

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**20-966/S-001, S-003, S-004**

**20-657/S-004, S-005**

**STATISTICAL REVIEW(S)**

S- 13 2000

## Statistical Review and Evaluation

**NDA:** 20-966 (S004)  
**Drug Name:** SPORANOX® (Itraconazole Injection 10 mg/mL followed by SPORANOX oral solution.)  
**Applicant:** Janssen Pharmaceutic Research Foundation  
**Indications:** Empiric therapy in febrile neutropenic patients with suspected fungal infections.  
**Documents Reviewed:** NDA volume 1 to 55 and electronic data dated April 28, 2000.  
**Medical Officer:** Alivisatos, M.D., HFD-590  
**Statistical Reviewer:** Liji Shen, Ph.D., HFD-725

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### 1. Introduction

Sporanox® (itraconazole) is a broad-spectrum triazole antifungal agent available in the United States in three formulations: oral capsule, oral solution and solution for intravenous injection. Itraconazole oral solution was approved for the treatment of oropharyngeal and esophageal candidiasis in 1997. The capsule formulation and intravenous injection are now indicated for the treatment of histoplasmosis and blastomycosis as well as for the treatment of *Aspergillus* infections in subjects who have failed treatment or cannot tolerate treatment with amphotericin B. In this supplemental NDA 20966, the applicant seeks for an indication of empiric treatment of febrile neutropenic patients with suspected fungal infections with a regimen of itraconazole I.V. injection followed by itraconazole oral solution. One pivotal trial, ITR-INT-62, was conducted and included in the submission to support the indication. ITR-INT-62 is a randomized open-label comparative multicenter trial which compares itraconazole I.V. injection followed by itraconazole oral solution with I.V. amphotericin B. Other trials of I.V. itraconazole followed by oral capsule/solution include ITR-INT-60, ITR-USA-113, ITR-USA-127, ITR-INT-58 and ITR-INT-59. These are uncontrolled clinical trials with sample sizes ranging from 16 to 32. This statistical review will focus on the controlled clinical trial, ITR-INT-62.

Summaries of clinical trials involving with itraconazole I.V. injection are presented in Table 1.

Table 1. Studies conducted with an itraconazole IV group

Study	Study design	Total enrolled	Population	Treatment
ITR-INT-62	Open-label randomized comparative trial	384 (192/arm)	Febrile neutropenic subjects with hematologic malignancies. The fever had to be greater than 38°C for 3 to 7 days and subjects had to be receiving broad-spectrum antibiotics.	Itraconazole IV injection followed by itraconazole oral solution vs. amphotericin B IV
ITR-INT-60	Non-comparative trial	31	Subjects with HIV, hematologic disorders, chronic granulomatous disease, and organ transplants who had invasive pulmonary or disseminated aspergillosis.	Itraconazole IV injection followed by itraconazole oral capsules
ITR-USA-113	Pharmacokinetic trial	30	Subjects with advanced HIV infection (CD4 counts < 300)	Itraconazole IV injection followed by itraconazole oral capsules
ITR-USA-127	Pharmacokinetic trial	32	Subjects with advanced HIV infection (CD4 counts < 300)	Itraconazole IV injection followed by itraconazole oral solution
ITR-INT-58	Pharmacokinetic trial	16	Subjects confined to the intensive care unit and required antifungal prophylaxis but had no signs or symptoms of fungal infection.	Itraconazole IV injection followed by itraconazole oral solution
ITR-INT-59	Pharmacokinetic trial	17	Subjects with hematologic malignancies and required antifungal prophylaxis but had no signs or symptoms of fungal infection.	Itraconazole IV injection followed by itraconazole oral solution

## 2. Statistical Review and Evaluation

### 2.1 Study ITR-INT-62

#### 2.1.1 Applicant's Methods

Study ITR-INT-62 is a multicenter, open-label, randomized clinical trial with centrally stratified randomization for the presence of sign and symptoms potentially attributable to deep fungal infection and for the underlying therapy: marrow transplant including peripheral stem cell infusion or chemotherapy only. The trial enrolled patients who were febrile neutropenic after 3 to 7 days of empiric antimicrobial treatment and still severely granulocytopenic without clinically documented infection. The objective of the trial was to show the efficacy and safety of intravenous itraconazole followed by oral itraconazole compared with intravenous amphotericin B as empiric therapy for

persistent fever of unknown origin. A patient could stop his/her treatment when his/her neutrophil count greater than  $0.5 \times 10^9/L$  and should stop his/her treatment when his/her neutrophil count once greater than  $1.0 \times 10^9/L$  up to 2 days.

The results of empiric antifungal therapy will be classified according to the following criteria:

Failure is defined as any of followings: Documented deep fungal infection or CT scan highly suggestive for deep fungal infection; Clinically and microbiologically documented bacterial or viral infection responsible for the fever; Death (any cause) after > 3 days of study medication; Persistent fever at the end of neutropenia or at day 28; Deterioration of the signs and symptoms potentially attributable to deep fungal infection whether the fever has disappeared or not at the end of neutropenia or at day 28; Fever requiring a change in the empirical antifungal regimen; Discontinuation of study medication due to poor tolerance.

Unevaluable is defined as treatment duration less than 4 days or any infection documented after the initiation of the empiric antifungal regimen resulting from investigations performed before its initiation.

Response is defined as not being classified into the failure or unevaluable criteria. Patients who have received 10 days of study medication and remained afebrile for 3 consecutive days will be included in the "response" category.

To analyze the equivalence between itraconazole and amphotericin B for the response and success rates, the Mantel-Haenszel-Type test was applied controlling for the stratification factors. The response rate is defined as response/(response + failure + unevaluable). The success rate is defined as response/(response + failure).

On-protocol population was amended and was defined as patients who took at least one drug administration and satisfied inclusion criteria 2 and 3 and exclusion criteria 4 and 8 specified in the protocol. (Source: Volume 2/page 42.)

Intention-to-treat population was also amended to be all randomized patients who satisfied inclusion criteria 2 and 3 and exclusion criteria 4 and 8. (Source: Volume 2/page 42.)

*Statistical Comments: The applicant's definition of ITT population and On-protocol population are very similar. Usually, ITT population should be all randomized patients who took at least one dose regardless of requirement of inclusion/exclusion, while On-protocol population is defined as the patients who meet inclusion/exclusion criteria, take sufficient medication and have efficacy evaluation at test-of-cure. The applicant's definition will not be used in the FDA's analysis.*

Safety database in this NDA includes all patients randomized in the enrollment and receiving at least one dose of study drug. Incidence rates of adverse events were recorded.

### 2.1.2 Statistical reviewer's analysis

The ITR-INT-62 trial ran from 22 March 1996 until 4 December 1997. Sixty investigators participated. A total of 394 subjects were recruited. Of these 394 subjects, 2 were neither randomized nor treated. Three subjects were not randomized but were treated with itraconazole. Eight patients were randomized to treatment group (5 with itraconazole and 3 with amphotericin B) but never received any trial medication. Another ten patients (5 in each group) from Dr. Bezwoda's

site were excluded from efficacy analysis because Dr. Bezwoda admitted to "a serious breach of scientific honesty and integrity" in regard to a study in breast cancer patients, a non-Janssen study. Therefore, 371 subjects were included in the FDA statistician's ITT population (184 with itraconazole and 187 with amphotericin B).

Table 2. FDA statistical reviewer's ITT population

Description of reasons for exclusion	Total number of subjects	Excluded subjects			
		Itraconazole group		Amphotericin B	
		N	CRF number	N	CRF number
Total subjects entered	394	197		197	
Not randomized and not treated	2	0		2	A03471 A09998
Not randomized but treated	3	3	A03094 A03204 A03429	0	
Randomized but never treated	8	5	A03159 A03272 A03441 A03450 A03571	3	A03242 A03268 A09999
Dr. Bezwoda's subjects	10	5	A03105 A03263 A03270 A03277 A03280	5	A03261 A03265 A03367 A03271 A03275
FDA statistician's ITT population	371	184		187	

Source: Volume 2/page 44.

The applicant's ITT population excluded an additional 11 patients who did not meet some inclusion/exclusion criteria. (See Volume 2/ page 44 for detail.) Therefore, the applicant's ITT population comprises of 179 patients in the itraconazole group and 181 patients in the amphotericin B group. Table 3 contains both the FDA's and the applicant's ITT analysis by stratification as well as by combining those stratification factors.

Table 3. Response rate of FDA and Applicant analyses (ITT population)

	FDA statistical reviewer's ITT		Applicant's ITT analysis	
	Itraconazole (n = 184)	Amphotericin B (n = 187)	Itraconazole (n = 179)	Amphotericin B (n = 181)
Sign:no/transplant:no	52/105(50%)	35/108(32%)	51/103(49%)	34/105(32%)
Sign:no/transplant:yes	25/53(47%)	24/49(49%)	24/52 (46%)	22/48 (46%)
Sign:yes/transplant:no	4/15(27%)	6/18(33%)	4/14 (29%)	6/18 (33%)
Sign:yes/transplant:yes	5/11(45%)	6/12(50%)	5/10 (50%)	6/10 (60%)
Total	86(47%)	71(38%)	84 (47%)	68 (38%)
Two-sided 95% CI*	(-1%, 18%)		(-1%, 19%)	

\*C.I. for difference in response rates, itraconazole minus amphotericin B. Unevaluable patients were treated as failures.

*Statistical Comments:* The response rate in the itraconazole group is greater than that in the

*amphotericin B group in both FDA and the applicant's ITT analysis, but the difference is not statistically significant. The difference occurs mainly in non-transplant patients who had no signs or symptoms of fungal infections at enrollment. Furthermore, all unevaluable patients were treated as failures for both treatments in the ITT analyses. Therefore, ITT analyses tends to show similar response rates. The FDA statistician's On-protocol analysis will exclude those patients who were not evaluable due to protocol violation.*

There are no statistical imbalances observed in gender, age, race, body weight or body height. Underlying diseases (e.g. acute lymphatic leukemia, acute myeloid leukemia, lymphoma, myeloma), predisposing factors (e.g. corticosteroids, diabetes, urinary tract catheter, central catheter, peripheral catheter, concomitant cases of aspergillosis, fungal colonization of digestive tract, mucositis) and status of hematologic disease are similar between the two treatment groups. The median days of chemotherapy before treatment start are 13 and 14 days, respectively in the itraconazole group and the amphotericin B group. The median days of neutropenia before treatment start are 7 days in both groups. The median number of previous febrile days unresponsive to antibiotics are 5 and 4 days, respectively in the itraconazole group and the amphotericin B group.

There are 69 patients (24 in the itraconazole group and 45 in the amphotericin B group) who were unevaluable but treated as failures in the FDA statistical reviewer's ITT analysis. In FDA statistical reviewer's On-protocol analysis, these patients are excluded. (See Table 4.)

Table 4. FDA statistical reviewer's On-protocol population

Description of reasons for exclusion	Total N	Excluded subjects			
		Itraconazole group		Amphotericin B	
		N	CRF number	N	CRF number
Total subjects in FDA's ITT	371	184		187	
Unevaluable	69	24	A03033 A03059 A03102 A03113 A03116 A03137 A03170 A03188 A03191 A03197 A03207 A03241 A03329 A03387 A03392 A03410 A03422 A03436 A03465 A03528 A03532 A03620 A03626 A03643	45	A03022 A03034 A03066 A03073 A03081 A03085 A03093 A03107 A03110 A03117 A03138 A03144 A03145 A03152 A03158 A03179 A03211 A03212 A03245 A03246 A03303 A03310 A03368 A03379 A03386 A03391 A03402 A03408 A03411 A03426 A03435 A03442 A03443 A03460 A03481 A03502 A03515 A03517 A03524 A03530 A03543 A03549 A03623 A03633 A03638
No post-baseline efficacy data	1	1	A03105	0	
Violate Inclusion or Exclusion	9	4	A03264 A03269 A03278 A03349	5	A03266 A03273 A03327 A03203 A03619
FDA On-protocol	292	155		137	

Source: SAS dataset and Volume 2/page 45.

The major reason why these 69 patients are unevaluable is that these patients were treated less

than 4 days. The applicant has included them in their On-protocol analysis. Therefore, their On-protocol analysis is essentially the same as their ITT analysis.

Response rate of itraconazole and amphotericin B for the On-protocol analysis are presented in Table 5.

Table 5. Response rate of FDA and Applicant analyses (On-protocol population)

	FDA statistical reviewer's PP		Applicant's PP analysis	
	Itraconazole (n = 155)	Amphotericin B (n = 137)	Itraconazole (n = 176)	Amphotericin B (n = 179)
Sign:no/transplant:no	51/90(57%)	34/79(43%)	51/102(50%)	34/105(32%)
Sign:no/transplant:yes	24/44(55%)	22/33(67%)	24/50 (48%)	22/46 (48%)
Sign:yes/transplant:no	4/11(36%)	6/15(40%)	4/14 (29%)	6/18 (33%)
Sign:yes/transplant:yes	5/10(50%)	6/10(60%)	5/10 (50%)	6/10 (60%)
Total	84(54%)	68(50%)	84 (48%)	68 (38%)
Two-sided 95% CI*	(-8%, 15%)		(-1%, 20%)	

\*C.I. for difference in response rates, itraconazole minus amphotericin B. Unevaluable patients were excluded in the FDA statistical reviewer's On-protocol analysis.

*Statistical Comments: When those unevaluable patients (mainly due to treatment duration less than 4 days) were excluded from FDA's On-protocol analysis, the response rates in the two treatment groups are much closer to each other than the rates in the Applicant's On-protocol analysis. This is because more amphotericin B patients than itraconazole patients were treated less than 4 days. (See Table 4.) Toxicity of amphotericin B made patients discontinue study early. Among those patients who did complete their treatment, the success rates are similar in the two groups. It is also noticed that response rate of itraconazole in the bone marrow transplant febrile neutropenic patients is lower than the rate of amphotericin B, although no conclusive results can be reached because of small sample size in the stratum.*

Further investigation of patient disposition shows that, among the patients who received medications(i.e., safety population, 192 in each group), there are 104 (54%) patients in the itraconazole group and 119 (62%) patients in the amphotericin B group who discontinued treatment. A higher percentage of amphotericin B patients (39%, or 74/192) than itraconazole patients (19% or 36/192) discontinued study because of adverse events. However, more itraconazole patients (46/192 or 24%) than amphotericin B patients (16/192 or 8%) discontinued study because they had insufficient response. Because ITR-INT-62 is an open label clinical trial, higher discontinuation rate in the amphotericin B group could be partially due to the subjective judgement of investigators. Under the suggestion of the medical reviewer of the FDA, an analysis was conducted on the population excluding those who discontinued study due to adverse events. When these patients are excluded, amphotericin B has a higher response rate than itraconazole in both ITT and On-protocol analyses. The lower bound of the 95% confidence intervals for the difference of response rates, itraconazole minus amphotericin B, are around -14% to -22% as shown in Table 6 and Table 7.

Table 6. Response rate of ITT population excluding those discontinued study due to AE

	FDA statistical reviewer's ITT		Applicant's ITT analysis	
	Itraconazole (n = 148)	Amphotericin B (n = 114)	Itraconazole (n = 144)	Amphotericin B (n = 111)
Sign:no/transplant:no	51/86(59%)	35/62(56%)	50/84(60%)	34/60(57%)
Sign:no/transplant:yes	25/53(58%)	23/36(64%)	24/43(56%)	21/35(60%)
Sign:yes/transplant:no	4/9(44%)	6/9(67%)	4/8 (50%)	6/9 (67%)
Sign:yes/transplant:yes	5/10(50%)	6/7(86%)	5/9 (56%)	6/7 (86%)
Total	85(57%)	70(61%)	83 (58%)	67 (60%)
Two-sided 95% CI*	(-15.9%, 7.9%)		(-14.8%, 9.4%)	

\*C.I. for difference in response rates, itraconazole minus amphotericin B. Unevaluable patients were treated as failures.

Table 7. Response rate of On-Protocol population excluding those discontinued study due to AE

	FDA statistical reviewer's		Applicant's analysis	
	Itraconazole (n = 130)	Amphotericin B (n = 90)	Itraconazole (n = 141)	Amphotericin B (n = 110)
Sign:no/transplant:no	50/77(65%)	34/48(71%)	50/83(60%)	34/60(57%)
Sign:no/transplant:yes	24/37(65%)	21/27(78%)	24/41(59%)	21/34 (62%)
Sign:yes/transplant:no	4/7(57%)	6/8(75%)	4/8 (50%)	6/9 (67%)
Sign:yes/transplant:yes	5/9(56%)	6/7(86%)	5/9 (56%)	6/7 (86%)
Total	83(64%)	67(74%)	83 (59%)	67 (61%)
Two-sided 95% CI*	(-22.9%, 1.6%)		(-14.2%, 10.1%)	

\*C.I. for difference in response rates, itraconazole minus amphotericin B. Unevaluable patients were excluded in the FDA statistical reviewer's On-protocol analysis.

**Summary of Efficacy:** In ITT analysis, response rate of itraconazole is higher, but not statistically significantly higher, than that of amphotericin B. Low response rate of amphotericin B may be caused by its toxicity. When only patients who were treated for more than 3 days are considered (i.e., FDA's On-protocol population), the response rates of itraconazole and amphotericin B are similar in terms of their response rates. Among them, patients with bone marrow transplants had a lower observed response rate in the itraconazole group than in the amphotericin B group. Furthermore, when patients who discontinued study due to adverse events were excluded from analysis, the response rate of amphotericin B becomes greater than that of itraconazole. We need to point out that the definition for "response" does not form a hard clinical endpoint although the two treatment groups have statistically comparable response rates. By definition, a response basically means that a patient has received 10 days of study medication and remained afebrile for 3 consecutive days. Microbiologic data were not submitted for evaluation. It is not clear in this clinical trial that fever was caused by fungal infection. Neither is it clear that resolution of fever is due to anti-fungal treatments or due to termination of immunology system suppression. Substantial microbiological evidence of anti-fungal activity of itraconazole was not clearly documented in this NDA. For supportive evidence for this empiric therapy indication, it is advised to consider the evidence of the approved first-line indications of itraconazole in treatment of oropharyngeal and esophageal candidiasis, histoplasmosis, blastomycosis and second-line treatment of *Aspergillus* infections.

FDA statistical reviewer checked the adverse events in Study ITR-INT-62 and found that the following events occurred more frequently in the amphotericin B group than in the itraconazole group: hypokalemia, rigors, creatinine in blood, abnormal renal function and increased blood urea nitrogen. In contrast, rates of adverse events in rash, coughing, bilirubinemia and pulmonary infiltration are higher in the itraconazole group. The clinical implication of these rates will be explained in the Medical Officer's review.

### 3. Summary of Conclusions

By definition of response as specified in this review, itraconazole IV demonstrates a comparable response rate with amphotericin B in a clinical setting to empirically treat patients who are febrile neutropenic. Evidence of anti-fungal activity of itraconazole also showed in the approved indications such as the oral solution formulation for the treatment of oropharyngeal and esophageal candidiasis, the capsule formulation and intravenous injection for the treatment of histoplasmosis and blastomycosis as well as for the treatment of *Aspergillus* infections in subjects who have failed treatment or cannot tolerate treatment with amphotericin B. The results from all these clinical trials favors the decision of approval of itraconazole for empiric use to treat febrile neutropenic patients.

IS/ 9/13/00  
Lijr Shen, Ph.D.  
Biostatistician, DBIII

Concur: IS/ 9/13/00  
Karen Higgins, Sc. D.  
Team Leader, DBIII

cc:  
Archival: NDA 20-966  
HFD-590/Dr. Alivisatos  
HFD-590/Dr. Leissa  
HFD-725/Dr. Huque  
HFD-725/Dr. Higgins  
HFD-725/Dr. Shen  
HFD-590/Dr. Albrecht  
HFD-590/Ms. Kimzey

This review contains 8 pages.