defect.

3.2.2.1 Deaths No deaths were reported during the study.

3.2.2.2 Other Serious Adverse Events During the trial, a total of 29 adverse events were listed as serious which occurred in 25 subjects. Thirteen serious adverse events (SAE's) occurred in subjects treated with Itraconazole Tablets, 13 SAE's were reported in subjects treated with Itraconazole Capsules, and 3 SAE's were reported in subjects treated with Placebo Tablets. Of the 29 SAE's reported, 6 occurred while subjects were taking drug. The remaining 23 SAE's were observed after subjects stopped taking treatment.

As a visualization of the SAE's and the timing in which they occurred, Figure 2 was constructed. This figure lists each of the SAE's (MedDRA preferred term) for each subject along with the timing of when subjects were treated with drug (gray lines) and the timing of the SAE (black lines). Sorting of the subjects is by treatment group. In instances when an SAE was unresolved by the end of the study, these lines in the figure were extended to the last date observed for all subjects who experienced an SAE.

Figure 2: Serious Adverse Events



4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

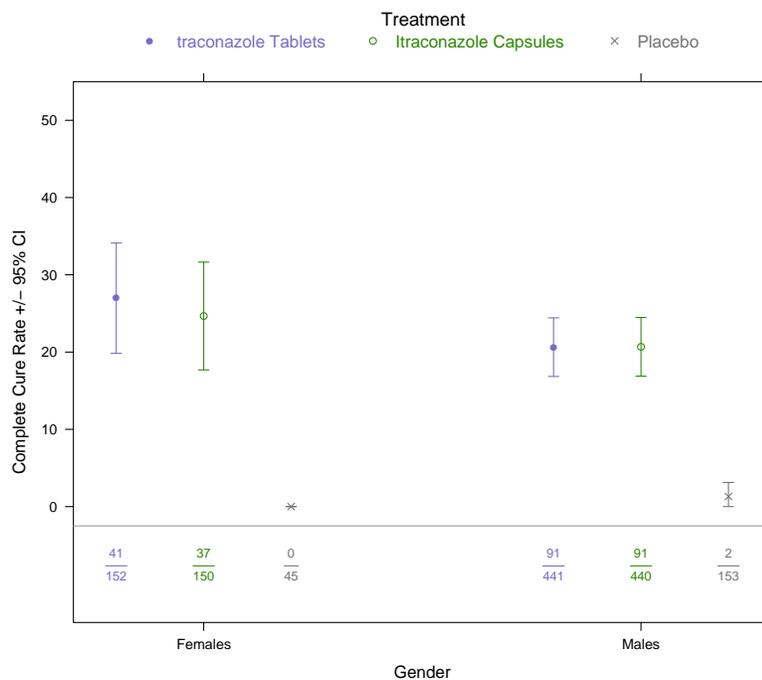
Sections 4.1 and 4.2 provide a graphical assessment of efficacy by subgroup as well tabular information listed in the lower section of each graph for Study 302. The efficacy summaries for the primary endpoint at Week 52 provided by gender, race, and age are similar to those used in the primary analysis: the population is ITT with missing data imputed using LOCF. Note that the protocol did not pre-specify any subgroup analysis which controlled the overall Type I error rate.

4.1 Gender, Race, and Age

4.1.1 Gender

Figure 3 depicts Complete Cure rates according to gender along with unadjusted 95% confidence intervals. Complete Cure rates for Itraconazole Tablets and Itraconazole Capsules were similar within each gender and these corresponding treatment effects were similar for both males and females. Note that no CI is presented for the female subjects treated with placebo as none of these subjects were defined as Complete Cure by Week 52.

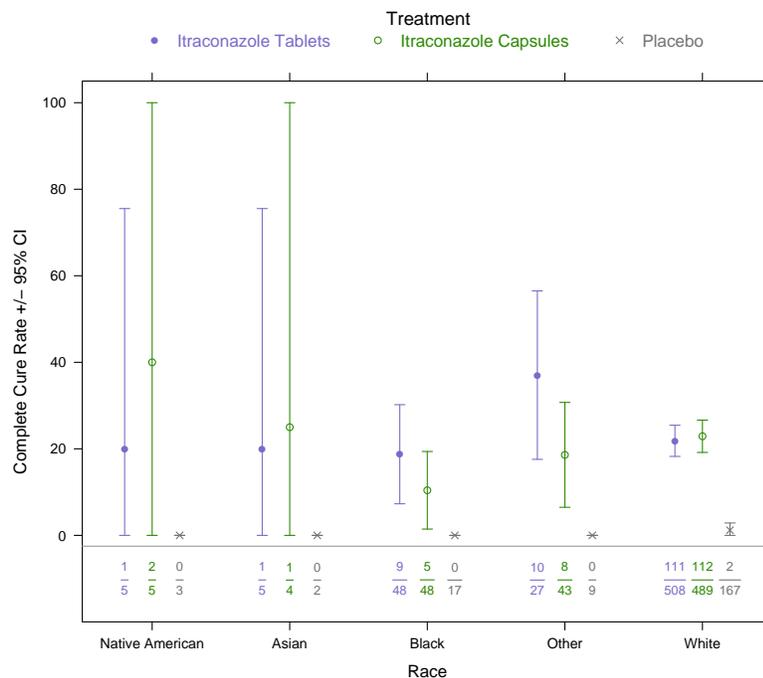
Figure 3: Efficacy Results According to Gender



4.1.2 Race

A small fraction of subjects were enrolled with races listed other than White. Figure 4 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 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 the limited sample sizes.

Figure 4: Efficacy Results According to Race

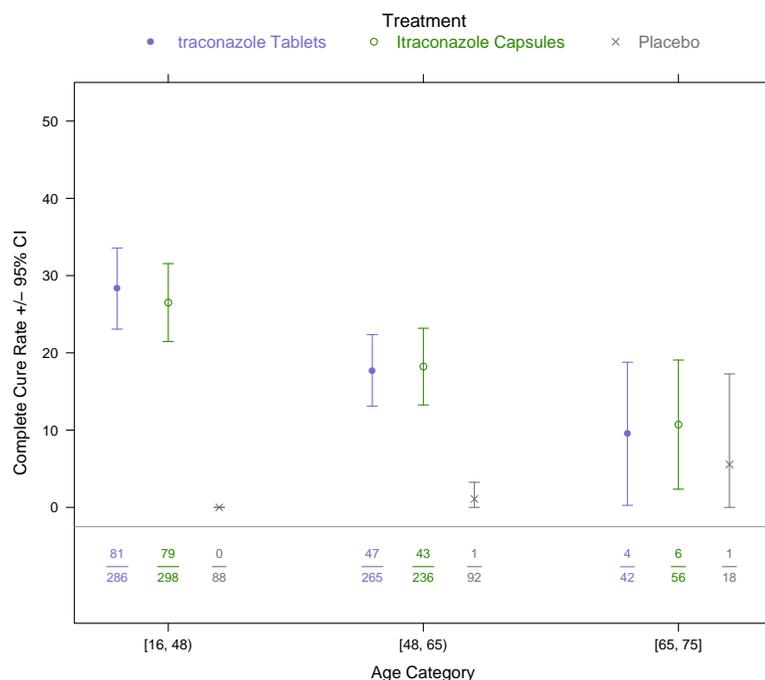


4.1.3 Age

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 guidances[2]. Complete Cure rates and unadjusted 95% confidence intervals are presented in Figure 5 for each of the three age groups. 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. 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 5: **Efficacy Results According to Age**



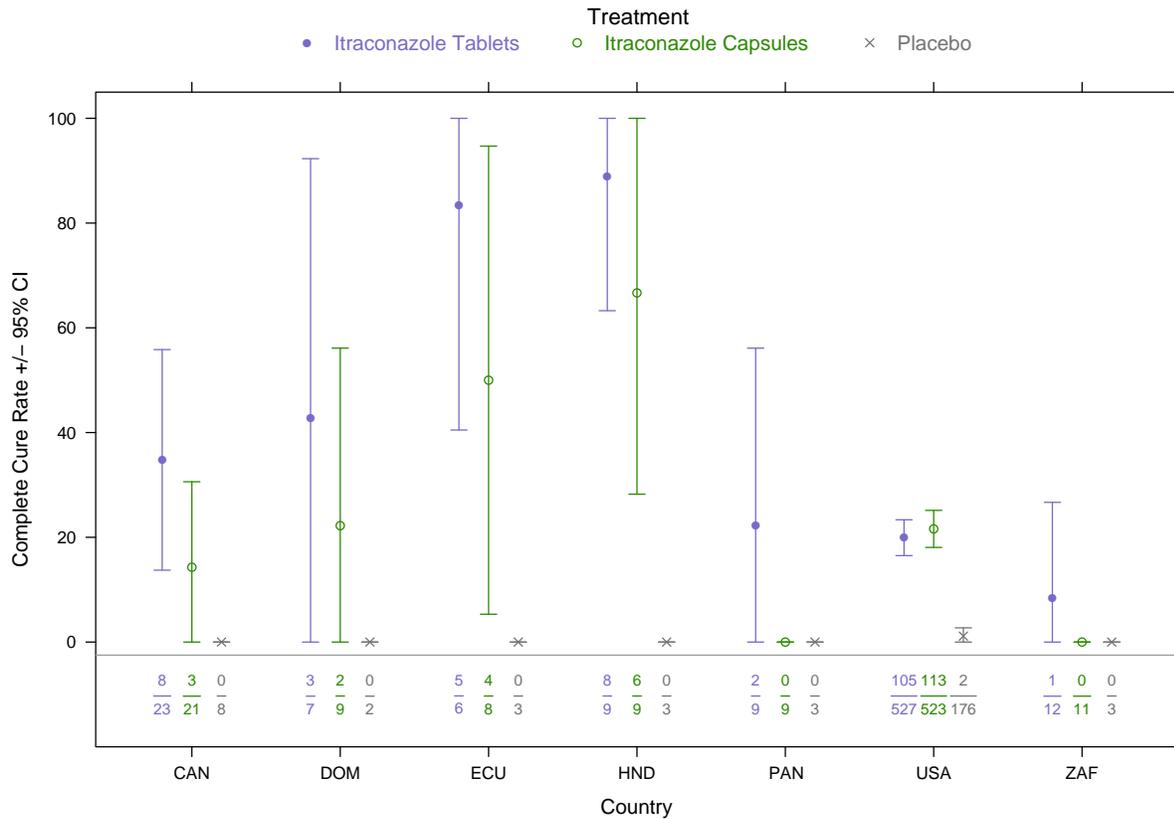
4.2 Other Special/Subgroup Populations

The following subgroup analyses are done post hoc to provide further descriptive information about the efficacy of Itraconazole Tablets on various other subgroups. Results are presented using the same methodology as that in Section 4.1 which includes estimates of the Complete Cure rate along with an unadjusted 95% confidence interval.

4.2.1 Efficacy by Country

Study 302 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 6 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 Itraconazole Tablets and Itraconazole Capsules for each country.

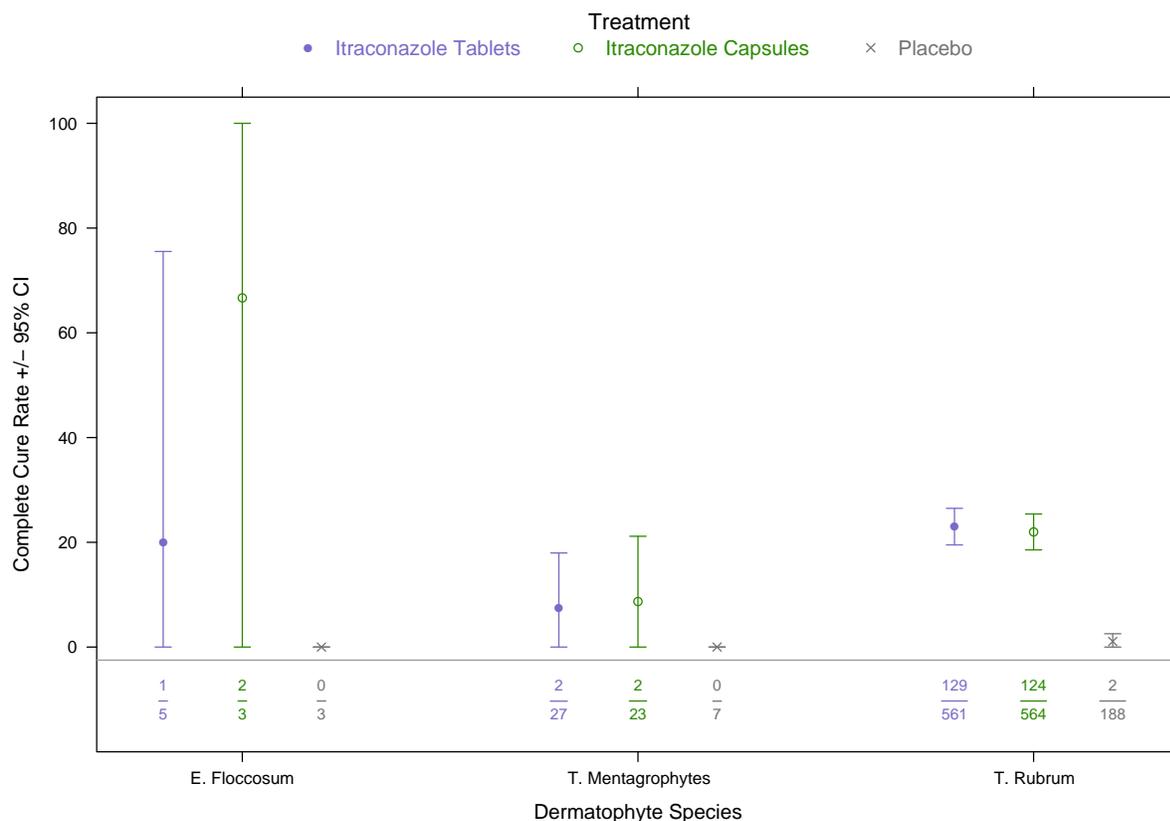
Figure 6: Efficacy Results According to Country



4.2.2 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 7 depicts Complete Cure rates for each of these species. With a limited number of subjects infected with dermatophytes other than *T. Rubrum*, Study 302 does not provide much information about effectiveness in these species. Consequently, the efficacy results are similar to those presented in the primary analysis.

Figure 7: Efficacy Results According to Dermatophyte Species

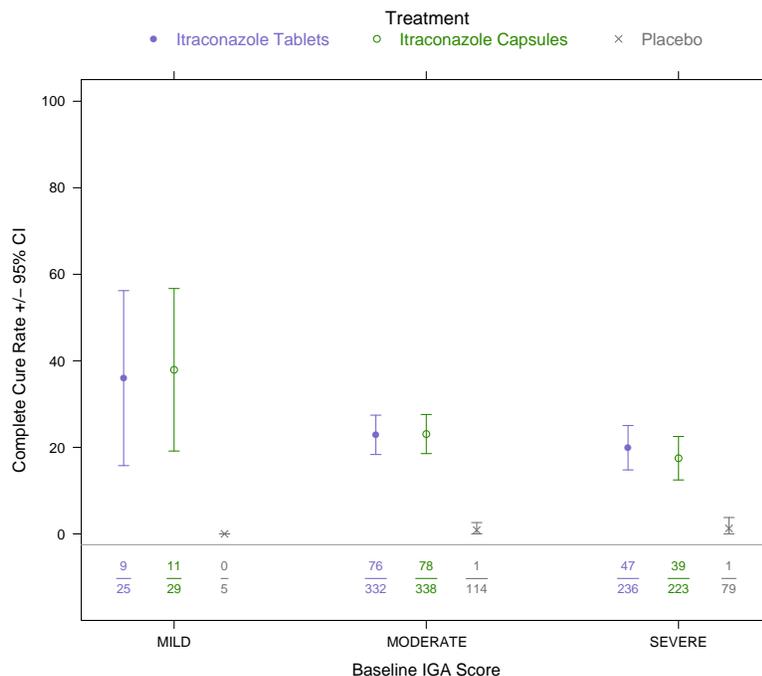


4.2.3 Efficacy by Baseline IGA Score

At baseline subjects enrolled with an IGA score of mild, moderate, and severe; Table 3 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 8 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 groups 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 rates for Itraconazole Tablets and Itraconazole Capsules which are both clearly superior to Placebo Tablets.

Figure 8: Efficacy Results by Baseline IGA Score

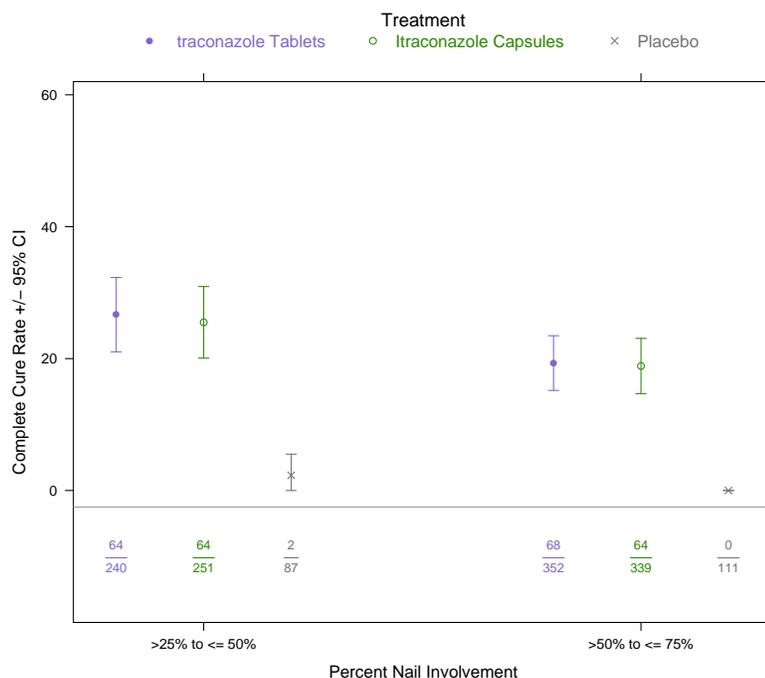


4.2.4 Efficacy by Nail Involvement

For the assessment of percent nail involvement, the target toenail was divided into three four categories: $\leq 25\%$, $> 25\%$ to $\leq 50\%$, $> 50\%$ to $\leq 75\%$, and $> 75\%$. At baseline all but one subject enrolled with a baseline percent nail involvement of $> 25\%$ to $\leq 50\%$ or $> 50\%$ to $\leq 75\%$. 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 9 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 Itraconazole Tablets and Itraconazole 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 9: Efficacy Results by Baseline Nail Involvement



5 SUMMARY AND CONCLUSIONS

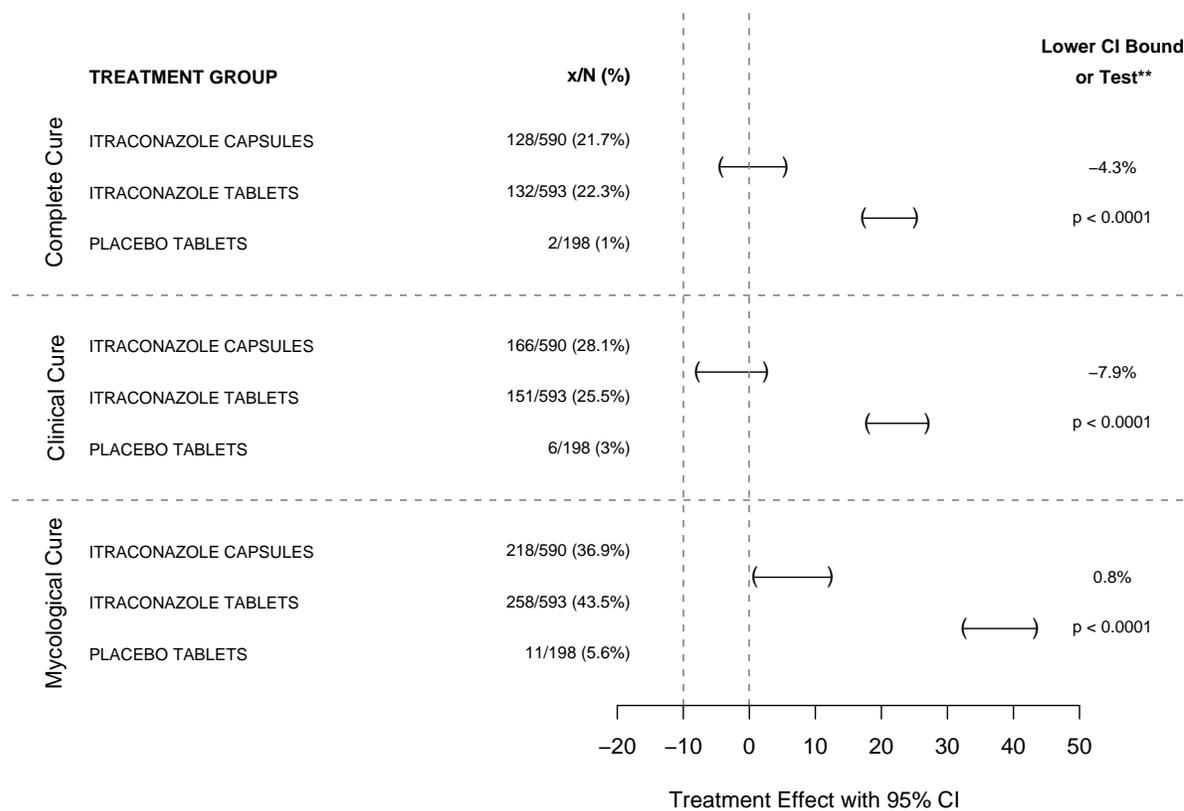
5.1 Statistical Issues and Collective Evidence

On 03/16/2006 (SN016) the sponsor submitted a revised protocol for Special Protocol Assessment to study itraconazole tablets in the treatment of *toenail* onychomycosis. Treatment for this indication is 200 mg QD for 12 weeks which follows the labeled treatment duration of Sporanox for toenail onychomycosis. In the SPA review, the primary analysis methods were agreed upon with only a few minor statistical recommendations such as increasing the number of subjects enrolled per site and the definition of the primary analysis population for the non-inferiority comparison.

Efficacy assessment was based upon the Complete Cure rate which is defined as a Clinical Cure (IGA = 0 on the target toenail) and Mycological Cure (negative KOH and negative culture for dermatophytes of the target toenail). The primary timepoint for efficacy evaluation was at Week 52. The comparison of Itraconazole Tablets to Itraconazole Capsules and placebo each met the pre-specified efficacy objectives (Figure 10; results are depicted for the ITT population only with missing data imputed using LOCF, results are consistent using the PP population).

The adverse event profile of both doses of itraconazole were similar. AE rates were compared for the duration of the trial as well as during the treatment phase of the study - time on treatment plus 14 days following last dose of drug. Several serious adverse events were reported though

Figure 10: Efficacy Result Summary



no major differences were observed in the Itraconazole Tablets treatment arm over Itraconazole Capsules and Placebo Tablets. Note that the study was not powered to detect any safety issues.

5.2 Conclusions and Recommendations

A single Phase 3 trial was conducted, Study 302, with the efficacy objective of demonstrating Itraconazole Tablets are non-inferior to Itraconazole 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 Study 302, Itraconazole 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). A conservative sensitivity analysis, removing these sites, still resulted in reaching pre-specified statistical criteria. Several other sensitivity analyses provided consistent efficacy results with

the primary analysis. The totality of the evidence supports: Itraconazole Tablets are superior to Placebo Tablets, and Itraconazole Tablets are non-inferior to Itraconazole Capsules when using a NI margin of -10%.

5.2.1 Labeling Comments

The following information is taken from the label submitted by the sponsor on August 28, 2009 for Section 14 of the label, Clinical Studies. This is followed by reviewer comments.



Reviewer Comment: The following are recommended changes to the proposed label submitted on 8/28/2009.

- *More description of the study should be provided including the following:*
 - *study design and the trial objectives,*
 - *population studied including descriptive statistics of the population, and*

- *description of the primary endpoint as well as the secondary endpoint (if the secondary endpoint is in agreement with the clinical review team).*
- *The efficacy results included in the sponsor’s proposed table in the label are based on the ITT population with missing data imputed using LOCF. Such a summary is acceptable, however, the following are some general recommendations for the table.*
 - *The primary endpoint should be clearly delineated in the summary of efficacy with other endpoints de-emphasized in the presentation of efficacy.*
 - *If Mycological Cure is included in the label, it is also recommended that Clinical Cure be included as these two components make up the primary endpoint (refer to table 5 for estimates).*
 - *Estimates of Mycological Cure should be rounded to one decimal place.*
- *The last sentence following the table may be deleted depending on recommendations from the clinical review team.*

References

- [1] Statistical Analysis and Graphics produced with R software. R Development Core Team (2009). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL <http://www.R-project.org>.
- [2] *Guideline for Industry - Studies in Support of Special Populations: Geriatrics*. Food and Drug Administration (1994).

APPENDIX

A.0.2 Baseline Demographic Tables

The following table presents tabulated data for the demographic factors (age, race, sex, and country) for the single pivotal Phase 3 trial.

Table 13: Baseline Demographic Factors by Treatment

	Itraconazole Tablets (<i>N</i> = 593)	Itraconazole Capsules (<i>N</i> = 590)	Placebo Tablets (<i>N</i> = 198)
Age	39.00 48.00 55.00	38.25 47.00 55.00	43.00 49.00 57.00
Sex :			
Male	74% (441)	75% (440)	77% (153)
Race :			
American Indian or Alaska Native	1% (5)	1% (5)	2% (3)
Asian	1% (5)	1% (4)	1% (2)
Black or African American	8% (48)	8% (48)	9% (17)
Native Hawaiian or other Pacific Islander	0% (0)	0% (1)	0% (0)
Other	5% (27)	7% (43)	5% (9)
White	86% (508)	83% (489)	84% (167)
Country :			
Canada	4% (23)	4% (21)	4% (8)
Dominican Republic	1% (7)	2% (9)	1% (2)
Ecuador	1% (6)	1% (8)	2% (3)
Honduras	2% (9)	2% (9)	2% (3)
Panama	2% (9)	2% (9)	2% (3)
United States	89% (527)	89% (523)	89% (176)
South Africa	2% (12)	2% (11)	2% (3)

a b c represent the lower quartile *a*, the median *b*, and the upper quartile *c* for continuous variables. Numbers after percents are frequencies.

Source: Study Report Table 14 and Reviewer Analysis.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Mat Soukup, Ph.D.

Date: November 2, 2009

Statistical Team Leader: Mohamed Alosh, Ph.D.

cc:

Archival NDA

DDDP/Walker

DDDP/Kettl

DDDP/Trajkovic

DDDP/Gould

DDDP/Owens

DDDP/Rashid

OBIO/Patrician

DB3/Wilson

DB3/Alosh

DB3/Soukup

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22484

ORIG-1

STIEFEL
LABORATORIES
INC

HYPHANOX 200MG FILM-
COATED TABLETS

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

/s/

MATTHEW J SOUKUP
11/02/2009

MOHAMED A ALOSH
11/02/2009

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22-484

Applicant: Steifel Laboratories

Stamp Date: 03/31/2009

Drug Name: Hyphanox tablets **NDA/BLA Type:** Original Supplement

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

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			eCTD
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			Single P3 Study BT0300-302-INT
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	X			On page 209 of study report
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			Uses a Define.XML file

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? YES

The NDA is filable from a statistics perspective.

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

In your study report you state the following, "During the course of the study, there were subjects for whom the study drug dispensation information was temporarily available to blinded personnel". Based upon the electronic data sets, this appears to have occurred for 93 subjects enrolled in 7 centers. The date of enrollment for these 93 subjects ranged from December 7, 2006 to September 12, 2007.

It should be noted that these 7 centers enrolled a total of 301 subjects of which 287 subjects were enrolled between December 7, 2006 and September 12, 2007. The trial as whole enrolled approximately 90% of subjects between these two dates as well.

The study report provides little details about the nature of the unblinding, and it is unclear how this may impact the study findings. The sponsor should provide all relevant information about the potential break of the blind. This information should include, but not be limited to the following.

- *Please clarify how the blind was broken and the date and time it was discovered.*
- *Define the corrective action taken to put the blind back in place and the date when this occurred for each center..*
- *Define the role of the personnel who became unblinded.*
- *Please clarify why the blind was only broken for some subjects within a center and not other centers.*
- *State whether or not the Agency was made aware of the unblinding issues prior to NDA submission.*

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

The Define.XML files for the listing of data sets and descriptions of individual data sets cannot be printed fully using Microsoft Internet Explorer (or any other known FDA supported software). The sponsor is requested to please submit Define.PDF files to the NDA.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			Superiority to placebo and NI (10% margin) to itraconazole capsules
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			Complete cure – agreed with during protocol review
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			X	
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			LOCF-primary Success and failure as sensitivity – agreed in protocol review

Brief summary of controlled clinical trials

A single study is submitted for the determination of efficacy. This is trial BT-0300-302-INT with the objective of establishing

- Itraconazole tablets are noninferior to itraconazole capsules (margin 10%)
- Itraconazole tablets are superior to placebo.

Study number	Design	Treatment arms/Sample size	Primary endpoint/Analysis	Sponsor's findings
BT0300-302-INT	Randomized, MC, DB, Active, Vehicle control	ITRA Tablets: 593 ITRA Capsules: 590 Placebo: 198	Complete Cure: Clinical Success (IGA = 0 or 1) and mycological success (negative KOH and negative culture)	See Table 17 of sponsor's study report provided below.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Table 17: Analysis of the Primary Endpoint

Non-Inferiority (ITT)			
<u>Complete Cure</u>	<u>Itraconazole Tablets</u>	<u>Itraconazole Capsules</u>	
Number of Subjects	593	590	
Success	132 (22.3%)	128 (21.7%)	
Failure	461 (77.7%)	462 (78.3%)	
	<u>Difference in Success Rates</u>	<u>Lower Limit 97.5% CI^a</u>	<u>Non-Inferior</u>
	0.56%	-4.3%	Yes
Superiority (ITT)			
<u>Complete Cure</u>	<u>Itraconazole Tablets</u>	<u>Placebo Tablets</u>	
Number of Subjects	593	198	
Success	132 (22.3%)	2 (1.0%)	
Failure	461 (77.7%)	196 (99.0%)	
P-Value ^b	<0.001		
Non-Inferiority (PP)			
<u>Complete Cure</u>	<u>Itraconazole Tablets</u>	<u>Itraconazole Capsules</u>	
Number of Subjects	502	488	
Success	126 (25.1%)	118 (24.2%)	
Failure	376 (74.9%)	370 (75.8%)	
	<u>Difference in Success Rates</u>	<u>Lower Limit 97.5% CI^a</u>	<u>Non-Inferior</u>
	0.92%	-4.7%	Yes
Superiority (PP)			
<u>Complete Cure</u>	<u>Itraconazole Tablets</u>	<u>Placebo Tablets</u>	
Number of Subjects	502	155	
Success	126 (25.1%)	2 (1.3%)	
Failure	376 (74.9%)	153 (98.7%)	
P-Value ^b	<0.001		

Mat Soukup, Ph.D.	05/14/2009
Reviewing Statistician	Date
Mohamed Alosh, Ph.D.	05/14/2009
Supervisor/Team Leader	Date

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/s/

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