CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: **20-966**

MEDICAL REVIEW(S)

TABLE OF CONTENTS NDA 20-966

APPEARS THIS WAY
ON ORIGINAL

Medical Officer's Review of NDA 20 - 966

Submission Date: April 27, 1998
CDER Stamp Date: April 30, 1998
Date Review Started: April 30, 1998
Date Review Completed: September 18, 1998

Applicant: Janssen Research Foundation
1125 Trenton-Harbourton Road
PO Box 200
Titusville, NJ 08560-0200

Generic Name: Itraconazole

Proprietary Name: Sporanox®

Pharmacologic Category: Antifungal

Chemical Name: (±)-1-[(RS)-sec-butyl]-4-[p-[[2R,4S)-2-2[2,4-dichlorophenyl)-2-(1H-1.2.4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]-Δ'2-1,2,4-triazolin-5-one

Dosage Form: Injection

Route of Administration: Intravenous

Strengths: 10 mg/mL

Proposed Indication and Usage (as per the proposed label): "SPORANOX® (itraconazole) Injection is indicated for the treatment of the following fungal infections in immunocompromised and non-immunocompromised patients:

1. Blastomycosis, pulmonary and extrapulmonary;
2. Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis; and
3. Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy."

Proposed Dosage and Administration: 200 mg IV BID (2 one-hour infusions) for 2 days, followed by 200 mg IV QD (one one-hour infusion)

MO Comment: The parenthetical statements are confusing to the reader. The MO was unclear if the 2 one-hour infusions referred to both doses or to only one. It is suggested that the applicant modify this statement to "infuse over 1 hour".

Related INDs and NDAs: NDA 20–083 (100 mg capsule for blastomycosis and histoplasmosis)
NDA 20–657 (oral solution 10 mg/mL for oropharyngeal candidiasis)
NDA 20– 510 (100 mg capsule for onychomycosis)
[redacted]

List of Currently Approved Indications: None for this formulation. Currently, the oral capsular formulation of itraconazole is approved for the proposed indications as well as for onychomycosis. Additionally the oral solution is approved for the treatment of oropharyngeal candidiasis.

Abbreviations used in this document:
ITR = Itraconazole
FLU = Fluconazole
AMP = Amphotericin B

AE = Adverse Event
Materials Reviewed: NDA 20–966, submitted 4/27/98, Volumes 33 – 67 and 88 through 155.
Electronic submission, submitted 5/24/98

MO Comment: In cases where the MO copied portions of the applicant's text, the font Arial 10 was utilized.

Regulatory Background: The intravenous formulation of itraconazole has not been approved for use in any country. Additionally, it has not been submitted for regulatory approval in any country at the present.

The development of this formulation and the submission of this NDA occurred in response to the FDA's request for a Phase IV commitment subsequent to the approval of the oral capsule formulation of itraconazole (NDA 20–083). In addition to the approved for the requested indications capsular formulation, an oral solution of itraconazole was also granted approval for the treatment of oral/esophageal candidiasis. The capsule is also approved for onychomycosis in non-immunocompromised patients.

This submission contains safety information on 255 patients treated with IV itraconazole for 7- 14 days in 9 clinical studies, 5 of which were still ongoing at the time of the submission. As noted above, the applicant has not submitted any information with regards to efficacy in this submission. Rather the approval of the intravenous formulation for the requested indications would be based upon pharmacokinetic data and safety data.

The 9 clinical trials included in the database are listed below (see Table 2):

- Two ongoing US open-label, active-controlled trials:

- Two ongoing international open-label, active-controlled trials:

➢ ITR-INT-62: A randomized, comparative, multicenter trial of itraconazole injection followed by itraconazole oral solution versus intravenous amphotericin B followed by oral [redacted] tablets for the treatment of febrile neutropenic patients with hematologic malignancy.

- One ongoing international open-label uncontrolled trial:

➢ ITR-INT-60. An efficacy and safety trial of itraconazole injection followed by oral itraconazole capsules in the treatment of hematologic, transplantation, acquired immunodeficiency syndrome, and chronic granulomatous disease patients with invasive pulmonary or disseminated aspergillosis.

- Two completed US open-label pharmacokinetic trials:

- ITR-USA-113: A pharmacokinetic trial of itraconazole injection followed by oral itraconazole capsules in patients with advanced human immunodeficiency virus infection.

- ITR-USA-127: A pharmacokinetic trial of itraconazole injection followed by oral itraconazole solution in patients with advanced human immunodeficiency virus infection.

- Two completed international open-label pharmacokinetic trials:

- ITR-INT-58: A pharmacokinetic trial of itraconazole injection followed by oral itraconazole solution in intensive care unit patients.

- INT-INT-59: A pharmacokinetic trial of itraconazole injection followed by oral itraconazole solution in patients with hematologic malignancy.

Itraconazole was administered intravenously for at least 1 week in all of the 9 aforementioned trials. The dosing regimen was the same, 200 mg BID for 2 days followed by 200 mg QD. Only the total duration (7 – 14 days) varied from trial to trial.

In addition to the above, the applicant submitted safety information for 71 patients in 6 pharmacokinetic trials who received single dose or limited 2 day dosing with itraconazole injection. These patients were not included in the integrated database.

Presented in Table 1 are the #s of patients included in the international safety database.

Table 1
Database by Treatment and Country

	All patients	Total Itraconazole	Controlled Clinical Trials			PK ITR	Uncontrolled Clinical Trials Itraconazole
			ITR	FLU	AMP		
Worldwide	393	255	137	32	106	95	23
US	156	108	46	29	19	62	-
Non-US	237	147	91	3	87	33	23

Medical Officer's Comment: The MO elected to review the safety of each trial separately and to provide an integrated safety summary. The MO's ISS, applicant's and MO's conclusions are presented below followed by Appendix I which contains the safety reviews of the individual trials. Please note that 5 of the 9 trials included in the submission were ongoing and only the pooled safety data from these trials could be reviewed (data cutoff date 5/1/97). At the time of the 4 month safety update, the applicant informed the division that trial ITR-INT-60 had been completed. The applicant submitted completed data from this trial (additional 8 patients) and updated the electronic submission to reflect the safety data on an additional 200 patients enrolled in the ongoing clinical trials.

Table 2
NDA 20-966 :Itraconazole injection
Summary of clinical safety experience submitted with NDA

	Study number	Study population	Itraconazole IV Dosing*	Comparator	Itraconazole 200 mg iv BID recipients (as of 5/1/97)	Comments
Pharmaco-Kinetic trials	USA113	HIV	14d	Non-comparative	30	completed
	USA127	HIV	14d	Non-comparative	32	completed
	INT58	ICU	14d	Non-comparative	16	completed
	INT59	Hematologic Malignancy	14d	Non-comparative	17	completed
Clinical efficacy trials	[redacted]					
	INT60	Pulmonary & Disseminated Aspergillosis	14d → PO caps	Non-comparative	23	Completed 5/98
	[redacted]					
	INT62	Febrile Neutropenia	14d → PO susp	Amphotericin B IV → PO Fluconazole	95	[redacted]
TOTAL					255	

*200 mg IV BID x 2 days followed by 200 mg IV QD until the end of IV therapy

Chemistry/Manufacturing Controls: Please see the Chemistry Review

Microbiology: No new information has been submitted. Briefly, itraconazole is an antifungal agent that inhibits the P-450-dependent synthesis of ergosterol, a component of fungal cell membranes. This agent exhibits *in vivo* activity against *Blastomyces dermatitidis, Histoplasma capsulatum, Histoplasma dudosii, Aspergillus flavus, Aspergillus fumigatus, Candida albicans*, and *Cryptococcus neoformans*. *In vitro* activity has been exhibited versus a number of other fungi however; correlation between *in vitro* activity and clinical outcome has not been shown.

Human Pharmacokinetics: Subsequent to administration, itraconazole is hepatically metabolized to the bioactive metabolite hydroxyitraconazole. The activity of this metabolite versus *Histoplasma capsulatum* and *Blastomyces dermatitidis* has not been evaluated. Plasma concentrations measured by HPLC may in reality be higher than those obtained because of the presence of the biometabolite.

PK studies were performed for the injectable formulation at a dose of 200 mg IV BID for 2 days and then 200 mg IV QD for 5 days. This regimen was followed by 200 my PO for an unspecified period. These PK studies were performed in patients with advanced HIV infection (USA 113 and USA 127). Steady state plasma concentrations were reached on day 3 for itraconazole and day 6 for hydroxyitraconazole. PK parameters for itraconazole and hydroxyitraconazole are presented in Table 3 below.

Table 3
PK Parameters (as per MO)

Parameter	Injection 200 mg BID x 2 days → 200 QD Day 7 N = 29		Capsule 200 mg BID Day 36 N = 12	
	Itraconazole	Hydroxyitraconazole	Itraconazole	Hydroxyitraconazole
C max (ng/mL)	2856 ± 866	1906 ± 612	2010 ± 1420	2614 ± 1703
T max (hr)	1.08 ± 0.14	8.53± 6.36	3.92 ± 1.83	5.92 ± 6.14
AUC 0 – 12 (ng-h/mL)	-	-	18768 ± 13933	28516 ± 19149
AUC 0 – 24 (ng-h/mL)	30605 ± 8961	42445 ±13282	-	-

As per the applicant " most patients had nondetectable plasma concentrations of hydroxypropyl-b-cyclodextrin by 24 hours after IV administration. Approximately 93 – 101% of the HP-b-cyclodextrin was excreted unchanged in the urine within 12 hours after dosing."

"The elimination half-life was not established in the previous study. Based on previous data, the mean elimination half-life for itraconazole at steady state after oral administration of 100 – 400 mg was 30 – 40 hours. Plasma protein binding is 99.8% for itraconazole and 99.5% for the biometabolite. The volume of distribution averaged 796 ± 185 L."

"3 – 18% of the dose is excreted via the fecal route and less than 0.03% of the parent compound is found in the urine. 80 – 90% of the hydroxypropyl-b-cyclodextrin is eliminated via the kidneys."

"In patients with mild to moderate renal insufficiency, the itraconazole plasma concentrations are similar to those obtained in healthy subjects. The same is true for patients receiving hemodialysis. Additionally, the majority of the cyclodextrin is eliminated within 120 hours in the above patient groups. In subjects however with severe renal impairment, the clearance of the cyclodextrin is reduced six-fold and therefore the injectable formulation of itraconazole is not indicated for patients with a creatinine clearance less than 30 mL/min.

The effect of hepatic insufficiency on plasma concentrations of itraconazole is unknown and therefore patients need to be monitored carefully."

Medical Officer's Comment: The applicant stated that the PK portion of the submission adequately demonstrated that the injectable formulation was equivalent to the oral. The MO deferred to the PK reviewer on this point.

Potential Safety Issues: Based on the known metabolism of the oral formulations of itraconazole (that is the CYP3A4-mediated route) and the well-established safety profile of the oral formulations, it was expected that the predominant number of AEs would be from the GI tract (nausea, vomiting, and diarrhea), as well as the liver (LFT elevations). Additionally, rash, hypokalemia and edema are amongst the more serious AEs encountered with the capsule. These events are usually reversible upon discontinuation. It has been well established, that the metabolism of other CYP3A4 dependent drugs such as midazolam, astemizole, cisapride, nifedipine, terfenadine, triazolam, can be inhibited by therapeutic concentrations of itraconazole and its metabolites, thereby leading to elevated plasma concentrations and exaggerated pharmacological effects of the affected agents.

A difference that exists for the injectable form of itraconazole (as opposed to the capsule) is the use of a cyclodextrin-solubilizing agent. This oligosaccharide is able to form inclusion complexes with different compounds and therefore is used as a host molecule for parenteral, oral, and local delivery of poorly soluble or unstable drugs. Once administered intravenously, this molecule is distributed in the extracellular fluids, and mainly eliminated via the kidney. Because excretion is primarily renal, there existed in the pre-clinical and early phases of human drug development, concerns with regard to the use of this agent in

patients with pre-existing renal dysfunction. PK studies in the severely renally impaired population revealed that there was a 6-fold decrease in clearance and a 6-fold increase in half-life. Therefore it is recommended that this formulation not be used in this group of patients. Other issues that are significant relative to the long-term use of the cyclodextrin molecule are its carcinogenic effects. This issue is not applicable to the current NDA given the short duration of therapy requested (see Pharm/Tox Review).

MO Overall Conclusions from the PK Studies (see Table 4):

Clinical and laboratory AEs seen with increased frequency in the PK trials:

Application Site Reactions or Vein Disorders: The incidence of application site disorders was higher in 1 of the US PK studies, #113 as compared to the 3 other PK trials reviewed (127, 58, and 59). Overall the incidence of application site disorders in the PK studies was 16/95 (16.8%/12 patients: study 113, 3 patients: study 127, 1 patient: Study 59). In addition, 1 patient in study 113 had an application site disorder coded as "implantation complication". Thus the total was 17/95 (17.9%). As noted above, the majority of these events occurred in study 113. 2 sites participated in this trial. 10 patients were enrolled at site 1 where 3 patients reported application site disorders (2 moderate, 1 mild), and 20 patients were enrolled at site 2 where 14 patients reported an application site disorder (14 mild, 3 moderate). All 17 reports were assessed as definitely or possibly-related to the study drug and all resolved. The verbatim adverse event reports included the following: IV site irritation, pain, edema, inflammation of skin, and vein hardness. In addition to the above, 11 events were coded as "vein disorder". All reports were from study 113 site 2. Verbatim terms included vein hardness and vein redness. The total # of patients from the PK trials with application site or vein disorders secondary to itraconazole infusion was 28/95 (29.5%). However, the data suggested that this event was site specific.

Granulocytopenia: 9/95 (9.5%) of patients from the PK studies developed granulocytopenia. All reports were from the US PK studies 113 and 127. Both of these trials were performed in HIV patients which suggests that the AE was patient population specific.

Overall Conclusions:

GI events were the most common on both the IV and PO arms of the PK studies. Diarrhea was the most frequent complaint overall 20/95 (21.1%) and appeared to be more frequent in the patients receiving oral itraconazole 19/95 (20%) as compared to those receiving IV 4/95 (4.2%). Interestingly, constipation also appeared with greater frequency on the IV arm 7/95 (7.4%) as compared to the PO arms 4/95 (4.2%) with an overall complaint rate of 8/95 (8.4%). Nausea, vomiting, abdominal pain, dyspepsia and the non-specified GI disorder were seen with increased frequency on the PO arms of the studies.

Fever was a frequent event on both the IV 7/95 (7.4%) and PO arms 13/95 (13.7%) with a total of 16/95 (16.8%) but the significance of this is unclear as most of the patient s with fever had underlying active malignant diseases.

As noted above, the most frequent complaint on the IV arm was application site or vein disorder.

From the laboratory standpoint, granulocytopenia was seen in 4/95 (4.2%) of the IV patients and 7/95 (7.4%) of the PO patients with a total of 9/95 (9.5%) frequency. However, the population in which this was seen most frequently was that of patients with hematologic malignancies and the significance is unknown.

Mild disturbances in hepatic function were noted in < 3% of the patients on both arms and no cases of significant renal dysfunction developed.

Overall it appeared as if patients on oral itraconazole developed more complaints from the GI tract as compared to the IV patients who developed more complaints associated with infusion.

Table 4
Overall Percent of Patients Enrolled in the PK trials Reporting Possibly or Definitely-Related AEs as per the Investigators (Table per the MO)

Adverse Event	IV Phase N = 95		PO Phase N = 95		Total N = 95	
	n	%	n	%	n	%
Gastrointestinal System Disorders						
Constipation	7	7.4	4	4.2	8	8.4
Nausea	5	5.3	8	8.4	11	11.6
Diarrhea	4	4.2	19	20	20	21.1
Abdominal Pain	3	3.2	7	7.4	8	8.4
Vomiting	2	2.1	4	4.2	4	4.2
Taste Perversion	2	2.1	3	3.2	3	3.2
GI Disorders	1	1			1	1
Dyspepsia	-	-	3	3.2	3	3.2
Body as a Whole-General Disorders						
Fever	7	7.4	13	13.7	16	16.8
Pain	3	3.2	2	2.1	3	3.2
Allergic Reaction	1	1	2	2.1	3	3.2
Pruritus	1	1	1	1	1	1
Central and Peripheral Nervous System Disorders						
Headache	5	5.3	4	4.2	8	8.4
Increased Sweating	2	2.1	-	-	2	2.1
Liver and Biliary Disorders						
Bilirubinemia	2	2.1	3	3.2	3	3.2
gGT	1	1	2	2.1	2	2.1
SGPT Increased	-	-	1	1	1	1
Jaundice	-	-	1	1	1	1
Cardiovascular Disorders						
Hypotension	3	3.2	2	2.1	3	3.2
Skin and Appendages Disorders						
Rash	2	2.1	6	6.3	2	2.1
Urticaria	-	-	1	1	1	1
WBC Disorders						
Granulocytopenia	4	4.2	7	7.4	9	9.5
Leucopenia	1	1	1	1	1	1
Marrow depression	1	1	1	1	1	1
RBC Disorders						
Anemia	1	1	3	3.2	3	3.2
Urinary System Disorders						
Albuminuria	4	4.2	2	2.1	4	4.2
Glycosuria	2	2.1	1	1	3	3.2
Hematuria	1	1	1	1	1	1
Metabolic and Nutritional System Disorders						
Hyperglycemia	4	4.2	3	3.2	5	5.3
Diabetes Insipidus	1	1	-	-	1	1
Vascular Disorders						
Application Site Reaction/Vein Disorder	25	26.3	13	13.7	25	26.3
Psychiatric Disorders						
Anxiety	2	2.1	3	3.2	3	3.2

*Total is not additive but per patient.

MO Conclusions from the Clinical Studies:

All trials included in the integrated database specified the same dosing regimen: 200 mg itraconazole injection twice daily for 2 days followed by 200 mg itraconazole injection once daily. Only the total duration of intravenous therapy varied across trials.
All controlled and uncontrolled trials specified a 7-day treatment duration with itraconazole injection that could be extended to 14 days or longer if the condition of the patient warranted additional intravenous therapy. In worldwide controlled trials, 53.3% of patients received itraconazole injection for up to one week and 40.9% received itraconazole injection between 8 and 14 days. Treatment durations beyond 2 weeks in worldwide were low; 5.8% and 17.4% of patients, respectively. In the single uncontrolled trial, ITR-INT-60, investigating the treatment of patients with disseminated aspergillosis, the majority of patients (73.9%) received between 8 and 14 days of intravenous therapy. The above were summarized in Table 5, copied from applicant table 2.1.

Table 5

Summary of IV Itraconazole Duration by Study Type

Total number of patients	n	Treatment Duration			
		≤7 days n (%)	>7-14 days n (%)	>14 days n (%)	Median days (min, max)
Worldwide					
Controlled	137	73 (53.3)	56 (40.9)	8 (5.8)	7 (2,28)
Uncontrolled	23	2 (8.7)	17 (73.9)	4 (17.4)	14 (4,28)

160 patients received IV itraconazole in 5 clinical studies (controlled and uncontrolled).
1249 AEs were experienced. 143 events were severe. 13 events (severe, moderate) were coded as definitely-related to the study drug and included: 1 event each of rigors, rash, abnormal renal function, headache, dizziness, nausea, medication error, increased SGPT, application site reaction and thrombosis. There were 2 events of injury definitely-associated to study drug.

220 events were coded as possibly-associated with the study drug and included with decreasing frequency:

Nausea: 19/160 (11.9%)
Diarrhea: 16/160 (10%)
Hypokalemia: 11/160 (6.9%)
Bilirubinemia: 12/160 (7.5%)
Vomiting: 11/160 (6.9%)
Increased creatinine: 6/160 (3.8%)
Dizziness: 4/160 (2.5%)
Jaundice: 5/160 (3.1%)
SGOT increased :5/160 (3.1%)
SGPT increased: 5/160 (3.1%)
Abdominal Pain: 4/160 (2.5%)
Increased BUN: 3/160 (1.9%)
Rash :3/160 (1.9%)
Constipation: 3/160 (1.9%)
Increased Alk. Phos.: 3/160 (1.9%)
1 event each of Hepatitis, Hepatocellular damage, Increased hepatic enzymes and Cholestasis or 4/160 (2.5%)
All other events occurred in 1/160 each or 0.6% and were not listed here.

There were a total of 18 deaths and 42 discontinuations due to an AE.

Below in Table 6 are all AEs that occurred during the IV phase in at least 2 patients in all clinical trials:

Table 6
Adverse Event Incidence with Onset in the IV Phase in all Clinical (Controlled and Uncontrolled) Trials reported by at Least 2 Patients

Body System/Adverse Event	Itraconazole IV N = 160 (100%)
Gastrointestinal System Disorders	
Nausea	37 (23%)
Diarrhea	34 (21%)
Vomiting	29 (18%)
Abdominal pain	16 (10%)
Constipation	12 (7.5%)
Stomatitis	11 (6.9%)
Mucositis	9 (5.6%)
Dyspepsia	6 (3.7%)
Melena	5 (3.1%)
Enterocolitis	4 (2.5%)
GI Hemorrhage	4 (2.5%)
Stomatitis Ulcerative	4 (2.5%)
Tooth Ache	3(1.8%)
Body as a whole - General Disorders	
Fever	24 (15%)
Chest Pain	10 (6.2%)
Edema	14 (8.8%)
Pain	13 (8.1%)
Rigors	11 (6.9%)
Back Pain	8 (5%)
Injury	8 (5%)
Fatigue	4 (2.5%)
Edema Peripheral	5 (3.1%)
Abdomen Enlarged	5 (3.1%)
Hot Flushes	3 (1.8%)
Anaphylactoid Reaction	3 (1.8%)
Condition Aggravated	4 (2.5%)
Syncope	4 (2.5%)
Respiratory System Disorders	
Coughing	24 (15%)
Dyspnea	22 (13.8%)
Pneumonia	12 (7.5%)
Pulmonary edema	14 (8.8%)
Pulmonary Infiltration	9 (5.6%)
Rhinitis	7 (4.4%)
Hypoxia	8 (5%)
Pharyngitis	6 (3.7%)
Respiratory Disorder	9 (5.6%)
Respiratory Insufficiency	6 (3.7%)
Pleural effusion	5 (3.1%)
Bronchospasm	7 (4.4%)
Hemoptysis	5 (3.1%)
Stridor	3 (1.8%)
Metabolic and Nutritional Disorders	
Hypokalemia	25(15.6%)
Hyperglycemia	11 (6.9%)
NPN increased	12 (7.5%)

Table 6
Adverse Event Incidence with Onset in the IV Phase in all Clinical (Controlled and Uncontrolled) Trials reported by at Least 2 Patients

Body System/Adverse Event	Itraconazole IV N = 160 (100%)
Fluid overload	10 (6.2%)
Hypomagnesemia	9 (5.6%)
Phosphatase Alkaline Increased	6 (3.7%)
BUN Increased	7 (4.4%)
Hypocalcemia	9 (5.6%)
Edema Generalized	7 (4.4%)
Hyperkalemia	3 (1.9%)
CPK Increased	3 (1.9%)
Hypernatremia	3 (1.9%)
Hyponatremia	3 (1.9%)
Acidosis	3 (1.9%)
Skin and Appendage Disorders	
Rash	20 (12.5%)
Rash Erythematous	11 (6.9%)
Sweating Increased	8 (5%)
Skin Disorder	3 (1.9%)
Pruritus	5 (3.1%)
Central & Peripheral Nervous System Disorders	
Headache	14 (8.8%)
Dizziness	8 (5%)
Tremor	5 (3.1%)
Psychiatric Disorders	
Insomnia	8 (5%)
Confusion	10 (6.2%)
Hallucination	6 (3.7%)
Anorexia	6 (3.7%)
Somnolence	6 (3.7%)
Anxiety	4 (2.5%)
Sleep Disorder	4 (2.5%)
Urinary System Disorders	
Hematuria	9 (5.6%)
Urine Abnormal	7 (4.4%)
Renal function Abnormal	6 (3.7%)
Urinary Incontinence	5 (3.1%)
Albuminuria	3 (1.9%)
Renal Failure Acute	4 (2.5%)
UTI	3 (1.9%)
Cardiovascular Disorders, General	
Hypotension	14 (8.8%)
Hypertension	9 (5.6%)
Cardiac Failure	6 (3.7%)
Heart Murmur	3 (1.9%)
Liver and Biliary System Disorders	
Bilirubinemia	16 (10%)
Jaundice	8 (5%)
SGPT Increased	7 (4.4%)
SGOT Increased	6 (3.7%)
Platelet, Bleeding & Clotting Disorders	
Epistaxis	12 (7.5%)
Purpura	6 (3.7%)
Resistance Mechanism Disorders	

Table 6
Adverse Event Incidence with Onset in the IV Phase in all Clinical (Controlled and Uncontrolled) Trials reported by at Least 2 Patients

Body System/Adverse Event	Itraconazole IV N = 160 (100%)
Infection Bacterial	9 (5.6%)
Herpes Simplex	6 (3.7%)
Infection	3 (1.9%)
Sepsis	4 (2.5%)
Heart Rate and Rhythm Disorders	
Tachycardia	6 (3.7%)
Bradycardia	4 (2.5%)
Red Blood Cell Disorders	
Anemia	14 (8.8%)
Vision Disorders	
Vision Abnormal	4 (2.5%)
Application Site Disorders	
Application Site Reaction	7 (4.4%)
Musculoskeletal System Disorders	
Skeletal pain	5 (3.1%)

Additionally: Hepatitis, Abnormal Hepatic Enzymes and Hepatocellular Damage: 5/160 (3.1%)

Comparison with PK Trials:

The most frequent AE in the PK trials was "Application Site Reaction/Vein Disorder". This event occurred in 25/95 subjects or 26.3%. In the clinical trials, the AE "Vein Disorder" did not appear and the AE "Application Site Disorder" appeared in 7/160 (4.4%) of patients. As noted in the MOR of the PK trials, this AE appeared to be site-specific, with 1 site in trial 113 accounting for the predominant number of complaints.

Gastrointestinal system disorders were overall as a group the most frequent events, with nausea, vomiting, diarrhea, constipation. GI disorders, abdominal pain, dyspepsia, mucositis, stomatitis and GI disorders accounting for 55/95 (58%) of the reported AEs in the PK trials. In the clinical trials there were a total of 144/160 (90%) similar events.

General symptoms such as fever, edema, chest pain, pain and rigors were reported in 26/95 (27.3%) of cases in the PK trials and from 72/160 (45%) of the cases in the clinical trials. The somewhat increased frequency of these events in the clinical trials is justified by the much iller population studied.

Respiratory system disorders were seen much less frequently in the PK trials with coughing and dyspnea accounting for 3/95 (3.2%) of events as compared to 46/160 (28.7%) of events in the clinical trials. Once again the overall iller population studied justified this difference. Pneumonia and pulmonary infiltration were not seen in the PK trials but had an incidence of 12/160 (7.5%) and 9/160 (5.6%) respectively in the clinical trials.

Metabolic disorders also had a much higher incidence in the clinical trials as compared to the PK trials. In the clinical trials, hypokalemia was seen most frequently 25/160 (15.6%), followed by hyperglycemia 11/160 (6.9%), increased creatinine 12/160 (7.5%), hypomagnesemia 9/160 (5.6%), fluid overload 10/160 (6.2%), increased Alk. Phos. 6/160 (3.7%), increased BUN 7/160 (4.4%). Hypocalcemia 9/160 (5.6%) and generalized edema 7/160 (4.4%). The respective values for the PK trials were: 0, 5/95 (5.3%), 0. 1 (1.1%), 0,0,0,0, and 0. Only glycosuria appeared in the PK trials at 3/95 (3.2%) as compared to 0 in the clinical trials. Hypo and hypernatremia appeared in 3/160 (1.9%) of patients each in the clinical trials and in none of the PK patients.

Rash occurred with an incidence of 20/160 (12.5%) in the clinical trials as compared to 6/95 (6.3%) in the PK trials. Erythematous rash appeared in 11/160 instances in the clinical trials as compared to 0 in the PK trials. Maculopapular rash (not listed above), appeared in 2/160 (1.2%) clinical trial patients as compared to 1/95 (1.1%) PK patients.

CNS disorders such as headache (14/160 (8.8%) clinical versus 8/95 (8.4%) PK) were relatively similar in both patient groups. Dizziness was seen in 8/160 (5%) clinical patients versus 0 PK patients .

Psychiatric disorders were of similar frequency with an increased incidence of confusion 10/160 (6.2%) in the clinical trials as compared to 0 in the PK trials.

Urinary system disorders had a much higher incidence in the clinical trials with 4/160 (2.5%) of patients developing ARF as compared to 0 in the PK trials. "Renal function abnormal" was seen in an additional 6/160 (3.8%) instances as compared to 0 in the PK trials. Thus there were 10/160 (6.2%) reports of disturbance of renal function in the clinical trials. Once again the MO questioned if the overall iller population could justify this difference. Albuminuria was seen in 4/95 (4.2%) of the PK cases as compared to 3/160 (1.9%) of the clinical cases.

Hypotension, hypertension, and cardiac failure were seen with a frequency of 29/160 (18%) in the clinical trials as compared to 6/95 (6.3%) in the PK trials. Additionally rhythm disturbances were seen in 14/160 (8.7%) of the clinical cases as compared to 0 of the PK cases. Thus the underlying disease processes may have contributed to the development of this group of AEs.

Bilirubinemia and jaundice were seen with an incidence of 24/160 (15%) in the clinical trials as compared to 4/95 (4.3%) in the PK trials. SGPT and SGOT increases were found to have a combined incidence of 13/160 (8.1%) as compared to 1/95 (1.1%) in the PK trials.

Bleeding and clotting disorders were seen in 0 of the PK patients as compared to 18 (11.3%) of the clinical patients.

Disturbances of immunity were seen much more frequently in the clinical trial patients as compared to the PK patients.

Granulocytopenia was seen in 9/95 (9.5%) of the PK patients as compared to 2/160 (1.2%) of the clinical patients. The PK patients were compromised of a large number of HIV patients which may justify this difference. Anemia was seen with a frequency of 14/160 (8.8%) in the clinical trials as compared to 3/95 (3.2%) in the PK trials.

In conclusion, The most frequent AEs in both the clinical and the PK recipients of IV itraconazole were from the GI tract, followed by general symptoms and application site reactions. Renal and hepatic dysfunction including metabolic disturbances developed much more frequently in the clinical trial population of patients, possibly due to significant predisposing underlying disease processes.

MO Conclusion of AE Incidence of Combined PK and Clinical Population:
Copied and modified by the MO below is the applicant's table 2-14, comparing the worldwide incidence of AEs by treatment arm of all populations studied. Please not that the clinical trials patients from the uncontrolled trial, #60, are listed separately (N = 23). The total of clinical trials patients is 160 (controlled and uncontrolled combined). The total # of all IV itraconazole treated patient was 255. The MO independently utilizing the electronic database recreated this table.

Table 7

Adverse Event Incidence With Onset in the IV Treatment Phase in Worldwide Trials, Reported by at Least Three Patients in Any Treatment Group, by Preferred Term, n(%)

(Applicant Table 2-14, modified by MO)

Body system/adverse event	Total	Controlled			PK	Uncontrolled
	ITR n=255	ITR n=137	FLU n=32	AMB n=106	ITR n=95	ITR n=23
Total number subjects with adverse event	209 (82.0)	128 (93.4)	31 (96.9)	101 (95.3)	64 (67.4)	17 (73.9)
Gastrointestinal System Disorders						
Nausea	40 (15.7)	33 (24.1)	8 (25.0)	32 (30.2)	5 (5.3)	2 (8.7)
Diarrhea	36 (14.1)	28 (20.4)	5 (15.6)	35 (33.0)	4 (4.2)	4 (17.4)
Vomiting	30 (11.8)	26 (19.0)	3 (9.4)	32 (30.2)	2 (2.1)	2 (8.7)
Abdominal Pain	18 (7.1)	14 (10.2)	5 (15.6)	13 (12.3)	3 (3.2)	1 (4.3)
Stomatitis	11 (4.3)	11 (8.0)	0 (0.0)	3 (2.8)	0 (0.0)	0 (0.0)
Constipation	19 (7.5)	9 (6.6)	4 (12.5)	4 (3.8)	7 (7.4)	3 (13.0)
Mucositis	8 (3.1)	7 (5.1)	2 (6.3)	7 (6.6)	0 (0.0)	1 (4.3)
Enterocolitis	4 (1.6)	4 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Melena	4 (1.6)	4 (2.9)	0 (0.0)	4 (3.8)	0 (0.0)	0 (0.0)
Dyspepsia	5 (2.0)	3 (2.2)	2 (6.3)	4 (3.8)	0 (0.0)	2 (8.7)
GI Hemorrhage	4 (1.6)	3 (2.2)	1 (3.1)	2 (1.9)	0 (0.0)	1 (4.3)
Stomatitis Ulcerative	4 (1.6)	3 (2.2)	0 (0.0)	2 (1.9)	0 (0.0)	1 (4.3)
Tooth Ache	3 (1.2)	3 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dysphagia	2 (0.8)	2 (1.5)	1 (3.1)	3 (2.8)	0 (0.0)	0 (0.0)
Hemorrhoids	1 (0.4)	1 (0.7)	0 (0.0)	4 (3.8)	0 (0.0)	0 (0.0)
Body as a whole – General Disorders						
Fever	30 (11.8)	18 (13.1)	7 (21.9)	11 (10.4)	7 (7.4)	5 (21.7)
Pain	16 (6.3)	13 (9.5)	3 (9.4)	7 (6.6)	3 (3.2)	0 (0.0)
Edema	14 (5.5)	12 (8.8)	3 (9.4)	6 (5.7)	0 (0.0)	2 (8.7)
Chest pain	11 (4.3)	10 (7.3)	1 (3.1)	6 (5.7)	1 (1.1)	0 (0.0)
Rigors	11 (4.3)	10 (7.3)	4 (12.5)	42 (39.6)	0 (0.0)	1 (4.3)
Injury	10 (3.9)	8 (5.8)	2 (6.3)	2 (1.9)	2 (2.1)	0 (0.0)
Back Pain	8 (3.1)	7 (5.1)	2 (6.3)	0 (0.0)	1 (1.1)	0 (0.0)
Abdomen Enlarged	5 (2.0)	5 (3.6)	1 (3.1)	2 (1.9)	0 (0.0)	0 (0.0)
Edema Peripheral	5 (2.0)	5 (3.6)	1 (3.1)	5 (4.7)	0 (0.0)	0 (0.0)
Anaphylactoid Reaction	3 (1.2)	3 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	3 (1.2)	3 (2.2)	1 (3.1)	5 (4.7)	0 (0.0)	0 (0.0)
Hot Flushes	3 (1.2)	3 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Condition Aggravated	4 (1.6)	2 (1.5)	0 (0.0)	3 (2.8)	0 (0.0)	2 (8.7)
Malaise	2 (0.8)	2 (1.5)	0 (0.0)	4 (3.8)	0 (0.0)	0 (0.0)
Syncope	5 (2.0)	2 (1.5)	0 (0.0)	1 (0.9)	1 (1.1)	2 (8.7)
Allergic Reaction	3 (1.2)	1 (0.7)	0 (0.0)	2 (1.9)	1 (1.1)	1 (4.3)

Table 7

Adverse Event Incidence With Onset in the IV Treatment Phase in Worldwide Trials, Reported by at Least Three Patients in Any Treatment Group, by Preferred Term, n(%)

(Applicant Table 2-14, modified by MO)

Body system/adverse event	Total	Controlled			PK	Uncontrolled
	ITR n=255	ITR n=137	FLU n=32	AMB n=106	ITR n=95	ITR n=23
Lab values Abnormal	1 (0.4)	0 (0.0)	0 (0.0)	3 (2.8)	0 (0.0)	1 (4.3)
Respiratory System Disorders						
Coughing	24 (9.4)	20 (14.6)	3 (9.4)	8 (7.5)	0 (0.0)	4 (17.4)
Dyspnea	22 (8.6)	15 (10.9)	1 (3.1)	15 (14.2)	1 (1.1)	6 (26.1)
Pneumonia	10 (3.9)	10 (7.3)	1 (3.1)	8 (7.5)	0 (0.0)	0 (0.0)
Pulmonary Infiltration	9 (3.5)	9 (6.6)	1 (3.1)	2 (1.9)	0 (0.0)	0 (0.0)
Pulmonary Edema	14 (5.5)	9 (6.6)	2 (6.3)	5 (4.7)	0 (0.0)	5 (21.7)
Rhinitis	8 (3.1)	7 (5.1)	2 (6.3)	2 (1.9)	1 (1.1)	0 (0.0)
Hypoxia	8 (3.1)	6 (4.4)	1 (3.1)	1 (0.9)	0 (0.0)	2 (8.7)
Pharyngitis	6 (2.4)	6 (4.4)	1 (3.1)	3 (2.8)	0 (0.0)	0 (0.0)
Respiratory Disorder	9 (3.5)	6 (4.4)	0 (0.0)	6 (5.7)	0 (0.0)	3 (13.0)
Pleural Effusion	5 (2.0)	5 (3.6)	3 (9.4)	4 (3.8)	0 (0.0)	0 (0.0)
Respiratory Insufficiency	6 (2.4)	5 (3.6)	0 (0.0)	1 (0.9)	1 (1.1)	0 (0.0)
Bronchospasm	7 (2.7)	4 (2.9)	1 (3.1)	4 (3.8)	0 (0.0)	3 (13.0)
Hemoptysis	5 (2.0)	3 (2.2)	1 (3.1)	5 (4.7)	0 (0.0)	2 (8.7)
Pneumonitis	3 (1.2)	2 (1.5)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
Stridor	3 (1.2)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.7)
Pleural Pain	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.8)	0 (0.0)	0 (0.0)
Sinusitis	1 (0.4)	0 (0.0)	0 (0.0)	4 (3.8)	1 (1.1)	0 (0.0)
Metabolic and Nutritional Disorders						
Hypokalemia	22 (8.6)	21 (15.3)	4 (12.5)	32 (30.2)	0 (0.0)	1 (4.3)
Hyperglycemia	14 (5.5)	10 (7.3)	4 (12.5)	5 (4.7)	4 (4.2)	0 (0.0)
NPN increased	12 (4.7)	10 (7.3)	2 (6.3)	29 (27.4)	0 (0.0)	2 (8.7)
Fluid Overload	11 (4.3)	8 (5.8)	3 (9.4)	9 (8.5)	1 (1.1)	2 (8.7)
Hypomagnesemia	8 (3.1)	7 (5.1)	2 (6.3)	9 (8.5)	0 (0.0)	1 (4.3)
Bun Increased	6 (2.4)	6 (4.4)	0 (0.0)	14 (13.2)	0 (0.0)	0 (0.0)
Hypocalcemia	7 (2.7)	6 (4.4)	2 (6.3)	6 (5.7)	0 (0.0)	1 (4.3)
Edema Generalized	6 (2.4)	6 (4.4)	1 (3.1)	9 (8.5)	0 (0.0)	0 (0.0)
Phosphatase Alkaline Increased	6 (2.4)	6 (4.4)	5 (15.6)	3 (2.8)	0 (0.0)	0 (0.0)
CPK Increased	3 (1.2)	3 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperkalemia	3 (1.2)	3 (2.2)	1 (3.1)	3 (2.8)	0 (0.0)	0 (0.0)
Hypernatremia	3 (1.2)	3 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Acidosis	3 (1.2)	2 (1.5)	0 (0.0)	2 (1.9)	0 (0.0)	1 (4.3)
Skin and Appendages Disorders						
Rash	21 (8.2)	16 (11.7)	3 (9.4)	8 (7.5)	2 (2.1)	3 (13.0)
Rash Erythematous	11 (4.3)	10 (7.3)	1 (3.1)	6 (5.7)	0 (0.0)	1 (4.3)
Sweating Increased	10 (3.9)	8 (5.8)	0 (0.0)	2 (1.9)	2 (2.1)	0 (0.0)
Pruritus	6 (2.4)	5 (3.6)	1 (3.1)	4 (3.8)	1 (1.1)	0 (0.0)
Skin Disorder	3 (1.2)	3 (2.2)	2 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric Disorders						
Confusion	10 (3.9)	8 (5.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.7)

Table 7

Adverse Event Incidence With Onset in the IV Treatment Phase in Worldwide Trials, Reported by at Least Three Patients in Any Treatment Group, by Preferred Term, n(%)

(Applicant Table 2-14, modified by MO)

Body system/adverse event	Total	Controlled			PK	Uncontrolled
	ITR n=255	ITR n=137	FLU n=32	AMB n=106	ITR n=95	ITR n=23
Insomnia	8 (3.1)	8 (5.8)	0 (0.0)	6 (5.7)	0 (0.0)	0 (0.0)
Anorexia	6 (2.4)	6 (4.4)	1 (3.1)	2 (1.9)	0 (0.0)	0 (0.0)
Hallucination	6 (2.4)	6 (4.4)	0 (0.0)	2 (1.9)	0 (0.0)	0 (0.0)
Somnolence	6 (2.4)	6 (4.4)	2 (6.3)	3 (2.8)	0 (0.0)	0 (0.0)
Sleep Disorder	4 (1.6)	4 (2.9)	0 (0.0)	3 (2.8)	0 (0.0)	0 (0.0)
Anxiety	5 (2.0)	3 (2.2)	0 (0.0)	5 (4.7)	2 (2.1)	0 (0.0)
Depression	3 (1.2)	2 (1.5)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
Central & Peripheral Nervous System Disorder						
Headache	17 (6.7)	10 (7.3)	0 (0.0)	13 (12.3)	5 (5.3)	2 (8.7)
Dizziness	8 (3.1)	7 (5.1)	0 (0.0)	5 (4.7)	0 (0.0)	1 (4.3)
Tremor	5 (2.0)	5 (3.6)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Liver and Biliary System Disorders						
Bilirubinemia	17 (6.7)	15 (10.9)	5 (15.6)	5 (4.7)	2 (2.1)	0 (0.0)
Jaundice	7 (2.7)	7 (5.1)	1 (3.1)	1 (0.9)	0 (0.0)	0 (0.0)
SGPT Increased	7 (2.7)	7 (5.1)	1 (3.1)	2 (1.9)	0 (0.0)	0 (0.0)
SGOT Increased	5 (2.0)	5 (3.6)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Hepatic Function Abnormal	2 (0.8)	2 (1.5)	0 (0.0)	5 (4.7)	0 (0.0)	0 (0.0)
Gamma-GT Increased	2 (0.8)	1 (0.7)	3 (9.4)	2 (1.9)	1 (1.1)	0 (0.0)
Cardiovascular Disorders, General						
Hypotension	16 (6.3)	12 (8.8)	3 (9.4)	10 (9.4)	3 (3.2)	1 (4.3)
Hypertension	8 (3.1)	8 (5.8)	6 (18.8)	6 (5.7)	0 (0.0)	0 (0.0)
Cardiac Failure	7 (2.7)	6 (4.4)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
Heart Murmur	3 (1.2)	3 (2.2)	0 (0.0)	2 (1.9)	0 (0.0)	0 (0.0)
Edema Dependent	1 (0.4)	1 (0.7)	0 (0.0)	3 (2.8)	0 (0.0)	0 (0.0)
Urinary System Disorders						
Hematuria	10 (3.9)	9 (6.6)	2 (6.3)	6 (5.7)	1 (1.1)	0 (0.0)
Urine Abnormal	7 (2.7)	7 (5.1)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Renal Function Abnormal	6 (2.4)	5 (3.6)	0 (0.0)	11 (10.4)	0 (0.0)	1 (4.3)
Urinary Incontinence	5 (2.0)	5 (3.6)	0 (0.0)	3 (2.8)	0 (0.0)	0 (0.0)
ARF	4 (1.6)	4 (2.9)	0 (0.0)	3 (2.8)	0 (0.0)	0 (0.0)
Albuminuria	7 (2.7)	3 (2.2)	1 (3.1)	1 (0.9)	4 (4.2)	0 (0.0)
UTI	2 (0.8)	2 (1.5)	3 (9.4)	2 (1.9)	0 (0.0)	0 (0.0)
Nephropathy Toxic	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.8)	0 (0.0)	0 (0.0)
Platelet, Bleeding & Clotting Disorders						
Epistaxis	12 (4.7)	10 (7.3)	3 (9.4)	11 (10.4)	0 (0.0)	2 (8.7)
Purpura	6 (2.4)	6 (4.4)	0 (0.0)	5 (4.7)	0 (0.0)	0 (0.0)
Hemorrhage	1 (0.4)	1 (0.7)	1 (3.1)	3 (2.8)	0 (0.0)	0 (0.0)
Resistance Mechanism Disorders						
Infection Bacterial	10 (3.9)	6 (4.4)	0 (0.0)	2 (1.9)	3 (3.2)	1 (4.3)
Herpes Simplex	7 (2.7)	5 (3.6)	0 (0.0)	0 (0.0)	1 (1.1)	1 (4.3)
Infection	3 (1.2)	3 (2.2)	2 (6.3)	3 (2.8)	0 (0.0)	0 (0.0)

Table 7

Adverse Event Incidence With Onset in the IV Treatment Phase in Worldwide Trials, Reported by at Least Three Patients in Any Treatment Group, by Preferred Term, n(%)

(Applicant Table 2-14, modified by MO)

Body system/adverse event	Total	Controlled			PK	Uncontrolled
	ITR n=255	ITR n=137	FLU n=32	AMB n=106	ITR n=95	ITR n=23
Sepsis	5 (2.0)	2 (1.5)	4 (12.5)	4 (3.8)	2 (2.1)	1 (4.3)
RBC Disorders						
Anemia	12 (4.7)	11 (8.0)	1 (3.1)	2 (1.9)	1 (1.1)	0 (0.0)
Heart Rate and Rhythm Disorders						
Tachycardia	6 (2.4)	6 (4.4)	2 (6.3)	8 (7.5)	0 (0.0)	0 (0.0)
Bradycardia	3 (1.2)	3 (2.2)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Application Site Disorders						
Application Site Reaction	23 (9.0)	7 (5.1)	0 (0.0)	5 (4.7)	16 (16.8)	0 (0.0)
Vision disorders						
Vision Abnormal	4 (1.6)	4 (2.9)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Conjunctivitis	0 (0.0)	0 (0.0)	1 (3.1)	5 (4.7)	0 (0.0)	0 (0.0)
Vascular (extracardiac) Disorders						
Flushing	2 (0.8)	2 (1.5)	0 (0.0)	3 (2.8)	0 (0.0)	0 (0.0)
Phlebitis	1 (0.4)	1 (0.7)	0 (0.0)	3 (2.8)	0 (0.0)	0 (0.0)
Vein Disorder	9 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)	9 (9.5)	0 (0.0)
Musculoskeletal system disorders						
Skeletal pain	5 (2.0)	5 (3.6)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
WBC and *Reticuloendothelial* Disorders						
Granulocytopenia	5 (2.0)	2 (1.5)	0 (0.0)	1 (0.9)	3 (3.2)	0 (0.0)
Special Senses Other, Disorders						
Taste Perversion	3 (1.2)	1 (0.7)	0 (0.0)	0 (0.0)	2 (2.1)	0 (0.0)

MO Comment: The MO previously compared the incidence of AEs seen in the clinical trial patient population compared to that seen in the PK trial population. In this section the MO limited comment to the overall population (N = 255) and AEs that developed during the IV phase as compared to the control amphotericin and fluconazole groups.

GI System AEs: There was a high frequency of GI-related AEs across the treatment groups. Nausea and vomiting were the most frequent AEs with an incidence of 40/255 (15.7%), 36/255 (14.1%), and 30/255 (11.8%) of IV itraconazole patients respectively. As noted previously, these events had the highest incidence in the clinical and PK trial populations respectively. However, although these events were among the most frequent in the PK trials populations, overall the incidence was lower than that seen in the clinical trials population. The MO postulated that this occurrence might be accounted for by the underlying illnesses of the clinical trial populations. Comparing these events to the comparator arms revealed a similarly high incidence in those patients treated with amphotericin (32/106, 35/106, and 32/106 or 30.2%, 33%, and 30.2%) per AE respectively. The incidence per respective AE for the fluconazole patients was 8/32, 5/32, and 3/32 or 25%, 15.6%, and 9.4%) or somewhat lower than that seen on the 2 comparator arms.

The incidence of all GI events with onset in the IV phase was 115/255 (45.1%) itraconazole, 16/32 (50%) fluconazole and 78/106 (73.6%) amphotericin. The MO determined that these percentages were consistent with those expected from the comparators.

Body as a whole: Overall incidence of all reported events was similar between the 3 study drugs (itraconazole: 93/255 (36.5%), fluconazole 16/32 (50%), and amphotericin 64/106 (60.4%). The breakdown of the incidence in the clinical trials itraconazole patients versus the PK trials patients was 79/160 (49.4%) versus 14/95 (14.7%). Thus, although the overall incidence for the total itraconazole population was 36% the clinical trials incidence is similar to that of the other 2 clinical arms. The 60.4% incidence reported for the amphotericin group is justified by the increased frequency of reporting of rigors 42/106 (39.6%) for this group as compared to 11/160 (6.9%) for itraconazole clinical trials patients and 4/32 (12.5%) for fluconazole-treated patients. Rigors and fever are commonly reported AEs for amphotericin.

Anaphylactoid reaction was reported in 3 (1.2%) itraconazole patients. In all 3 patients a review of the CRFs revealed that these events were related to platelet transfusions.

Respiratory: There were no major difference in the reported frequencies of any of the events that compromised this group/ Overall incidence was: itraconazole 78/255 (30.6%), fluconazole 13/32 (40.6%), and amphotericin 43/106 (40.6%). A breakdown of the itraconazole patients into all clinical: 72/160 (45%), PK: 6/95 (6.3%) and uncontrolled 13/23 (56.5%) versus controlled 59/137 (43.1%) revealed that there was a higher frequency in the uncontrolled trial. The underlying disease process of the uncontrolled population, disseminated or pulmonary aspergillosis, justified this difference. Overall coughing and dyspnea had the highest incidence of reported events (itraconazole 24/255 (9.4%) and 22/255 (8.6%).

Metabolic and Nutritional Disorders: Overall incidence for this category by treatment arm was: itraconazole: 61/255 (23.9%) versus fluconazole 18/32 (56.3%) and amphotericin 63/106 (59.4%). The breakdown for all clinical itraconazole patients versus PK patients was 56/160 (35%) versus 5/95 (5.3%). The most frequently reported event was hypokalemia, occurring in 22/255 (8.6%) of all itraconazole patients (clinical 22/160 (13.8%), PK 0), as compared to 32/106 (30.2%) amphotericin patients and 4/32 (12.5%) fluconazole patients. The high incidence of hypokalemia on the amphotericin arm in conjunction with the high incidences of increased creatinine: 29/106 (27.4%) and increased BUN 14/106 (13.2%) are consistent with this agent's known renal toxicity profile (renal tubular acidosis). The respective incidences for the itraconazole-treated patents were 12/255 (4.7%) and 6/255 (2.4%) as compared to those for the fluconazole patients: 2/32 (6.3%) and 0.

Overall the frequencies of other reported events in this category were similar between the arms.

Skin and Appendages Disorders: Overall incidence for this group for the itraconazole-treated patients was 47/255 (18.4%) as compared to 9/32 (28.1%) for the fluconazole-treated patients and 25/106 (23.6%) for the amphotericin-treated patients. 3 verbatim terms were primarily utilized for this category: rash, rash erythematous, and rash maculopapular. The combined frequency for these 3 events was 42/255(16.4%) for the itraconazole-treated patients. As per the applicant, the overall incidence of these events was higher than expected. The breakdown for rash events alone was 9.4% for controlled clinical trials, 17.4% for the uncontrolled trial and 6.3% for the PK trials. The PK frequency was similar to that reported for the oral formulations of itraconazole (solution 4%, and capsules 8.6%). The applicant postulated that the high incidence of rash seen in the clinical patients could be justified on the basis of underlying disease and other medications. The MO cannot comment on this given that the type of patients evaluated for safety in the clinical trials of the oral formulations of itraconazole are not known at the present. The overall frequency of these events as compared to the fluconazole and amphotericin arms was not unusual.

Urinary System Disorders: The IV itraconazole formulation for which the applicant is seeking approval solubilized itraconazole in hydroxypropyl-b-cyclodextrin. This differs from the oral formulations and because the oral formulations do not contain this chemical compound, they contain no precautionary labeling with regard to their use in patients with renal dysfunction. All of the clinical trials for the IV formulation were conducted excluding patients with severe renal insufficiency because of the excretion of HP-b-CD by glomerular filtration. The frequency of urinary system AEs was 33/255 (12.9%) for all IV itraconazole patients (27/160 (27.8% clinical and 6/95 (6.3%) PK) as compared to 8/32 (25%) fluconazole patients and 33/106 (31.1%) amphotericin patients. Events captured in this category included hematuria

(8/255 (7.4%), ARF 4/255 (3.7%), UTI 4/255 (3.7%), albuminuria 3/255 (2.8%) and abnormal renal function 3/255 (2.8%). All reported cases of hematuria were determined to be unrelated to the study drug. All patients who developed ARF were reviewed previously. 2 of these patients died, #0402 due to ARDS and multiorgan failure and #1163 who also died to multiorgan failure secondary to worsening colon Ca. This patient entered the trial with underlying renal insufficiency (Cr. 1.4). The remaining 2 patients #0051 entered the trial with a Cr. Of 3.8 received 2 days of IV therapy and then PO itraconazole, followed by rhabdomyolysis, and #1111 also with a baseline Cr. of 2,6 which rose to 3.5 on day 4 of therapy. In neither case was the elevation of the creatinine attributed to the IV itraconazole use. The last 2 patients discontinued therapy for worsening renal failure.

In addition to the above, there were 2 patients with an AE coded " creatinine clearance decreased." The first #03031, an aspergillosis patient, discontinued the trial for this reason as well as for dyspnea and stridor. The other patient #1163 was described previously.

Overall the renal dysfunction found on all 3 arms was expected and in none of the itraconazole cases was a definite relationship to the study drug established.

Cardiovascular Disorders: The incidence of this group of disorders was 31/255 (12.2%) for all itraconazole patients as compared to 8/32 (25%) fluconazole patients and 21/106 919.8%) of amphotericin patients. The breakdown of for clinical itraconazole patients versus PK patients was 26/160 (16.2%) versus 5/95 (5.3%). Overall there appeared to be no difference s between the clinical trial treatment groups. None of the cardiac events were attributed to IV itraconazole.

Liver and Biliary System Disorders: The incidence of disorders from this system was 34/255 (13.3%) for all itraconazole patients (31/160 (19.3%) clinical trials patients and 3/95 (3.2%) PK patients) as compared to 10/32 (31.3%) for all fluconazole patients and 14/106 (13.2%) for all amphotericin patients. The fluconazole incidence was higher than expected and most likely reflective of the severity of the underlying disease in the patient population as well as the small sample size. However the incidence reported for IV itraconazole was also higher then expected. In worldwide esophageal and oral candidiasis trials the incidence of abnormal hepatic function was 0.3% for the oral solution and an incidence of 2.7% is reported in the prescribing information for the capsules. Most of the patients with liver abnormalities were enrolled in trial 62. These patients had underlying hematologic malignancies

Application Site Disorders: 23/255 (9%) of all itraconazole patients reported an application site disorder. Additionally, 9/255 (3.5%) reported a vein disorder. As noted previously in the PK section, these events appear to be synonymous and therefore the total incidence was 32/255 (12.5%). None of the fluconazole patients developed this AE and the incidence in the amphotericin patients was 5/106 (4.7%). As noted previously this event appeared to be site specific (Study 113) with all vein disorders from that PK study as well as 16 of the application site disorders.

WBC Disorders: Granulocytopenia was observed in 5/255 (2%) of the IV itraconazole patients as compared to none of the fluconazole patents and 1/106 (0.9%) of the amphotericin patients. 3 of the 5 events on the itraconazole arm were from the PK trials performed in HIV patients.

Assessment of AEs by relationship to study drug:

Overall AE reporting was high across the treatment arms with total AE reporting of 95.3% for the amphotericin-treated patients, 100% for the fluconazole-treated patients and 91.8% for the itraconazole-treated patients. Almost 50% of all reported itraconazole adverse events were assessed as possibly or definitely-related to study drug. A higher association of drug relationship to adverse event was noted for amphotericin B with 82.1% of adverse events assessed as possibly or definitely-related. The association of adverse event with study drug was not as great for fluconazole, 21.9% assessed as possibly-related, but the sample size was small making conclusions difficult. Copied and modified below is the applicant's table 2-17. The MO modified this table to reflect all clinical trials patients instead of controlled and uncontrolled.

Table 8
All AEs Considered Possibly or Definitely Related to Study Drugs (As per the MO)

Body system/ Adverse event	Total ITR n=255	Clinical (Controlled and Uncontrolled) ITR n=160	FLU n=32	AMB n=106	PK ITR n=95
Total number patients with adverse event	**118 (46.3)**	**79 (49.4)**	**7 (21.9)**	**87 (82.1)**	**39 (41.1)**
Gastrointestinal System Disorders	**45 (17.6)**	**34 (21.2)**	**2 (6.3)**	**37 (34.9)**	**11 (11.6)**
Nausea	23 (9.0)	18 (11.2)	0 (0.0)	23 (21.7)	5 (5.3)
Diarrhea	19 (7.5)	15 (9.4)	1 (3.1)	14 (13.2)	4 (4.2)
Vomiting	11 (4.3)	10 (6.2)	0 (0.0)	16 (15.1)	1 (1.1)
Abdominal Pain	7 (2.7)	4 (2.5)	0 (0.0)	5 (4.7)	3 (3.2)
Constipation	3 (1.2)	3 (1.9)	1 (3.1)	1 (0.9)	0 (0.0)
Liver and Biliary System Disorders	**26 (10.2)**	**23 (14.4)**	**4 (12.5)**	**9 (8.5)**	**3 (3.2)**
Bilirubinemia	13 (5.1)	11 (6.9)	3 (9.4)	4 (3.8)	2 (2.1)
SGPT Increased	6 (2.4)	6 (3.8)	1 (3.1)	2 (1.9)	0 (0.0)
Jaundice	4 (1.6)	4 (2.5)	0 (0.0)	1 (0.9)	0 (0.0)
SGOT Increased	4 (1.6)	4 (2.5)	0 (0.0)	1 (0.9)	0 (0.0)
Hepatic Function Abnormal	2 (0.8)	2 (1.2)	0 (0.0)	3 (2.8)	0 (0.0)
Metabolic and Nutritional Disorders	**27 (10.6)**	**25 (15.6)**	**2 (6.3)**	**47 (44.3)**	**2 (2.1)**
Hypokalemia	11 (4.3)	11 (6.9)	0 (0.0)	29 (27.4)	0 (0.0)
Increased Creatinine	6 (2.4)	6 (3.8)	1 (3.1)	27 (25.5)	0 (0.0)
Increased BUN	3 (1.2)	3 (1.9)	0 (0.0)	11 (10.4)	0 (0.0)
Increased Alk. Phos.	3 (1.2)	3 (1.9)	1 (3.1)	2 (1.9)	0 (0.0)
Fluid Overload	1 (0.4)	1 (0.6)	0 (0.0)	3 (2.8)	0 (0.0)
Hyperglycemia	3 (1.2)	1 (0.6)	0 (0.0)	1 (0.9)	2 (2.1)
Hypomagnesemia	2 (0.8)	2 (1.2)	0 (0.0)	7 (6.6)	0 (0.0)
Hypocalcemia	1 (0.4)	1 (0.6)	0 (0.0)	3 (2.8)	0 (0.0)
Body as a Whole – General Disorders	**17 (6.7)**	**15 (9.3)**	**0 (0.0)**	**38 (35.8)**	**2 (2.1)**
Pain	3 (1.2)	3 (1.9)	0 (0.0)	1 (0.9)	0 (0.0)
Rigors	2 (0.8)	2 (1.2)	0 (0.0)	36 (34.0)	0 (0.0)
Syncope	3 (1.2)	2 (1.2)	0 (0.0)	0 (0.0)	1 (1.1)
Fever	1 (0.4)	1 (0.6)	0 (0.0)	5 (4.7)	0 (0.0)
Central & Peripheral Nervous System Disorder	**15 (5.9)**	**12 (7.5)**	**0 (0.0)**	**7 (6.6)**	**3 (3.2)**
Dizziness	5 (2.0)	5 (3.1)	0 (0.0)	2 (1.9)	0 (0.0)
Headache	5 (2.0)	2 (1.2)	0 (0.0)	3 (2.8)	3 (3.2)
Urinary System Disorders	**13 (5.1)**	**8 (5.0)**	**0 (0.0)**	**19 (17.9)**	**5 (5.3)**
Renal Function Abnormal	3 (1.2)	3 (1.9)	0 (0.0)	11 (10.4)	0 (0.0)
Albuminuria	4 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	4 (4.2)
Nephropathy Toxic	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.8)	0 (0.0)
Skin and Appendages Disorders	**12 (4.7)**	**9 (5.6)**	**2 (6.3)**	**9 (8.5)**	**3 (3.2)**
Rash	5 (2.0)	4 (2.5)	1 (3.1)	4 (3.8)	1 (1.1)
Pruritus	1 (0.4)	0 (0.0)	0 (0.0)	3 (2.8)	1 (1.1)
Cardiovascular Disorders, General	**2 (0.8)**	**2 (1.2)**	**0 (0.0)**	**8 (7.5)**	**0 (0.0)**

Body system/ Adverse event	Total ITR n=255	Clinical (Controlled and Uncontrolled) ITR n=160	FLU n=32	AMB n=106	PK ITR n=95
Hypertension	0 (0.0)	0 (0.0)	0 (0.0)	4 (3.8)	0 (0.0)
Heart Rate and Rhythm Disorders	**2 (0.8)**	**2 (1.2)**	**0 (0.0)**	**4 (3.8)**	**0 (0.0)**
Tachycardia	2 (0.8)	2 (1.2)	0 (0.0)	3 (2.8)	0 (0.0)
Respiratory System Disorders	**3 (1.2)**	**3 (1.9)**	**0 (0.0)**	**9 (8.5)**	**0 (0.0)**
Bronchospasm	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.8)	0 (0.0)
Vascular (extracardiac) Disorders	**12 (4.7)**	**2 (1.2)**	**0 (0.0)**	**6 (5.7)**	**10 (10.5)**
Flushing	1 (0.4)	1 (0.6)	0 (0.0)	3 (2.8)	0 (0.0)
Phlebitis	1 (0.4)	1 (0.6)	0 (0.0)	3 (2.8)	0 (0.0)
Vein Disorder	9 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)	9 (9.5)
Application Site Disorders	**16 (6.3)**	**1 (0.6)**	**0 (0.0)**	**0 (0.0)**	**15 (15.8)**
Application Site Reaction	16 (6.3)	1 (0.6)	0 (0.0)	0 (0.0)	15 (15.8)
Special Senses other, Disorders	**3 (1.2)**	**1 (0.6)**	**0 (0.0)**	**1 (0.9)**	**2 (2.1)**
Taste Perversion	3 (1.2)	1 (0.6)	0 (0.0)	0 (0.0)	2 (2.1)

MO Comment: There was a less than 5% point difference between the incidence of all events related to study drug for the total itraconazole population and the clinical population only. This applied to all body systems as well as separate events. As noted previously, the highest incidence of relatedness was seen on the amphotericin arm and the lowest on the fluconazole arm. The most frequent AEs were from the GI tract and there appeared to be a significant difference between the reported AE rate for the itraconazole patients versus the fluconazole patients. Additionally the difference between itraconazole and fluconazole in terms of hypokalemia and disturbances of renal function appeared to be significant. The MO requested that the FDA statistical reviewer evaluate this table for significance.

Laboratory Abnormalities:

As per the applicant, a total of 255 patients were treated with itraconazole, 32 with fluconazole, and 106 with amphotericin B.

The mean duration of IV itraconazole was 8.33 days; the mean duration of IV fluconazole was 8.66 days; and the mean duration of amphotericin B treatment was 8.84 days. There were a variety of patient populations studied in the individual trials. The majority of patients had hematological malignancies and neutropenia or advanced HIV infection; additionally patients enrolled with candidemia, histoplasmosis, blastomycosis, active invasive pulmonary or disseminated aspergillosis, as well as intensive care unit patients requiring antifungal prophylaxis. Therefore the laboratory data were obtained from a heterogeneous and ill population, making the separation of effects of treatment from those of the underlying diseases and concomitant therapies difficult. Additionally, the PK trials were not performed in a normal volunteer population but in patients with advanced HIV disease. However for the purposes of these studies the HIV patients represented the most stable population studied.

Preclinical studies of IV itraconazole suggested that toxicity appeared related mainly to the itraconazole component rather than the hydroxypropyl-β-cyclodextrin component. No increased toxicity was seen with IV itraconazole than with an equivalent quantity of itraconazole alone. Known laboratory changes associated with the oral formulation of itraconazole include elevations of liver function tests (incidence of abnormal hepatic function of 2.7% in the itraconazole capsule prescribing information), and hypokalemia (incidence of 2.0% in the itraconazole capsule prescribing information).

Hemoglobin

Among all patients treated with itraconazole injection, approximately 80% had baseline hemoglobin values below the lower limit of normal. The incidence of NIH Grade 2 or 3 anemia (defined by hemoglobin value) was high across all treatment groups, as shown in applicant Table 2-33.

Table 2-33

Incidence of Grade 2 or 3 anemia, proportion (%)

NIH toxicity grade	Total ITR	FLU	AMB
Grade 2	63/152 (41.4)	11/21 (52.4)	21/40 (52.5)
Grade 3	31/231 (13.4)	5/29 (17.2)	18/89 (20.2)

MO Comment: Anemia is primarily associated with amphotericin therapy but not with fluconazole therapy or itraconazole therapy. The relatively high incidence of anemia on the fluconazole arm appeared to be associated with the type of patients treated and specifically affected by underlying diseases and concomitant therapies. Possibly the same could be said for the itraconazole arm. Overall the MO determined that the type of populations studied preclude an accurate assessment of this parameter.

Platelets

A large number of patients on all 3 treatment arms had abnormal baseline platelet values. Specifically, 55% of patients in the total itraconazole group had a baseline platelet count below the lower limit of the normal range, as did approximately 90% of the amphotericin B group. Copied below is the applicant's table 2.36 displaying the incidence of NIH grade 2 or 3 toxicity for all treatment arms.

Table 2-34:

Incidence of Grade 2 or 3 thrombocytopenia, proportion (%)

NIH toxicity grade	Total ITR	FLU	AMB
Grade 2	18/132 (13.6)	5/27 (18.5)	5/14 (35.7)
Grade 3	21/138 (15.2)	5/27 (18.5)	7/18 (38.9)

MO Comment: Overall rates of both grade 2 or 3 toxicity were lower for patients on the itraconazole arm as compared to the fluconazole and amphotericin arms. The significance of this however is unclear given the overall nature of the underlying disease of the populations studied as well as the concomitant therapies. Possible the itraconazole population's results were diluted by the results of the relatively normal PK populations. An analysis of only the HIV patients from trials 113 and 127 revealed that during the trials, 10.3% (6/58) of the patients developed a decrease from the normal to the below normal range and by day 8, 10.7% (6/56) had a similar decrease. The magnitude of these decreases did not appear to be clinically significant with the lowest value found of 113/mm'3.

WBC:

Almost all trials enrolled patients with baseline abnormal white blood cell counts (ITR-INT-62 and ITR-INT-59: hematological malignancies, bone marrow transplant recipients, ITR-USA-113 and ITR-USA-127: advanced HIV infection) thus making an assessment of WBC toxicity difficult. Only those patients from ITR-INT-58 (intensive care unit patients), ITR-INT-60 (patients with invasive pulmonary or disseminated aspergillosis),

During these trials the number of patients with decreases from a normal baseline to > 2.8/mm'3 were: 2/26 (7.7%) for itraconazole, 0/14 (0%) for fluconazole and 0/3 (0%) for Amphotericin B. Therefore it appeared as if the effect of all therapies on this parameter was minimal to non-existent.

Calcium

Copied below is applicant Table 2-35, displaying shifts in calcium levels during the course of IV therapy across all 3 treatment arms. Overall there was a trend towards the development of hypocalcemia for all

treatment arms. Additionally provided is applicant table 2.36 displaying the incidence of NIH grade 2 or 3 hypocalcemia.

Table 2-35

Calcium shift from within to below or above normal reference range, proportion (%)

Visit	Shift	Total ITR	FLU	AMB
Day 3	within→below	28/191 (14.7)	0/1 (0.0)	8/73 (11.0)
	within→above	0/191 (0.0)	0/1 (0.0)	0/73 (0.0)
Day 8	within→below	25/177 (14.1)	2/18 (11.1)	7/54 (13.0)
	within→above	0/177 (0.0)	0/18 (0.0)	1/54 (1.9)
Day 15	within→below	12/90 (13.3)	1/13 (7.7)	4/26 (15.4)
	within→above	0/90 (0.0)	1/13 (7.7)	0.26 (0.0)
Endpoint	within→below	27/230 (11.7)	3/25 (12.0)	11/84 (13.1)
	within→above	0/230 (0.0)	0/25 (0.0)	2/84 (2.4)

Table 2-36

Incidence of Grade 2 or 3 hypocalcemia, proportion (%)

NIH toxicity grade	Total ITR	FLU	AMB
Grade 2	47/211 (22.3)	7/25 (28.0)	16/68 (23.5)
Grade 3	10/239 (4.2)	0/27 (0.0)	10/86 (11.6)

MO Comment: Hypocalcemia is a known AE associated with amphotericin therapy but not with fluconazole therapy. The data collected from these trials for fluconazole appeared inconclusive due to the populations studied and the small number of patients provided for comparison. A review of only HIV PK itraconazole study patients revealed that by day 3 of therapy, 7/60 (11.7%) of patients had a decrease from normal to below normal limits and that by day 8 of therapy this had increased to 10/57 (17.5%). This indicated to the MO that IV itraconazole had a consistent effect on serum calcium leading to a decrease in levels on par with that of amphotericin therapy.

Potassium:

Hypokalemia is reported as an adverse event during treatment with itraconazole and amphotericin B. Downward shifts in potassium concentrations were greatest for patients in the amphotericin B group, but the percentage of patients who shifted from within to below the normal range during IV itraconazole therapy exceeded the incidence reported for itraconazole capsules and oral solution. The high frequency of hypokalemia across the itraconazole and amphotericin groups but not the fluconazole group suggested that either the sample size of the fluconazole population was too small to provide an accurate assessment of the influence of underlying disease and concomitant therapies on this parameter or that indeed there is a significant difference between the effect of fluconazole and itraconazole on this parameter. Copied below is applicant table 2-37.

Table 2-37

Potassium shift from within to below or above normal reference range, proportion (%)

Visit	Shift	Total ITR	FLU	AMB
Day 3	within→below	24/211 (11.4)	0/1 (0.0)	19/88 (21.6)
	within→above	2/211 (0.9)	0/1 (0.0)	2/88 (2.3)
Day 8	within→below	18/193 (9.3)	1/20 (5)	23/63 (36.5)
	within→above	6/193 (3.1)	0/20 (0.0)	1/63 (1.6)
Day 15	within→below	16/100 (16.0)	3/19 (15.8)	7/31 (22.6)
	within→above	1/100 (1.0)	1/19 (5.3)	1/31 (3.2)
Endpoint	within→below	30/245 (12.2)	4/27 (14.8)	22/96 (22.9)
	within→above	4/245 (1.6)	2/27 (7.4)	6/96 (6.3)

When only the values from the HIV PK patients were assessed the incidence of hypokalemia decreased to 0% by day 3, 1.8% or 1/57 by day 8 and to 6.6% or 4/61 by the end of the trials. Alternatively the incidence of hyperkalemia was 0% at day 3, 5.3% (3/57) by day 8 and 0% by the end of the study.

Glucose:
Elevations in serum glucose from a normal baseline were common during itraconazole treatment. A similar pattern of change in glucose values was seen for amphotericin B; as noted previously in the analysis of potassium, the sample size for fluconazole was too small to make meaningful comparisons. Copied below is the applicant's table 2-38 showing the incidence of NIH Grade 2 or 3 hyperglycemia across treatment groups.

Table 2-38

Glucose shift from within to below or above normal reference range, proportion (%)

Visit	Shift	Total ITR	FLU	AMB
Day 3	within→below	4/182 (2.2)	0/1 (0.0)	0/68 (0.0)
	within→above	37/182 (20.3)	0/1 (0.0)	9/68 (13.2)
Day 8	within→below	2/160 (1.3)	1/13 (7.7)	0/49 (0.0)
	within→above	32/160 (20.0)	0/13 (0.0)	6/49 (12.2)
Day 15	within→below	2/82 (2.4)	0/12 (0.0)	1/26 (3.8)
	within→above	10/82 (12.2)	0/12 (0.0)	5/26 (19.2)
Endpoint	within→below	2/214 (0.9)	1/19 (5.3)	1/78 (1.3)
	within→above	31/214 (14.5)	1/19 (5.3)	9/78 (11.5)

Table 2-39

Incidence of Grade 2 or 3 hyperglycemia, proportion (%)

NIH toxicity grade	Total ITR	FLU	AMB
Grade 2	30/194 (15.5)	3/15 (20.0)	16/76 (21.1)
Grade 3	12/217 (5.5)	2/19 (10.5)	5/83 (6.0)

The high incidence of NIH Grade 2 or 3 hyperglycemia in all treatment groups suggests underlying disease and/or concomitant therapies, such as multiple intravenous infusions of dextrose solutions, as the cause rather than study drug.

Table 2-40

Glucose shift from within to above normal reference range: pooled data from trials ITR-USA-113 and ITR-USA-127, proportion (%)

Visit	Shift	Total ITR
Day 3	within→above	14/59 (24)
Day 8	within→above	13/55 (23.6)
Endpoint	within→above	9/62 (14.5)

Table 2-41

Incidence of Grade 2 or 3 hyperglycemia; pooled data from trials ITR-USA-113 and ITR-USA-127, proportion (%)

NIH toxicity grade	Total ITR
Grade 2	6/61 (9.8)
Grade 3	0/61 (0.0)

MO Comment: Also copied above are the applicant's table of the incidence of hypoglycemia for the HIV patient sonly. As can be seen, the incidence of patients with glucose values shifting from within normal to above normal range during itraconazole therapy was not very different between the aggregate population from all trials and the HIV PK subpopulation. The significance of the development of hyperglycemia is questionable given that in all cases although the values were above normal, therapeutic intervention was not required.

BUN:

Elevations of BUN occurred across all groups during treatment as shown in applicant Table 2-42. As expected, the frequency of increased values was substantially higher for the amphotericin B group than for itraconazole injection or fluconazole

Table 2-42

BUN shift from within to above normal reference range, proportion (%)

Visit	Total ITR	FLU	AMB
Day 3	5/207 (2.4)	0/1 (0.0)	25/82 (30.5)
Day 8	7/188 (3.7)	3/20 (15)	32/59 (54.2)
Day 15	13/98 (13.3)	4/19 (21.1)	14/29 (48.3)
Endpoint	20/243 (8.2)	5/27 (18.5)	43/90 (47.8)

Creatinine:

The incidence of increases in serum creatinine during treatment is shown in applicant Table 2-43. Amphotericin B is known to cause decreased renal function and renal function abnormalities and, as expected, there was a higher incidence of increased serum creatinine than for fluconazole or itraconazole.

Table 2-43

Creatinine shift from within to above normal reference range, proportion (%)

Visit	Total ITR	FLU	AMB
Day 3	7/210 (3.3)	0/1 (0.0)	18/88 (20.5)
Day 8	6/192 (3.1)	1/20 (5)	24/63 (38.1)
Day 15	6/102 (5.9)	2/19 (10.5)	10/32 (31.3)
Endpoint	13/245 (5.3)	2/27 (7.4)	31/95 (32.6)

MO Comment: When only the HIV patients were assessed, only 1 patient developed an increase in serum creatinine (1/60, 1.7%). Thus the effect of itraconazole on this parameter appeared minimal.

LFTs:

LDH: There were no consistent patterns of change in serum lactate dehydrogenase.

Bilirubin: The incidence of increased bilirubin laboratory values and NIH Grade 2 or 3 tonicities, were comparable across treatment groups and suggested that possibly these changes were related in part to underlying disease processes.

Table 2-44

Bilirubin shift from within to above normal reference range, proportion (%)

Visit	Total ITR	FLU	AMB
Day 3	8/182 (4.4)	0/1 (0.0)	9/71 (12.7)
Day 8	17/172 (9.9)	3/19 (15.8)	9/59 (15.3)
Day 15	15/86 (17.4)	3/18 (16.7)	4/30 (13.3)
Endpoint	30/224 (13.4)	3/26 (11.5)	8/86 (9.3)

When only HIV patients were analyzed, 4.9% (3/61) patients had a shift from normal to above baseline by the end of therapy and of these patients the value was clinically significant in only 1 patient.

Liver enzymes:
Increased liver enzymes occurred across all treatment groups. The number of fluconazole-treated patients was small, but incidences of liver enzyme elevations and toxicity between the fluconazole and itraconazole injection treatment groups were comparable. In general, the amphotericin B treatment group developed liver enzyme elevation more frequently than either itraconazole or fluconazole. Liver enzyme abnormalities are reported to occur during amphotericin B therapy as well as with azole antifungals. Additionally the role played by the underlying diseases and concomitant therapies cannot be quantitated. Copied below are the applicant's tables pertaining to the respective liver enzymes:

Table 2-45

Alkaline phosphatase shift from within to above normal reference range, proportion (%)

Visit	Total ITR	FLU	AMB
Day 3	10/182 (5.5)	0/1 (0.0)	7/71 (9.9)
Day 8	18/173 (10.4)	2/19 (10.5)	14/58 (24.1)
Day 15	10/91 (11.0)	4/17 (23.5)	12/28 (42.9)
Endpoint	28/228 (12.3)	5/26 (19.2)	19/88 (21.6)

Table 2-46

ALT (SGPT) shift from within to above normal reference range, proportion (%)

Visit	Total ITR	FLU	AMB
Day 3	14/181 (7.7)	0/1 (0.0)	5/66 (7.6)
Day 8	19/162 (11.7)	1/13 (7.7)	9/57 (15.8)
Day 15	10/84 (11.9)	3/12 (25)	6/26 (23.1)
Endpoint	28/216 (13)	5/19 (26.3)	18/84 (21.4)

Table 2-47

AST (SGOT) shift from within to above normal reference range, proportion (%)

Visit	Total ITR	FLU	AMB
Day 3	12/180 (6.7)	0/1 (0.0)	5/67 (7.5)
Day 8	15/170 (8.8)	1/18 (5.6)	7/57 (12.3)
Day 15	6/87 (6.9)	1/17 (5.9)	4/24 (16.7)
Endpoint	25/226 (11.1)	6/26 (23.1)	8/85 (9.4)

Table 2-48

gGT shift from within to above normal reference range, proportion (%)

Visit	Total ITR	FLU	AMB
Day 3	9/169 (5.3)	0/1 (0.0)	6/56 (10.7)
Day 8	18/155 (11.6)	0/13 (0.0)	15/50 (30)
Day 15	12/70 (17.1)	1/12 (8.3)	7/23 (30.4)
Endpoint	20/207 (9.7)	3/19 (15.8)	18/74 (24.3)

MO Comment: If only the HIV-infected subjects were analyzed the incidence of increased liver function test values during IV itraconazole therapy was much lower with 1/57 (1.8%) of patients developing an increased Alk. Phos. by day 8 of therapy, 2/57 (3.5%) an increased ALT, 0% an increased AST and 0 an increased gGT.

MO Conclusion: As expected hypokalemia and disturbance of liver function developed with the usage of IV itraconazole. Additionally hypocalcemia occurred with some frequency. Most of the laboratory abnormalities that developed were without clinical significance.

Conclusion and Discussion as per the Applicant:

"We believe that the data presented in this Integrated Summary of Safety support a significant benefit in the use of itraconazole injection for histoplasmosis, blastomycosis, and aspergillosis with acceptable safety risks that are minimized in the setting of hospitalized patients who are observed closely and for whom laboratory test values are monitored frequently.

As expected, the overall adverse event incidence in worldwide trials during the intravenous treatment phase of itraconazole was high, but did not differ substantially from those reported for fluconazole and amphotericin B in the controlled clinical trials. Importantly, the adverse event incidence was considerably lower for every body system, other than Application site disorders, among patients treated in the pharmacokinetics trials compared with the total itraconazole population, supporting the assumption that the vast majority of adverse events were more closely attributable to the underlying condition.

Gastrointestinal adverse events were reported with the greatest frequency (12.9%) during the intravenous treatment phase in the "signal" population of relatively healthy patients enrolled to the US pharmacokinetic trials (ITR-USA-113 and -127). Nausea, abdominal pain, and diarrhea were reported most often. Likewise for the total

population, gastrointestinal events were observed frequently among all treatment groups.

For purposes of presenting the adverse event profile of itraconazole injection in the package insert, we propose that adverse events considered possibly or definitely related to itraconazole injection and reported with a frequency of ≥2% among all itraconazole patients be presented in tabular format. For purposes of comparison, the incidence of adverse events among patients treated with itraconazole or an active comparator in active controlled studies will be presented as well. Thus, the proposed labeling is:

ADVERSE REACTIONS:

The adverse events listed below are based on the experience of 255 patients treated with Sporanox® injection in four pharmacokinetic, one uncontrolled and four active controlled studies where the control was amphotericin B or fluconazole. Nearly all patients were neutropenic or were otherwise immunocompromised and were treated empirically for febrile episodes, for documented systemic fungal infections, or in trials to determine pharmacokinetics. The dose of Sporanox® injection was 200 mg twice daily for the first two days followed by a single daily dose of 200 mg for the remainder of the intravenous treatment period. The majority of patients received between 7 and 14 days of Sporanox® injection.

SUMMARY OF POSSIBLY OR DEFINITELY DRUG-RELATED ADVERSE EVENTS REPORTED BY ≥2% OF SPORANOX® INJECTION PATIENTS (TOTAL)			
	TOTAL	COMPARATIVE STUDIES	
ADVERSE EVENT	SPORANOX INJECTION (N=255) %	SPORANOX INJECTION (N=137) %	ACTIVE CONTROLS* (N=138) %
Gastrointestinal system disorders			
Nausea	9	12	17
Diarrhea	8	9	11
Vomiting	4	7	12
Abdominal pain	3	3	4
Metabolic and nutritional disorders			
hypokalemia	4	8	21
NPN increased	2	3	20
Liver and biliary system disorders			
bilirubinemia	5	8	5
SGPT increased	2	4	2
Central & peripheral nervous system disorders			
Dizziness	2	3	1
Headache	2	2	2
Skin and appendages disorders			
Rash	2	2	4
Vascular (extracardiac) disorders			
Vein disorder	4	0	0
Application site disorder			
Application site disorder	6	1	0

*Amphotericin B (106 patients) or fluconazole (32 patients)

The following adverse events also occurred in 5% or more of Sporanox® Injection patients; however, the causal relationship of these events to the administration of Sporanox® Injection is uncertain:

Body as a whole: edema, fever, pain

Gastrointestinal system disorders: constipation

Metabolic and nutritional disorders: hyperglycemia

Respiratory system disorders: coughing, dyspnea, and pulmonary edema

Cardiovascular disorders: hypotension

CONCLUSIONS

Itraconazole is effective for treatment of histoplasmosis, blastomycosis, and aspergillosis. Data from 255 patients treated for indications ranging from systemic antifungal disease (histoplasmosis, blastomycosis, aspergillosis, candidemia) to fever in the setting of neutropenia, to prophylaxis of fungal infection, support the safety of itraconazole injection for patients requiring intravenously administered itraconazole. Adverse events most frequently associated with the use of itraconazole injection include gastrointestinal effects and rashes. Alterations of serum potassium and liver function test values attributable to treatment occur infrequently, but risks are minimized because most patients will be closely monitored in a hospital setting while receiving itraconazole injection.

MO Conclusion: As noted in the introduction, this submission contained safety information on 255 patients treated with IV itraconazole for 7- 14 days in 9 clinical studies, 5 of which were still ongoing at the time of the submission. Additionally, the applicant did not submit any information with regards to efficacy in this submission. Rather the approval of the intravenous formulation for the requested indications would be based upon pharmacokinetic data and safety data.

Overall the MO agreed with the applicant's determination of the safety of the IV formulation of itraconazole. Most frequent AEs were from the GI tract. Overall itraconazole had less renal and hepatic toxicity as compared to amphotericin B. Sample sizes were inadequate to draw any conclusions with regard to fluconazole. Hypokalemia, hypocalcemia, hyperglycemia, and LFT abnormalities appeared to be the laboratory abnormalities most frequently associated with IV itraconazole. Additionally renal dysfunction was also occasionally seen although not to the degree expected by the applicant due to the excretion of the cyclodextrin molecule via the kidney. The *a priori* exclusion of patients with renal dysfunction (serum creatinine > 4 mg/dL 0r creatinine clearance < 30) most likely led to a decreased incidence of renal toxicity. The MO agreed that the IV formulation of itraconazole should not be given to patients with renal dysfunction as described above.

With regard to efficacy, the applicant stated that the PK portion of the submission adequately demonstrated that the IV formulation was equivalent to the oral. The MO deferred to the PK reviewer with regard to a final determination of effectiveness.

The MO disagreed with the applicant's proposal with regard to labeling. The MO determined that a table of possibly or definitely-related AEs was appropriate but only for patients from clinical trials, i. e. itraconazole N = 160.

Additionally, the MO determined that the comparator arms, amphotericin B and fluconazole, should be listed separately as the current table presents the fluconazole arm in conjunction with the amphotericin arm and presents an inaccurate picture of the AE profile of their comparator agents.

The MO determined that it was inappropriate to include the results of the PK patients (N = 95) because these studies were of shorter duration and the patient populations differed from those in the clinical trials.

As per the FDA statistician, Dr. Liji Shen,
"A higher proportion of patients with itraconazole 70/160 (49.4%) than patients with fluconazole 7/32 (21.9%) experienced adverse events associated with study drug (p=0.06). Patients treated with amphotericin B had even higher drug-related adverse events 87/106 (82.1%) than those treated with itraconazole, (p=0.000). Adverse events according to body system showed statistically significantly higher occurrences in amphotericin patients in the following body systems: GI (p=0.021), Metabolic and

nutritional disorders (p=0.000), Body as a whole (p=0.000), Urinary system disorders (p=0.002), Cardiovascular disorders (p=0.021) and Respiratory system disorders (p=0.026). No statistically significant difference in the frequency of drug-related adverse events according to body system was found between itraconazole and fluconazole."

The MO proposes that a table of all investigator-determined, treatment-related AEs by study arms be added to the label and to include only clinical trial patients. It should be noted that the values in the table below are only tentative pending the applicant's submission and the MOR of the 4-month safety update.

SUMMARY OF POSSIBLY OR DEFINITELY DRUG-RELATED ADVERSE EVENTS REPORTED BY ≥2% OF SPORANOX® INJECTION PATIENTS (%)			
ADVERSE EVENT	**IV Itraconazole N = 160**	**IV Fluconazole N = 32**	**Amphotericin B N = 106**
Total number patients with adverse event	**79 (49)**	**7 (22)**	**87 (82)**
Gastrointestinal System Disorders	**34 (21)**	**2 (6)**	**37 (35)**
Nausea	18 (11)	0 (0)	23 (22)
Diarrhea	15 (9)	1 (3)	14 (13)
Vomiting	10 (6)	0 (0)	16 (15)
Abdominal Pain	4 (3)	0 (0)	5 (5)
Liver and Biliary System Disorders	**23 (14)**	**4 (13)**	**9 (9)**
Bilirubinemia	11 (7)	3 (9)	4 (4)
SGPT Increased	6 (4)	1 (3)	2 (2)
Jaundice	4 (3)	0 (0)	1 (1)
SGOT Increased	4 (3)	0 (0)	1 (1)
Hepatic Function Abnormal	2 (1)	0 (0)	3 (3)
Metabolic and Nutritional Disorders	**25 (16)**	**2 (6)**	**47 (44)**
Hypokalemia	11 (7)	0 (0)	29 (27)
Increased Creatinine	6 (4)	1 (3)	27 (25)
Central & Peripheral Nervous System Disorder	**12 (8)**	**0 (0)**	**7 (7)**
Dizziness	5 (3)	0 (0)	2 (2)
Skin and Appendages Disorders	**9 (6)**	**2 (6)**	**9 (9)**
Rash	4 (3)	1 (3)	4 (4)

The following adverse events also occurred in 5% or more of Sporanox® Injection patients (N = 255); however, the causal relationship of these events to the administration of Sporanox® Injection is uncertain:
Body as a whole: Edema 14/255 (5.5%), Fever 30/255 (11.8%), Pain 16/255 (6.3%)
Gastrointestinal system disorders: Constipation 19/255 (7.5%)
Metabolic and nutritional disorders: Hyperglycemia 14/255 (5.5%)
Respiratory system disorders: Coughing 24/255 (9.4%), Dyspnea 22/255 (8.6%), Pulmonary edema 14/255 (5.5%)
Cardiovascular disorders: Hypotension 16/255 (6.3%)
CNS: Headache 17/255 (7.3%)
Application site disorders: 23/255 (9%)

RECOMMENDED REGULATORY ACTION:

The MO recommends approval of the IV itraconazole formulation for the treatment of blastomycosis (pulmonary and extrapulmonary), histoplasmosis (including chronic cavitary pulmonary disease and disseminated non-meningeal histoplasmosis), and aspergillosis (pulmonary and extrapulmonary in patients refractory to amphotericin B) in immunocompromised and non-immunocompromised patients at a dose of 200 mg IV BID for 2 days followed by 200 mg IV QD for a maximum of 14 days.

The following changes should be incorporated into the applicant's proposed labeling:

1) Under **DOSAGE and ADMINISTRATION** the sentence " Treatment of blastomycosis, histoplasmosis, and aspergillosis: The recommended intravenous dose is 200 mg BID (2 one-hour infusions) for 2 days followed by 200 mg QD (one one-hour infusion)"

   should be modified to:

2) Under **ADVERSE REACTIONS** the applicant's table and text (see page 103) should be modified to reflect clinical trial patients only and the comparator arms, amphotericin B and fluconazole, should be listed separately (see MO table and text page 105).

/S/

Regina Alivisatos, MD
DSPIDP, HFD-590

/S/

Concurrence only:
HFD-590/DIVDir/MGoldberger

Cc:
Orig. NDA 50-762
HFD-590
HFD-590/DepDIVDir/RAlbrecht
HFD-590/MTL/BLeissa 9/30/98
HFD-590/Biopharm/PColangelo
HFD-590/Micro/
HFD-590/Chem/
HFD-590/Pharm/
HFD-590/CSO/KimeyR
HFD-725/Biostat/Chakravarty
HFD-520/Biopharm/McMasterO

8/12/98

APPENDIX I: Individual Studies/Safety Review:

Pharmacokinetic trials of short duration:

The MO elected to present the data on the following 6 trials/71 patients who received 1 – 2 doses of itraconazole intravenous solution. These patients were not included in the safety database but the safety data addresses acute toxicity.

Protocol 80 (N=6):

Protocol 80 was an open-label, cross-over designed trial to investigate the intravenous pharmacokinetics and absolute oral bioavailability of itraconazole in six healthy patients. Itraconazole injection was administered as a single-dose one-hour infusion of a 100 mL solution containing 100 mg itraconazole (1 mg/mL). Oral itraconazole was administered as a 10 mL solution containing 100 mg itraconazole. As per the applicant, no information on adverse event reporting is available for this study.

Laboratory data (serum biochemistry, hematology, and urinalyses) were performed on blood and urine samples and collected immediately before drug administration and one day after dosing. Analysis of the data revealed no clinically significant effects on any laboratory safety parameter examined. The clinical trial report referenced one patient (#5329) with an important laboratory abnormality during treatment; a rise in triglyceride from 162 mg/dL during the washout phase to 259 mg/dL during treatment with itraconazole injection (normal reference range 40-230 mg/dL). The patient had an elevated triglyceride of 238 mg/dL at baseline and 236 mg/dL during treatment with oral itraconazole.

MO Comment: None of the 6 patients received the proposed itraconazole dose or the proposed concentration of 10 mg/mL.

ITR-BEL-1 (N = 10):

ITR-BEL-1 was a cross-over designed trial to investigate the pharmacokinetics and oral bioavailability of itraconazole in ten bone marrow transplant patients. Patients were randomized to receive either a single oral or intravenous 100 mg dose of itraconazole (1 mg/mL) 1 to 2 days after bone marrow transplantation followed by cross-over to the other treatment 7 to 10 days after bone marrow transplantation. The intravenous infusions were administered over one hour. All patients received a second oral dose of itraconazole 14 to 23 days after transplantation.

Two of the 10 patients enrolled in the trial discontinued for adverse events, but only one received itraconazole injection. Patient #3 was withdrawn from the study after the second administration of itraconazole (100 mg orally on Day 2 post-transplant followed by 100 mg intravenously on Day 8 post-transplant), because of a graft-versus-host reaction and renal failure. The investigator determined these events were not related to itraconazole but related to complications of the transplantation.

Patient #7 was withdrawn from the study after the first oral dose of itraconazole due to a cutaneous rash on the neck, thorax and legs which appeared eight hours after dosing.

Clinical laboratory data was not collected in this trial.

MO Comment: None of 10 patients received the proposed itraconazole dose the proposed concentration. The development of a rash however was an AE that was noted in the 200 mg PK and clinical trials.

ITR-BEL-18 (N=2):

ITR-BEL-18 was a two-phase pilot study to investigate the *in vivo* hemolytic effect of itraconazole injection. In Phase 1, itraconazole injection, 100 mg (1 mg/mL), was administered to two patients as an infusion over 10 minutes using an automatic syringe pump. In Phase 2, itraconazole injection was administered to the same two patients as a manual injection over three minutes.

Both patients completed the study. No information on adverse event reporting is available for this study.

No clinically relevant laboratory abnormalities (hemolysis, LDH, potassium, and haptcglobin) were observed, and no clinically significant hemolysis was induced.

MO Comment: Neither of the 2 patients received the proposed itraconazole dose or the proposed concentration. However, the dose utilized was infused rapidly without problems.

ITR-BEL-57 (N=4):

ITR-BEL-57 was an open-label trial designed to assess safety and tolerability and to describe the pharmacokinetics of itraconazole, hydroxy-itraconazole, and hydroxypropyl-β-cyclodextrin. Four one-hour infusions of 200 mg itraconazole injection (10 mg/mL) were administered over two days to four healthy patients.

All four patients completed the study. One patient complained of headache on Day 3. He also developed inflammation at the site of the intravenous catheter insertion between days 3 and 7. This inflammation occurred bilaterally, at both the catheter site used to infuse itraconazole and at the catheter site in the opposite arm used only to draw blood.

There were no changes in heart rate, blood pressure or ECG intervals during the trial.

Hematology, biochemistry, and urinalysis were performed at recruitment, immediately prior to drug infusion, and 24, 48 and 96 hours, and 15 days after first drug infusion.

One patient had low values for total protein (range: 5.7-6.2 g/dL) at baseline and throughout the entire trial (normal reference range: 6.6-8.0 g/dL).

There were no other clinically relevant or consistent changes observed in any of the investigated hematology, biochemistry, or urinary variables. This included plasma creatinine concentrations and creatinine clearances.

MO Comment: 4 healthy subjects received the proposed itraconazole dose for only 2 days. No significant events occurred. The development of an application site reaction is consistent with the AE profile as seen in the PK and clinical trials.

ITR-BEL-77 (N=36):

ITR-BEL-77 was an open-label, three-way crossover trial designed to assess dose proportionality and pharmacokinetics of itraconazole and hydroxypropyl-β-cyclodextrin in healthy patients. Itraconazole injection was administered as single doses of 50 mg, 100 mg, or 200 mg in volumes of 15 mL, 30 mL, or 60 mL, respectively. Each dose was administered as a one-hour infusion.

Adverse events were reported by four of the 12 patients receiving the 50 mg dose; by two of the 12 patients receiving the 100 mg dose; and by four of the 12 patients receiving the 200 mg dose. Headache was the most frequently reported event; three patients after the 50 mg dose and one patient after the 100 mg dose. Two patients reported diarrhea; one each in the 50- and 200-mg groups. Other adverse events reported only once included: vertigo, nausea, vomiting and muscle pain after the 50 mg dose; dyspepsia after the 100 mg dose; and dizziness, abdominal pain, flatulence and erythematous rash after the 200 mg dose.

The severity of the adverse events ranged from mild to moderate. No death or other serious adverse events occurred during the study.

Clinical laboratory data were available for all patients for all three treatment periods. There were no consistent changes in blood chemistry, hematology, or urinalysis test results.

MO Comment: No significant AEs were reported. GI dysfunction (diarrhea, abdominal pain, flatulence) and rash are expected AEs with the agent under study.

ITR-USA-116 (N=37):

ITR-USA-116 was an open-label trial designed to determine the pharmacokinetic profile of itraconazole injection in patients with normal and impaired renal function. Patients were stratified into four groups based on their renal function as determined by urine creatinine clearance: normal renal function (I), mildly impaired (II), moderately impaired (III), or severely impaired (IV).

Itraconazole injection was administered as single dose of 200 mg (10 mg/mL) infused over one hour.

All 37 patients were included in the safety analysis. Sixteen patients (43.2%) reported at least one adverse event during the trial. Incidence rates by renal function group were 28.6% (Group I), 55.6% (Group II), 28.6% (Group III), and 71.4% (Group IV). The most common adverse events, each reported by two patients, were rhinitis (14.3% in Group I) and headache (22.2% and 28.6% in Groups II and IV, respectively). In general, the type and incidence of adverse events appeared to be distributed evenly among the four treatment groups. All adverse events were mild in severity with the following two exceptions:

Patient #0125 (Group I): 74 YO who developed a maculo-papular, non-pruritic, erythematous rash of moderate severity on her abdomen, breast, and back that spread to the groin and axilla. This rash was associated with a mild fever and resolved with hydroxyzine treatment.

Patient #0135 (Group IV): 70 YO patient was hospitalized for septicemia 8 days after receiving the itraconazole dose.

Six patients experienced seven adverse events that the investigator considered possibly-related to study drug. One patient (#0125) in the normal renal function group experienced an erythematous rash and another in the same group (#0122) developed nausea; both events were considered possibly-related. Two patients in the mild renal impairment group had events the investigator considered drug-related: dry mouth (#0132, possibly-related) and prolonged QT interval (#0128, definitely-related). One patient in the moderate renal impairment group (#0108) had two possibly-related events: nausea and taste perversion. One patient in the severe renal impairment group reported headache (#0119, possibly-related).

Clinical laboratory data were available for screening and the final study day (Day 6) for all patients with normal renal function, for eight of nine patients with mild renal impairment, for five of seven patients with moderate renal impairment, and for all patients with severe renal impairment. There were no consistent changes noted over time in blood chemistry or hematology values.

A shift in blood urea nitrogen from within normal limits at screening to above normal limits at Day 6 was seen in three patients, one with mild renal impairment (#0133) and two with moderate renal impairment (#0123 and #0136). Similarly, two patients, one in the mild impairment group (#0133) and one in the moderate impairment group (#0123) had increases in creatinine from within normal limits at baseline to above normal limits on Day 6. No other clinically significant changes in blood chemistry or hematology were observed.

Conclusions as per the applicant:

(Copied from the electronic submission):

> Adverse event information was available for four of the six clinical pharmacology and pharmacokinetic trials of short duration (ITR-BEL-1, ITR-BEL-57, ITR-BEL-77 and ITR-USA-116). Twenty-three of the 63 patients in these four trials reported one or more adverse events during the trials. Headache was the most common adverse event, reported in three of the four trials. The majority of the reported events were mild to moderate in severity.
>
> Three patients prematurely discontinued from a trial due to adverse events: two patients in ITR-BEL-1 (graft-versus-host reaction/renal failure and cutaneous rash) and one patient in ITR-USA-116 (prolonged QT interval). One serious adverse event of

severe sepsis was reported in ITR-USA-116; the event was considered unrelated to study drug.

Adverse events appeared to be distributed evenly among the treatment groups in the dose-proportionality trial (ITR-BEL-77), suggesting that there was no dose-related effect on the adverse event profile of itraconazole injection. In addition, there did not appear to be a difference in the incidence of adverse event reporting among patients with mild, moderate or severe renal impairment (ITR-USA-116). Results of the analysis of cardiovascular safety from ITR-BEL-57 showed that there were no relevant changes in heart rate, blood pressure, or ECG intervals during that trial.

Clinical laboratory data were available from all trials except ITR-BEL-1. In general, there were few clinically relevant or consistent changes over time in blood chemistry tests, hematology, urinalyses, or tests for hemolysis. Nine patients, four in ITR-BEL-77 and five in ITR-USA-116, had laboratory test values that were normal at baseline and outside the normal limits at sometime during the study. As with adverse events, there did not appear to be any relationship between renal status and laboratory test results.

MO Comment: 53 of the 71 patients received the proposed dose and concentration of intravenous itraconazole, 200 mg(10 mg/mL)although for a short duration only. The most frequently reported AEs that appeared to be treatment-related were rash, nausea and headache. From a laboratory standpoint, an increase in serum creatinine and BUN was noted in 3 patients with previously-documented mild to moderate renal dysfunction.

Pharmacokinetic Studies of Longer Duration:

- **ITR-USA-127:** A pharmacokinetic trial of itraconazole injection followed by oral itraconazole solution in patients with advanced human immunodeficiency virus infection.

Study Dates: October 7, 1996 – March 12, 1997

Investigators: A Miro, MD
Pittsburgh, PA

M. Shelton, Ph.D.
Buffalo, NY

Study Summary: Study 127 was the first of 4 open-label, randomized, comparison, IV and oral solution pharmacokinetic studies. The population studied was 32 patients with advanced HIV disease. This population was evaluated because of the frequent need for the use of long term itraconazole. The inclusion and exclusion criteria were standard and excluded those patients who were taking medications incompatible with itraconazole or who had laboratory abnormalities > 2 x normal.

The study objective was to determine the pharmacokinetics of the intravenous formulation of itraconazole in 36 HIV positive subjects with CD4 lymphocyte counts < 300 cells/mm3 at a dose of 200 mg twice daily for two days and once daily for 5 days, followed by randomization to one of two dosing regimens of itraconazole oral solution, (200 mg QD or BID for an additional 28 days). Parameters obtained were

compared with those observed after continued dosing for 28 days using two oral dosing regimens of itraconazole capsules, 200 mg twice daily and 200 mg once daily. A secondary objective was to obtain preliminary safety data in patients with advanced HIV disease (CD4 lymphocyte count < 300 cells/mm3).

Adverse events occurring any time on study were recorded and assessed by the investigator with respect to their severity and relationship to study medication.

In the pre-study period (2 weeks prior to the first dose), the subjects underwent (Copied from the original protocol)

1. A complete and current medical history.
2. Physical examination including height, body weight and vital signs.
3. CD4 lymphocyte count
4. Laboratory safety tests:
   a. Hematology
      Complete blood count with differential; platelet count.
   b. Blood chemistry
      SMAC 22 (sodium, potassium, chloride, calcium, phosphorus, glucose, total bilirubin, direct bilirubin, alkaline phosphatase, ASAT, ALAT, gGT, LDH, blood urea nitrogen, creatinine, uric acid, total protein, albumin, globulin, A/G ratio, total cholesterol, triglycerides).
   c. Urinalysis
4. Urine Drug Screening
   amphetamine, barbiturate, benzodiazepine, cannabinoids, cocaine, methaqualone, opiates, phencyclidine. Subjects will be notified that additional samples may be taken at random during the study.
5. Serum pregnancy test
6. Electrocardiogram ONLY if the patient is 45 years old or has a history of cardiac disease.

On days 1, 7, and 36 of the study, the subjects were admitted to the clinical research center where they remained for a minimum of 24 hours. PK sampling was performed and vital signs and body weight were measured.

Subjects then received IV itraconazole, 200 mg twice daily for two days, and 200 mg once daily for 5 more days. Intravenous itraconazole was administered over a one hour time period. Vital signs were obtained prior to, once during, and at the end of each infusion, and subjects were observed clinically for the occurrence of any adverse events during the infusion and for one hour after each infusion. Subjects returned to clinic weekly during oral dosing.

After admission, prior to dosing the next morning, serum chemistry, hematology, and urinalysis were performed. These analyses were repeated on days 3 and 8. In addition to PK blood sampling, urine for cyclodextrin was collected at the time of infusion and for 12 hours subsequent. This was repeated on days 7 – 8.

After the last IV infusion and randomization to an oral regimen, the subjects returned weekly for

monitoring. Laboratory analyses were again performed on day 36 after the last dose.

Any discontinuations were reported to the study monitor and recorded on the CRF.

Safety

All randomized patients were included in safety analysis.

All reported adverse events were evaluated with respect to the severity and relationship to study drug. Adverse events were graded according to the toxicity table in Appendix 2 (see below). The incidence for each reported adverse experience was presented for each dose regimen.

Laboratory tests were performed during the study and descriptive statistics calculated for each laboratory test. Normal reference ranges were used in the summary of laboratory data. Abnormal laboratory test results were summarized in the report. Laboratory data were cross-classified into below, within, and above the reference range according to their values at baseline and during the study.

Copied and modified below is the applicant's schedule of events:

SCHEDULE OF EVENTS (OVERALL)

Procedure	Screening	1	2	3-6	7	15-35	36
History and Physical Exam	xa						
CD4 lymphocyte count	xb						
Laboratory Safety Tests	xa	x		xh	xh		x
Calculated Creatinine Clearance	xa	x			x		x
Electrocardiogramf	xa						
Drug Screening	xa						
Vital Signs and AEsg	x	x	x	x	x	x	x
Trough Levels			xd	xd		xd	
Full PK sampling		xc			xc		xe

a. Within two weeks prior to the first dose Calculated Creatinine clearance on the evening prior to dosing.

b. Within two weeks prior to the first dose

c. For pharmacokinetics: blood samples will be obtained prior to and at the end of dosing, and at 15 and 30 minutes and 1, 2, 4, 6, 8, and 11 hours after the end of the i.v. dose (Day 7 includes a 23 hour sample)

d. Prior to each i.v. dose and weekly during oral dosing.

e. For pharmacokinetics: blood samples will be obtained prior to and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12 and 24 hours after the last oral dose.

f. Only for patients _ 45 years of age or with a history of cardiac disease

g. Prior to and during each infusion, observe for one-hour post infusion, and weekly during oral dosing

h. Morning of Day 3 and on the morning of Day 8 with 23 hour PK specimen

Copied below is the applicant's appendix 2 outlining the scoring system used to assess severity of AEs:

APPENDIX 2: TABLE FOR GRADING SEVERITY OF ADVERSE EXPERIENCES

ITEM	GRADE 1 TOXICITY	GRADE 2 TOXICITY	GRADE 3 TOXICITY	GRADE 4 TOXICITY
HEMATOLOGY				
HEMOGLOBIN	9.5 - 10.5 gm/Dl	8.0 - 9.4 gm/dL	6.5 - 7.9 gm/dL	< 6.5 gm/dL
ABSOLUTE NEUTROPHIL COUNT	1000 - 1500/mm3	750 - 999/mm3	500 - 749/mm3	< 500/mm3
PLATELETS	75,000 - 99,000/mm3	50,000 - 74,999/mm3	20,000 - 49,000/mm3	< 20,000/mm3 or diffuse petechiae
PROTHROMBIN TIME (PT)	1.01 - 1.25 x upper normal limit	1.26 - 1.5 x upper normal limit	1.51 - 3.0 x upper normal limit	> 3 x upper normal limit
ACTIVATED PARTIAL THROMBOPLASTIN TIME (APTT)	1.01 - 1.66 x upper normal limit	1.67 - 2.33 x upper normal limit	2.34 - 3 x upper normal limit	> 3 x upper normal limit
FIBRINOGEN	0.75 - 0.99 x lower normal limit	0.50 - 0.74 x lower normal limit	0.25 x 0.49 x lower normal limit	< 0.25 x lower normal limit
FIBRIN SPLIT PRODUCT	20 - 40 mcg/ml	41-60 mcg/ml	61 - 80 mcg/ml	> 80 mcg/ml
METHEMOGLOBIN	5 - 9.9 %	10.0 - 14.9 %	15.0 - 19.9%	> 20 %
ENZYMES				
AST (SGOT)	1.25 - 2.5 x upper normal limit	2.6 - 5 x upper normal limit	5.1 - 10 x upper normal limit	> 10 x upper normal limit
ALT (SGPT)	1.25 - 2.5 x upper normal limit	2.6 - 5 x upper normal limit	5.1 - 10 x upper normal limit	> 10 x upper normal limit
GGT	1.25 - 2.5 x upper normal limit	2.6 - 5 x upper normal limit	5.1 - 10 x upper normal limit	> 10 x upper normal limit
ALKALINE PHOSPHATASE	1.25 - 2.5 x upper normal limit	2.6 - 5 x upper normal limit	5.1 - 10 x upper normal limit	> 10 x upper normal limit
AMYLASE	1.1 - 1.5 x upper normal limit	1.6 - 2.0 x upper normal limit	2.1 - 5.0 x upper normal limit	> 5.1 x upper normal limit
CHEMISTRIES				
HYPONATREMIA	130 - 135 meq/L	123 - 129 meq/L	116 - 122 meq/L	< 116 meq/L or mental status changes or seizures
HYPERNATREMIA	146 - 150 meq/L	151 - 157 meq/L	158 - 165 meq/L	> 165 meq/L or mental status changes or seizures
HYPERKALEMIA	5.6 - 6.0 meq/L	6.1 - 6.5 meq/L	6.6 - 7.0 meq/L	> 7.0 meq/L or life-threatening arrhythmias
HYPOGLYCEMIA	55 - 64 mg/dL	40 - 54 mg/dL	30-39 mg/dL	< 30 mg/dL or mental status changes or coma
HYPERGLYCEMIA (note if fasting)	116 - 160 mg/dL	161 - 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or ketoacidosis or seizures
HYPOCALCEMIA correct for albumin	7.8 - 8.4 mg/dL	7.0 - 7.7 mg/dL	6.1 - 6.9 mg/dL	< 6.1 mg/dL or life-threatening arrythmia or tetany
HYPERCALCEMIA correct for albumin	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL or life-threatening arrhythmia
HYPOMAGNESEMIA	1.2 - 1.4 meq/L	0.9 - 1.1 meq/L or replacement Rx re.	0.6 - 0.8 meq/L or intensive Rx re. or hospitalization	< 0.6 meq/L or life-threatening arrhythmia
HYPOPHOSPHATEMIA	2.0 - 2.4 mg/dL	1.5 - 1.9 mg/dL or replacement Rx re.	1.0 - 1.4 mg/dL or intensive Rx re. or hospitalization re.	< 1.0 mg/dL or life-threatening arrhythmias
HYPERBILIRUBINEMIA	1.1 - 1.5 x upper normal limit	1.6 - 2.5 x upper normal limit	2.6 - 5 x upper normal limit	> 5 x upper normal limit
BLOOD UREA NITROGEN (BUN)	1.25 - 2.5 x upper normal limit	2.6 - 5 x upper normal limit	5.1 - 10 x upper normal limit	> 10 x upper normal limit
CREATININE	1.1 - 1.5 x upper normal limit	1.5 - 3.0 x upper normal limit	3.1 - 6 x upper normal limit	> 6 x upper normal or dialysis required
URINALYSIS				
PROTEINURIA	1+ or < 0.3% or < 3 g/L or 200 mg - 1 gm loss/day	2 - 3+ or 0.3 - 1.0% or 3 - 10 g/L or 1 - 2 gm loss/day	4+ or > 1.0% or > 10 g/L or 2 - 3.5 gm loss/day	> 3.5 gm loss/day or nephrotic syndrome
HEMATURIA	microscopic only	gross, no clots	gross + clots	requires transfusion or obstructive