Discontinuations due to AEs occurred in 11 subjects (36%). 5 during the IV phase and the remaining during the PO phase.

Laboratory abnormalities occurred but with less frequency as compared to previously reviewed studies, possibly due to the large number of discontinuations.

Prophylaxis studies:

As part of the safety dataset the applicant submitted study reports and supporting data from 5 prophylaxis studies where ITR oral solution was used. The MOR of these studies can be found in Appendix B. The MO elected not to include the safety information from these studies in the ISS and labeling recommendations for the empiric therapy of febrile neutropenia indication because of the incompatibility of the dosing regimens including dosage and duration of treatment between the subjects that received the IV/PO formulation and those that received only oral solution.

APPEARS THIS WAY
ON ORIGINAL

Integrated Summary of Safety:

As noted in the introduction, ITR is a broad-spectrum triazole antifungal agent available in three formulations: oral capsule, oral solution, and solution for intravenous injection (itraconazole I.V. injection). This integrated summary of safety (ISS) addresses the safety considerations relevant to the application's proposed indication and dosing recommendations: a regimen of itraconazole I.V. injection followed by itraconazole oral solution for the empiric treatment of febrile neutropenic patients with suspected fungal infections. The ISS focuses on data from the applicant's pivotal trial, ITR-INT-62, in which itraconazole injection plus oral solution were compared with amphotericin B.

The safety data in the submission were derived from subjects treated with one of two regimens:

Table 33
Organization of safety data in the integrated summary of safety

GROUP 1: ITRACONAZOLE I.V. INJECTION FOLLOWED BY ORAL SOLUTION			
Clinical trials of therapeutic and prophylaxis regimens			**Extended-exposure clinical pharmacology trials**
Comparative		Non-comparative	Non-comparative
Active control	Placebo control		
ITR-INT-62	not applicable	ITR-INT-58 ITR-INT-59 ITR-INT-60	ITR-USA-113 ITR-USA-127
GROUP 2: ITRACONAZOLE ORAL SOLUTION ONLY			
Comparative			Non-comparative
Active control	Placebo control		
ITR-BEL-4 ITR-INT-54 ITR-GBR-17	ITR-ITA-18		ITR-CAN-15

Group 1—itraconazole I.V. injection followed by itraconazole oral solution or capsules (N = 318),

Group 2—itraconazole oral solution only (N = 868).

The complete safety database as submitted by the applicant consisted of 1186 ITR subjects. This constituted the "all trials/all subjects" population. The comparators database consisted of 1043 subjects, 204 received placebo, 229 received fluconazole, 192 received IV AMP B and 417 received oral AMP B alone or in combination with oral nystatin.

The subjects in Group 1 were primarily derived from pivotal trial ITR-INT-62, where subjects were diagnosed with a hematologic malignancy. The remaining Group 1 subjects came from trials where the patients were immunocompromised for other reasons, including invasive aspergillosis, AIDS, and ICU care (Trial 60). Additionally included in

Group 1 were subjects in extended-exposure clinical pharmacology trials, in which the dose and duration of itraconazole were similar to those in ITR-INT-62. In all Group 1 trials, itraconazole I.V. injection was administered for 1 to 2 weeks, followed by oral solution or capsules.

The subjects in Group 2 were from the 5 oral prophylaxis trials. These subjects had hematologic malignancies and were given itraconazole oral solution only(868 subjects, 943 treatment courses)..

Note: The ITR-INT-62 clinical research report, which constituted the efficacy portion of this SNDA, was amended to exclude the efficacy data from 10 subjects (5 receiving itraconazole; 5 receiving amphotericin B). These subjects were entered in the South African site of Dr. Bezwoda who admitted to clinical misconduct in another, non-Janssen trial. The data from these subjects was retained in the safety database.

Medical Officer's Comment: *The MO elected to primarily present only data from Group I subjects, those that received the regimen requested by the applicant for the indication of ETFN. Although the subjects in Group 2 suffered primarily from hematologic malignancies, the treatment regimens both between the Group 2 studies as well as between groups 1 and 2 were sufficiently different. Therefore combining the populations was not feasible. Additionally, during the MO review of the applicant's ISS, discrepancies were noted in the cumulative AE tables most commonly due to the omission of studies. The sponsor was requested to resubmit this information and to verify the accuracy of all submitted data. Only in the introduction to the ISS (below) did the MO present general AE data from the total ITR population as well as from Group 2. The data presented was accurate in that all numbers were generated by the MO utilizing 2 independent search tools.*

Demographics:

Table 34
Demographics Groups 1 and 2
As per the MO

All Trials/All Subjects		Group 1		Group 2	
	ITR N = 1186 (100%)	**ITR N = 318 (100%)**	**AMP B N = 192 (100%)**	**ITR N = 868 (100%)**	**Comparators N = 842 (100%)**
Sex					
Male	730 (61.6%)	213 (67%)	110 (57.3%)	517 (59.5%)	463 (55%)
Female	456 (38.4%)	105 (33%)	82 (42.7%)	351 (40.5%)	379 (45%)
Race					
White	409 (34.5%)	268 (84.3%)	165 (88%)	141 (16.2%)	132 (15.7%)
Black	30 (2.5%)	29 (9.1%)	15 (7.8%)	1(0.1%)	-
Hispanic	10 (0.8%)	9 (2.8%)	3 (1.6%)	1(0.1%)	-
Oriental	5 (0.4%	5(1.6%)	-	-	
Other	7 (0.6%)	7(2.2%)	5 (2.6%)	-	-
Unknown	725 (61.1%)	-	-	725 (83.6%)	710 (84.3%)
Age					
Mean	44.9	43	49.2	45.6	45.7
Median	45	42.7	50	Not provided	Not provided
≥ 65	137 (11.6%)	29 (9.1%)	33 (17.2%)	98 (11.3%)	86 (10.2%)

Medical Officer's Comment: *The demographics of the all trials/all subjects ITR population were similar to those of subjects in groups 1 and 2. There was a 10% difference in males between the ITR arm and the AMP B arm in group 1. Race was not collected in a large number of prophylaxis trials that were conducted primarily in Europe.*

Duration of Therapy: The mean duration for the all trials/all subjects population was 27 days (median 20). However, the duration for subjects in Group 1 was much shorter with a mean of 20 days and a median of 13 days. When this group was broken down into subjects from trial 62 and subjects in the PK trials, the mean duration for trial 62 was 10.6 days (median 8.5) as compared to a mean of 34.5 days (median 35) for PK trial subjects. For subjects in Group 2, the mean duration was 28 days of oral solution (median 17).

Adverse Events:

IV followed by oral solution (GROUP I):

The MO elected to present and discuss the AEs reported by the subjects that received the dosing regimen proposed by the applicant for the indication of ETFN. This regimen consisted of IV ITR 200 mg BID for the first 2 days followed by IV ITR QD for 5 – 12 days, followed by oral ITR 20 mL (200 mg oral solution) BID. 318/1186 (26.8%) of the

subjects in the safety database received this regimen. As noted above, 192 ITR subjects were patients treated in trial 62 and were diagnosed with hematologic malignancies. The remaining 126 ITR subjects were obtained from PK trials and trial 60 that included ICU patients, patients with aspergillosis, patients with stable HIV disease, and patients with hematologic malignancies. Included in this analysis are 192 AMP B treated subjects. All AEs reported by at least 2% of subjects are listed below.

Table 35
Kind and incidence of adverse events by body system by at least 2% of subjects

ADVERSE EVENT	ITR N= 192 (100%)	AMP B N = 192 (100%)	ALL Group 1 N= 318 (100%)	All ITR Uncont'ed N = 126 (100%)
GASTRO-INTESTINAL SYSTEM	**115 (59.9%)**	**115(59.9%)**	**168 (52.8%)**	**53 (42.1%)**
Diarrhea	39 (20%)	53 (28%)	66 (20.8%)	27 (21.4%)
Nausea	46 (24%)	45 (23%)	63 (19.8%)	17 (13.5%)
Vomiting	37 (19%)	40 (21%)	47 (14.8%)	10 (7.9%)
Abdominal Pain	15 (8%)	19 (10%)	27 (8.5%)	12 (9.5%)
Dyspepsia	3 (1.6%)	8 (4.2%)	8 (2.5%)	5 (4%)
Stomatitis	13 (7%)	7 (3.6%)	13 (4.1%)	-
Constipation	11(5.7%)	8 (4.2%)	23 (7.2%)	12 (9.5%)
Mucositis Nos	7 (3.6%)	11(5.7%)	8 (2.5%)	1 (0.8%)
Dry Mouth	5 (2.6%)	4 (2%)	5 (1.6%)	-
Ulcerative Stomatitis	4 (2%)	5 (2.6%)	5 (1.6%)	1 (0.8%)
Hemorrhoids	4 (2%)	4 (2%)	4 (1.3%)	-
GI disorder NOS	6 (3%)	4 (2%)	7 (2.2%)	1 (0.8%)
Oral Hemorrhage	2 (1%)	4 (2%)	2 (0.6%)	-
Enterocolitis	4 (2%)	4 (2%)	4 (1.3%)	-
Colitis	2 (1%)	2 (1%)	3 (0.9%)	1 (0.8%)
BODY AS A WHOLE - GENERAL DISORDERS	**89 (46.4%)**	**119 (62%)**	**141 (44.3%)**	**52 (41.3%)**
Rigors	19 (10%)	78 (40.6%)	25 (7.9%)	6 (4.8%)
Fever	12 (6%)	20 (10.4%)	38 (11.9%)	26 (20.6%)
Chest Pain	15 (8%)	8 (4.2%)	19 (6%)	4 (3.2%)
Edema	29 (15.1%)	24 (12.5%)	34 (10.7%)	5 (4%)
Edema Peripheral	8 (4.2%)	15 (7.8%)	9 (2.8%)	1 (0.8%)
Back Pain	9 (4.7%)	9 (4.7%)	10 (3.1%)	1 (0.8%)
Injury	7 (3.6%)	6 (3%)	16 (5%)	9 (7.1%)
Allergic Reaction	6 (3%)	5 (2.6%)	10 (3.1%)	5 (4%)
Pain	6 (3%)	7 (3.6%)	11 (3.5%)	5 (4%)
Condition Aggravated	3 (1.6%)	7 (3.6%)	8 (2.5%)	5 (4%)
Abdomen Enlarged	5 (2.6%)	4 (2%)	6 (1.9%)	1 (0.8%)
Fatigue	3 (1.6%)	5 (2.6%)	9 (2.8%)	6 (4.2%)

Malaise	2 (1%)	5 (2.6%)	2 (0.6%)	-
Syncope	5 (2.6%)	3 (1.6%)	6 (1.9%)	1 (0.8%)
Asthenia	4 (2%)	1 (0.5%)	4 (1.3%)	-
METABOLIC AND NUTRITIONAL DISORDERS	**65 (34%)**	**113 (58.9%)**	**78 (24.5%)**	**13 (10.3%)**
Hypokalemia	34 (17.7%)	60 (31.3%)	36 (11.3%)	2 (1.6%)
Creatinine Increased	8 (4.2%)	50 (26%)	10 (3.1%)	2 (1.6%)
Hypomagnesemia	14 (7.3%)	17 (9%)	15 (4.7%)	1 (0.8%)
Edema generalized	16 (8%)	13 (7%)	16 (5%)	-
Fluid Overload	10 (5.2%)	15 (7.8%)	13 (4.1%)	3 (2.4%)
BUN Increased	4 (2%)	15 (7.8%)	4 (1.3%)	3 (2.1%)
Hyperglycemia	6 (3%)	9 (4.7%)	12 (3.8%)	6 (4.8%)
Hypocalcemia	7 (3.6%)	8 (4.2%)	8 (2.5%)	3 (2.1%)
Alkaline Phosphatase Increased	9 (4.7%)	5 (2.6%)	9 (2.8%)	-
Hypophosphatemia	6 (3%)	6 (3%)	6 (1.9%)	-
LDH Increased	5 (2.6%)	-	6 (1.9%)	1 (0.8%)
Hypocalcemia	7 (3.6%)	8 (4.2%)	6 (1.9%)	1 (0.8%)
RESPIRATORY SYSTEM DISORDERS	**77 (40%)**	**71 (375)**	**107 (33.6%)**	**30 (23.8%)**
Dyspnea	17 (9)	22 (11.5)	26 (8.2%)	9 (7.1%)
Coughing	25 (13)	10 (5.2)	30 (9.4%)	5 (4%)
Pulmonary Edema	10 (5)	12 (6)	15 (4.7%)	5 (4%)
Pneumonia	10 (5)	11 (5.7)	13 (4.1%)	3 (2.4%)
Pulmonary Infiltration	13 (6.8)	4 (2%)	13 (4.1%)	-
Respiratory Disorder	7 (3.6%)	10 (5.2)	10 (3.1%)	3 (2.4%)
Pleural Effusion	6 (3%)	5 (2.6%)	7 (2.2%)	1 (0.8%)
Pneumonitis	5 (2.6%)	6 (3%)	9 (2.8%)	4 (3.2%)
Hemoptysis	4 (2%)	6 (3%)	8 (2.5%)	4 (3.2%)
Bronchospasm	3 (1.6%)	6 (3%)	6 (1.9%)	3 (2.4%)
CxR Abnormal	4 (2%)	5 (2.6%)	5 (1.6%)	1 (0.8%)
Respiratory Insufficiency	4 (2%)	5 (2.6%)	6 (1.9%)	2 (1.6%)
Hypoxia	5 (2.6%)	2 (1%)	8 (2.5)	2 (1.6%)
Pharyngitis	5 (2.6%)	3 (1.6%)	6 (1.9%)	1 (0.8%)
SKIN AND APPENDAGES DISORDERS	**56 (29%)**	**49 (25.5%)**	**76 (23.9%)**	**20 (15.9%)**
Rash	25 (13%)	15 (7.8%)	36 (11.3%)	11 (8.7%)
Rash Erythematous	13 (6.8%)	10 (5.2%)	14 (4.4%)	1 (0.8%)
Sweating Increased	11 (5.7%)	4 (2%)	14 (4.45%)	3 (2.4%)
Bullous Eruption	4 (2%)	2 (1%)	4 (1.3%)	-
Pruritus	7 (3.6%)	6 (3%)	8 (2.5%)	1 (0.8%)
Skin Disorder	4 (2%)	3 (1.6%)	4 (1.3%)	-

Skin Discoloration	1 (0.5%)	4 (2%)	1 (0.3%)	-
URINARY SYSTEM DISORDERS	**36 (18.8%)**	**49 (26%)**	**50 (15.7%)**	**14 (11.1%)**
Renal Function Abnormal	9 (4.7%)	24 (12.5%)	10 (3.15)	1 (0.8%)
Hematuria	8 (4.2%)	8 (4.2%)	10 (3.1%)	2 (1.6%)
Urine Abnormal	8 (4.2%)	2 (1%)	8 (2.5%)	-
Incontinence	5 (2.6%)	4 (2%)	6 (1.9%)	1 (0.8%)
Albuminuria	4 (2%)	1 (0.5%)	8 (2.5%)	4 (3.2%)
ARF	1 (0.5%)	4 (2%)	1 (0.3%)	-
PSYCHIATRIC DISORDERS	**43 (22%)**	**35 (18%)**	**56 (17.6%)**	**13 (10.3%)**
Confusion	10 (5.2%)	7 (3.6%)	12 (3.8%)	2 (1.6%)
Anxiety	9 (4.7%)	8 (4.2%)	13 (4.1%)	4 (3.2%)
Somnolence	5 (2.6%)	8 (4.2%)	5 (1.6%)	-
Insomnia	5 (2.6%)	7 (3.6%)	9 (2.8%)	4 (3.2%)
Hallucination	6 (3%)	5 (2.6%)	6 (1.9%)	-
Agitation	8 (4.2%)	1 (0.5%)	8 (2.5%)	-
Sleep disorder	4 (2%)	3 (1.6%)	4 (1.3%)	-
Anorexia	3 (1.6%)	3 (1.6%)	3 (0.9%)	-
Depression	3 (1.6%)	-	5 (1.6%)	2 (1.6%)
LIVER AND BILIARY SYSTEM DISORDERS	**35 (18%)**	**30 (16%)**	**44 (13.8%)**	**9 (7.1%)**
Bilirubinemia	19 (10%)	9 (4.7%)	23 (7.2%)	6 (3.2%)
Hepatic Function Abnormal	6 (3%)	9 (4.7%)	8 (2.5%)	2 (1.6%)
Jaundice	5 (2.6%)	6 (3%)	6 (1.9%)	1 (0.8%)
SGPT Increased	5 (2.6%)	3 (1.6%)	6 (1.9%)	1 (0.8%)
SGOT Increased	4 (2%)	1 (0.5%)	4 (1.3%)	1 (0.8%)
gGT Increased	4 (2%)	3 (1.6%)	6 (1.9%)	2 (1.6%)
CENTRAL & PERIPH. NERVOUS SYSTEM DISORDERS	**36 (19%)**	**25 (13%)**	**57 (17.9%)**	**21 (16.7%)**
Headache	13 (6.8%)	15 (7.8%)	25 (7.9%)	12 (9.5%)
Dizziness	9 (4.7%)	7 (3.6%)	10 (3.1%)	1 (0.8%)
Tremor	8 (4.2%)	3 (1.6%)	9 (2.8%)	1 (0.8%)
Convulsions	-	1 (0.5%)	3 (0.9%)	3 (2.4%)
CARDIOVASCULAR DISORDERS, GENERAL	**27 (14%)**	**32 (16.7%)**	**37 (11.6%)**	**10 (7.9%)**
Hypotension	13 (6.8%)	21 (11%)	17 (5.3%)	4 (3.2%)
Hypertension	4 (2%)	7 (3.6%)	7 (2.2%)	3 (2.4%)
Cardiac Failure	7 (3.6%)	2 (1%)	8 (2.5%)	1 (0.8%)
PLATELET, BLEEDING & CLOTTING DISORDERS	**19 (10)**	**23 (12)**	**21 (6.6%)**	**2 (1.6%))**
Epistaxis	9 (4.7%)	15 (8%)	11 (3.5%)	2 (1.6%)

Purpura	6 (3%)	6 (3%)	6 (1.9%)	-
RESISTANCE MECHANISM DISORDERS	**20 (10%)**	**23 (12%)**	**19 (12.3%)**	**19 (15.1%)**
Bacterial Infection	7 (3.6%)	3 (1.6%)	13 (4.1%)	6 (4.8%)
Sepsis	2 (1%)	8 (4.2%)	5 (1.6%)	3 (2.4%)
Herpes Simplex	5 (2.6%)	3 (1.6%)	11 (3.5%)	6 (4.8%)
Fungal Infection	1 (0.5%)	6 (3%)	8 (2.5%)	7 (5.6%)
HEART RATE AND RHYTHM DISORDERS	**12 (6.3%)**	**19 (10%)**	**13 (4.1%)**	**1 (0.8%)**
Tachycardia	6 (3%)	12 (6%)	6 (1.9%)	-
Atrial fibrillation	5 (2.6%)	3 (1.6%)	5 (1.6%)	-
VISION DISORDERS	**13 (6.8%)**	**15 (7.8%)**	**15 (4.7)**	**2 (1.6%)**
Conjunctivitis	4 (2%)	6 (3%)	5 (1.6%)	1 (0.8%)
Abnormal Vision	3 (1.6%)	4 (2%)	3 (0.9%)	-
APPLICATION SITE DISORDERS	**10 (5.2%)**	**7 (3.6%)**	**28 (8.8)**	**18 (14.3%)**
Application Site reaction	7 (3.6%)	6 (3%)	23 (7.2%)	16 (12.7%)
Injection Site Inflammation	3 (1.6%)	-	4 (1.3%)	1 (0.8%)
VASCULAR	**6 (3%)**	**7 (3.6%)**	**19 (6%)**	**13 (10.3%)**
Vein disorders	-	-	9 (2.85)	9 (7.1%)
Flushing	4 (2%)	3 (1.6%)	4 (1.3%)	-
WHITE CELL DISORDERS	**4 (2%)**	**1 (0.5%)**	**17 (5.3%)**	**13 (9%)**
Granulocytopenia	3 (1.6%)	1 (0.5%)	13 (4.1%)	10 (6.9%)
No. (%) with any AE	**174 (90.6%)**	**182 (94.8%)**	**288 (90.6%)**	**114 (90.5%)**

GI events were the most commonly reported AEs both on the ITR arm of trial 62 as well as in the total ITR population and the uncontrolled trial subjects. The most commonly reported AE was diarrhea followed by nausea, vomiting, and abdominal pain. Such events are the most frequently reported with both ITR IV and PO. The incidence of diarrhea was higher on the AMP B arm of trial 62 (28%) versus the ITR arm (20%). There were no discontinuations dues to this AE.

The incidence of nausea was similar on both study arms of trial 62 (24% ITR versus 23% AMP B) and marginally higher that that seen for the overall ITR population (20%). 6/192 (3.1%) of the ITR patients as compared to 1/192 (0.5%) of the AMP B patients discontinued treatment because of this AE.

The incidence of AEs reported from the category of "Body as a Whole" was lower on the ITR arm (46.4%) as compared to the AMP B arm (62%) in study 62. The incidence of such events was similar for the overall ITR population as well as for the uncontrolled trial population. The reason for the difference seen between the AMP B arm and the ITR arm was due to the higher incidence of rigors reported by the AMP B patients (40.6% AMP B versus 10% ITR). 8/192 (4.2%) AMP B subjects discontinued treatment due to rigors.

Other events of note that occurred in this category were fever (6% ITR arm versus 10% AMP B arm versus 20% uncontrolled ITR). The reason for the higher incidence of fever in the uncontrolled population was unclear. Chest pain was reported with a higher frequency (8%) from the ITR trial 62 population as compared to 4.2% on the AMP B arm. None of the events reported were determined to be related to therapy and there were no treatment discontinuations due to this AE.

Events from the respiratory tract were reported with a higher frequency from the ITR arm of trial 62 (40%) versus 37% AMP B. The frequency of these events was higher than that reported in the uncontrolled trials (23.8%) and higher than that of the total ITR population (33.6%). Coughing and pulmonary infiltration were the 2 events reported more frequently in study 62 that appeared to lead to this difference. The incidence of both these events on the ITR arm of trial 62 (13% coughing and 7% pulmonary infiltration) was higher than that seen on the AMP B arm (5% and 2% respectively). There were no discontinuations due to these events.

Dyspnea was reported by 9% of ITR subjects in trial 62 as compared to 11.5% of AMP B subjects. This event was reported by 7% of the ITR uncontrolled subjects. In trial 62, 5/192 (2.6%) of AMP B subjects versus 6/192 (3%) of ITR subjects discontinued treatment due to this event. In 3 of the ITR subjects the event was determined to be severe and was determined to be of moderate severity in the remaining 3. In one of the moderate subjects the dyspnea was categorized as possibly related to treatment.

The frequency of metabolic and nutritional AEs was higher on the AMP B arm of trial 62 (59%) as compared to the ITR arm (34%). The incidence of such events in the uncontrolled ITR population was 10% and in the overall ITR population it was 25%. The etiology of the differences between the populations was due to the higher incidence of renal tubular acidosis and its sequelae in the AMP B population as well as to the higher incidence of renal dysfunction/failure (increased creatinine 26% AMP B versus 4.2% ITR).

Hypokalemia was the most frequently reported laboratory event on both trial 62 treatment arms (17.7% ITR versus 31.3%) AMP B). Hypokalemia has been associated with ITR previously. In all ITR subjects this event was determined to be of mild to moderate severity and there were no discontinuations due to this event.

Of the subjects with increased creatinine, 50 (26%) AMP B versus 8 (4.2%) ITR in trial 62, 24 of the AMP B subjects discontinued treatment as compared to 1 of the ITR subjects.

Other expected events consistent with the known AE profile of ITR that were reported in this category included hypocalcemia, hypomagnesemia, and increased alkaline phosphatase.

The incidence of AEs from the skin and appendages was 29% ITR versus 25.5% AMP B in trial 62 as compared with 16% ITR uncontrolled and 24% for the total ITR population. Rah was the most frequently reported event followed by the more specific erythematous rash. 1/192 (0.5%) AMP B subjects discontinued treatment due to this event as compared to 5/192 (2.6%) of ITR subjects in trial 62. In all 5 ITR subjects the event was determined to be possibly related to treatment and varied in severity from mild to severe.

Psychiatric events were reported from 22% ITR subjects versus 18% AMP B subjects in trial 62. The incidence of such events for the ITR uncontrolled population was 10% and for the overall ITR population 17.6%. Agitation was reported more frequently on the ITR trial 62 arm (4.2%) versus 0.5% on the AMP B arm and appeared to account for the difference in the reported incidence of such events. There were no discontinuations due to this event.

As expected, AEs from the urinary system including "renal function abnormal", were reported more frequently on the AMP B arm of trial 62 (12.5%) as compared to the ITR arm (4.7%). 18 of the 24 AMP B subjects reporting this event discontinued treatment as compared to 1 of 9 ITR subjects.

Acute renal failure was reported in 4 (2%) of AMP B subjects I trial 62 as compared to 1 (0.5%) ITR subjects. ARF was not reported in any uncontrolled ITR subjects.

Of note was the incidence of events reported from the liver and biliary systems. 18% of ITR subjects in trial 62 developed such events as compared to 16% of AMP B subjects. The incidence of these events was 7.1% in the uncontrolled ITR population and 13.8% for the total ITR population.

Bilirubinemia was the most frequently reported event occurring in 19/192 (10%) of ITR trial 62 subjects as compared to 9/192 (4.7%) of AMP B subjects. 3 of the ITR subjects discontinued treatment due to this event and in 2 of the subjects the event was determined to be severe and possibly related to treatment.

Increased SGOT was seen in 4 (2%) of ITR subjects in trail 62 as compared to 1 (0.5%) of the AMP B subjects. 2 of the ITR patients discontinued treatment due to this event and in both cases the event was determined to be possibly related to treatment.

From the cardiovascular system, the incidence of events was higher on the 32/192 (16.7%) AMP B arm as compared to the ITR arm (37/318 (11.6%). This difference was primarily due to the higher frequency of hypotension on the AMP B arm.

Application site disorders were reported most frequently from the uncontrolled ITR subjects (14%) as compared to 5% ITR trial 62 subjects and 3.6% AMP B subjects. As noted in the MOR of NDA 20-966, most events were reported from a US site in trial USA-113. The applicant is postulating that such events were due to the narrow ratio of ITR to cyclodextrin in normal saline that can lead to precipitation.

The overall incidence of any reported AE was similar between the ITR (90.6%) and AMP B (95%) arms of trial 62 although more events were reported on the AMP B arm. The overall incidence of events on the ITR arm of trial 62 was similar to that reported from the ITR uncontrolled trials population (90.5%).

AEs (possibly and definitely) Related to Treatment in IV to PO ITR subjects:

The incidence of drug related AEs for ALL ITR subjects was 563/1186 (47.5%). This was comparable to the incidence of drug related AE on the ITR arm in trial 62 (87/192, 45.3%) as well as to the incidence of the All IV to PO ITR (Group 1) category (159/318, 50%). Presented in the table below are all drug related AEs for ≥ 1% of IV to PO ITR subjects.

Table 36

AEs (possibly and definitely) Related to Treatment in ≥ 1% IV to PO ITR subjects

ADVERSE EVENT	ITR N= 192 (100%)	AMP B N = 192 (100%)	ALL Group 1 N= 318 (100%)	All ITR Uncont'ed N = 126 (100%)
Total # with a related AE	**87 (45.3%)**	**157 (81.8%)**	**159 (50%)**	**72 (57.1%)**
GASTRO-INTESTINAL SYSTEM	**40 (20.8%)**	**48 (25%)**	**72 (22.6%)**	**32 (25.4%)**
Diarrhea	19 (10%)	17 (8.9%)	39 (12.3%)	20 (15.9%)
Nausea	21 (10.9%)	29 (15.1%)	34 (10.7%)	13 (10.3%)
Vomiting	13 (6.8%)	19 (10%)	16 (5%)	3 (2.4%)
Abdominal Pain	5 (2.6%)	6 (3.1%)	13 (4.1%)	8 (6.3%)
Constipation	3 (1.6%)	1 (0.5%)	4 (1.3%)	1 (0.8%)
BODY AS A WHOLE - GENERAL DISORDERS	**11 (5.7%)**	**76 (39.6%)**	**26 (8.2%)**	**15 (11.9%)**
Rigors	1 (0.5%)	65 (33.9%)	2 (0.6%)	1 (0.8%)
Fever	-	13 (6.8%)	5 (1.6%)	5 (4%)
Chest Pain	-	-	2 (0.6%)	2 (1.6%)
Edema	4 (2%)	4 (2%)	7 (2.2%)	3 (2.4%)
Edema Peripheral	1 (0.5%)	2 (1%)	2 (0.6%)	1 (0.8%)
Malaise	-	2 (1%)	-	-
Syncope	1 (0.5%)	-	3 (0.9%)	2 (1.6%)
Lab values abnormal	-	2 (1%)	1 (0.3%)	1 (0.8%)
METABOLIC AND NUTRITIONAL DISORDERS	**31 (16.1%)**	**86 (44.8%)**	**36 (11.3%)**	**5 (4%)**
Hypokalemia	18 (9.4%)	54 (28.1%)	18 (5.7%)	-
Creatinine Increased	5 (2.6%)	48 (25%)	7 (2.2%)	2 (1.6%)
Hypomagnesemia	3 (1.6%)	8 (4.2%)	4 (1.3%)	1 (0.8%)
Electrolyte Abnormality	-	2 (1%)	-	-
Fluid Overload	2 (1%)	5 (2.6%)	2 (0.6%)	-
BUN Increased	2 (1%)	12 (6.3%)	2 (0.6%)	-

Hyperglycemia	1 (0.5%)	1 (0.5%)	3 (0.9%)	2 (1.6%)
Enzyme Abnormality	-	2 (1%)	-	-
Alkaline Phosphatase Increased	4 (2%)	4 (2%)	4 (1.3%)	-
Hypophosphatemia	2 (1%)	3 (1.6%)	2 (0.6%)	-
LDH Increased	4 (2%)	-	5 (1.6%)	1 (0.8%)
Hypocalcemia	2 (1%)	4 (2%)	3 (0.9%)	1 (0.8%)
Acidosis	1 (0.5%)	2 (1%)	2 (0.6%)	1 (0.8%)
Glycosuria	-	-	2 (0.6%)	2 (1.6%)
RESPIRATORY SYSTEM DISORDERS	**5 (2.6%)**	**16 (8.3%)**	**9 (2.8%)**	**4 (3.2%)**
Dyspnea	2 (1%)	6 (3.1%)	3 (0.9%)	1 (0.8%)
Pulmonary Edema	1 (0.5%)	3 (1.6%)	1 (0.3%)	-
Pulmonary Infiltration	2 (1%)	-	2 (0.6%)	-
Respiratory Disorder	-	2 (1%)	1 (0.3%)	1 (0.8%)
Bronchospasm	1 (0.5%)	3 (1.6%)	1 (0.3%)	-
SKIN AND APPENDAGES DISORDERS	**16 (8.3%)**	**12 96.3%)**	**24 (7.5%)**	**8 (6.3%)**
Rash	9 (4.7%)	5 (2.6%)	15 (4.7%)	6 (4.8%)
Rash Erythematous	3 (1.6%)	1 (0.5%)	3 (0.9%)	-
Sweating Increased	4 (2%)	1 (0.5%)	4 (1.3%)	-
Pruritus	2 (1%)	2 (1%)	3 (0.9%)	1 (0.8%)
URINARY SYSTEM DISORDERS	**5 (2.6%)**	**31 (16.1%)**	**13 (4.1%)**	**8 (6.3%)**
Renal Function Abnormal	1 (0.5%)	22 (11.5%)	2 (0.6%)	1 (0.8%)
Albuminuria	1 (0.5%)	-	5 (1.6%)	4 (3.2%)
ARF	-	2 (1%)	-	-
Decreased CrCl	1 (0.5%)	2 (1%)	2 (0.6%)	1 (0.8%)
Toxic Nephropathy	-	3 (1.6%)	-	-
PSYCHIATRIC DISORDERS	**3 (1.6%)**	**9 (4.7%)**	**4 (1.3%)**	**1 (0.8%)**
Confusion	1 (0.5%)	3 (1.6%)	1 (0.3%)	-
Somnolence	1 (0.5%)	2 (1%)	1 (0.3%)	-
Anorexia	-	2 (1%)	-	-
LIVER AND BILIARY SYSTEM DISORDERS	**25 (13%)**	**15 (7.8%)**	**33 (10.4%)**	**8 (6.3%)**
Bilirubinemia	11 (5.7%)	6 (3.1%)	14 (4.4%)	3 (2.4%)
Hepatic Function Abnormal	5 (2.6%)	4 (2%)	7 (2.2%)	2 (1.6%)
Jaundice	4 (2%)	1 (0.5%)	5 (1.6%)	1 (0.8%)
SGPT Increased	5 (2.6%)	2 (1%)	6 (1.9%)	1 (0.8%)
SGOT Increased	4 (2%)	1 (0.5%)	4 (1.3%)	-
gGT Increased	2 (1%)	1 (0.5%)	4 (1.3%)	2 (1.6%)
Hepatomegaly	2 (1%)	1 (0.5%)	2 (0.6%)	-

CENTRAL & PERIPH. NERVOUS SYSTEM DISORDERS	**12 (6.3%)**	**8 (4.2%)**	**20 (6.3%)**	**8 (6.3%)**
Headache	4 (2%)	4 (2%)	9 (2.8%)	5 (4%)
Dizziness	2 (1%)	2 (1%)	3 (0.9%)	1 (0.8%)
Tremor	2 (1%)	1 (0.5%)	2 (0.6%)	-
CARDIOVASCULAR DISORDERS, GENERAL	**2 (1%)**	**13 (6.8%)**	**2 (0.6%)**	**0**
Hypotension	2 (1%)	6 (3.1%)	2 (0.6%)	-
Hypertension	-	4 (2.1%)	-	-
RBC DISORDERS	**0**	**0**	**4 (1.3%)**	**4 93.2%)**
Anemia	-	-	2 (0.6%)	2 (1.6%)
RESISTANCE MECHANISM DISORDERS	**0**	**2 (1%)**	**3 (0.9%)**	**3 (2.4%)**
Fungal Infection	-	1 (0.5%)	3 (0.9%)	3 (2.4%)
HEART RATE AND RHYTHM DISORDERS	**2 (1%)**	**8 (4.2%)**	**2 (0.6%)**	**0**
Tachycardia	2 (1%)	5 (2.6%)	2 (0.6%)	-
SPECIAL SENSES DISORDERS	**1 (0.5%)**	**2 (1%)**	**4 (1.3%)**	**3 (2.4%)**
Taste Perversion	1 (0.5%)	**1 (0.5%)**	4 (1.3%)	3 (2.4%)
APPLICATION SITE DISORDERS	**0**	**0**	**15 (4.7%)**	**15 (11.9%)**
Application Site reaction	-	-	15 (4.7%)	15 (11.9%)
VASCULAR	**1 (0.5%)**	**3 (1.6%)**	**11 (3.5%)**	**10 (7.9%)**
Vein disorders	-	-	9 (2.8%)	9 (7.1%)
Flushing	1 (0.5%)	3 (1.6%)	1 (0.3%)	-
WHITE CELL DISORDERS	**0**	**1 (0.5%)**	**7 (2.2%)**	**7 (5.6%)**
Granulocytopenia	-	-	7 (2.2%)	7 (5.6%)

As expected, the most frequent drug related AEs on the ITR arms were from the GI tract. The incidence of such events was lower on the ITR arm of trial 62 (21%) as compared to the AMP B arm (25%). However, the incidence of such events in the uncontrolled ITR group was 25.4%. The difference between the ITR groups could be attributed to the higher frequency of abdominal pain in the uncontrolled trials (8/126, 6.3%) as compared to the frequency in trial 62 (ITR 5/192 (2.6% versus AMP B 6/192 (3%). Nausea, vomiting, and diarrhea were the most frequently reported drug related AEs in all patient groups.

The most frequently reported drug related AEs on the AMP B arm of study 62 were from the body-as-a-whole (76/192, 39.6%) and metabolic/nutritional disorders (86/192, 44.8%). The frequency of these events was consistent with the AE profile of AMP B.

The frequency of related AEs from the body-as-a-whole from the ITR arm of trial 62 was 11/192 (5.7%) as compared to 15/126 (11.9%) for the uncontrolled ITR population and 26/318 (8.2%) for the All IV to PO ITR population. The AEs that primarily contributed to the difference in frequencies between the ITR and AMP B populations were rigors (AMP B 65/192, 33.9% versus ITR 1/192, 0.5%) and fever (AMP B 13/192 (6.8%) versus 0 ITR).

The frequency of metabolic/nutritional events on the ITR arm of trial 62 was 31/192 (16.1%) as compared to 5/126 (4%) from the uncontrolled ITR population and 36/318 (11.3%) from the total ITR IV to PO population.

The event most frequently attributed to treatment on both the ITR and AMP B arms of trial 62 was hypokalemia (18/192 ITR (9.4%) versus 54/192 (28.1%) AMP B). There were no occurrences of hypokalemia attributed to treatment from the uncontrolled ITR patients. Hypokalemia is an AE known to be associated with both ITR and AMP B. The other AE in this category that contributed to the difference in the frequency of drug related AEs was increased creatinine (AMP B 48/192 (25%) versus ITR 5/192 (2.6%). A difference was also noted between the treatment arms for increased BUN attributable to treatment (AMP B 12/192 (6.3%) versus ITR 2/192 (1%).

The incidence of other events reported as drug related in this category was similar between all groups. AEs attributed to treatment included hypocalcemia, hypomagnesemia, hypophosphatemia, and increases in alkaline phosphatase and LDH.

ITR subjects had a higher incidence of drug related AEs from the biliary system (25/192 (13%) in trial 62. The incidence of such events on the AMP B arm was 15/192 (7.8%). The incidence for the uncontrolled ITR population was 8/126 (6.3%) and for All IV to PO subjects it was 33/318 (10.4%). There were 11/192 (5.7%) ITR subjects in trial 62 with bilirubinemia attributed to treatment as compared to 6/192 (3%) on the AMP B arm. There were 3/126 (2.4%) subjects with bilirubinemia from the uncontrolled ITR trials. Similar differences were noted for jaundice 9ITR 4/192 (2%) as compared to AMP B 1/192 (0.5%).

Additionally, there was at least a 50% difference between the treatment arms in trial 62 with regards to drug related gGT, SGOT, and SGPT increases. All cases were reviewed and synopses can be found in the section of the MOR pertaining to trial 62.

ITR subjects in trial 62 had a higher incidence of rash (9/192 (4.7%) as compared to AMP B subjects (5/192 (2.6%). There were 6/126 (4.8%) reports of rash attributable to treatment from the uncontrolled ITR population. The incidence of rash for the all ITR IV to PO population was 15/318 (4.7%).

Psychiatric drug related AEs were reported more frequently on the AMP B arm (9/192 (4.7%) as compared to 3/192 (1.6%) ITR (trial 62) and 1/126 (0.8%) uncontrolled ITR. The incidence of such events for the all ITR IV to PO population was 9/318 (4.7%).

Confusion was more common on the AMP B arm and accounted for the difference in the frequency of such events.

Drug related urinary system AEs were more frequent on the AMP B arm (31/192 (16.1%) as compared to the ITR arm of trial 62 (5/192 (2.6%) and the uncontrolled ITR population 8/126 (6.3%). The incidence for such events for the all ITR IV to PO population was 13/318 (4.1%). Accounting for the difference between the populations was the high incidence of abnormal renal function on the AMP B arm in study 62. In the uncontrolled ITR population there were 4 subjects with albuminuria (3.2%) that led to an increased frequency of such events.

Cardiovascular disorders were attributed more frequently to treatment on the AMP B arm and application site disorders were attributed to treatment more frequently in the ITR uncontrolled population. Application site disorders attributed to treatment were not reported in trial 62 on either arm.

Adverse events by gender: IV followed by PO ITR (Group 1):

Table 37
Gender Breakdown of Group 1

Gender	All Group 1 N = 318 (100%)	ITR Trial 62 N = 192 (100%)	AMP B Trial 62 N = 192 (100%)	Uncontrolled ITR N = 126 (100%)
Male	213 (67%)	119 (62%)	110 (57%)	94 (75%)
Female	105 (33%)	73 (38%)	82 (43%)	32(25%)

Approximately two thirds of the group 1 subjects were male. Additionally, in trial 62 there were more males than females on both study arms with a greater difference on the ITR arm. In the uncontrolled group, males represented three quarters of the population.

AEs were more frequent in females than males. Specifically, 100/105 (95.2%) of all group 1 female subjects sustained AEs as compared to 188/213 (88.3%) male ITR subjects. This difference was noted on the ITR arm of trial 62 (ITR males with AE 106/119 (89%) versus ITR females 73/192 (93.2%) and in the uncontrolled ITR group (males with AE 82/94 (87%) versus females 32/32 (100%). This difference was not seen on the AMP B arm of trial 62 where similar numbers of males and females sustained AEs (males 104/110 (94.5%), females 78/82 (95%).
There did not appear to be a specific event leading to this difference in rates. Overall it appeared as if female subjects in the uncontrolled population sustained more GI events including diarrhea as well as an increased incidence of hypokalemia. This difference did not extend to the controlled trial 62 population.

Adverse events by Race (Group 1):

The 268/318 (84%) of subjects in the I.V. followed by oral itraconazole trials were white and 29/318 (9%) were black. 21/318 (7%) had race designated as "other". AEs were reported by 245/268 (91.4%) of white subjects and 20/21 (95.2%) of "other" subjects, compared with 23/29 (79.3%) of black subjects. Overall, black subjects sustained fewer AEs in all body systems without a specific AE difference found.

AEs by Age (Group 1):

The age range for Group 1 subjects was 17 years of age or greater. Pediatric subjects were not studied. 289/318 (91%) of subjects were between 17 and 64 years of age and 29/318 (9%) were ≥ 65.

AEs were reported in 288/318 (91%) of the total population as compared to 260/290 (90%) of subjects aged 17 – 64 and 28/29 (97%) of subjects ≥ 65. This difference extended to both components of the ITR population, trial 62 and the uncontrolled ITR group as well as to the AMP B arm. There did not appear to be a specific category of events accounting for this differential. A review of all AEs indicated that those subjects ≥ 65 had a greater incidence of hypokalemia (7/29 (24%) versus all ITR 29/318 (10%), fluid overload (4/29 (14%) versus 9/318 (3.1%), and hyperglycemia (3/29 (10%) versus 9/318 (3.1%). Similar differences did not exist for BUN and creatinine changes although under the generic category of "renal function abnormal" there were 3/29 (10%) of those ≥ 65 as compared to 7/318 (2.4%) of the remaining subjects.

In the category of metabolic and nutritional disorders, 6/29 (20%) of elderly subjects sustained bilirubinemia as compared to 17/318 (6%) of the younger population.

Similar differences were not noted for neuro-psychiatric events.

Table 38
Comparison of adverse events between age groups treated with itraconazole
As per the FDA

	Age from 17 to 64	Age > 64	p-value*
AEs reported	260/289 (90%)	28/29 (97%)	0.499
Hypokalemia	22/289 (8%)	7/29 (24%)	0.010
Fluid overload	5/289 (2%)	4/29 (14%)	0.005
Hyperglycemia	6/289 (2%)	3/29 (10%)	0.039
Renal function abnormal	4/289 (1%)	3/29 (10%)	0.019

*p-value is base on the two-sided Fisher's exact test.

Among the patients treated with itraconazole, elderly subjects (age ≥ 65) had statistically significantly higher rates of hypokalemia, fluid overload, hyperglycemia and renal function abnormal than the younger patients (age from 17 to 64). Similar differences were not observed between the younger and elder patients treated with amphotericin B.

Table 39
Comparison of adverse events between age groups treated with amphotericin B
As per the FDA

	Age from 17 to 64	Age > 64	p-value*
AEs reported	149/159 (93.7%)	33/33 (100%)	0.216
Hypokalemia	51/159 (32.1%)	9/33 (27.3%)	0.682
Fluid overload	11/159 (6.9%)	4/33 (12.1%)	0.296
Hyperglycemia	7/159 (4%)	2/33 (6.1%)	0.654
Renal function abnormal	20/159 (12.6%)	4/33 (12.1%)	1.000

*p-value is base on the two-sided Fisher's exact test.

As per the FDA statistician, among patients who were older than 64, the incidence rates of hypokalemia, fluid overload, hyperglycemia, and renal function abnormal in the two treatment groups were both similarly alarming. The incidence rates are lower in the younger group of itraconazole patients compared to the younger patients in the amphotericin B group. Due to the small denominator utilized in this analysis, statistically valid conclusions could not be drawn.

Conclusion regarding are-related differences:

Elderly patients in both treatment groups experienced similarly higher adverse event rates in hypokalemia, fluid overload, hyperglycemia, and renal function abnormal, while younger patients in the itraconazole group had lower rates of these adverse events compared to the younger patients in the amphotericin B group as well as to the older patients in either treatment group. Regarding the specific AEs of hyperkalemia, fluid overload, hyperglycemia and renal function abnormal, itraconazole was no more toxic than amphotericin B.

Serious AEs:
(For by trial listings of AEs and specific case histories, Please refer to the MO's safety review of each trial).

As per the applicant 120/1186 (10%) of subjects from the total database (All trials/All subjects) sustained serious AEs. A by study review by the MO found that 162/1186 (13.6%) of all ITR treated subjects sustained a serious AE as compared to 56/318 (17.6%) of group 1 subjects. Specifically for group 1, 32/192 (17%) ITR trial 62 subjects as compared to 46/192 (24%) AMP B subjects and 24/126 (19%) of uncontrolled trial ITR subjects sustained serious AEs.

Table 40
Cumulative Serious AEs Group 1

Serious AEs	Group 1 N = 318 (100%)	ITR Trial 62 N = 192 (100%)	AMP B Trial 62 N = 192 (100%)	ITR Uncontrolled N = 126 (100%)
# with Serious AE	**56 (17.6%)**	**32 (16.7%)**	**46 (24%)**	**24 (19%)**
GASTRO-INTESTINAL SYSTEM	**9 (2.8%)**	**3 (1.6%)**	**2 (1%)**	**6 (4.8%)**
Nausea	5 (1.6%)	2 (1%)	-	3 (2.4%)
Vomiting	3 (0.9%)	1 (0.5%)	-	2 (1.6%)
Constipation	2 (0.6%)	-	-	2 (1.6%)
Diarrhea	1 (0.3%)	-	-	1 (0.8%)
Enterocolitis	1 (0.3%)	1 (0.5%)	-	-
GI Hemorraghe	1 (0.3%)	-	-	1 (0.8%)
Abdominal Pain	-	-	1 (0.5%)	-
Bloody diarrhea	-	-	1 (0.5%)	-
BODY AS A WHOLE – GENERAL DISORDERS	**15 (4.7%)**	**7 (3.6%)**	**9 (4.7%)**	**8 (6.3%)**
Condition Aggravated	6 (1.9%)	2 (1%)	6 (3.1%)	4 (3.2%)
Fever	6 (1.9%)	3 (1.6%)	1 (0.5%)	3 (2.4%)
Asthenia	2 (0.6%)	2 (1%)	-	-
Rigors	2 (0.6%)	-	-	2 (1.6%)
Drug Interaction	1 (0.3%)	1 (0.5%)	-	-
Pain	1 (0.3%)	-	-	1 (0.8%)
Enlarged Abdomen	-	-	1 (0.5%)	-
Hyperpyrexia	-	-	1 (0.5%)	-
Injury	-	-	1 (0.5%)	-
METABOLIC AND NUTRITIONAL DISORDERS	**4 (1.3%)**	**3 (1.6%)**	**5 (2.6%)**	**1 (0.8%)**
Hypernatremia	2 (0.6%)	2 (1%)	-	-
CPK Increased	1 (0.3%)	1 (0.5%)	-	-
Dehydration	1 (0.3%)	1 (0.5%)	-	-
Hyperglycemia	1 (0.3%)	1 (0.5%)	-	-
Xerophthalmia	1 (0.3%)	-	-	1 (0.8%)
Hyperkalemia	-	-	1 (0.5%)	-
Creatinine Increased	-	-	4 (2.1%)	-
RESPIRATORY SYSTEM DISORDERS	**34 (10.7%)**	**22 (11.5%)**	**19 (9.9%)**	**12 (9.5%)**
Dyspnea	10 (3.1%)	6 (3.1%)	7 (3.6%)	4 (3.2%)
Pneumonia	6 (1.9%)	4 (2.1%)	3 (1.6%)	2 (1.6%)
Respiratory Insufficiency	6 (1.9%)	4 (2.1%)	3 (1.6%)	2 (1.6%)
Hypoxia	5 (1.6%)	4 (2.1%)	2 (1%)	1 (0.8%)

Pneumonitis	4 (1.3%)	1 (0.5%)	1 (0.5%)	3 (2.4%)
Pulmonary Infiltration	3 (0.9%)	3 (1.6%)	-	-
Pulmonary Edema	3 (0.9%)	3 (1.6%)	1 (0.5%)	-
Abnormal CxR	2 (0.6%)	1 (0.5%)	-	1 (0.8%)
Coughing	2 (0.6%)	1 (0.5%)	-	1 (0.8%)
Hemoptysis	2 (0.6%)	-	1 (0.5%)	2 (1.6%)
Respiratory Disorder	2 (0.6%)	1 (0.5%)	1 (0.5%)	1 (0.8%)
Pneumothorax	1 (0.3%)	-	-	1 (0.8%)
Respiratory Depression	1 (0.3%)	-	1 (0.5%)	1 (0.8%)
Bronchospasm	-	-	1 (0.5%)	-
Pulmonary Hemorraghe	-	-	1 (0.5%)	-
Sinusitis		-	1 (0.5%)	-
SKIN AND APPENDAGES DISORDERS	**2 (0.6%)**	**0**	**1 (0.5%)**	**2 (1.6%)**
Rash	1 (0.3%)	-	-	1 (0.8%)
Rash Maculopapular	1 (0.3%)	-	-	1 (0.8%)
Sweating Increased	-	-	1 (0.5%)	-
URINARY SYSTEM DISORDERS	**2 (0.6%)**	**2 (1%)**	**11 (5.7%)**	**0**
ARF	1 (0.3%)	1 (0.5%)	3 (1.6%)	-
Renal Function Abnormal	1 (0.3%)	1 (0.5%)	8 (4.2%)	-
Oliguria	-	-	1 (0.5%)	-
PSYCHIATRIC DISORDERS	**4 (1.3%)**	**2 (1%)**	**1 (0.5%)**	**2 (1.6%)**
Confusion	3 (0.9%)	2 (1%)	-	1 (0.8%)
Hallucination	1 (0.3%)	1 (0.5%)	-	-
Suicide Attempt	1 (0.3%)	-	-	1 (0.8%)
Somnolence	-	-	1 (0.5%)	-
LIVER AND BILIARY SYSTEM DISORDERS	**8 (2.5%)**	**6 (3.1%)**	**2 (1%)**	**2 (1.6%)**
Bilirubinemia	4 (1.3%)	3 (1.6%)	2 (1%)	1 (0.8%)
Hepatic Function Abnormal	3 (0.9%)	2 (1%)	-	1 (0.8%)
Hepatic Enzymes Increased	1 (0.3%)	1 (0.5%)	-	-
Hepatic Failure	1 (0.3%)	-	-	1 (0.8%)
Hepatocellular Damage	1 (0.3%)	1 (0.5%)	-	-
Jaundice	1 (0.3%)	1 (0.5%)	-	-
SGOT Increased	1 (0.3%)	1 (0.5%)	-	-
SGPT Increased	1 (0.3%)	1 (0.5%)	-	-
CENTRAL & PERIPH. NERVOUS SYSTEM DISORDERS	**3 (0.9%)**	**0**	**2 (1%)**	**3 (2.4%)**

Coma	1 (0.3%)	-	-	1 (0.8%)
Convulsions	1 (0.3%)	-	1 (0.5%)	1 (0.8%)
Encephalopathy	1 (0.3%)	-	1 (0.5%)	1 (0.8%)
Gait Abnormal	1 (0.3%)	-	-	1 (0.8%)
Hypokinesia	1 (0.3%)	-	-	1 (0.8%)
CARDIOVASCULAR DISORDERS, GENERAL	**8 (2.5%)**	**4 (2.1%)**	**2 (1%)**	**2 (1.6%)**
Cardiac Failure	4 (1.3%)	3 (1.6%)	-	1 (0.8%)
Circulatory Failure	3 (0.9%)	1 (0.5%)	1 (0.5%)	2 (1.6%)
Hypotension	2 (0.6%)	1 (0.5%)	6 (3.1%)	1 (0.8%)
RBC DISORDERS	**1 (0.3%)**	**1 (0.5%)**	**0**	**0**
Spleen Disorder	1 (0.3%)	1 (0.5%)	-	-
RESISTANCE MECHANISM DISORDERS	**12 (3.8%)**	**4 (2.1%)**	**9 (4.7%)**	**8 (6.3%)**
Fungal Infection	4 (1.3%)	1 (0.5%)	2 (1%)	3 (2.4%)
Sepsis	4 (1.3%)	2 (1%)	6 (3.1%)	2 (1.6%)
Bacterial Infection	3 (0.9%)	-	-	3 (2.4%)
Herpes simplex	1 (0.3%)	-	-	1 (0.8%)
Infection	1 (0.3%)	1 (0.5%)	-	-
Moniliasis	-	-	2 (1%)	-
HEART RATE AND RHYTHM DISORDERS	**3 (0.9%)**	**2 (1%)**	**3 (1.6%)**	**1 (0.8%)**
Atrial fibrillation	2 (0.6%)	2 (1%)	-	-
Arrythmia	1 (0.3%)	-	-	1 (0.8%)
Cardiac Arrest	-	-	2 (1%)	-
Tachycardia	-	-	2 (1%)	-
VISISON DISORDERS	**2 (0.6%)**	**2 (1%)**	**0**	**0**
Mydriasis	1 (0.3%)	1 (0.5%)	-	-
Vision Abnormal	1 (0.3%)	1 (0.5%)	-	-
APPLICATION SITE DISORDERS	**1 (0.3%)**	**0**	**0**	**1 (0.8%)**
Application Site reaction	1 (0.3%)	-	-	1 (0.8%)
VASCULAR	**3 (0.9%)**	**2 (1%)**	**2 (1%)**	**1 (0.8%)**
Cerebral Hemorraghe	1 (0.3%)	2 (1%)	-	-
CVA	1 (0.3%)	-	1 (0.5%)	-
Thrombophlebitis Leg	1 (0.3%)	-	-	1 (0.8%)
Thrombophlebitis	-	-	1 (0.5%)	-
PLATELET DISORDERS	**1 (0.3%)**	**1 (0.5%)**	**0**	**0**
Thrombocytopenia	1 (0.3%)	1 (0.5%)	-	-
MYOCARDIAL DISORDERS	**1 (0.3%)**	**0**	**0**	**1 (0.8%)**

Infarction	1 (0.3%)	-	-	1 (0.8%)
SECONDARY TERMS	**1 (0.3%)**	**1 (0.5%)**	**0**	**0**
Medication Error	1 (0.3%)	1 (0.5%)	-	-

Premature discontinuations:

The incidence of premature discontinuation for any reason was lower for the total itraconazole population (143/318, 45%) than for the amphotericin B subjects (119/192, 62%), as was the incidence of premature discontinuation due to an adverse event (total itraconazole: 66/318 (20.8%); amphotericin B: 73/192 (38%). When only controlled trial subjects were assessed, the incidence of premature discontinuation remained higher on the AMP B arm 119/192 (62%) as compared to the ITR arm 104/192 (54%). However, the difference was more extreme when discontinuations due to an AE were assessed (ITR 36/192 (18.8%) versus AMP B 73/192 (38%). As noted in the efficacy review, more ITR patients discontinued treatment due to insufficient response as compared to the AMP B subjects where the primary reason for discontinuation was an AE.

Table41
Cumulative Premature Discontinuations Group 1

	All ITR	**ITR**	**AMP B**	**Uncontrolled ITR**
Total	N = 318 (100%)	N = 192 (100%)	N = 192 (100%)	N = 126 (100%)
Completed	175 (55%)	88 (46%)	73 (38%)	87 (69%)
Discontinued	143 (45%)	104 (54%)	119 (62%)	39 (31%)
Discontinued for AE	66 (21%)	36 (19%)	73 (38%)	30 (24%)

For the ALL ITR population, the most common AEs leading to premature discontinuation were coded to the respiratory (41/318 (12.9%), gastrointestinal (29/318 (12.3%), and body-as-a-whole (38/318 (11.9%) categories. Dyspnea, nausea, diarrhea, vomiting, fever, and edema were the most frequently reported events.

The subjects receiving amphotericin B had a higher incidence of premature discontinuations due to metabolic/nutritional disorders (43/192 (22.4%) and urinary system disorders (27/192 (14.1%), compared with itraconazole subjects, and the adverse events most frequently reported were rigors, hypokalemia, increased BUN and abnormal renal function.

Liver and biliary system disorders were a cause of premature discontinuation in 15/318 (4.7%) of ALL ITR subjects as compared to 9/192 (4.7%) AMP B subjects in trial 62 (ITR trial 62: 13/192 (6.8%), uncontrolled ITR: 2/126 (1.6%).

DEATHS:
All deaths and summaries were reviewed previously and can be found in the MOR of each study).

The total number of deaths during trial 62 was 19/192 (10%) in the itraconazole group and 27/192 (14%) in the amphotericin B group. 16 of the ITR deaths and 23 of the AMP

B deaths occurred during the treatment period. Of these, all but two amphotericin B subjects were included in the survival analysis. All death summaries can be found in the Appendix to the MOR of NDA 20,966 (pp. 72 – 74). The MO concluded that none of the deaths on either study arm were related to study drug.

An additional 9 ITR deaths were reported from the remaining studies that constituted the uncontrolled portion of Group 1. Thus the total number of deaths for all group I subjects was 28/318 (0%). As above, no death appeared attributable to treatment.

Laboratory:

As noted previously, the most common laboratory abnormalities associated with ITR are hypokalemia, hyperbilirubinemia, increased transaminases, and hypocalcemia. The data provided by the sponsor in the SNDA under review was consistent with this profile.

Hematology: The assessment of the effect of ITR on any parameters in this category was difficult given the underlying disease processes of the subjects and the MO determined that the type of populations studied preclude an accurate assessment.

Regarding hemoglobin, 85% of ITR subjects entered the trial with an abnormal value. In the PK trial subjects (ITR-USA-113 and ITR-USA-127) with stable HIV infection, 4/62 (6.5%) of subjects developed and NIH grade II toxicity regarding hemoglobin values and none developed grade III. Overall it appeared as if ITR did not have a significant effect on hemoglobin levels.

Similar problems existed with an assessment of ITR effects on platelet counts where 75% of all IRR patients had abnormal platelet counts at study entry. Once again an assessment of only those subjects with stable HIV disease revealed that 11.7%) of the subjects entered the trials with thrombocytopenia. There appeared to be a trend towards lower counts during ITR administration with 6/58 (10.3%) of subjects with initially normal values decreasing to below normal by day 3 of ITR. The lowest value seen in this population was 113,000/mm^3 (normal range 130,000 – 400, 000/ mm^3.

Granulocytopenia/neutropenia was an entry criterion for trial 62 and as above, any effect of IV ITR on WBC counts was difficult. 31/80 ALL ITR subjects from the subgroup that had normal baseline values developed values that fell below normal during ITR treatment. In trial 62, similar percentages of ITR patients (14/16 (87.5%) and AMP B patients (18/21 (85.7%), fell into this category. From the uncontrolled population composed primarily of HIV patients, 17/64 (26.6%) fell into this group.

In summary any effect f ITR on hematologic parameters was difficult to assess in the populations studied.

Hypokalemia:

As stated above, hypokalemia is a known AE associated with both AMP B and with ITR. Hypokalemia was reported as an AE in 34/192 (17.7%) of ITR subjects and 60/192 (31.3%) of AMP b subjects in trail 62. 36/318 (11.3%) of ALL ITR subjects reported hypokalemia and 2/126 ITR uncontrolled subjects reported this event. This difference suggests that hypokalemia reported during trial 62 may have been due to other causes on the ITR arm. In 18/192 (9.4%) ITR trial 62 subjects as compared to 54/192 (28.1%) of AMP B subjects, the AE was determined to be related to therapy. In none of the uncontrolled subjects did this occur and therefore the total number of hypokalemia events determined to be related to ITR in group I was 18/318 (5.7%). Of note, 3 of the AMP B subjects discontinued treatment due to hypokalemia as compared to none of the ITR subjects.

Hypocalcemia:

Hypocalcemia has also been associated with ITR and AMP B administration and was reported in 7/192 (3.6%) of trial 62 ITR subjects as compared to 8/192 (4.2%) of AMP B subjects, 3/126 (2.1%) of uncontrolled ITR subjects and 8/318 (2.5%) of all ITR subjects in group I. A larger proportion of AMP B subjects developed grade 3 NIH toxicity (26/153 (17%) as compared to 10/168 (6%) of ITR subjects in trial 62 or 6/124 (4.8%) of uncontrolled ITR subjects. This event was attributed to treatment in 2/192 (1%) of trial 62 ITR subjects as compared to 4/192 (4%) AMP B subjects and 1/126 (0.8%) of uncontrolled ITR subjects. The total number of reports of hypocalcemia attributable to treatment for group 1 was 3/318 (0.9%).

Phosphorus:

Hypophosphatemia was reported in 2/192 (1%) of ITR subjects as compared to 3/192 (1.6%) of AMP B trial 62 subjects and n none of the uncontrolled trial subjects (Total group 1 2/318 (0.6%). All reported cases were attributed to treatment. There were no discontinuations due to this event. A larger number of AMP B patients developed hyperphosphatemia with a shift from normal to above normal by the end of week 1 of 13.2%) as compared to 3/156 (1.9%) of ITR trial 62 subjects.

Glucose:

Hyperglycemia has been observed previously in ITR-treated populations and less frequently in AMP B-treated subjects. This event occurred in 6/192 (3%) ITR trial 62 subjects and 9/192 (4.7%) of AMP B subjects. Additionally it was reported in 6/126 (4.8%) of uncontrolled ITR subjects or 12/318 (3.8%) of all group 1 subjects. A relationship to treatment was determined in 1 subject each on ITR and AMP B (0.5%) in trial 62 and in 2/126 (1.6%) of uncontrolled trial ITR subjects (3/318 (0.9%) of group 1 ITR). None of the subjects prematurely discontinued treatment due to this event.

Uric Acid: there was no consistent or remarkable change in this parameter.

Albumin and total protein were expectedly low in the population studied.

Cholesterol and Triglycerides: No consistent changes were noted.

LFTs:
6/318 (1.9%) of all group 1 ITR subjects discontinued treatment prematurely due to LFT abnormalities including "abnormal hepatic function, increased gGT, increased ALT or AST, hepatocellular damage, hepatitis, and increased hepatic enzymes." In 4 the event was rated as "severe". Overall, 6/192 (3%) of trial 62 ITR subjects as compared to 9/192 (4.7%) of AMP B subjects reported abnormal hepatic function. An additional 2/126 (1.6%) of uncontrolled ITR subjects were reported, with a total group 1 reporting rate of 8/318 (2.5%). For ALT increases, 5/192 (2.6%) of trial 62 ITR patients were reported as compared to 3/192 (1.6%) of AMP B subjects and 1 /126 (0.9%) of uncontrolled ITR subjects or 6/318 (1.9%) of all group 1 ITR subjects. Similar numbers were reported for AST and gGT abnormalities and can be found in the preceding tables.

Increased alkaline phosphatase was reported in 9/192 (4.7%) of ITR trial 62 subjects, 5/192 (2.6%) AMP B subjects, and in none of the 126 uncontrolled ITR subjects (TOTAL Group 1 9/318 (2.8%).

The above were considered serious in only 1 ITR subject per event or 1/318 (0.3%).

Abnormal hepatic function attributed to therapy was documented in 5/192 (2.6%) of ITR subjects, 4/192 (2%) of AMP B subjects, 2 (1.6%) of uncontrolled ITR subjects, and 7/318 (2.2%) of all group 1 ITR subjects. For further attributions to treatment, see above table.

Bilirubin:

Increased bilirubin was reported in 19/192 (10%) of trial 62 ITR subjects, 9/192 (4.7%) AMP B subjects, 6/126 (3.2%) of uncontrolled ITR subjects, and 23/318 (7.2%) of all group 1 ITR subjects. This event was attributed to therapy in 11/192 (5.7%) of ITR trial 62 subjects, 6/192 (3.1%) AMP B subjects, 3/126 (2.4%) uncontrolled ITR subjects and 14/318 (4.4%) of all ITR subjects. 4 ITR subjects discontinued treatment prematurely due to this event as compared to 1 AMP B subject.

BUN and Creatinine:

Abnormalities associated with renal function have been primarily reported in subjects receiving AMP B treatment and the reported cases in this SNDA were consistent with that trend with 50/192 (26%) of AMP B subjects developing an increased creatinine and 15/192 (7.8%) an increased BUN as compared to 8/192 (4.2%) of ITR trial 62 subjects with increased creatinine and 4 (2%) with an increased BUN. 2/126 (1.6%) of uncontrolled ITR subjects developed an increased creatinine and 3 (2.1%) an increased

BUN. The total for group 1 ITR was10/318 (3.1%) with increased creatinine and 4/318 (1.3%) with increased BUN.

In 48/192 (25%) of AMP b subjects the increased creatinine was attributed to treatment as compared to 5/192 (2.6%) of trial 62 ITR subjects. Similarly attribution for BUN increased was found in 12/192 (6.3%) of AMP B subjects compared to 2 (1%) of ITR trial 62 subjects.

3/318 (0.9%) of all group 1 ITR subjects discontinued treatment due to abnormal renal function as compared to 42/192 (22%) of AMP B subjects.

ISS Conclusions:

The MO ISS primarily pertained to an ITR IV to PO safety database of 318 subjects, 192 from trial 62 and 126 from PK trials. The subjects from trial 62 were diagnosed with hematologic malignancies and were febrile and neutropenic at the time of enrollment. The PK study subjects were immunocompromised for a variety of reasons including invasive aspergillosis, AIDS, and ICU care. In all group 1 studies, subjects received the proposed for the indication of empiric therapy of febrile neutropenia regimen of IV itraconazole 200 mg IV BID for 2 days followed by 200 mg IV QD for up to 14 days followed by itraconazole oral solution 200 mg PO BID for a maximum duration of 28 days total. Only those subjects from ITR trial 60 received capsules as opposed to oral solution.

The sponsor also submitted data from 868 subjects treated with oral solution alone. Although these subjects had similar underlying conditions as those in group 1 (hematologic malignancies with resultant neutropenia), the MO elected not to include this group in the ISS and recommendations for the following reasons:

- Variability in dosing and duration of treatment regimens between the trials that compromised group 2 and their lack of comparability to the proposed IV to PO ITR regimen.

- Discrepancies in the analyses provided by the sponsor including omissions of whole studies in calculations of serious AEs or deaths.

- The adequacy of group 1 as a safety database in order to update the labels of both the IV and oral solution for the proposed indication.

Therefore, although the review occasionally refers to the complete database of 1186 subjects it was done merely to point out that the AE profile of group 1 subjects was comparable to that seen in previous itraconazole submissions.

Overall, the incidence of adverse events within the subjects treated with itraconazole was lower than that seen in the subjects treated with amphotericin B. The differentiation of AEs due to treatment as opposed to events due to the subjects underlying disease

processes and treatments was not always clear-cut however the AE profiles of both study drugs were consistent with those previously seen.

The two most common adverse events among ITR subjects were rash and gastrointestinal disorders and led to premature discontinuation from trial for some subjects.

Previously reported trials with all itraconazole formulations (IV, capsules, and oral solution) have revealed two laboratory abnormalities associated with itraconazole therapy: elevated liver function parameters and hypokalemia. These abnormalities, especially bilirubinemia, were seen within this itraconazole subject population as well, and led to premature discontinuation from trial for some subjects.

AEs were reported from 288/318 (90.6%) ITR patients and 182/192 (94.8%) AMP B patients. AEs on both arms were primarily from the GI tract or the body-as-a-whole.

Specifically, 168/318 (53%) of ITR subjects as compared to 115/192 (60%) of AMP B subjects had AEs from the GI tract including diarrhea (AMP B 53/192 (28%) versus ITR 66/318 (21%), nausea (AMP B 45/192 (23%) versus ITR 63/318 (20%), and vomiting (AMP B 40/192 (21%) versus ITR 47/318 (15%). Other GI events that occurred included abdominal pain, dyspepsia, and constipation.

AEs from the body-as-a-whole occurred in 141/318 (44.3%) ITR subjects as compared to 119/192 (62%) of AMP B subjects. The large difference in incidence of AEs of this category could be attributed to the higher incidence of rigors on the AMP B arm (78/192 (40.6%) AMP B versus 25/318 (7.9%) ITR).

AEs from the category of metabolic and nutritional disorders occurred in 78/318 (24.5%) ITR subjects versus 113/192 (59%) AMP B subjects. As expected abnormalities associated with renal dysfunction accounted for the large difference in the incidence of such events (hypokalemia (AMP B 60/192 (31.3%) versus ITR 36/318 (11.3%), creatinine increased in 10/318 (4%) ITR versus 50/192 (26%) AMP B).

The investigators considered one or more adverse events to be definitely drug-related in 9/192 (5%) itraconazole subjects and 103/192 (54%) amphotericin B subjects. The most frequently reported drug-related adverse events were rigors (0 versus 50 subjects), creatinine increased (0 versus 29 subjects), hypokalemia (1 versus 24 subjects), abnormal renal function (0 versus 12 subjects) and fever (0 versus 11 subjects). Nausea was the AE most frequently related to therapy in the ITR-treated patients (3 or 1.5%) vs. 1 (0.5%) AMP B).

As noted above, rash also occurred frequently on the ITR arm with an incidence of 36/318 (11.3%) versus 15/192 (7.8%) AMP B.

Possibly or definitely drug-related adverse events were noted in 159/318 (50%) itraconazole subjects and 157/192 (82%) amphotericin B subjects. GI events including nausea, vomiting, and diarrhea were the most frequent events possibly related to therapy on both study arms. Additionally, hypokalemia was found in 18/318 (6%) of ITR

subjects versus 54/192 (28%) of AMP B subjects. Other events possibly associated with treatment on the AMP B arm included rigors 65/192 (34%) versus ITR 2/318 (0.6%), increased creatinine 48/192 (25%) versus ITR 7/318 (2%), and abnormal renal function 22/192 (11.5%) versus ITR 2/318 (0.6%). On the ITR arm, bilirubinemia attributable to treatment was reported in 14/318 (4.4%) of patients as compared to 6/192 (3.1%) on the AMP B arm. Additionally, there were more reports of transaminase elevations, hepatitis, hepatomegaly, and cholestatic hepatitis on the ITR arm.

The total number of deaths was 19/192 (10%) in the itraconazole group and 27/192 (14%) in the amphotericin B group. 16 ITR deaths (8.3%) and 23/192 (12%) of the AMP B deaths occurred during the treatment phase or the immediate 14 days following treatment. The main causes of death were condition aggravated (two itraconazole subjects and nine amphotericin B subjects), pneumonia (five and four subjects, respectively), dyspnea (four subjects in each group) and respiratory insufficiency (three subjects in each group).

Apart from adverse events leading to death, other serious adverse events were reported in a total of 23/192 (12%) ITR subjects and 28/192 (14.6%) AMP B subjects. The most remarkable difference between the two groups was noted for abnormal renal function (1 ITR (0.5%) subject vs. 7/192 (3.6%) AMP B).

36 (19%) itraconazole subjects and 73 (38%) amphotericin B subjects discontinued treatment permanently because of adverse events. The most remarkable differences between the two groups were noted for creatinine increased (1 (0.5%) ITR subject and 24 (12.5%) AMP B subjects) and abnormal renal function (0 ITR and 16 (8.3%) subjects).

Gastrointestinal adverse events noted by toxicity grades were noted in 114 subjects (59%) in each group. The majority of these cases were rated as either grade 1 or grade 2 toxicity.

For clinical laboratory data, from baseline to end point, there was a tendency toward hyperchloremia, hyperphosphatemia, hypernatremia, hypoglycemia, hypokalemia, hypouricemia, and decreased BUN as well as increased liver function tests (alkaline phosphatase, lactate dehydrogenase, AST and ALT in the ITR group. In the amphotericin B group, there was a tendency towards hyperchloremia, hyperphosphatemia, hypernatremia, and hypokalemia. Additionally patients had increases in liver function tests (alkaline phosphatase, gGT, lactate dehydrogenase, AST and ALT) and a tendency towards an increase in renal function tests (blood urea nitrogen, urea, uric acid and creatinine). Renal toxicity was noted in 10 (5%) itraconazole subjects and 46 (24%) amphotericin B subjects.

The toxicities sustained by the patients in both study groups were expected given the well-known safety profiles of each agent. Overall, subjects on ITR had fewer dose or treatment limiting toxicities. AMP B-treated subjects experienced more severe adverse events, drug-related adverse events, and premature discontinuation of treatment due to adverse events. Adverse events that were reported more in the amphotericin B group

were rigors, hypokalemia, increased BUN, and abnormal renal function as evidenced by intergroup difference in renal toxicity. On the ITR arm, more patients developed bilirubinemia and LFT abnormalities.

In conclusion, the adverse event and laboratory data indicate that the proposed regimen (itraconazole I.V. injection followed by oral itraconazole solution) is safe for the empiric treatment of febrile neutropenic patients with suspected fungal infections, provided that the patients are hospitalized and/or closely monitored and promptly treated for adverse events and laboratory abnormalities.

Overall Conclusions and Recommendations:

SNDA 20-966 (S-004) and SNDA 20-657 (S-005) were submitted in order to obtain the indication of empiric therapy in febrile neutropenia for both the IV and oral solution formulations of itraconazole.

Imperative in the support of an application for this indication is that the applicant provide adequate evidence of antifungal activity of the compound under study. Itraconazole has demonstrated such activity versus *Histoplasma capsulatum, Blastomyces dermatitidis,* and *Aspergillus* spp. and the IV formulation is approved for the treatment of histoplasmosis, blastomycosis and as second line in patients with Aspergillosis. Additionally, the oral solution is currently approved for the treatment of oropharyngeal candidiasis. Based on previous applications, itraconazole has demonstrated clinical and *in vitro* activity versus the aforementioned pathogens.

As per FDA advisory committee recommendations, in order to obtain such an indication, the applicant should in addition to the demonstration of antifungal activity also demonstrate efficacy in the ETFN via one adequate and well-controlled study. The applicant has done so in this application by submitting the results of ITR-INT-62, a comparative trial of IV followed by PO itraconazole versus amphotericin B in febrile neutropenic patients.

In addition, an applicant must also demonstrate an adequate safety profile for the proposed regimen. The applicant has also met this requirement with a safety database of 318 subjects that received the proposed regimen. Of note, the safety database submitted by the applicant was compromised of 1186 subjects however, 318 actually received the proposed regimen. Although this database is smaller than that requested of other sponsors, itraconazole has a well-known safety profile that has been well studied since its initial approval (oral solution 3/96, IV 14/99, and capsules 9/92).

Regarding the need for alternative treatments for the indication of empiric therapy of febrile neutropenia, it is well established that patients with acute leukemia, patients undergoing bone marrow transplantation, and patients receiving cytotoxic chemotherapy are at substantial risk for developing systemic fungal infections during periods of neutropenia. Other risk factors that increase the susceptibly of such patients to invasive

fungal infections include the use of broad-spectrum antimicrobials as prophylaxis or empiric therapy, radiation therapy, and breaks of the cutaneous barriers due, for example, to central venous catheters utilized for the administration of chemotherapy, antimicrobial therapy and antifungal therapy. Additionally, it has been shown that the presence of superficial fungal infections such as oropharyngeal candidiasis lead to an increased risk of systemic candidal infections.

Diagnosis of fungal infections in these patient populations is difficult and delays in the institution of treatment may increase morbidity and mortality. Without treatment, mortality can exceed 90%. Therefore, the standard of care is to institute empiric therapy when these patients develop fever, which may be the only sign of infection. The most common pathogens causing systemic fungal infections in these patients are *Candida albicans* and *Aspergillus fumigatus*; any agent selected as empiric therapy should have as stated above *in vitro* activity against these organisms and proven clinical efficacy for treatment of established infections. At present amphotericin B remains the gold standard. Amongst the marketed azoles, fluconazole has not been proven effective in infections caused by *Aspergillus* spp. Of the marketed azoles, only itraconazole is active against *Aspergillus fumigatus.*

Other fungi have been increasingly recognized for their pathogenic role including *Trichosporon* spp., *Malassezia furfur*, agents of phaeohyphomycosis, *Fusarium* spp., and *Scedosporium* spp. No single antifungal agent, including amphotericin B, is active against all these organisms. Some, such as the dermatacious fungi of phaeohyphomycosis and *Scedosporium* are susceptible to itraconazole.

At present, the only antifungal agent approved for the empiric therapy of febrile neutropenia is the liposomal amphotericin B, AmBisome®. The approval was based on the submission of 3 comparative studies one of which was blinded. The applicant of the current submissions received verbal approval from the agency in 1996 that 1 comparative study would be adequate to support their application in light of the previous proven antifungal activity of itraconazole.

The primary benefits to the approval of the proposed itraconazole regimen are the lower toxicity and increased tolerability as compared to the conventional AMP B regimen. Additionally, there is the potential for increased outpatients use if patients stabilize.

ITR-INT-62, the pivotal trial on which an approval will be based was primarily compromised of adults diagnosed with hematologic malignancies with or without bone marrow transplantation. The efficacy assessment of response was based on a composite endpoint and required survival of the patient with resolution of fever and neutropenia within 28 days of treatment, the absence of EFIs, and no discontinuation due to toxicity or failure. Response was assessed in the ITT population (subjects who received 1 dose of study medication, met the inclusion/exclusion criteria, and who had follow-up information). As can be seen in the table below, itraconazole was non-inferior to amphotericin B in the ITT population.

Overview of Efficacy

Efficacy Parameters	ITR	AMP B	95% CI (FDA)
Response Rate ITT	84/179 (47%)	68/181 (38%)	- 1.4%, 20%, $\Delta = \pm 15$
Fever Resolution	131/179 (73%)	127/181 (70%)	- 6.8%, 12.9%, $\Delta = \pm 15$
Without EFI	169/179 (94%)	172/181 (95%)	- 5.8%, 4.5%, $\Delta = \pm 15$
Survival	161/179 (90%)	156/181 (86%)	- 3.5%, 11%, $\Delta = \pm 5$
No premature discontinuation due to toxicity	144/179 (80.4%)	111/181 (61.3%)	- 9.4%, 28.8%, $\Delta = \pm 15$

In an analysis performed by the FDA statistician, assessing response where those subjects who discontinued treatment due to an AE were excluded, amphotericin B-treated subjects had higher response rates (67/111 (60%) than those on the itraconazole arm (83/144 (58%). However, the difference was not statistically significant (95% CI -14.8%, 9.4% $\Delta = \pm 15$).

Overview of Outcome

	ITR N = 179	AMP B N = 181
Cure	84 (47%)	68 (38%)
Failure because unevaluable	24 (13%)	44 (24%)
Failure due to intolerance	12 (7%)	37 (20%)
Failure due to lack of efficacy	59 (33%)	32 (18%)

A larger number of itraconazole subjects (itraconazole 59/179 (33%) versus 32/181 (18%) of the amphotericin B patients). were assessed as failures due to lack of efficacy (including insufficient response, persistent fever, change in therapy due to fever, emergent fungal infections, deterioration of signs and symptoms, or death. However, a larger number of amphotericin B-treated subjects were assessed as failures due to toxicity (12/179 (7%) itraconazole versus 37/181 (20%) amphotericin B).

When patients were assessed by transplant status the response rate of the itraconazole-treated subjects was numerically similar to that of the AMP B-treated group but non-inferiority was not established. It should be noted however that the denominator in this analysis was too small to allow for statistically reliable conclusions. The opposite was shown for those subjects without a transplant where ITR was numerically superior to AMP B.

Efficacy in the ITT Transplant and Non-Transplant Populations

Transplant Status	Itraconazole	Amphotericin B	95% CI (Δ = ± 15%)
Response Rate with transplant	29/62 (46.7%)	28/58 (48.3%)	- 21%, 18%
Response Rate without transplant	55/117 (47%)	40/123 (32.5%)	1.4%, 27.6%

If success was assessed by use of antifungal prophylaxis (primarily azole derivatives), itraconazole was equivalent to the comparator in those subjects who had received prophylaxis but NOT in those who had not received it.

Success Rate by Antifungal Prophylaxis
ITT Population

Antifungal Prophylaxis	Itraconazole	Amphotericin B	95% CI (Δ = 15%)
YES	63/132 (48%)	48/139 (35%)	- 2%, 25%
NO	21/47 (45%)	20/42 (48%)	- 26%, 20%

Subgroup analyses of subjects at higher risk versus lower risk (due to ANC of < 100, duration of neutropenia > 7 days, duration of previous antibiotic therapy) revealed non-inferiority between the treatment arms with numerical superiority of itraconazole in many groups. However, the numbers of subjects analyzed was small due to the larger number of amphotericin B subjects who discontinued due to toxicity. Of note was the more prolonged duration of neutropenia in the ITR-treated patients (> 14 days). An explanation for this finding has not been found.

10 (6%) ITR-treated subjects as compared to 9 (5%) AMP B-treated subjects developed EFIs, primarily due to *Candida* or *Aspergillus* spp.

Survival was similar between the study arms (ITR death rate 19/187 (10%) versus 25/187 (13%) AMP B).

Regarding safety, subjects on both study arms exhibited known toxicities of the treatment agents including renal dysfunction on the amphotericin B arm and hepatic abnormalities on the itraconazole arm. Overall none of the events were unusual and the analyses of the laboratory data suggest that the risks of the proposed dosing regimen of itraconazole are less than those seen for amphotericin B.

Given the safety data submitted in this application, the efficacy profile of itraconazole, and the limited number of approved alternative treatments for the indication of empiric therapy of febrile neutropenia, a risk benefit analysis supports the dosing regimen of Sporanox® injection followed by oral therapy with Sporanox® oral solution as empiric therapy of suspected fungal infections in febrile neutropenic patients with hematologic malignancies.

Labeling recommendations for SNDAs 20-966 (S-004) and 20-657 (S-005):

The proposed **Indications and Usage** section should be modified by omission of the strikethrough text and by the addition of all underscored

INDICATIONS AND USAGE

SPORANOX®(itraconazole) Injection/Solution is [redacted] indicated for empiric therapy of febrile neutropenic patients with suspected fungal infections. [redacted]

The proposed **Clinical Studies** section should be modified by the omission of strikethrough text and the addition of all underscored and of the Overview of Efficacy table.

Description of Clinical Studies:
Empiric Therapy in Febrile Neutropenic Patients: [redacted] An open, randomized trial, compared the efficacy and safety of itraconazole (intravenous followed by oral solution) with intravenous amphotericin B for empiric therapy in 384 febrile, neutropenic patients with hematologic malignancies [redacted] who had suspected fungal infections. Patients received either itraconazole (injection, 200 mg BID for 2 days followed by 200 mg once daily for up to 14 days, followed by oral solution, 200 mg BID), or amphotericin B (total daily dose of 0.7-1.0 mg/kg body weight). [redacted]

emergent fungal infections, deterioration of signs and symptoms, or death). However, a larger number of amphotericin B-treated subjects were assessed as failures due to toxicity.

29% of the itraconazole-treated subjects as compared to 17% of the amphotericin B-treated subjects had prolonged duration of neutropenia (> 14 days) despite comparability between the groups at baseline. The significance of this finding is unknown.

The **ADVERSE REACTIONS** section should be modified by the omission of text with strikethrough and the addition of underscored text.

The **DOSAGE and ADMINSTRATION** section should be modified by the addition of the underscored:

Empiric Therapy in Febrile, Neutropenic Patients: The recommended dose of SPORANOX® Injection is 200 mg BID for four doses, followed by 200 mg once daily for up to 14 days. Each intravenous dose should be infused over 1 hour. Treatment should be continued with SPORANOX® Oral Solution 200 mg (20 mL) BID until resolution of the clinically significant neutropenia
1/31/01

APPEARS THIS WAY
ON ORIGINAL

RECOMMENDED REGULATORY ACTION:

The MO recommends approval of the IV itraconazole formulation itraconazole oral solution (20 mg/mL) for the empiric therapy of febrile neutropenia in febrile neutropenic subjects at a dose of 200 mg IV BID for 2 days followed by 200 mg IV QD for a maximum of 14 days.

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

Regina Alivisatos, MD
DSPIDP, HFD-590

Concurrence only:
HFD-590/DIVDir/MGoldberger

Cc:
Orig. NDA 20-966, NDA 20-657
HFD-590
HFD-590/DIVDir/RAlbrecht
HFD-590/MTL/BLeissa
HFD-590/CSO/KimeyR
HFD-725/Biostat/HigginsK
HFD-520/Biopharm/McMasterO
2/15/01

APPENDIX A:

DEATH SUMMARIES:

ITR-BEL- 4

ITR (N = 16):

#11:61-year old, Caucasian male patient entered the trial on 21MAR90. The patient was diagnosed with acute myeloid leukemia. No medical history was noted. 43 days after randomization and 8 days after the patient had dropped out, a serious adverse event occurred: the patient died suddenly, probably due to acute gastro-intestinal bleeding. The investigator considered the adverse event to be not drug-related.

#15:72-year old, Caucasian female patient entered the trial on 03MAR90. The patient was diagnosed with acute myeloid leukemia. No medical history was noted. There was a discontinuation of the trial medication from 02APR90 until 10APR90 (discontinued). On 29APR90, 57 days after randomization, 27 days after discontinuation of the treatment and 19 days after the patient had dropped out, a serious adverse event occurred: the patient died due to thrombocytopenia and infection. The investigator considered the adverse event to be not drug-related.

#37:42-year old, Caucasian male patient entered the trial on 18JUN90. The patient was diagnosed with a solid tumor and had had a bone marrow transplant. No medical history was noted. There was a discontinuation of the trial medication from 08JUL90 until 11JUL90 (discontinued). The patient stopped the trial on 11JUL90, i.e. 23 days after randomization and 3 days after discontinuation of the treatment, because of death; this was reported as a serious adverse event. The patient had developed severe veno-occlusive disease.

#72:49-year old, Caucasian female patient entered the trial on 19JUL91. The patient was diagnosed with acute myeloid leukemia. Medical history showed appendectomy. The patient stopped the trial on 28JUL91, i.e. 9 days after randomization, because of death; this was reported as a serious adverse event. The patient died after a relapse of leukemia and severe, acute cardiac decompensation (WHO preferred term: myocardial decompensation). The investigator considered the adverse event to be not drug-related.

#95: 70-year old, Caucasian female patient entered the trial on 12DEC90. The patient was diagnosed with acute myeloid leukemia. No medical history was noted. The patient stopped the trial on 16DEC90, i.e. 4 days after randomization, because of death; this was reported as a serious adverse event. The patient died after a fall; there was no cerebral lesion.

#103: 58-year old, Caucasian male patient entered the trial on 17NOV90. The patient was diagnosed with acute myeloid leukemia. No medical history was noted. On 15DEC90, 28 days after randomization and 21 days after the patient had dropped out due to inefficacy (suspicion of a disseminated deep fungal infection), a serious adverse event occurred: the patient died. The patient had developed *Aspergillus* pneumopathy (aspergillosis with acute pulmonary edema) and cardiac failure.

#142: 61-year old, Caucasian male patient entered the trial on 11JAN91. The patient was diagnosed with acute myeloid leukemia. No medical history was noted. There was a discontinuation of the trial medication from 22JAN91 until 23JAN91 (discontinued). The patient stopped the trial on 23JAN91, i.e. 12 days after randomization, because of both inefficacy (superficial fungal infection) and death (this was reported as a serious adverse event). The patient had developed an intracerebral bleeding due to thrombocytopenia resulting in paraplegia.

#177: 67-year old, Caucasian female patient entered the trial on 26NOV93. The patient was diagnosed with acute lymphatic leukemia. Medical history showed appendectomy, ovarian cyst. The patient stopped the trial on 06DEC93, i.e. 10 days after randomization, because of death; this was reported as a serious adverse event. The patient had developed a cerebral hemorrhage.

#246: 37-year old, Caucasian male patient entered the trial on 30SEP91. The patient was diagnosed with acute lymphatic leukemia. Medical history showed a bone marrow transplant in 1988. There was a discontinuation of the trial medication from 12OCT91 until 13OCT91 (discontinued), because of a superficial fungal infection; on 13OCT91, the patient dropped out of the trial because of the same reason, i.e., inefficacy. On 26OCT91, 26 days after randomization, a serious adverse event occurred: the patient had a cerebral hemorrhage and died.

#274: 76-year old, Caucasian male patient entered the trial on 11JAN92. The patient was diagnosed with acute myeloid leukemia. No medical history was noted. On 11JAN92, the day of randomization, a serious adverse event occurred: the patient had developed dyspnea (respiratory distress; no further details available); the patient died on 09FEB92, 29 days after randomization, due to a septic shock, pneumopathy and respiratory distress.

#288: 21-year old, Hispanic male patient entered the trial on 09APR92. The patient was diagnosed with acute myeloid leukemia. No medical history was noted. On 14APR92, five days after randomization and one day after the patient had dropped out due to inefficacy (deep fungal infection), a serious adverse event occurred: the patient had developed an acute respiratory disease and died.

#292:41-year old, Caucasian male patient entered the trial on 05MAY92. The patient was diagnosed with acute myeloid leukemia. No medical history was

noted. There was a discontinuation of the trial medication from 21MAY92 until 25MAY92 (discontinued) because of inefficacy (deep fungal infection). The patient stopped the trial on 25MAY92, i.e. 20 days after randomization, because of both inefficacy (deep fungal infection) and death (reported as a serious adverse event). Chest X-ray revealed bilateral lung infiltrates (hypervolaemia *vs* infection) and bibasal lung congestion; the patient also suffered from fever and dyspnea. Death was probably due to either intestinal hemorrhage or myocardial infarction.

#293: 47-year old, Caucasian female patient entered the trial on 15MAY92.The patient was diagnosed with acute myeloid leukemia. Medical history showed bilateral pneumonia. There was a discontinuation of the trial medication from 17MAY92 until 07JUN92 (discontinued) and the patient stopped the trial on 07JUN92, both because of ineligibility (the patient was febrile at trial entry, with a history of bilateral pneumonia possibly of fungal etiology; a high risk of relapse of fungal infection justified prophylactic amphotericin B administration). On 10JUN92, 26 days after randomization and three days after the patient had dropped out of the trial, a serious adverse event occurred: the patient died of progression of leukemia.

#298: 33-year old, Caucasian male patient entered the trial on 01JUN92. The patient was diagnosed with acute myeloid leukemia. No medical history was noted. There was a discontinuation of the trial medication from 10JUN92 until 14JUN92 (discontinued) and the patient stopped the trial on 14JUN92, both because of inefficacy (deep fungal infection). On 15JUN92, 14 days after randomization and one day after the patient had dropped out, a serious adverse event occurred: the patient died. The patient experienced pulmonary hemorrhage; an acute respiratory disease seemed to be the cause of death.

#310: 57-year old, Caucasian female patient entered the trial on 17AUG92. The patient had had a bone marrow transplant. No medical history was noted. The patient interrupted the intake of the trial medication from 22AUG92 to 24AUG92 and from 28AUG92 to 29AUG92 (interruption), because of vomiting. The patient stopped the trial on 03SEP92 because of inefficacy (deep fungal infection). On 30SEP92, 44 days after randomization and 27 days after the patient had dropped out, a serious adverse event occurred: the patient died. The patient had developed a *Candida* infection (hepato-splenic).

#356: 68-year old, Caucasian female patient entered the trial on 13NOV92. The patient was diagnosed with acute myeloid leukemia. No medical history was noted. There was a discontinuation of the trial medication from 19NOV92 until 22NOV92 (discontinued), i.e., the patient permanently stopped the intake of the trial medication on 19NOV92, 6 days after randomization, because of both severe pulmonary edema and condition aggravated (both continuous); the investigator considered the adverse events to be not drug-related. She stopped the trial on 22NOV92, i.e., 9 days after randomization, because of death

(reported as a serious adverse event). The patient died due to multiple organ failure.

AMP B/Nystatin (N = 11):

#141: 70-year old, Caucasian male patient entered the trial on 11JAN91. The patient was diagnosed with acute myeloid leukemia. No medical history was noted. On 28JAN91, 17 days after randomization, a serious adverse event occurred: the patient died. The patient had developed pneumonia due to multiresistant *Staphylococcus spp.* (non-aureus).

#148: 78-year old, Caucasian female patient entered the trial on 09MAR91. The patient was diagnosed with acute myeloid leukemia. No medical history was noted. The patient stopped the trial on 14MAR91, i.e. 5 days after randomization, because of death; this was reported as a serious adverse event. The patient died of primary disease (acute myeloid leukemia).

#153: 54-year old, Caucasian female patient entered the trial on 17MAY91. The patient was diagnosed with acute lymphatic leukemia. No medical history was noted. The patient stopped the trial on 19JUN91, i.e. 33 days after randomization, because of death; this was reported as a serious adverse event. The patient had developed neurological problems due to chemotherapy, and died due to a cerebrovascular disorder (intracranial hemorrhage). The investigator considered the adverse event to be not drug-related.

#174: 65-year old, Caucasian male patient entered the trial on 19JUL93. The patient was diagnosed with acute myeloid leukemia. No medical history was noted. On 22AUG93, 34 days after randomization, a serious adverse event occurred: the patient died. The patient had developed pulmonary infiltration (RX thorax). The patient was ventilated for a short time for respiratory insufficiency. The trial medication was discontinued and was changed to fluconazole and amphotericin B, but with the sustained neutropenia, the patient developed more pulmonary infiltrates and died from respiratory insufficiency.

#203: 60-year old, Caucasian male patient entered the trial on 13AUG91. The patient was diagnosed with acute myeloid leukemia. No medical history was noted. There was a discontinuation of the trial medication from 21AUG91 until 22AUG91 (discontinued), i.e. the patient permanently stopped the intake of the trial medication on 21AUG91, and stopped the trial on 22AUG91, 8 days after randomization, because he was unable to swallow. On 28AUG91, 15 days after randomization, and 6 days after the patient had dropped out, a serious adverse event occurred: the patient died after septicemia due to *Candida*. The investigator considered the adverse event to be not drug-related.

#219: 77-year old, Caucasian male patient entered the trial on 12DEC91. The patient was diagnosed with acute myeloid leukemia. No medical history was

noted. From 12DEC91 to 30DEC91, the patient did not take the trial medication as described in the protocol (irregular intake); on 30DEC91, the patient stopped the trial (inefficacy). On 05JAN92, 24 days after randomization and 6 days after the patient had dropped out, the following serious adverse events were reported: abscess (bacterial; groin), and *Candida* septicemia; the patient died. The investigator considered the adverse events to be not drug-related.

#263: 69-year old, Caucasian female patient entered the trial on 09JAN92. The patient was diagnosed with acute myeloid leukemia. No medical history was noted. The patient stopped the trial on 23JAN92, i.e., 14 days after randomization, because of a serious adverse event: death. The patient had developed septicemia with *Pseudomonas aeruginosa.*

#289: 48-year old, Caucasian male patient entered the trial on 15APR92. The patient was diagnosed with acute myeloid leukemia. No medical history was noted. There was a discontinuation of the trial medication from 27APR92 until 26MAY92 (discontinued), i.e., the patient permanently stopped the intake of the trial medication on 27APR92 and he stopped the trial on 26MAY92 because of inefficacy (deep fungal infection). On 28MAY92, 43 days after randomization and two days after the patient had dropped out, a serious adverse event occurred: the patient died. He died with sepsis syndrome and multi-organ failure (acute respiratory disease, renal insufficiency, ...) and had persistent blastosis.

#300: 44-year old, Caucasian male patient entered the trial on 13JUN92. The patient was diagnosed with acute myeloid leukemia. No medical history was noted. There was a discontinuation of the nystatin treatment (mouthwash solution, permanently stopped) from 17JUN92 until 07AUG92 (discontinued), because of moderate nausea (intermittent); the investigator considered the adverse event to be possibly drug-related. The patient recovered without residual effects. There was a discontinuation of the amphotericin B treatment (capsules, permanently stopped) from 27JUN92 until 07AUG92 (discontinued), because of inefficacy (deep fungal infection). The patient stopped the trial on 07AUG92, i.e. 55 days after randomization), because of both inefficacy (deep fungal infection) and death (reported as a serious adverse event). The patient had developed septicemia due to *Serratia marcescens.*

#363: 68-year old, Caucasian male patient entered the trial on 30JUL93. The patient was diagnosed with acute myeloid leukemia. Medical history showed gastrectomy (Billroth II) 1975, resection epididymis 1989. There was a discontinuation of the trial medication from 04AUG93 until 09AUG93 (discontinued), i.e., the patient permanently stopped the intake of the trial medication on 04AUG93, i.e. 5 days after randomization, because of adverse experiences: pulmonary hemorrhage, septicemia and pulmonary edema (all severe and continuous); these adverse events resulted in the patient's death (serious adverse event) on 09AUG93 (drop-out date). The patient had also developed an abnormal renal function.

#373: 65-year old, Caucasian male patient entered the trial on 28JAN93. The patient was diagnosed with acute myeloid leukemia. No medical history was noted. The patient stopped the trial on 12FEB93, i.e., 15 days after randomization, because of both inefficacy (deep fungal infection) and death (reported as a serious adverse event). The patient had developed *Candida* stomatitis and severe, continuous *Candida* pneumonia. The investigator considered the pneumonia to be not drug-related.

ITR-GBR-17:

Fluconazole (N = 20):

#0105: 14 year old male with acute lymphoblastic leukemia was entered into the trial on the 24th January 1994 in error as he was below the minimum age. One dose of fluconazole was administered before the error was noted at which point the patient was withdrawn from the study as a protocol violator. The patient subsequently died the same day of probable cardiac arrest associated with tumor lysis syndrome. No comment was made on the association with the trial medication.

#0106: 69 year old male with acute myeloid leukemia entered the trial on 19th September 1994. He received fluconazole 100mg once daily for 17days. During therapy he developed platelet refractoriness and had a gastro-intestinal bleed at the time of platelet nadir and maximal mucositis. Despite platelet swamping and HLA matched platelet support he died of the GI hemorrhage on 6th October 1994. The SAE was thought not to be related to treatment with fluconazole.

#0262: 45 year old high-risk female with acute myeloid leukemia entered the study on 21st December 1992 and received fluconazole 100mg daily for 23 days. She then re-entered the study on the 1st February 1993 receiving fluconazole at the same dose for a further 19 days. During this period she developed renal failure and died on 20th February.

#0302: 26 year old male undergoing an allogenic bone marrow transplant for acute myeloid leukemia entered the study for the third time on 13th September and received fluconazole 100mg once daily for 10 days. The patient became febrile and subsequently died. No further details available

#0326: 28 year old male undergoing an allogenic bone marrow transplant for acute lymphoblastic leukemia entered the study for the third time on 8th August and received fluconazole 100 mg daily on 3 occasions over a period of 14 weeks. During his third course of chemotherapy it was discovered he had been receiving off study fluconazole from another source between courses of chemotherapy and was withdrawn as a protocol violator. The patient died 6 weeks later of culture positive invasive aspergillosis.

#0371: 37 year old female undergoing an allogenic bone marrow transplant for chronic granulocytic leukemia entered the study on 10th December 1993 and received fluconazole 100mg daily for 12 days. The patient was withdrawn from the study due to liver function tests greater than 5 times the upper limit of normal. The patient subsequently died of aspergillosis.

#0380: 20 year old male undergoing an allogenic bone marrow transplant for acute myeloid leukemia entered the study on 30th November 1994 and received fluconazole 100mg daily for 4 weeks. The patient died 23 days after the end of the study from *Enterobacter cloacae* septicemia isolated from the cerebrospinal fluid, blood and stools.

#0462: 39 year old female undergoing an allogenic bone marrow transplant entered the study on the 6th February 1993 and received fluconazole 100mg daily for 18 days. After 15 days treatment the patient developed hepato-renal failure. Treatment with the trial medication was withdrawn. The Patient subsequently died on 8th March from an intracranial hemorrhage.

#0536: 36 year old male undergoing an autologous bone marrow transplant for acute lymphoblastic leukemia entered the study on 30th August 1994 and received fluconazole 100mg daily. The patient developed bronchial pneumonia and although was appearing to respond to antibacterial therapy subsequently died following what was thought to be a pulmonary hemorrhage. No post-mortem was performed.

#0602: 80 year old female with acute myeloid leukemia entered the study on the 12th February 1993 and received fluconazole 100mg daily for 24 days. The patient developed a cellulitis of the left arm with a clinical neutropenic sepsis requiring intravenous antibiotics. The patient developed abnormal liver and impaired renal function and subsequently died on 15th March. Clinical complications thought not to be related to the study medication.

#0632: 50 year old male with acute myeloid leukemia entered the study on 26th March 1993 and received fluconazole 100mg once daily for 2 days. On March 25th the patient became shocked and despite resuscitation his condition deteriorated and he died on 31st March. Cause of death was given as shock secondary to dehydration from a profound neutropenic enterocolitis associated with the acute myeloid leukemia and chemotherapy.

#0708:48 year old male with acute myeloid leukemia entered the trial on June 15th 1993 and received fluconazole 100mg daily for 4 weeks. The patient discontinued the study medication on July 18th. The patient subsequently started intravenous amphotericin B for a suspected fungal pneumonia but his condition deteriorated progressively primarily due to failure of bone marrow regeneration

post-chemotherapy. The patient died on August 27th from a cerebral bleed. No post-mortem was completed so fungal infection could not be proven

#0710: 59 year old female with acute lymphoblastic leukemia entered the study on 28th July 1993 and received fluconazole 100mg once daily for 4 weeks. During a prolonged pancytopenic phase she developed extensive skin infections and septicemia with *Xanthomonas*. These were controlled but not cleared with antibiotic combination therapy. On 1st September she developed prolonged fitting and became comatose. The patient died the following day.

#0732: 54 year old male undergoing an autologous bone marrow transplant for myeloma entered the study on 8th July 1993 and received fluconazole 100mg once daily for 13 days. The patient developed liver, cardiac and renal failure associated with problems of pancytopenia post chemotherapy and died on 21st July due to multi-organ failure.

#0806:60 year old male with acute myeloid leukemia entered the study on 4th June 1993 and received fluconazole 100mg once daily for 25 days. Before entry into the study the patient had a history of abdominal pain and possibly biliary colic. A CT scan indicated multiple gallstones and ultrasound indicated a dilated colon with a question of biliary sepsis. As the patient had neutropenia and AML surgery was not regarded as an option. The patient died on 29th June from sepsis and cardiac arrest. Not considered to be related to the study medication.

#0931: 51 year old female with acute lymphoblastic leukemia entered the study on 10th February 1993 and received fluconazole 100mg once daily for a total of 28 days. Subsequent to developing septicemia (case reference 15624 previous SAE) the patient had a gastro-intestinal bleed on 2nd March and was given haemacell, plasma, platelets and erythrocytes. The patient was transferred to intensive care due to general deterioration in her condition and died on 21st March

#1562: 48 year old male receiving an autologous bone marrow transplant for a myeloma entered the study on the 8th May 1993 and received itraconazole 2.5 mg/kg twice daily for 3 days. The patient was found to be ineligible as was known to have renal disease and was immediately withdrawn from the study and no further trial medication given. The patient died 25 days after withdrawal from renal failure. In view of the disease and the short exposure time to the study medication a disease related cause is the most likely.

#1811: 52 year old male with acute myeloid leukemia entered the study on 29th April 1994 and received fluconazole 100mg once daily on one occasion. Intravenous amphotericin B was introduced. The patient died on the 28th May from respiratory failure.

#1961: 53 year old male undergoing an allogenic bone marrow transplant for myelodysplastic syndrome entered the study on 13 April 1994 and received fluconazole 100mg once daily for 11 days. The patient died on 24th April from a cerebral bleed.

#2014: 44 year old male with acute lymphoblastic leukemia entered the study on 26th October 1994 and received fluconazole 100mg once daily for 15 days. On 24th November, 14 days after the last dose of study medication, he had a pyrexia which was unresponsive to antibiotic, antifungal and antiviral therapy. There was a possibility of herpes simplex isolated at bronchoscopy. The patient initially developed respiratory distress, abnormal liver function and finally renal failure. The patient continued to deteriorate despite dialysis and he died on 7th December. A post-mortem was refused by the relatives.

Itraconazole (N = 23):

#0107: 80 year old female with acute myeloid leukemia entered the study on 16th December 1994 and received itraconazole 2.5 mg/kg twice daily for 18 days. She developed melena from 31/12/94 to 03/01/95. Platelet counts were low throughout the study period. Septicemia was diagnosed from a positive culture although the patient showed no outward sign of infection. There was severe hemorrhagic large bowel problems requiring considerable blood product support. The patient had a cardiac arrest on 04/01/95 one day after stopping the trial medication. Cause of death was given as septicemia culminating in cardiac arrest. No causality to the trial medication was given. No further follow-up available

#0161: 20 year old high-risk female was entered the study on October 18th 1993 and received itraconazole 2.5 mg/kg twice daily for 5 days. The patient developed septicemia whilst on therapy and went into shock. There was no response to therapy and she died within 6 hours. The death was expected and not related to the study medication.

#0202: 54 year old high-risk male with acute myeloid leukemia entered the study on the 6th January 1993 with a bone marrow transplant and received itraconazole 2.5 mg/kg twice daily for 16 days. On entry to the study the patients liver function tests and triglycerides were elevated (SGOT 91, SGPT 167, Triglycerides 2.1) and LFTs were further increased after I weeks therapy (SGOT 182, SGPT 504). On his last day of itraconazole LFTs had normalized or improved significantly (SGPT 65) and triglycerides had normalized (1.2 MMOL/L). The patient died from cardio-respiratory arrest 2 days after completing the full prophylactic course of itraconazole. No further follow-up available.

#0208: 21 year old male with acute lymphoblastic leukemia entered the study on the 2nd April 1993 and received itraconazole 2.5 mg/kg twice daily for 13 days.

The patient died on 27th April, 12 days after the last dose of the study medication due to septicemia.

#0243: 23 year old female undergoing an autologous bone marrow transplant for Hodgkin's disease entered the study on the 24th June 1993 with and received itraconazole 2.5 mg/kg twice daily for 2 days. The patient died of cardio-respiratory arrest 10 days after receiving treatment with itraconazole. No further details available.

#0366:47 year old male with CML undergoing an allogeneic bone marrow transplant entered the study on 16th August 1993 and received itraconazole 2.5 mg/kg twice daily for 2 days. On the 2nd September he developed Budd-Chiari syndrome and 9 days later a portal-caval shunt was performed for a thrombosed splenic vein. Post-operatively the patient became anuric and developed capillary leak syndrome. The patient died 2 days later

#0503: 48 year old female with acute myeloid leukemia entered the study on 28th October 1994 and received itraconazole 2.5 mg/kg twice daily. The patient developed colitis and septicemia and was transferred to intensive care where the trial drug was temporarily stopped as the patient removed her naso-gastric tube. The patient remained on intensive care and died of pneumonia related to the underlying condition.

#0554: 60 year old male receiving an autologous bone marrow transplant for non-Hodgkin's lymphoma entered the study on 26th October and received itraconazole 2.5mg/kg twice daily for 15 days. The patient was withdrawn from the study on 10th November 1993 with a suspected systemic fungal infection. Two days later the patient was found in bed with cardiac failure and resuscitation was attempted which was unsuccessful and the patient died. The differential cause of death was septicemia, pancytopenia due to chemotherapy or congestive heart failure. At post-mortem findings were consistent with congestive heart failure. Mycological cultures were performed which were negative.

#0562: 41 year old female undergoing an allogenic bone marrow transplant for acute lymphoblastic leukemia entered the study on 2nd November 1993 and received itraconazole 2.5 mg/kg twice daily for 25 days. She underwent the bone marrow transplant 10 days after starting treatment with itraconazole. The patient deteriorated with acute graft versus host disease and metabolic disturbance secondary to treatment with cyclosporin A. High dose prednisolone was introduced without success and the patient died of graft versus host disease on 27th November. Cause of death was confirmed at post-mortem.

#0605: 59 year old high-risk male with acute myeloid leukemia entered the study on 7th May 1993 and received itraconazole 2.5 mg/kg twice daily for 11 days. The patient developed an opportunistic respiratory infection not thought to be related to the study medication on 16th May. Erythromycin and cotrimoxazole

were started. The respiratory problems appeared to have improved 2 days later but he remained pyrexial with widespread crackles and the chest X-ray showed patchy shadowing and linear collapse in both lower zones. Itraconazole was withdrawn. The patient had also developed watery diarrhea, epistaxis and hemoptysis. He died on 6th June.

#0607: 62 year old female with acute myeloid leukemia entered the study on 27th August 1993 and received itraconazole 2.5 mg/kg twice daily for 3 days. The patient developed pneumonia during the initial chemotherapy and deteriorated despite intensive respiratory and antibiotic support and subsequently died. Causality was thought to be unrelated to the trial medication and the unfortunate complication of chemotherapy.

#0609: 64 year old high-risk male with acute myeloid leukemia entered the study on 19th October 1993 and received itraconazole 2.5 mg/kg twice daily for 2 days. The patient had existing leukemia and developed pneumonia and was admitted to intensive care 3 days after starting the study. The patient died 6 days later of cardiorespiratory, renal and bone marrow failure.

#0635: 52 year old high-risk male with acute myeloid leukemia entered the study on 26th August 1993 and received itraconazole 2.5 mg/kg twice daily for 19 days. The patient developed pneumonia during the initial chemotherapy that was initially stabilized with antibiotics and medical support. The patient deteriorated rapidly on the 12-13th September and became unresponsive to therapy and died on the 14th September. Post-mortem gave cause of death pneumonia and acute myeloid leukemia. No causality was attributed to the study medication.

#0702:46 year old female with acute myeloid leukemia entered the study on February 2nd 1993 and received itraconazole 2.5 mg/kg twice daily for 16 days. The patient had an intracerebral hemorrhage and itraconazole was stopped on 15th February. The patient subsequently died as a result of the cerebral hemorrhage. The investigator considered the event to be unrelated to the study medication.

#0707:44 year old male with acute myeloid leukemia entered the study on 15th June 1993 and received itraconazole 2.5 mg/kg twice daily for 19 days. The patient complained of abdominal pain and itraconazole was stopped. The abdominal pain settled rapidly. On July 2nd the patient's condition deteriorated rapidly with features of infection pyrexia, cough and hypoxia) despite receiving broad-spectrum antibiotics. The patient died the following after a cardiac arrest. No post-mortem was carried out.

#0716: 46 year old female with acute lymphoblastic leukemia entered the study on 18th February 1994 and received itraconazole 2.5 mg/kg twice daily. She subsequently successfully completed 2 courses of chemotherapy. During these 2 courses the AEs reported were epigastric pain and discomfort during the first