Glucose: 6 patients developed hyperglycemia.
Hemoglobin: 19 patients were found to have anemia.
Hematocrit: 1 patient developed a clinically significant decrease.
LDH: 1 patients developed a clinically significant increase.
WBC: no patient became granulocytopenic.
Platelets: 2 patients developed borderline thrombocytopenia.
Sodium: 2 patients developed hypernatremia and 1 patient hyponatremia.
Bilirubin: 9 patient had bilirubinemia.
Urea: 9 patients developed an increase in BUN.
Uric Acid: 13 patients developed a clinically significant decrease.

Amphotericin B:

Albumin: 8 patients developed clinically significant hypoalbuminemia.
Alkaline Phosphatase: 5 patients developed clinically significant elevations.
ALT: 10 patients developed clinically significant elevations.
AST: 3 patients developed clinically significant elevations.
Calcium: 7 patients developed hypocalcemia.
Chloride: 18 patients developed hyperchloremia.
gGT: 12 patients developed clinically significant elevations.
Glucose: 9 patients developed hyperglycemia.
Hemoglobin: 14 patients were found to have anemia.
Hematocrit: 2 patients developed a clinically significant decrease.
LDH: 2 patients developed a clinically significant increase.
WBC: no patient became granulocytopenic.
Platelets: 3 patients developed borderline thrombocytopenia.
Sodium: 2 patients developed hypernatremia and 1 patient hyponatremia.
Bilirubin: 7 patient had bilirubinemia.
Urea: 43 patients developed an increase in BUN.
Uric Acid: 1 patient developed a clinically significant decrease.

MO Comment: As noted previously, patients on the amphotericin arm developed renal dysfunction consistent with that commonly seen with this agent. Additionally patients on this arm developed hepatic dysfunction more frequently than those on the itraconazole arm.

Interestingly, patients on itraconazole had a higher incidence of hypocalcemia, hypouricemia and marginally higher hyperbilirubinemia.

MO Conclusion:

AEs from the GI tract were the most frequently seen AEs on both arms of the study. On the itraconazole arm, 21 or 22.2% of patients complained of diarrhea, 25 or 26.3%, complained of nausea, 6 or 6.3% of constipation, and 21 or 22.1% of vomiting. Other events were seen but only the previously listed were seen in > 5% of patients. On the amphotericin arm, 31 or 32.3% complained of diarrhea, 29 or 32% of nausea, 7 or 7.3% of constipation, 39or 30.2% of vomiting, and 7 or 7.3% of mucositis. As above, other events from the GI tract were seen but in less than 5% of the patients.

Rash was seen in12 or 12.6% of patients on itraconazole as compared to 8 or 8.3% on amphotericin B. Other allergic dermatologic phenomena such as erythematous rash (8 or 8.4% itraconazole versus 6 or 6.3% amphotericin), and increased sweating (8 or 8.4% itraconazole versus 2 or 2.1% amphotericin) were also seen.

Notable differences were seen in the incidence of fever and rigors with 7 or 7.4% of itraconazole patients complaining of fever versus 11 or 11.5% amphotericin patients and 9 or 9.5% itraconazole patients complaining of rigors versus 37 or 38.5% amphotericin patients. This difference was expected based on the known AE profiles of both agents.

Application site reactions were seen in approximately the same number of patients on both arms (5 or 5.3% itraconazole versus 5 or 5.2% amphotericin).

Major differences were seen in the incidence of electrolyte abnormalities and renal dysfunction between the arms. Specifically, on the itraconazole arm 16 or 16.8% of patients developed hypokalemia, 4 or 4.2% hypomagnesemia, 2 or 2.1% hypocalcemia 4 or 4.2% had an increased creatinine. On the amphotericin arm the respective numbers were: hypokalemia 26 or 27.1%, hypomagnesemia 8 or 8.3%, hypocalcemia 4 or 4.2%, increased BUN 11 or 11.5%, increased creatinine 24 or 25%, and hyperglycemia 5 or 5.2%. These abnormalities are consistent with the development of a renal tubular acidosis in patients on amphotericin B and its overall renal toxicity profile.

From a general standpoint, 6 or 6.3% of itraconazole patients developed fluid overload and 6 or 6.3% generalized edema. The respective numbers on the amphotericin arm were 9 or 9.4% for both AEs.

Abdominal pain was seen in 9 or 9.5% of itraconazole patients as compared to 13 or 13.5% amphotericin patients. Stomatitis was seen in 11 or 11.5% itraconazole patients as compared to 3 or 3.1% amphotericin patients. Headache was seen in 6 or 6.5% of itraconazole patients and 11 or 11.5% amphotericin patients. Dizziness was also seen in > 5% on both arms (7.1% oral itraconazole versus 5 or 5.2% amphotericin).

Abnormal renal function coded as such was seen in 10 or 10.4% of amphotericin patients and hematuria in 6 or 6.3%. These events were seen in < 5% of patients on the IV itraconazole arm and only hematuria was seen in 3 or 7.1% of the oral itraconazole patients. Insomnia and anorexia were seen in 5.2% of patients on the amphotericin arm and in less than 5% of patients on the itraconazole arm. Edema was seen in approximately 5% on both arms.

Pain and chest pain were seen in approximately 6% of amphotericin patients as compared to < 5% of itraconazole patients for pain and 8 or 8.3% for chest pain

From the respiratory tract, 9 or 9.5% of itraconazole patients had pulmonary infiltrates as compared to 2 or 2.1% amphotericin patients. Hypoxia was also seen more frequently on the itraconazole arm 5 or 5.3% as compared to 1 or 1% on the amphotericin arm, Respiratory insufficiency however was seen more frequently in the amphotericin patients 6 or 6.3% compared to 2 or 2.1% itraconazole patients. Pneumonia was diagnosed in 6 or 6.3% of patients on itraconazole and 8 or 8.3% on amphotericin. Coughing (15.8% itraconazole versus 8.3% amphotericin), dyspnea (8.4% itraconazole versus 14.6% amphotericin), pulmonary edema (6.3% amphotericin), and hemoptysis (5.2% amphotericin) were also seen in > 5% of patients.

From the eye, only conjunctivitis was seen in > 5% of the amphotericin patients.

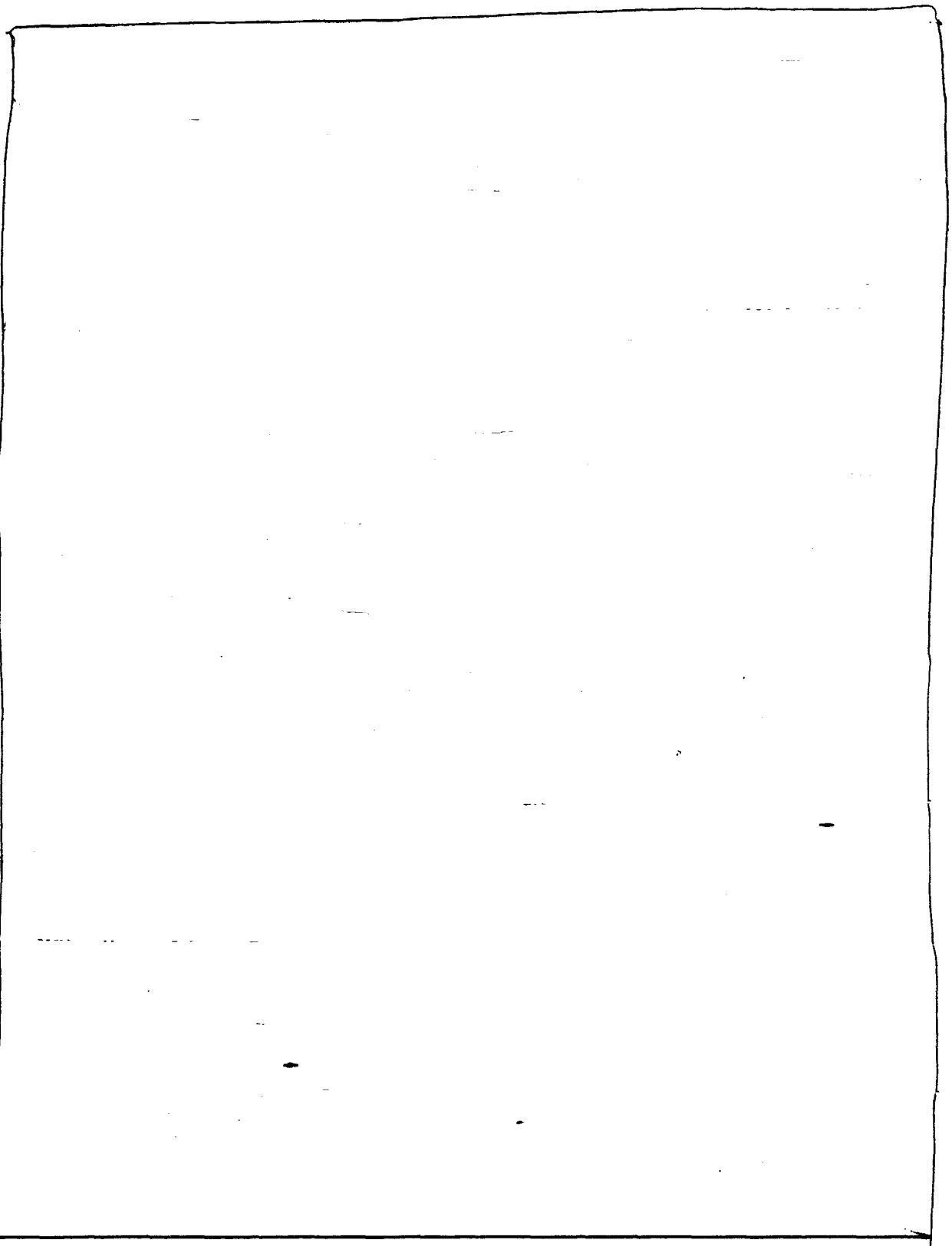
Both arms had a number of complaints of hepatic dysfunction. Specifically, on the itraconazole arm 10 or 10.5% of patients had an elevated bilirubin as compared to 5 or 5.2% of amphotericin patients. 5 or 5.2% of amphotericin patients were coded as having hepatitis and 3 or 7.1% or oral itraconazole patients as having an elevated LDH.

Other events seen in > than 5% of patients were: epistaxis 5.3% itraconazole versus 11 or 11.5% amphotericin, purpura (5.3% amphotericin), hypotension (9.4% amphotericin), hypertension (6.3%) amphotericin), and tachycardia (7.3%) amphotericin).

From a laboratory standpoint, patients on the amphotericin arm developed renal dysfunction consistent with that commonly seen with this agent. Additionally patients on this arm developed hepatic dysfunction more frequently than those on the itraconazole arm.

Interestingly, patients on itraconazole had a higher incidence of hypocalcemia, hypouricemia and marginally higher hyperbilirubinemia.

Overall, the AEs seen in this study were consistent with those seen in previously reviewed studies with a higher frequency of hyperbilirubinemia.



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Addendum to MOR of NDA 20- 966

Submission Date: September 10, 1998
CDER Stamp Date: September 16, 1998
Date Review Started: September 16, 1998
Date Review Completed: October 8, 1998

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

Generic Name: Itraconazole

Proprietary Name: Sporanox® Injection

Pharmacologic Category: Antifungal

Materials Reviewed: NDA 20-966, 4-month safety update, submitted 9/10/98 Volumes 1 –7. Update contained data tabulations on the initial 255 patients included in the 4/27/98 submission as well as information on 8 additional patients from the completed ITR-INT-60 trial (An efficacy and safety trial of itraconazole injection followed by oral itraconazole capsules in the treatment of hematologic, transplantation, acquired immunodeficiency syndrome and chronic granulomatous disease patients with invasive pulmonary or disseminated aspergillosis (uncontrolled). Additionally included were individual patient narratives as well as CRFs of serious AEs including deaths reported to the applicant between October 1, 1997 through May 1, 1998.

Safety Review for ITR-INT-60 patients not included in original database (N = 8):

All patients with proven pulmonary or disseminated aspergillosis in this phase III, open, uncontrolled, multicenter trial received IV itraconazole 200 mg BID x 2 days followed by 200 mg IV QD x 12 days Subsequent to the IV phase, patients received itraconazole capsules 200 mg PO QD (two 100 mg capsules) for 12 weeks. Safety assessments were scheduled prior to the institution of therapy, after 2 days, 7 days, and 14 days of therapy (conclusion of IV phase), and at 6 and 12 weeks. All investigators, sites and patients were non-US. 23 patients were enrolled at the time of the original submission. The primary objective was to study the efficacy and safety of IV itraconazole followed by itraconazole capsules in 30 patients with aspergillosis.

All 8 additional patients developed AEs during the IV phase of the trial. 3 of the events were considered severe by the investigators. None of the severe AEs were considered related to study drug. There were 2 deaths, both during the post-treatment period and neither considered related to itraconazole (#3027:sepsis, #3030:hepatic failure). Both of these patients were also coded as discontinuations due to an AE.

Listed below are the patients, AEs, severity, relationship to study medication and outcome.

#A03008: mild: diarrhea, swollen face, fever, moderate: fever, severe: rash. Patient recovered from all AEs. 2 episodes of fever were considered possibly-related to IV itraconazole.

#A03052, #A03057, #A03058: Patients hospitalized for diagnostic pulmonary biopsy, no relationship to study drug.

#A03074: Severe: hemoptysis, moderate: left femoral thrombophlebitis. No relation to study drug. Patient recovered.

#A03072: Severe: right thigh abscess, headache, aggravation of aspergillosis. No relation to study drug for abscess and headache. Investigator considered the patient's worsening condition possibly-related to IV itraconazole and discontinued therapy. Patient recovered.

#A03030: Severe: hyperbilirubinemia (conjugated) with jaundice, liver failure due to underlying Hodgkin's disease or aspergillosis, moderate: hematuria, mild: hematuria, superficial thrombophlebitis right upper extremity. Patient died due to liver failure and was discontinued from the study at the time of development of jaundice. None of the AEs were considered related to the study drug.

#A03027: Severe: multiorgan failure, septic shock, post-operative pneumonia, respiratory failure, surgical excision of left upper lobe, moderate: fever, mild: fever. Patient died from pneumonia and sepsis post-operatively. Only febrile episodes were considered possibly-related to study drug.

Reviewer Conclusion: None of the events recorded above were unexpected given the underlying disease status of the patients reviewed. The addition of these 8 patients to the database had minimal impact on the incidence of AEs by body system. None of the AEs were new or unexpected for itraconazole.

DEATHS:
Included in the safety update were 17 deaths from ongoing clinical itraconazole trials. There were 10 deaths from patients who received fluconazole and 6 from patients who received amphotericin B. Synopses are provided below:

Itraconazole N = 17:

Patient #0127: 40 YO female initiated treatment with study medication on September 18, 1997. On October 16, 1997 the patient was admitted to the ICU with cyclosporin toxicity. The study medication was temporarily stopped. She subsequently developed a perforated duodenal ulcer requiring surgery. Post operative chest x-rays revealed bilateral opacities. She required increasing amounts of supplemental oxygen and developed hemothoraces one week prior to death. The patient's family decided to withdraw further care on December 30, 1997 and the patient expired the same day.

Patient #0130: 40 YO male received an allogeneic bone marrow transplant for AML. He began treatment with the study medication on October 16, 1997. On October 29, 1997, the patient developed respiratory distress secondary to pulmonary hemorrhage, and was admitted to the ICU. He also developed acute renal failure that required hemodialysis, and imipenem-resistant *Xanthamonas maltophilia* bacteremia. On November 27, 1997 the patient became hypotensive and his respiratory status began to deteriorate. The patient developed a tension pneumothorax. Thoracentesis was preformed immediately to relieve the tension pneumothorax, but the patient's blood pressure continued to drop and he became asystolic. The cause of death was sepsis.

Patient #0138: 57 YO male began treatment with study medication on December 23, 1997. During his hospital stay, the patient was found to be in respiratory distress and was transferred to the ICU. He was found to be fungemic. Treatment with itraconazole was discontinued on January 4, 1998, and the patient was started on amphotericin intravenously. His condition continued to deteriorate. On January 9,1998, the patient became severely hypotensive despite maximal pressor support and he expired.

Patient #0140: 24 YO female received a bone marrow transplant and began treatment with study medication on January 22, 1998. Two days later, she developed respiratory distress. A series of chest x-rays showed extensive right lung tumor growth and subsequent pleural effusion. On January 29,1998, she was found to be tachypneic and somnolent. One hour later she was found unresponsive and cyanotic. Despite aggressive resuscitation attempts, the patient expired. An autopsy revealed a large tumor involving the anterior mediastinum and both the upper and middle lobes of the right lung. Microscopic sections confirmed the presence of lymphoma with extensive necrosis.

Patient #0148: 37 YO female began treatment with study medication on February 27, 1998. On March 4, 1998, the patient developed an alveolar hemorrhage secondary to thrombocytopenia and platelet

dysfunction secondary to acute renal failure. She was transferred to the ICU and intubated for respiratory support. On March 9, 1998, the patient was noted to have fixed and dilated pupils with a hypertensive crisis. A CT scan revealed a subarachnoid hemorrhage with complete brainstem herniation. Subsequently she developed an asystolic rhythm and expired on March 10, 1998.

Patient #0151: 30 YO male received an allogeneic bone marrow transplant for AML and began study drug on March 24, 1998. His post-transplant course was complicated by neutropenic fevers, hemorrhagic cystitis, severe mucositis, pancytopenia, gastrointestinal bleeding, and acute renal failure. On April 4, 1998, the patient was transferred to the ICU with respiratory distress and hypotension. On April 7, 1998, he developed severe hypotension and third degree heartblock with a junctional rhythm and expired secondary to multi-organ failure.

Patient #0308: 47 YO male was started on study medication on 19 November 19, 1997. The patient was hospitalized with a pulmonary infiltrate on December 1, 1997. A bronchoscopy was performed and the patient became increasingly short of breath. He was intubated on December 5, 1997, and was transferred to the medical intensive care unit. Sputum cultures were positive for CMV, mold, *Klebsiella* spp., and Gram (-) bacilli. The study medication was temporarily stopped. The patient expired on December 11, 1997.

Patient #0311: 54 YO male received an allogeneic bone marrow transplant for AML. He started treatment with study medication on March 26, 1998. During administration of his morning dose on March 28, 1998, the patient complained of shortness of breath, dizziness and a sensation of puffiness in his hands. He had diminished breath sounds in the mid and lower lungs bilaterally. His oxygen saturation on room air was 80-89%. An ECG showed sinus tachycardia and a heart rate of 105. A chest X-ray showed 'no overt congestion' and 'no pneumonic infiltrates'. After treatment with oxygen and Benadryl, the shortness of breath subsided. The investigator felt that the events were possibly-related to the study medication, and the patient was discontinued from trial drug. On April 6, 1998, the patient was transferred to the ICU when his respiratory status again began to deteriorate. The patient was intubated and put on a ventilator on April 7, 1998. The patient expired on April 10, 1998. An autopsy report indicated the causes of death to be veno-occlusive disease, disseminated intravascular coagulation, neutropenia, pulmonary infiltrate, and acute renal failure.

Patient #0109: 44 YO male began treatment with study medication on May 8, 1997. On May 15, 1997, he experienced an episode of hypoglycemia with tachycardia and tachypnea. Study medication was discontinued. The investigator believed the event was most probably due to pneumonia or sepsis. On June 5, 1997, the patient developed oliguric renal failure with an increasing creatinine. He expired upon removal from life support. The cause of death was disseminated histoplasmosis, respiratory and renal failure.

Patient #3027: 47 YO male had a medical history of duodenal ulcer, pulmonary tuberculosis, and rheumatoid arthritis. Treatment with study medication was initiated on April 16, 1998 and discontinued on May 16, 1997. On May 19, 1997, the patient underwent a right upper lobectomy but could not be successfully extubated because of poor lung function attributed to pulmonary fibrosis secondary to rheumatoid arthritis. The patient developed bilateral pneumonia. Despite treatment with antibiotics, his condition continued to deteriorate and he expired due to septic shock and multi-organ failure on June 3,1997.

Patient #3030: 51 YO male had a medical history of Hodgkin's disease and myopathy. He began treatment with study medication on May 21, 1997. On June 9, 1997, he was hospitalized with bilirubinemia due to either liver infiltration of Hodgkin's disease or cholestasis due to aspergillosis. The patient developed hepatic failure and died on July 1, 1997

Patient # 0323: 82 YO female entered the study on December 5, 1997. Medical history included vulvar cancer. While in the hospital, she developed unspecified complications secondary to underlying metastatic vulvar cancer and was placed on a "do not resuscitate status." All treatments were withdrawn on December 17, 1997 and the patient expired on December 20, 1997.

Patient #0608: 72 YO male entered the study June 16, 1997. Medical history included recurrent sinusitis, myocardial infarctions, colon cancer, enterocutaneous and rectovesical fistulas, transurethral resection of the prostate, hematuria, and diabetes mellitus. The patient received study medication from June 16, 1997 to June 20, 1997. On June 21, 1997, he developed fever, hypotension, leukocytosis, and respiratory distress. Urine and sputum cultures revealed *Enterobacter* spp. He expired despite support with vasopressors and fluid.

Patient # 0705: 62 YO female entered the study on March 27, 1997. Medical history included hypertension, pneumonia, G-tube infection, chronic dysphagia, paraplegia, seizures, kyphoscoliosis, urinary tract infection, arthrogryposis, depression, anxiety, and anemia. The patient received study until April 13, 1997. On May 11, 1997, the patient was hospitalized with hypotension, Enterococcal sepsis, and bleeding from an abdominal wall fistula. Chest x-ray showed pneumonia. The patient was treated with antibiotics, intravenous support and dopamine for hypotension. She was discharged to a nursing home in stable condition on May 22, 1997, and the study medication continued. On May 23, 1997, the patient developed a sudden onset of respiratory distress and expired.

Patient #0709: 77 YO female entered the trial on December 19, 1997. Medical history included coronary artery disease, hypertension, abdominal aortic aneurysm repair, chronic obstructive pulmonary disease, total abdominal hysterectomy, hematoma in the retroperitoneal space post sarcoma removal, and leiomyosarcoma of the small intestine. After suffering a respiratory arrest, she was intubated on December 18 1997. Blood cultures were positive for yeast and she began treatment with study medication. Blood cultures were still positive for yeast on December 21, 1997. The study medication was discontinued on December 22, 1997, and the patient was started on amphotericin B. The patient was removed from life support on December 23, 1997 and expired. The cause of death was sited as cardio-respiratory arrest due to poor cardio-respiratory reserve, multi-organ failure, fungal sepsis, and pulmonary emboli.

Patient # 3558: 71 YO male entered the trial on August 20, 1997. The patient was being treated for AML and had been hospitalized on August 15, 1997 for chemotherapy. During the hospitalization, he experienced neutropenic fevers with negative blood cultures. An echocardiogram showed grossly diminished left ventricular function with probable left ventricular enlargement. The patient underwent a right heart catheterization and was diagnosed with fluid overload and sepsis. On August 22, 1997, the patient required intubation for respiratory distress. Treatment with study medicine was discontinued on August 23, 1997. On August 24, 1997, the patient was found to be in atrial fibrillation with a rapid ventricular rate and hypotension and he expired the same day.

Patient #3634: 52 YO male received study medication from October 6, 1997 to October 9, 1997. He was admitted to the ICU on October 8, 1997 for rehydration following a diagnosis of hypernatremia and hyperglycemia secondary to dehydration. On October 10, he developed pulmonary edema and he expired on October 27, 1997 due to respiratory failure after a period of gradual multi-organ decline.

Medical Officer's Comment: All deaths in the itraconazole-treated patients appeared related to the underlying disease processes and not to the study drug. Patient #0311 appeared to have experienced an acute allergic reaction to IV itraconazole which resolved with appropriate therapeutic measures and the patient subsequently expired from other causes.

Fluconazole (N = 10):

Patient #0116: 30 YO male started treatment with study medication on May 1, 1997. On August 4, 1997, the patient was hospitalized with a near syncopal episode, orthostatic hypotension, and progressive icterus and was found to be septic. An abdominal CT showed ascites and thickening of the small bowel, ascending

colon, and cecum, consistent with graft versus host disease. The patient became increasingly encephalopathic and aspirated on August 15, 1997. The patient subsequently became unresponsive and expired.

Patient #0124: 49 YO male started study medication on 1 August 1, 1997. On August 13, 1997, the patient was admitted to the ICU with respiratory distress. Blood cultures were positive for Gram (-) organisms. Study medication was stopped on August 14, 1997 and the patient expired on August 15, 1997 due to Gram (-) sepsis.

Patient #0132: 35 YO male started treatment with study medication on November 5, 1997. While recovering from his bone marrow transplant, the patient developed jaundice and ascites secondary to veno-occlusive disease and renal failure secondary to hepatorenal syndrome. On November 28, 1997, the patient had an episode of hypotension, and was transferred to the ICU for vasopressor support. The patient continued to require increasing vasopressor support and remained hypotensive despite large doses of dopamine and norepinephrine bitartrate injection. On December 1, 1997 the patient became asystolic and expired.

Patient #0137: 36 YO male received a bone marrow transplant for non-Hodgkin's lymphoma and his medical history included chronic fevers, upper respiratory infections, a right sided-pleural effusion, pancytopenia requiring multiple platelet and red blood cell transfusions, and a splenectomy. He began treatment with study medication on December 23, 1997. On January 8, 1998, he developed paroxysmal atrial fibrillation with shortness of breath. Two days later, his atrial fibrillation recurred with a rapid ventricular heart rate of greater than 200 beats per minute. He was hypotensive and became progressively bradycardic. The patient expired on January 10, 1998. An autopsy cited the immediate cause of death to be septic shock secondary to pneumonia resulting from complications of chemotherapy and bone marrow transplantation.

Patient #0146: 38 YO male received study medication from 19 February 19, 1998 to April 14, 1998. The patient had received a bone marrow transplant for recurrent Hodgkin's lymphoma. On April 18, 1998, the patient expired from multi-organ failure secondary to graft versus host disease.

Patient #0410: 36 YO female with a PMH of cardiomyopathy with cardiac decompensation began study medication on November 1, 1997. On November 11, 1998, the patient developed septic shock with hepatic and renal insufficiency requiring vasosuppressive support and continuous ultrafiltration for treatment of fluid overload. She suffered from arrhythmias requiring cardioversion and was admitted to the ICU. On November 25, 1997, the patient was intubated for shortness of breath. On November 30, 1997, the patient expired due to hepatic failure, renal failure, and pulmonary hemorrhage.

Patient #0413, 38 YO male began study medication on December 23, 1997. On February 6, 1998, he was hospitalized due to a relapse of AML, fever, and pain. While hospitalized, he was temporarily given intravenous fluconazole. On February 19, 1998, the patient was hospitalized again for relapse of AML, fever, and pain. Study medication was temporarily held on February 23, 1998. The patient expired due to his underlying condition on February 26, 1998.

Patient #0415: 36 YO female received an allogeneic bone marrow transplant for non-Hodgkin's lymphoma. Treatment with study medication was started on March 11, 1998. On March 26, 1998, the patient was hospitalized with diarrhea, fever, rash, lethargy, decreased oral intake, emesis, sinus tachycardia, and hypotension. A colonoscopy was performed and the findings were consistent with graft versus host disease. On April ~~15~~, 1998, she was hospitalized with a left jugular venous thrombosis and was treated with heparin therapy. Tachycardia and an ejection murmur were present. The patient was febrile and was treated with antibiotics. On May 8, 1998, she was hospitalized with progressive ARDS and she expired the next day due to respiratory failure. An autopsy revealed *Aspergillus.*

Patient # 0322: 74 YO male entered the study on October 17, 1997. Medical history included atrial fibrillation, shortness of breath, hyperglycemia, anemia, and generalized edema. The patient received study medication through October 24, 1997. The study medication was stopped on October 25, 1997 due to a

positive blood culture. On November 18, 1997, the patient had an episode of severe hypotension and bradycardia. On December 4, 1997, the patient developed acidosis, which could not be successfully treated. The patient developed multi-organ failure and expired on December 5, 1997.

Patient #0710: 80 YO female entered the trial on March 4, 1998. The patient had a history of COPD. On February 18, 1998, prior to beginning treatment with study drug, the patient had undergone surgery to repair a perforated duodenal ulcer and required intubation. On March 4, 1998, the physician discussed a tracheostomy with the patient and her family. A decision was made to discontinue life support. The patient expired on March 5, 1998. An autopsy report sited the causes of death to be cardiopulmonary arrest and fungal sepsis.

Medical Officer's Comment: All deaths in the fluconazole-treated patients appeared related to the patients' underlying disease processes.

Amphotericin (N = 6):

Patient #3408: 63 YO male with AML entered the study on February 13 1997 and continued until February 15, 1997. The patient received high dose methotrexate as part of his chemotherapy regimen. He subsequently developed methotrexate toxicity and acute renal failure. Dialysis was started on February 18, 1997. The patient developed sepsis and multi-organ failure and expired on February 26, 1997. The investigator determined that the acute renal failure was possibly related to both amphotericin B and methotrexate.

Patient # 3615: 21 YO male entered the trial on September 30, 1997. The patient was being treated for acute lymphocytic leukemia and had received peripheral blood stem cell transplantation in February 1996. Medical history included mucositis, left eye pain, left heel amputation, cervical adenopathy, and severe bone and joint pain. On October 25, 1997, the patient expired due to documented *Candida albicans* fungemia and possible *Aspergillus* pneumonia. An x-ray and CT of the chest both showed upper lobe infiltrates consistent with *Aspergillus* pneumonia.

Patient # 3619: 73 YO male with a history of AML entered the trial on 10 October 1997. On October 31, 1997, the patient was admitted to the ICU for observation of respiratory status. Amphotericin B was permanently discontinued on November 1, 1997, at the request of the patient's family. The patient expired on November 3, 1997 from respiratory failure, *Aspergillus* pneumonia and a possible CNS hemorrhage.

Patient #3199: 44 YO male received study medication from November 17, 1997 to November 27, 1997. He developed pneumonia, which continued to worsen throughout the course of the trial. He expired on November 28, 1997.

Patient #3534: 65 YO male became febrile following consecutive peripheral blood stem cell transplants on October 17, 1997 and October 23, 1997. He began treatment with study medication on October 31, 1997. Treatment was discontinued after 4 days due to renal impairment. The patient remained febrile and was admitted to the ICU on November 11, 1997 with renal dysfunction, hypotension and atrial fibrillation. His condition continued to worsen and he expired on November 24, 1997 due to multi-organ failure.

Patient #3644: 53 YO female was being treated for relapsed leukemia after an 18 year remission. She received study medication from October 14, 1997 to October 19, 1997. On November 8, 1997, she expired due to end stage leukemia with chemotherapy-related pancytopenia, sepsis, and neutropenic enterocolitis.

Medical Officer's Comments: Most deaths in the amphotericin-B-treated patients appeared unrelated to the study drug. Only patient #3408 developed acute renal failure which appeared to be related to therapy and which played a role in the patient's ultimate death.

Serious Adverse Events:

Between October 1, 1997 and May 1, 1998 27 itraconazole patients, 12 fluconazole patients, and 9 amphotericin B patient developed AEs that were classified as serious by the investigators. 18 of the 27 itraconazole patients, 10 of the 12 fluconazole patients and 6 of the 9 amphotericin B patients were listed above in the death summaries. None of the events that occurred in the remaining 9 itraconazole, 2 fluconazole, or 3 amphotericin B patients appeared related to study medication. All events were associated with the underlying disease processes in these severely ill patients.

Specifically, of the remaining 9 itraconazole-treated patients with serious AEs, 4 (#0120, #0201, #3312, and #3642) developed septic events, 2 (#0307 and #0414) developed hemoptysis and anemia, 1 (#0212) developed CHF, 1 (#0120) developed hyperglycemia, and 1 (#0412) required surgery for AV insufficiency.

Of the remaining 2 fluconazole-treated patients, 1 (#0122) developed dehydration secondary to diarrhea and 1 (#0410) was hospitalized for exacerbation of sickle cell disease.

Of the remaining 3 amphotericin-B-treated patients, 1 (#3435) developed severe hypotension and pulmonary edema, 1 (#3638) developed sepsis, and 1 (#3211) experienced acute renal failure probably attributable to dehydration.

Reviewer Conclusion:

The adverse events summarized in the MOR of the 4-month safety update were consistent with the type and severity of adverse events summarized in the MOR of the NDA. In general, the adverse events reflect the severity of disease of the patient population under investigation. No new or unexpected adverse events were reported for itraconazole or the comparator agents fluconazole and amphotericin B.

The MO continues to propose that a table of all investigator-determined, treatment-related AEs be added to the label by study arms and to include only clinical trial patients (controlled and uncontrolled). It should be noted that the values proposed in the table on page 30 of the original MOR were tentative pending the sponsor's submission and the MOR of the 4-month safety update reviewed herein as well as the submission of a final update in late October 1998. Minor changes have been made to the table, specifically the itraconazole denominator was changed to 168 (previously 160) and the total number of itraconazole patients with an AE possibly or definitely-related to therapy was changed to 82. As noted above, 1 itraconazole patient had worsening of his underlying condition which was possibly-attributed to study drug and 2 patients had 5 episodes of fever attributed to study drug. None of these events were seen in > 2% of itraconazole-treated patients and therefore no further changes were deemed necessary.

SUMMARY OF POSSIBLY OR DEFINITELY DRUG-RELATED ADVERSE EVENTS REPORTED BY ≥2% OF SPORANOX® INJECTION PATIENTS (TOTAL)			
ADVERSE EVENT	**IV Itraconazole N = 168**	**IV Fluconazole N = 32**	**Amphotericin B N = 106**
Total number patients with adverse event	**82 (49)**	**7 (22)**	**87 (82)**
Gastrointestinal System Disorders	**34 (21)**	**2 (6)**	**37 (35)**
Nausea	18 (11)	0 (0)	23 (22)
Diarrhea	15 (9)	1 (3)	14 (13)
Vomiting	10 (6)	0 (0)	16 (15)
Abdominal Pain	4 (2)	0 (0)	5 (5)
Liver and Biliary System Disorders	**23 (14)**	**4 (12)**	**9 (8)**
Bilirubinemia	11 (7)	3 (9)	4 (4)
SGPT Increased	6 (4)	1 (3)	2 (2)
Jaundice	4 (2)	0 (0)	1 (1)
SGOT Increased	4 (2)	0 (0)	1 (1)
Hepatic Function Abnormal	2 (1)	0 (0)	3 (3)
Metabolic and Nutritional Disorders	**25 (16)**	**2 (6)**	**47 (44)**
Hypokalemia	11 (7)	0 (0)	29 (27)
Increased Creatinine	6 (4)	1 (3)	27 (25)
Central & Peripheral Nervous System Disorder	**12 (7)**	**0 (0)**	**7 (7)**
Dizziness	5 (3)	0 (0)	2 (2)
Skin and Appendages Disorders	**9 (6)**	**2 (6)**	**9 (8)**
Rash	4 (2)	1 (3)	4 (4)

RECOMMENDED REGULATORY ACTION:

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

The MO continues to propose that the following changes be incorporated into the applicant's proposed labeling:

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

   should be modified to:

2) Under **ADVERSE REACTIONS** the applicant's table and text (see MOR page 30 and MOR addendum page 8) should be modified to reflect clinical trial patients only and the comparator arms, amphotericin B and fluconazole, should be listed separately (see MO table and text page 30).

/S/

Regina Allvisatos, MD
DSPIDP, HFD-590

Cc:
Orig. NDA 50-762
HFD-590
HFD-520
HFD-590/DIVDir/MGoldberger
HFD-590/DepDIVDir/RAlbrecht
HFD-590/MTL/BLeissa 4/2/99
HFD-590/Biopharm/PColangelo
HFD-590/Chem/Holbert
HFD-590/Pharm/McMaster
HFD-590/CSO/Kimzey
HFD-725/Biostat/Shen

10/8/98

Addendum II to MOR of NDA 20- 966

Submission Date: November 10, 1998
CDER Stamp Date: November12, 1998
Date Review Started: November 16, 1998
Date Review Completed: November 30, 1998

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

Generic Name: Itraconazole

Proprietary Name: Sporanox®

Pharmacologic Category: Antifungal Injection

Materials Reviewed: NDA 20-966, 6-month safety update, submitted November /98 Volumes 1 – 32. Update contained data tabulations on an additional 193 patients from the now completed trial ITR-INT-62 (A randomized, comparative, multicenter trial of itraconazole injection followed by itraconazole oral solution versus intravenous amphotericin B followed by oral fluconazole tablets for the treatment of febrile neutropenic patients with hematologic malignancy), as well as on the initial 255 patients included in the 4/27/98 submission and the 8 additional patients from the completed ITR-INT-60 trial included in the 4-month safety update (An efficacy and safety trial of itraconazole injection followed by oral itraconazole capsules in the treatment of hematologic, transplantation, acquired immunodeficiency syndrome and chronic granulomatous disease patients with invasive pulmonary or disseminated aspergillosis (uncontrolled). Additionally included were individual patient narratives as well as CRFs of patients with serious AEs including deaths reported to the applicant between October 1, 1997 through September 1, 1998 on patients from 3 additional ongoing clinical trial[redacted]

In addition to the paper submission the applicant updated the electronic database and the reviewer was independently able to generate AE tables. Notable however was that the electronic potion of the submission was incomplete with regards to total # of deaths. For a summary of the total number of patients included in the NDA database, see Table 1 below.

Table 1
Summary of IV Itraconazole Duration by Study Type

Total number of patients	n	Treatment Duration			
		≤7 days n (%)	>7-14 days n (%)	>14 days n (%)	Median days (min, max)
Worldwide					
Controlled	234	133 (56.8)	88 (37.6)	13 (5.6)	7 (2, 28)
Uncontrolled	31	2 (6.5)	25 (80.6)	4 (12.9)	14 (4, 28)

The 95 PK patients who were treated with IV itraconazole were reviewed in the original MOR and will not be referred to in this appendix. This portion of the review pertains only to those itraconazole-treated patients from controlled and uncontrolled clinical trials (N = 265).

Copied from the submission in table 2 are patients' demographics and baseline characteristics. There was general homogeneity in the populations treated with a slight preponderance of males.

Table 2
Summary of patient demographics participating in itraconazole injection trials (6-month safety update)

	Total ITR	Controlled			PK ITR	Uncontrolled ITR
		ITR	FLU	AMB		
Number of patients	360	234	32	202	95	31
Age, mean (years)	44.4	46.5	56.3	48.9	37.3	50.2
Gender, % male	66.1	61.5	62.5	56.9	77.9	64.5
Race						
Black, %	11.1	8.1	15.6	9.4	21.1	3.2
White, %	81.9	85.0	75.0	86.6	71.6	90.3
Hispanic, %	3.6	3.4	3.1	1.5	5.3	0.0
Other, %	3.3	3.4	6.3	2.5	2.1	6.5

Results:
The addition of the 97 new itraconazole-treated patients from trial ITR-INT-62 had minimal impact on the overall incidence of AEs. There was an overall incidence of 82% (209) reported in the original 255 patients as compared to 83.6% (301) reported for the 360 patients included in this update.

Specifically, 265 patients received IV itraconazole in 5 clinical studies (controlled and uncontrolled). 1951 AEs were experienced during the IV phase of the trials and 191 of these events were severe. 18 events (severe, moderate, mild) were coded as definitely-related to the study drug and included: 3 events of hypokalemia, 2 events each of rigors, rash, 1 event each of abnormal renal function, headache, dizziness, nausea, medication error, increased SGPT, pain, drug level increased, application site reaction and thrombosis. There were 2 events of injury definitely-associated to study drug.

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

Nausea: 22/265 (8.3%)
Diarrhea: 19/265 (7.2%)
Hypokalemia: 17/265 (6.4%)
Bilirubinemia: 14/265 (5.3%)
Vomiting: 13/265 (4.9%)
Rash: 8/265 (3%)
Increased Creatinine: 6/265 (2.3%)
Jaundice: 5/265 (1.9%)
SGOT increased: 5/265 (1.9%)
SGPT increased: 5/265 (1.9%)
Increased Alk. Phos.: 5/265 (1.9%)
Increased sweating: 4/265 (1.5%)
Headache: 4/265 (1.5%)
Dizziness: 4/265 (1.5%)
Hypomagnesemia: 4/265 (1.5%)
Edema 4/265: (1.5%)
Abnormal Hepatic Function: 4/265 (1.5%)
Abdominal Pain: 4/265 (1.5%)
Hypocalcemia: 3/265 (1.1%)
Dyspnea: 3/265 (1.1%)
Fever: 3/265 (1.1%)
Renal Function Abnormal: 3/265 (1.1%)
Increased BUN: 3/265 (1.1%)

Pain: 3/265 (1.1%)
Tachycardia: 3/265 (1.1%)
Erythematous Rash: 3/265 (1.1%)
Constipation: 3/265 (1.1%)
Acidosis: 2/265 (0.7%)
Fluid Overload: 2/265 (0.7%)
Hepatocellular Damage: 2/265 (0.7%)
Myalgia: 2/265 (0.7%)
Rigors: 2/265 (0.7%)
Abnormal Vision: 2/265 (0.7%)
Syncope: 2/265 (0.7%)

All other events occurred in 1/265 each or 0.4% and were not listed here.

There were a total of 29 deaths and 60 discontinuations due to an AE.

Below in Table 3 are all AEs that occurred during the IV itraconazole phase in at least 2 patients in all clinical trials (all causality):

Table 3
Adverse Event Incidence with Onset in the IV Phase in all Clinical (Controlled and Uncontrolled) Trials reported by at Least 2 Patients/All Causality

Body System/Adverse Event	Itraconazole IV N = 265 (100%)
Gastrointestinal System Disorders	
Nausea	52 (19.6%)
Diarrhea	46 (17.4%)
Vomiting	44 (16.6%)
Abdominal pain	22 (8.3%)
Constipation	17 (6.4%)
Stomatitis	13 (4.9%)
Mucositis	12 (4.5%)
Dyspepsia	9 (3.4%)
Pharyngitis	8 (3%)
Melena	6 (2.3%)
Enterocolitis	4 (1.5%)
GI Hemorrhage	5 (1.9%)
Stomatitis Ulcerative	6 (2.3%)
Tooth Ache	3 (1.1%)
Dry Mouth	5 (1.9%)
C. difficile Diarrhea	2 (0.8%)
Dysphagia	3 (1.1%)
Gingival Bleeding	2 (0.8%)
Hemorrhoids	3 (1.1%)
Rectal Disorder	3 (1.1%)
Eructation	2 (0.8%)
Fecal Incontinence	2 (0.8%)
GI Disorder	2 (0.8%)
Hematemesis	2 (0.8%)
Rectal Hemorraghe	2 (0.8%)
Oral Hemorrhage	2 (0.8%)
Tenesmus	2 (0.8%)
Body as a whole – General Disorders	
Fever	30 (11.3%)
Chest Pain	17 (6.4%)
Edema	21 (7.9%)

Table 3
Adverse Event Incidence with Onset in the IV Phase in all Clinical (Controlled and Uncontrolled) Trials reported by at Least 2 Patients/All Causality

Body System/Adverse Event	Itraconazole IV N = 265 (100%)
Generalized Edema	17 (6.4%)
Fluid Overload	13 (4.9%)
Pain	16 (6%)
Rigors	23 (8.7%)
Back Pain	12 (4.5%)
Leg Pain	2 (0.8%)
Leg Edema	2 (0.8%)
Mouth Edema	2 (0.8%)
Injury	13 (4.9%)
Fall	4 (1.5%)
Fatigue	9 (3.4%)
Edema Peripheral	8 (3%)
Edema Facial	4 (1.5%)
Abdomen Enlarged	8 (3%)
Hot Flushes	4 (1.5%)
Flushing	4 (1.5%)
Anaphylactoid Reaction	3 (1.1%)
Allergic Reaction	6 (2.3%)
Condition Aggravated	6 (2.3%)
Syncope	5 (1.9%)
Asthenia	4 (1.5%)
Weight Increase	2 (0.8%)
Weight Decrease	2 (0.8%)
Alopecia	2 (0.8%)
Leg Cramps	2 (0.8%)
Malaise	2 (0.8%)
Respiratory System Disorders	
Coughing	32 (12.1%)
Dyspnea	31 (11.7%)
Pneumonia	15 (5.7%)
Pulmonary Edema	18 (6.8%)
Pulmonary Infiltration	12 (4.5%)
Rhinitis	7 (2.6 %)
Hypoxia	9 (3.4%)
Pharyngitis	6 (3.7%)
Pneumonitis	6 (2.3%)
Respiratory Disorder	11 (4.2%)
Respiratory Insufficiency	7 (2.6%)
Pleural Effusion	8 (3%)
Bronchospasm	8 (3%)
Hemoptysis	8 (3%)
Abnormal CxR	5 (1.9%)
Stridor	3 (1.1%)
Dysphonia	2 (0.8%)
Lobar Pneumonia	2 (0.8%)
Atelectasis	2 (0.8%)
Decreased Breath Sounds	2 (0.8%)
Cyanosis	2 (0.8%)
Increased Sputum	2 (0.8%)
Metabolic and Nutritional Disorders	
Hypokalemia	42 (15.8%)

Table 3
Adverse Event Incidence with Onset in the IV Phase in all Clinical (Controlled and Uncontrolled) Trials reported by at Least 2 Patients/All Causality

Body System/Adverse Event	Itraconazole IV N = 265 (100%)
Hyperglycemia	15 (5.7%)
NPN Increased	13 (4.9%)
Fluid Overload	10 (6.2%)
Hypomagnesemia	18 (6.8%)
Phosphatase Alkaline Increased	11 (4.1%)
BUN Increased	8 (3%)
Hypocalcemia	13 (4.9%)
Edema Generalized	7 (4.4%)
Hyperkalemia	4 (1.5%)
CPK Increased	3 (1.1%)
Hypernatremia	5 (1.9%)
Hyponatremia	4 (1.5%)
Acidosis	3 (1.1%)
Hypophosphatemia	6 (2.3%)
Decreased CrCl	2 (0.8%)
Hypochloremia	2 (0.8%)
Dehydration	2 (0.8%)
Electrolyte Abnormality	2 (0.8%)
Hypercholesteremia	2 (0.8%)
Uremia	2 (0.8%)
Skin and Appendage Disorders	
Rash	31 (11.7%)
Rash Erythematous	16 (6%)
Rash Mac/Pap	2 (0.8%)
Sweating Increased	12 (4.55%)
Skin Disorder	6 (2.3%)
Pruritus	9 (3.4%)
Bullous Eruption	4 (1.5%)
Skin Discoloration	3 (1.1%)
Skin Ulceration	3 (1.1%)
Cellulitis	2 (0.8%)
Urticaria	3 (1.1%)
Photosensitivity Reaction	2 (0.8%)
Dry Skin	2 (0.8%)
Central & Peripheral Nervous System Disorders	
Headache	22 (8.3%)
Dizziness	11 (4.2%)
Tremor	9 (3.4%)
Abnormal Gait	2 (0.8%)
Involuntary Muscle Contractions	2 (0.8%)
Mydriasis	2 (0.8%)
Paresthesia	2 (0.8%)
Psychiatric Disorders	
Insomnia	12 (4.5%)
Confusion	16 (6%)
Hallucination	7 (2.6%)
Anorexia	6 (2.3%)
Somnolence	7 (2.6%)
Anxiety	12 (4.5%)
Sleep Disorder	4 (1.5%)
Agitation	7 (2.6%)

Table 3
Adverse Event Incidence with Onset in the IV Phase in all Clinical (Controlled and Uncontrolled) Trials reported by at Least 2 Patients/All Causality

Body System/Adverse Event	Itraconazole IV N = 265 (100%)
Depression	4 (1.5%)
Delirium	2 (0.8%)
Urinary System Disorders	
Hematuria	12 (4.5%)
Urine Abnormal	10 (3.8%)
Renal function Abnormal	12 (4.5%)
Urinary Incontinence	5 (1.9%)
Albuminuria	4 (1.5%)
Renal Failure Acute	5 (1.9%)
UTI	3 (1.1%)
Dysuria	3 (1.1%)
Oliguria	2 (0.8%)
Cardiovascular Disorders, General	
Hypotension	23 (8.7%)
Hypertension	12 (4.5%)
Cardiac Failure	8 (3%)
Heart Murmur	4 (1.5%)
Cardiomegaly	2 (0.8%)
Liver and Biliary System Disorders	
Bilirubinemia	24 (9%)
Jaundice	9 (3.4%)
SGPT Increased	7 (4.4%)
SGOT Increased	6 (2.3%)
gGT Increased	4 (1.5%)
Abnormal Hepatic Function	5 (1.9%)
Hepatocellular Damage	3 (1.1%)
Hepatitis	2 (0.8%)
Increased LDH	3 (1.1%)
Platelet, Bleeding & Clotting Disorders	
Epistaxis	15 (5.7%)
Purpura	8 (3%)
Trombocytopenia	2 (0.8%)
Hematoma	2 (0.8%)
Thrombosis	2 (0.8%)
Resistance Mechanism Disorders	
Infection Bacterial	13 (4.9%)
Herpes Simplex	7 (2.6%)
Infection	4 (1.5%)
Sepsis	5 (1.9%)
Moniliasis	3 (1.1%)
Conjunctivitis	3 (1.1%)
Fungal Infection	2 (0.8%)
Heart Rate and Rhythm Disorders	
Tachycardia	10 (3.8%)
Bradycardia	4 (1.5%)
Atrial Fibrillation	7 (2.6%)
Arrythmia	4 (1.5%)
Supraventricular Tachycardia	3 (1.1%)
Extrasystole	2 (0.8%)
Red Blood Cell Disorders	
Anemia	14 (5.3%)

Table 3
Adverse Event Incidence with Onset in the IV Phase in all Clinical (Controlled and Uncontrolled) Trials reported by at Least 2 Patients/All Causality

Body System/Adverse Event	Itraconazole IV N = 265 (100%)
White Blood Cell Disorders	
Granulocytopenia	3 (1.1%)
Vision Disorders	
Vision Abnormal	4 (1.5%)
Retinal Hemorraghe	2 (0.8%)
Application Site Disorders	
Application Site Reaction	8 (3%)
Injection Site Inflammation	4 (1.5%)
Musculoskeletal System Disorders	
Skeletal pain	6 (2.3%)
Myalgia	3 (1.1%)
Genital System Disorders	
Vaginal Hemorraghe	3 (1.1%)

Copied below from the submission is applicant table 4.3 or MO table 4 with AE incidence by treatment arm for the entire database. This table includes updated information on the amphotericn-B-treated patients. Minimal discrepancies between MO tables 3 and 4 are due to inaccuracies by the applicant in the electronic portion of the submission as well as by the use of a denominator of 3 (applicant) as opposed to 2 (MO).

Table 4
Adverse event incidence with onset in the intravenous treatment phase in worldwide trials, reported by at least three patients in any treatment group, by preferred term, n(%)

Body system/adverse event	Total		Controlled				Uncontrolled	
	ITR NDA N=255	ITR Update N=360	ITR NDA N=137	ITR Update N=234	FLU NDA N=32	AMB Update N=202	ITR NDA N=23	ITR Update N=31
Total number of subjects with adverse event	**209 (82.0)**	**301 (83.6)**	**128 (93.4)**	**209 (89.3)**	**31 (96.9)**	**191 (94.6)**	**17 (73.9)**	**28 (90.3)**
Gastrointestinal								
Nausea	40 (15.7)	55 (15.3)	33 (24.1)	46 (19.7)	8 (25.0)	48 (23.8)	2 (8.7)	4 (12.9)
Diarrhea	36 (14.1)	48 (13.3)	28 (20.4)	39 (16.7)	5 (15.6)	57 (28.2)	4 (17.4)	5 (16.1)
Vomiting	30 (11.8)	45 (12.5)	26 (19.0)	39 (16.7)	3 (9.4)	43 (21.3)	2 (8.7)	4 (12.9)
Abdominal Pain	18 (7.1)	24 (6.7)	14 (10.2)	19 (8.1)	5 (15.6)	19 (9.4)	1 (4.3)	2 (6.5)
Stomatitis	11 (4.3)	13 (3.6)	11 (8.0)	13 (5.6)	0 (0.0)	7 (3.5)	0 (0.0)	0 (0.0)
Constipation	19 (7.5)	23 (6.4)	9 (6.6)	13 (5.6)	4 (12.5)	8 (4.0)	3 (13.0)	3 (9.7)
Mucositis nos	8 (3.1)	11 (3.1)	7 (5.1)	10 (4.3)	2 (6.3)	11 (5.4)	1 (4.3)	1 (3.2)
Enterocolitis	4 (1.6)	4 (1.1)	4 (2.9)	4 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Melena	4 (1.6)	5 (1.4)	4 (2.9)	5 (2.1)	0 (0.0)	8 (4.0)	0 (0.0)	0 (0.0)
Dyspepsia	5 (2.0)	8 (2.2)	3 (2.2)	6 (2.6)	2 (6.3)	8 (4.0)	2 (8.7)	2 (6.5)
GI Hemorrhage	4 (1.6)	5 (1.4)	3 (2.2)	4 (1.7)	1 (3.1)	3 (1.5)	1 (4.3)	1 (3.2)
Stomatitis Ulcerative	4 (1.6)	6 (1.7)	3 (2.2)	5 (2.1)	0 (0.0)	5 (2.5)	1 (4.3)	1 (3.2)
Tooth Ache	3 (1.2)	3 (0.8)	3 (2.2)	3 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dysphagia	2 (0.8)	3 (0.8)	2 (1.5)	3 (1.3)	1 (3.1)	3 (1.5)	0 (0.0)	0 (0.0)
Hematemesis	2 (0.8)	2 (0.6)	2 (1.5)	2 (0.9)	0 (0.0)	3 (1.5)	0 (0.0)	0 (0.0)
Oral Hemorrhage	2 (0.8)	2 (0.6)	2 (1.5)	2 (0.9)	0 (0.0)	4 (2.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorder nos	2 (0.8)	3 (0.8)	1 (0.7)	2 (0.9)	0 (0.0)	2 (1.0)	0 (0.0)	0 (0.0)

Table 4

Adverse event incidence with onset in the intravenous treatment phase in worldwide trials, reported by at least three patients in any treatment group, by preferred term, n(%)

Body system/adverse event	Total		Controlled				Uncontrolled	
	ITR	ITR	ITR	ITR	FLU	AMB	ITR	ITR
	NDA N=255	Update N=360	NDA N=137	Update N=234	NDA N=32	Update N=202	NDA N=23	Update N=31
Total number of subjects with adverse event	209 (82.0)	301 (83.6)	128 (93.4)	209 (89.3)	31 (96.9)	191 (94.6)	17 (73.9)	28 (90.3)
Hemorrhoids	1 (0.4)	3 (0.8)	1 (0.7)	3 (1.3)	0 (0.0)	4 (2.0)	0 (0.0)	0 (0.0)
Mouth Dry	1 (0.4)	5 (1.4)	1 (0.7)	5 (2.1)	0 (0.0)	4 (2.0)	0 (0.0)	0 (0.0)
Rectal disorder	1 (0.4)	3 (0.8)	1 (0.7)	3 (1.3)	1 (3.1)	1 (0.5)	0 (0.0)	0 (0.0)
Body as a whole-general disorders								
Fever	30 (11.8)	36 (10.0)	18 (13.1)	22 (9.4)	7 (21.9)	20 (9.9)	5 (21.7)	7 (22.6)
Pain	16 (6.3)	19 (5.3)	13 (9.5)	16 (6.8)	3 (9.4)	8 (4.0)	0 (0.0)	0 (0.0)
Edema	14 (5.5)	21 (5.8)	12 (8.8)	19 (8.1)	3 (9.4)	10 (5.0)	2 (8.7)	2 (6.5)
Chest Pain	11 (4.3)	18 (5.0)	10 (7.3)	15 (6.4)	1 (3.1)	8 (4.0)	0 (0.0)	2 (6.5)
Rigors	11 (4.3)	23 (6.4)	10 (7.3)	20 (8.5)	4 (12.5)	82 (40.6)	1 (4.3)	3 (9.7)
Injury	10 (3.9)	15 (4.2)	8 (5.8)	11 (4.7)	2 (6.3)	6 (3.0)	0 (0.0)	2 (6.5)
Back Pain	8 (3.1)	12 (3.3)	7 (5.1)	11 (4.7)	2 (6.3)	9 (4.5)	0 (0.0)	0 (0.0)
Abdomen Enlarged	5 (2.0)	8 (2.2)	5 (3.6)	8 (3.4)	1 (3.1)	4 (2.0)	0 (0.0)	0 (0.0)
Edema Peripheral	5 (2.0)	8 (2.2)	5 (3.6)	8 (3.4)	1 (3.1)	14 (6.9)	0 (0.0)	0 (0.0)
Anaphylactoid Reaction	3 (1.2)	3 (0.8)	3 (2.2)	3 (1.3)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Fatigue	3 (1.2)	8 (2.2)	3 (2.2)	4 (1.7)	1 (3.1)	6 (3.0)	0 (0.0)	4 (12.9)
Hot Flushes	3 (1.2)	4 (1.1)	3 (2.2)	3 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.2)
Asthenia	2 (0.8)	4 (1.1)	2 (1.5)	4 (1.7)	1 (3.1)	1 (0.5)	0 (0.0)	0 (0.0)
Condition Aggravated	4 (1.6)	6 (1.7)	2 (1.5)	4 (1.7)	0 (0.0)	7 (3.5)	2 (8.7)	2 (6.5)
Malaise	2 (0.8)	2 (0.6)	2 (1.5)	2 (0.9)	0 (0.0)	5 (2.5)	0 (0.0)	0 (0.0)
Syncope	5 (2.0)	6 (1.7)	2 (1.5)	3 (1.3)	0 (0.0)	1 (0.5)	2 (8.7)	2 (6.5)
Allergic Reaction	3 (1.2)	7 (1.9)	1 (0.7)	5 (2.1)	0 (0.0)	5 (2.5)	1 (4.3)	1 (3.2)
Chest Pain Substernal	0 (0.0)	3 (0.8)	0 (0.0)	3 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lab Values Abnormal	1 (0.4)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.0)	1 (4.3)	1 (3.2)
Respiratory system disorders								
Coughing	24 (9.4)	32 (8.9)	20 (14.6)	28 (12.0)	3 (9.4)	10 (5.0)	4 (17.4)	4 (12.9)
Dyspnea	22 (8.6)	31 (8.6)	15 (10.9)	24 (10.3)	1 (3.1)	22 (10.9)	6 (26.1)	6 (19.4)
Pneumonia	10 (3.9)	13 (3.6)	10 (7.3)	13 (5.6)	1 (3.1)	11 (5.4)	0 (0.0)	0 (0.0)
Pulmonary Infiltration	9 (3.5)	12 (3.3)	9 (6.6)	12 (5.1)	1 (3.1)	4 (2.0)	0 (0.0)	0 (0.0)
Pulmonary Edema	14 (5.5)	18 (5.0)	9 (6.6)	13 (5.6)	2 (6.3)	12 (5.9)	5 (21.7)	5 (16.1)
Rhinitis	8 (3.1)	8 (2.2)	7 (5.1)	7 (3.0)	2 (6.3)	4 (2.0)	0 (0.0)	0 (0.0)
Hypoxia	8 (3.1)	9 (2.5)	6 (4.4)	7 (3.0)	1 (3.1)	2 (1.0)	2 (8.7)	2 (6.5)
Pharyngitis	6 (2.4)	8 (2.2)	6 (4.4)	8 (3.4)	1 (3.1)	3 (1.5)	0 (0.0)	0 (0.0)
Respiratory Disorder	9 (3.5)	11 (3.1)	6 (4.4)	8 (3.4)	0 (0.0)	10 (5.0)	3 (13.0)	3 (9.7)
Pleural Effusion	5 (2.0)	8 (2.2)	5 (3.6)	8 (3.4)	3 (9.4)	5 (2.5)	0 (0.0)	0 (0.0)
Respiratory Insufficiency	6 (2.4)	7 (1.9)	5 (3.6)	6 (2.6)	0 (0.0)	5 (2.5)	0 (0.0)	0 (0.0)
Bronchospasm	7 (2.7)	8 (2.2)	4 (2.9)	5 (2.1)	1 (3.1)	6 (3.0)	3 (13.0)	3 (9.7)
Hemoptysis	5 (2.0)	8 (2.2)	3 (2.2)	6 (2.6)	1 (3.1)	6 (3.0)	2 (8.7)	2 (6.5)
Pneumonitis	3 (1.2)	7 (1.9)	2 (1.5)	6 (2.6)	0 (0.0)	6 (3.0)	0 (0.0)	0 (0.0)
Chest X-ray Abnormal	2 (0.8)	5 (1.4)	1 (0.7)	4 (1.7)	0 (0.0)	5 (2.5)	1 (4.3)	1 (3.2)
Stridor	3 (1.2)	3 (0.8)	1 (0.7)	1 (0.4)	0 (0.0)	0 (0.0)	2 (8.7)	2 (6.5)

Table 4

Adverse event incidence with onset in the intravenous treatment phase in worldwide trials, reported by at least three patients in any treatment group, by preferred term, n(%)

Body system/adverse event	Total		Controlled				Uncontrolled	
	ITR	ITR	ITR	ITR	FLU	AMB	ITR	ITR
	NDA N=255	Update N=360	NDA N=137	Update N=234	NDA N=32	Update N=202	NDA N=23	Update N=31
Total number of subjects with adverse event	209 (82.0)	301 (83.6)	128 (93.4)	209 (89.3)	31 (96.9)	191 (94.6)	17 (73.9)	28 (90.3)
Pleural Pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.5)	0 (0.0)	0 (0.0)
Sinusitis	1 (0.4)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.0)	0 (0.0)	0 (0.0)
Metabolic and nutritional disorders								
Hypokalemia	22 (8.6)	39 (10.8)	21 (15.3)	38 (16.2)	4 (12.5)	65 (32.2)	1 (4.3)	1 (3.2)
Hyperglycemia	14 (5.5)	18 (5.0)	10 (7.3)	14 (6.0)	4 (12.5)	9 (4.5)	0 (0.0)	0 (0.0)
NPN Increased	12 (4.7)	13 (3.6)	10 (7.3)	11 (4.7)	2 (6.3)	55 (27.2)	2 (8.7)	2 (6.5)
Fluid Overload	11 (4.3)	14 (3.9)	8 (5.8)	11 (4.7)	3 (9.4)	15 (7.4)	2 (8.7)	2 (6.5)
Hypomagnesemia	8 (3.1)	17 (4.7)	7 (5.1)	16 (6.8)	2 (6.3)	18 (8.9)	1 (4.3)	1 (3.2)
Bun Increased	6 (2.4)	7 (1.9)	6 (4.4)	7 (3.0)	0 (0.0)	18 (8.9)	0 (0.0)	0 (0.0)
Hypocalcemia	7 (2.7)	11 (3.1)	6 (4.4)	10 (4.3)	2 (6.3)	10 (5.0)	1 (4.3)	1 (3.2)
Edema Generalized	6 (2.4)	16 (4.4)	6 (4.4)	16 (6.8)	1 (3.1)	13 (6.4)	0 (0.0)	0 (0.0)
Phosphatase Alkaline Increased	6 (2.4)	11 (3.1)	6 (4.4)	11 (4.7)	5 (15.6)	5 (2.5)	0 (0.0)	0 (0.0)
CPK Increased	3 (1.2)	3 (0.8)	3 (2.2)	3 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperkalemia	3 (1.2)	4 (1.1)	3 (2.2)	4 (1.7)	1 (3.1)	3 (1.5)	0 (0.0)	0 (0.0)
Hypernatremia	3 (1.2)	5 (1.4)	3 (2.2))	5 (2.1)	0 (0.0)	2 (1.0)	0 (0.0)	0 (0.0)
Acidosis	3 (1.2)	3 (0.8)	2 (1.5)	2 (0.9)	0 (0.0)	3 (1.5)	1 (4.3)	1 (3.2)
Electrolyte Abnormality	2 (0.8)	2 (0.6)	2 (1.5)	2 (0.9)	0 (0.0)	3 (1.5)	0 (0.0)	0 (0.0)
Hypophosphatemia	2 (0.8)	6 (1.7)	2 (1.5)	6 (2.6)	2 (6.3)	6 (3.0)	0 (0.0)	0 (0.0)
LDH Increased	2 (0.8)	3 (0.8)	2 (1.5)	3 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyponatremia	2 (0.8)	3 (0.8)	1 (0.7)	2 (0.9)	1 (3.1)	3 (1.5)	1 (4.3)	1 (3.2)
Hypoproteinemia	1 (0.4)	1 (0.3)	1 (0.7)	1 (0.4)	0 (0.0)	3 (1.5)	0 (0.0)	0 (0.0)
Dehydration	0 (0.0)	2 (0.6)	0 (0.0)	2 (0.9)	0 (0.0)	3 (1.5)	0 (0.0)	0 (0.0)
Skin and appendages disorders								
Rash	21 (8.2)	32 (8.9)	16 (11.7)	26 (11.1)	3 (9.4)	14 (6.9)	3 (13.0)	4 (12.9)
Rash Erythematous	11 (4.3)	16 (4.4)	10 (7.3)	15 (6.4)	1 (3.1)	10 (5.0)	1 (4.3)	1 (3.2)
Sweating Increased	10 (3.9)	14 (3.9)	8 (5.8)	11 (4.7)	0 (0.0)	4 (2.0)	0 (0.0)	1 (3.2)
Pruritus	6 (2.4)	10 (2.8)	5 (3.6)	9 (3.8)	1 (3.1)	6 (3.0)	0 (0.0)	0 (0.0)
Skin Disorder	3 (1.2)	6 (1.7)	3 (2.2)	6 (2.6)	2 (6.3)	3 (1.5)	0 (0.0)	0 (0.0)
Skin Discoloration	2 (0.8)	3 (0.8)	2 (1.5)	3 (1.3)	2 (6.3)	4 (2.0)	0 (0.0)	0 (0.0)
Skin ulceration	2 (0.8)	3 (0.8)	2 (1.5)	2 (0.9)	1 (3.1)	2 (1.0)	0 (0.0)	1 (3.2)
Rash Maculopapular	2 (0.8)	3 (0.8)	1 (0.7)	2 (0.9)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Skin dry	2 (0.8)	3 (0.8)	1 (0.7)	2 (0.9)	0 (0.0)	3 (1.5)	0 (0.0)	0 (0.0)
Urticaria	1 (0.4)	3 (0.8)	1 (0.7)	3 (1.3)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Bullous Eruption	0 (0.0)	4 (1.1)	0 (0.0)	4 (1.7)	0 (0.0)	2 (1.0)	0 (0.0)	0 (0.0)
Psychiatric disorders								
Confusion	10 (3.9)	16 (4.4)	8 (5.8)	14 (6.0)	0 (0.0)	7 (3.5)	2 (8.7)	2 (6.5)
Insomnia	8 (3.1)	12 (3.3)	8 (5.8)	10 (4.3)	0 (0.0)	8 (4.0)	0 (0.0)	2 (6.5)
Anorexia	6 (2.4)	6 (1.7)	6 (4.4)	6 (2.6)	1 (3.1)	4 (2.0)	0 (0.0)	0 (0.0)
Hallucination	6 (2.4)	7 (1.9)	6 (4.4)	7 (3.0)	0 (0.0)	5 (2.5)	0 (0.0)	0 (0.0)

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Body system/adverse event	Total		Controlled				Uncontrolled	
	ITR	ITR	ITR	ITR	FLU	AMB	ITR	ITR
	NDA N=255	Update N=360	NDA N=137	Update N=234	NDA N=32	Update N=202	NDA N=23	Update N=31
Total number of subjects with adverse event	**209 (82.0)**	**301 (83.6)**	**128 (93.4)**	**209 (89.3)**	**31 (96.9)**	**191 (94.6)**	**17 (73.9)**	**28 (90.3)**
Somnolence	6 (2.4)	7 (1.9)	6 (4.4)	7 (3.0)	2 (6.3)	8 (4.0)	0 (0.0)	0 (0.0)
Sleep Disorder	4 (1.6)	4 (1.1)	4 (2.9)	4 (1.7)	0 (0.0)	3 (1.5)	0 (0.0)	0 (0.0)
Anxiety	5 (2.0)	12 (3.3)	3 (2.2)	9 (3.8)	0 (0.0)	8 (4.0)	0 (0.0)	1 (3.2)
Agitation	2 (0.8)	7 (1.9)	2 (1.5)	7 (3.0)	1 (3.1)	1 (0.5)	0 (0.0)	0 (0.0)
Depression	3 (1.2)	5 (1.4)	2 (1.5)	4 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Central and peripheral nervous system disorders								
Headache	17 (6.7)	25 (6.9)	10 (7.3)	17 (7.3)	0 (0.0)	17 (8.4)	2 (8.7)	3 (9.7)
Dizziness	8 (3.1)	10 (2.8)	7 (5.1)	9 (3.8)	0 (0.0)	7 (3.5)	1 (4.3)	1 (3.2)
Tremor	5 (2.0)	9 (2.5)	5 (3.6)	8 (3.4)	0 (0.0)	3 (1.5)	0 (0.0)	1 (3.2)
Fecal Incontinence	1 (0.4)	2 (0.6)	1 (0.7)	2 (0.9)	0 (0.0)	3 (1.5)	0 (0.0)	0 (0.0)
Liver and biliary system disorders								
Bilirubinemia	17 (6.7)	25 (6.9)	15 (10.9)	23 (9.8)	5 (15.6)	10 (5.0)	0 (0.0)	0 (0.0)
Jaundice	7 (2.7)	8 (2.2)	7 (5.1)	8 (3.4)	1 (3.1)	6 (3.0)	0 (0.0)	0 (0.0)
SGPT Increased	7 (2.7)	7 (1.9)	7 (5.1)	7 (3.0)	1 (3.1)	3 (1.5)	0 (0.0)	0 (0.0)
SGOT Increased	5 (2.0)	5 (1.4)	5 (3.6)	5 (2.1)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Hepatic Function Abnormal	2 (0.8)	5 (1.4)	2 (1.5)	5 (2.1)	0 (0.0)	9 (4.5)	0 (0.0)	0 (0.0)
Gamma-GT Increased	2 (0.8)	5 (1.4)	1 (0.7)	4 (1.7)	3 (9.4)	3 (1.5)	0 (0.0)	0 (0.0)
Hepatitis Cholestatic	1 (0.4)	1 (0.3)	1 (0.7)	1 (0.4)	0 (0.0)	3 (1.5)	0.(0.0)	0 (0.0)
Hepatocellular Damage	1 (0.4)	3 (0.8)	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)	1 (4.3)	1 (3.2)
Cardiovascular disorders, general								
Hypotension	16 (6.3)	25 (6.9)	12 (8.8)	21 (9.0)	3 (9.4)	22 (10.9)	1 (4.3)	1 (3.2)
Hypertension	8 (3.1)	11 (3.1)	8 (5.8)	11 (4.7)	6 (18.8)	7 (3.5)	0 (0.0)	0 (0.0)
Cardiac Failure	7 (2.7)	9 (2.5)	6 (4.4)	8 (3.4)	0 (0.0)	2 (1.0)	0 (0.0)	0 (0.0)
Heart Murmur	3 (1.2)	4 (1.1))	3 (2.2)	4 (1.7)	0 (0.0)	2 (1.0)	0 (0.0)	0 (0.0)
Edema Dependent	1 (0.4)	1 (0.3)	1 (0.7)	1 (0.4)	0 (0.0)	5 (2.5)	0 (0.0)	0 (0.0)
Urinary system disorders								
Hematuria	10 (3.9)	13 (3.6)	9 (6.6)	11 (4.7)	2 (6.3)	8 (4.0)	0 (0.0)	1 (3.2)
Urine Abnormal	7 (2.7)	10 (2.8)	7 (5.1)	10 (4.3)	0 (0.0)	2 (1.0)	0 (0.0)	0 (0.0)
Renal Function Abnormal	6 (2.4)	11 (3.1)	5 (3.6)	10 (4.3)	0 (0.0)	25 (12.4)	1 (4.3)	1 (3.2)
Urinary Incontinence	5 (2.0)	5 (1.4)	5 (3.6)	5 (2.1)	0 (0.0)	4 (2.0)	0 (0.0)	0 (0.0)
Renal Failure Acute	4 (1.6)	5 (1.4)	4 (2.9)	5 (2.1)	0 (0.0)	4 (2.0)	0 (0.0)	0 (0.0)
Albuminuria	7 (2.7)	8 (2.2)	3 (2.2)	4 (1.7)	1 (3.1)	1 (0.5)	0 (0.0)	0 (0.0)
Oliguria	2 (0.8)	2 (0.6)	2 (1.5)	2 (0.9)	0 (0.0)	3 (1.5)	0 (0.0)	0 (0.0)
Urinary Tract Infection	2 (0.8)	2 (0.6)	2 (1.5)	2 (0.9)	3 (9.4)	2 (1.0)	0 (0.0)	0 (0.0)
Face Edema	1 (0.4)	4 (1.1)	1 (0.7)	2 (0.9)	0 (0.0)	2 (1.0)	0 (0.0)	2 (6.5)
Nephropathy Toxic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.5)	0 (0.0)	0 (0.0)

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	ITR	ITR	ITR	ITR	FLU	AMB	ITR	ITR
	NDA N=255	Update N=360	NDA N=137	Update N=234	NDA N=32	Update N=202	NDA N=23	Update N=31
Total number of subjects with adverse event	**209 (82.0)**	**301 (83.6)**	**128 (93.4)**	**209 (89.3)**	**31 (96.9)**	**191 (94.6)**	**17 (73.9)**	**28 (90.3)**
Platelet, bleeding and clotting disorders								
Epistaxis	12 (4.7)	15 (4.2)	10 (7.3)	13 (5.6)	3 (9.4)	15 (7.4)	2 (8.7)	2 (6.5)
Purpura	6 (2.4)	8 (2.2)	6 (4.4)	8 (3.4)	0 (0.0)	6 (3.0)	0 (0.0)	0 (0.0)
Coagulation Disorder	1 (0.4)	2 (0.6)	1 (0.7)	2 (0.9)	0 (0.0)	3 (1.5)	0 (0.0)	0 (0.0)
Hemorrhage nos	1 (0.4)	1 (0.3)	1 (0.7)	1 (0.4)	1 (3.1)	3 (1.5)	0 (0.0)	0 (0.0)
Resistance mechanism disorders								
Infection Bacterial	10 (3.9)	14 (3.9)	6 (4.4)	10 (4.3)	0 (0.0)	3 (1.5)	1 (4.3)	1 (3.2)
Herpes Simplex	7 (2.7)	8 (2.2)	5 (3.6)	6 (2.6)	0 (0.0)	3 (1.5)	1 (4.3)	1 (3.2)
Infection	3 (1.2)	4 (1.1)	3 (2.2)	4 (1.7)	2 (6.3)	2 (1.0)	0 (0.0)	0 (0.0)
Moniliasis	2 (0.8)	3 (0.8)	2 (1.5)	3 (1.3)	1 (3.1)	2 (1.0)	0 (0.0)	0 (0.0)
Sepsis	5 (2.0)	6 (1.7)	2 (1.5)	3 (1.3)	4 (12.5)	9 (4.5)	1 (4.3)	1 (3.2)
Infection Fungal	1 (0.4)	2 (0.6)	0 (0.0)	1 (0.4)	1 (3.1)	6 (3.0)	1 (4.3)	1 (3.2)
Red blood cell disorders								
Anemia	12 (4.7)	12 (3.3)	11 (8.0)	11 (4.7)	1 (3.1)	2 (1.0)	0 (0.0)	0 (0.0)
Heart rate and rhythm disorders								
Tachycardia	6 (2.4)	10 (2.8)	6 (4.4)	10 (4.3)	2 (6.3)	13 (6.4)	0 (0.0)	0 (0.0)
Bradycardia	3 (1.2)	3 (0.8)	3 (2.2)	3 (1.3)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Arrhythmia	2 (0.8)	4 (1.1)	2 (1.5)	3 (1.3)	0 (0.0)	3 (1.5)	0 (0.0)	1 (3.2)
Fibrillation Atrial	1 (0.4)	6 (1.7)	1 (0.7)	6 (2.6)	0 (0.0)	3 (1.5)	0 (0.0)	0 (0.0)
Application site disorders								
Application Site reaction	23 (9.0)	24 (6.7)	7 (5.1)	8 (3.4)	0 (0.0)	6 (3.0)	0 (0.0)	0 (0.0)
Cellulitis	2 (0.8)	2 (0.6)	1 (0.7)	1 (0.4)	0 (0.0)	4 (2.0)	1 (4.3)	1 (3.2)
Injection Site Inflammation	0 (0.0)	4 (1.1)	0 (0.0)	3 (1.3)	0 (0.0)	1 (0.5)	0 (0.0)	1 (3.2)
Vision disorders								
Vision Abnormal	4 (1.6)	4 (1.1)	4 (2.9)	4 (1.7)	0 (0.0)	3 (1.5)	0 (0.0)	0 (0.0)
Conjunctivitis	0 (0.0)	3 (0.8)	0 (0.0)	3 (1.3)	1 (3.1)	6 (3.0)	0 (0.0)	0 (0.0)
Vascular (extracardiac) disorders								
Flushing	2 (0.8)	4 (1.1)	2 (1.5)	4 (1.7)	0 (0.0)	3 (1.5)	0 (0.0)	0 (0.0)
Phlebitis	1 (0.4)	1 (0.3)	1 (0.7)	1 (0.4)	0 (0.0)	3 (1.5)	0 (0.0)	0 (0.0)
Vein Disorder	9 (3.5)	9 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Muscle-skeletal disorders								
Skeletal Pain	5 (2.0)	6 (1.7)	5 (3.6)	6 (2.6)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Myalgia	1 (0.4)	3 (0.8)	0 (0.0)	2 (0.9)	1 (3.1)	3 (1.5)	1 (4.3)	1 (3.2)
Secondary Terms								
Fall	1 (0.4)	4 (1.1)	1 (0.7)	4 (1.7)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
White cell and res disorders								
Granulocytopenia	5 (2.0)	6 (1.7)	2 (1.5)	3 (1.3)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Reproductive Disorders, Female								
Vaginal Hemorrhage	2 (0.8)	4 (1.1)	0 (0.0)	2 (0.9)	0 (0.0)	1 (0.5)	1 (4.3)	1 (3.2)

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Total number of subjects with adverse event	209 (82.0)	301 (83.6)	128 (93.4)	209 (89.3)	31 (96.9)	191 (94.6)	17 (73.9)	28 (90.3)
Special senses other, disorders								
Taste perversion	3 (1.2)	3 (0.8)	1 (0.7)	1 (0.4)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)

MO Comment: Highlighted in gray was any event observed with increased incidence in the 6-month update as compared to the original NDA database. The following AEs were observed with an incidence greater than or equal to twice that observed in the original database: dry mouth, allergic reaction, abnormal CxR, agitation, increased gGT, and atrial fibrillation. A review of the CRFs revealed that of the allergic reactions, none were attributed to itraconazole infusion. 3 of these events were transfusion-related and all were mild. Of the 3 events of increased gGT, only one was attributed to the study drug.

As noted in addendum I to the MOR (MOR of 4-month safety update), rigors and fatigue were observed in 3 patients and with an incidence greater than twice that observed in the original database. The investigators attributed there events to the patients' underlying disease, aspergillosis.

Overall and as stated previously, there were no significant or unexpected differences in the AE profiles for any of the antifungal agents utilized.

Adverse Event Incidence by Relationship to Study Medication:

In MO table 5 are the AEs assessed by the investigators as possibly or definitely-related to study medication by treatment arm. This table included all amphotericn-B-treated patients, all controlled and uncontrolled itraconazole–treated patients and the original 32 fluconazole-treated patients. Additionally columns have been added to represent all 360 itraconazole-treated patients as well as the 95 PK patients.

Table 5
All AEs Considered Possibly or Definitely Related to Study Drugs (As per the MO)

Body system/ Adverse event	Total	Clinical (Controlled and Uncontrolled)			PK
	ITR n=360	ITR n=265	FLU n=32	AMB n= 202	ITR n=95
Total number patients with adverse event	151 (41.9)	112 (42.3)	7 (21.9)	166 (82.2)	39 (41.1)
Gastrointestinal System Disorders	54 (15)	43 (16.2)	2 (6.3)	49 (24.3)	11 (11.6)
Nausea	42 (11.7)	23 (8.7)	0 (0.0)	31 (15.3)	5 (5.3)
Diarrhea	44 (12.3)	19 (7.2)	1 (3.1)	18 (8.9)	4 (4.2)
Vomiting	19 (5.3)	13 (4.9)	0 (0.0)	21 (10.4)	1 (1.1)

Body system/ Adverse event	Total ITR n=360	Clinical (Controlled and Uncontrolled) ITR n=265	FLU n=32	AMB n= 202	PK ITR n=95
Abdominal Pain	13 (3.6)	4 (1.5)	0 (0.0)	6 (3.0)	3 (3.2)
Constipation	4 (1.2)	3 (1.1)	1 (3.1)	1 (0.5)	0 (0.0)
Dyspepsia	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
GI Disorder	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
C. difficile Diarrhea	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Pharyngitis	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Colitis	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Melena	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Liver and Biliary System Disorders	**30 (8.3)**	**27 (10.2)**	**4 (12.5)**	**15 (7.4)**	**3 (3.2)**
Bilirubinemia	18 (5)	14 (5.3)	3 (9.4)	6 (3.0)	2 (2.1)
SGPT Increased	8 (2.3)	6 (2.3)	1 (3.1)	2 (1.0)	0 (0.0)
Jaundice	6 (1.7)	5 (1.9)	0 (0.0)	1 (0.5)	0 (0.0)
SGOT Increased	6 (1.7)	5 (1.9)	0 (0.0)	1 (0.5)	0 (0.0)
Hepatic Function Abnormal	7 (2)	4 (1.5)	0 (0.0)	3 (1.5)	0 (0.0)
Increased gGT	4 (1.2)	2 (0.7)	0 (0.0)	1 (0.5)	0 (0.0)
Increased LDH	5 (1.4)	5 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatocellular Damage	2 (0.6)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Venoocclusive Liver Disease	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Bilirubinuria	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatitis	1 (0.3)	1(0.4)	0 (0.0)	1 (0.5)	0 (0.0)
Cholestatic Hepatitis	1 (0.3)	1(0.4)	0 (0.0)	1 (0.5)	0 (0.0)
Hepatomegaly	2 (0.6)	2 (0.7)	0 (0.0)	1 (0.5)	0 (0.0)
Aggravated Bilirubinemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Abnormal Hepatic Function	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Enzyme Abnormalities	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)
Metabolic and Nutritional Disorders	**39 (10.8)**	**37 (14)**	**2 (6.3)**	**96 (47.5)**	**2 (2.1)**
Hypokalemia	19 (5.3)	20 (7.5)	0 (0.0)	60 (29.7)	0 (0.0)
Increased Creatinine	9 (2.5)	6 (2.3)	1 (3.1)	53 (26.2)	0 (0.0)
Increased CrCl	2 (0.6)	2 (0.7)	0 (0.0)	2 (1.0)	0 (0.0)
Increased BUN	3 (0.9)	3 (1.1)	0 (0.0)	15 (7.4)	0 (0.0)
Increased Alk. Phos.	6 (1.7)	5 (1.9)	1 (3.1)	4 (2.0)	0 (0.0)
Fluid Overload	2 (0.7)	2 (0.7)	0 (0.0)	5 (2.5)	0 (0.0)
Hyperglycemia	3 (0.9)	1 (0.4)	0 (0.0)	1 (0.5)	2 (2.1)
Hypomagnesemia	4 (1.2)	4 (1.5)	0 (0.0)	9 (4.5)	0 (0.0)
Hypocalcemia	3 (0.9)	3 (1.1)	0 (0.0)	5 (2.5)	0 (0.0)
Glycosuria	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Acidosis	2 (0.6)	2 (0.7)	0 (0.0)	2 (1.0)	0 (0.0)
Hypochloremia	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Hyponatremia	1 (0.3)	1 (0.4)	0 (0.0)	1 (0.5)	0 (0.0)
Hyperchloremia	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypophosphatemia	2 (0.6)	1 (0.4)	0 (0.0)	3 (1.5)	0 (0.0)
Hyperuricemia	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperphosphatemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Hyperkalemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)

Body system/ Adverse event	Total ITR n=360	Clinical (Controlled and Uncontrolled) ITR n=265	FLU n=32	AMB n= 202	PK ITR n=95
Hypoproteinemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Hypoglycemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Hypertriglyceridemia	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)
Electrolyte Abnormalities	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)
Body as a Whole – General Disorders	**26 (7.2)**	**24 (9)**	**0 (0.0)**	**77 (38.1)**	**2 (2.1)**
Pain	4 (1.2)	4 (1.5)	0 (0.0)	1 (0.5)	0 (0.0)
Rigors	3 (0.9)	4 (1.5)	0 (0.0)	71 (35.1)	0 (0.0)
Syncope	3 (0.9)	2 (0.7)	0 (0.0)	0 (0.0)	1 (1.1)
Fever	5 (1.4)	3 (1.1)	0 (0.0)	14 (6.9)	0 (0.0)
Enlarged Abdomen	2 (0.6)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Malaise	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)
Back Pain	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0))	0 (0.0)
Central & Peripheral Nervous System Disorder	**19 (5.3)**	**16 (6.0)**	**0 (0.0)**	**10 (5.0)**	**3 (3.2)**
Dizziness	5 (1.9)	5 (1.9)	0 (0.0)	2 (1.0)	0 (0.0)
Headache	10 (2.8)	5 (1.9)	0 (0.0)	5 (2.5)	3 (3.2)
Urinary System Disorders	**14 (3.9)**	**9 (3.4)**	**0 (0.0)**	**32 (15.8)**	**5 (5.3)**
Renal Function Abnormal	1 (0.3)	4 (1.5)	0 (0.0)	24 (11.9)	0 (0.0)
Albuminuria	5 (1.9)	1 (0.4)	0 (0.0)	0 (0.0)	4 (4.2)
Nephropathy Toxic	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.5)	0 (0.0)
Edema	5 (1.9)	4 (1.5%)	0 (0.0)	1 (0.5)	0 (0.0)
Peripheral edema	2 (0.6)	2 (0.7)	0 (0.0)	2 (1.0)	0 (0.0)
General Edema	1 (0.3)	1 (0.4)	0 (0.0)	2 (1.0)	0 (0.0)
Oral Edema	1 (0.3)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Dependent Edema	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Pyuria	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Uremia	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Dysuria	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Hematuria	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Oliguria	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Leg Edema	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Periorbital Edema	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal Urine	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Cystitis	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Interstitial Nephritis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
ARF	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)
Micturition Disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Glomerular RF Abnormality	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Dehydration	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)

Body system/ Adverse event	Total ITR n=360	Clinical (Controlled and Uncontrolled) ITR n=265	FLU n=32	AMB n= 202	PK ITR n=95
Skin and Appendages Disorders	**21 (5.8)**	**18 (6.8)**	**2 (6.3)**	**12 (5.9)**	**3 (3.2)**
Rash	15 (4.2)	10 (3.8)	1 (3.1)	7 (3.5)	1 (1.1)
Pruritus	1 (0.3)	0 (0.0)	0 (0.0)	2 (1)	1 (1.1)
Rash (erythematous)	3 (0.9)	3 (1.1)	0 (0.0)	1 (0.5)	0 (0.0)
Rash (mac/pap)	2 (0.6)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Localized Skin Reaction	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Increased Sweating	4 (1.2)	4 (1.5)	0 (0.0)	1 (0.5)	0 (0.0)
Skin Disorder	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Dry Skin	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Acne	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Urticaria	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Allergic Reaction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Cardiovascular Disorders, General	**4 (1.1)**	**4 (1.5)**	**0 (0.0)**	**15 (7.4)**	**0 (0.0)**
Hypertension	1 (0.3)	1 (0.4)	0 (0.0)	4 (2.0)	0 (0.0)
Aggravated Hypertension	1 (0.3)	1 (0.4)	0 (0.0)	1 (0.5)	0 (0.0)
Hypotension	2 (0.6)	2 (0.7)	0 (0.0)	6 (3.0)	0 (0.0)
Cardiac Failure	1 (0.3)	1 (0.4)	0 (0.0)	1 (0.5)	0 (0.0)
Cardiac Arrest	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Chest Pain	2 (0.6)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary Edema	1 (0.3)	1 (0.4)	0 (0.0)	3 (1.5)	0 (0.0)
Postural Hypotension	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)
Heart Rate and Rhythm Disorders	**3 (0.9)**	**3 (1.1)**	**0 (0.0)**	**8 (4.0)**	**0 (0.0)**
Tachycardia	3 (0.9)	3 (1.1)	0 (0.0)	5 (2.5)	0 (0.0)
Arrythmia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Atrial Fibrillation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Respiratory System Disorders	**6 (1.8)**	**6 (2.3)**	**0 (0.0)**	**16 (7.9)**	**0 (0.0)**
Dyspnea	3 (0.9)	3 (1.1)	0 (0.0)	6 (3.0)	0 (0.0)
Bronchospasm	1 (0.3)	1 (0.4)	0 (0.0)	3 (1.5)	0 (0.0)
Hemoptysis	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pleural Effusion	1 (0.3)	1 (0.4)	0 (0.0)	1 (0.5)	0 (0.0)
Pulmonary Infiltrate	2 (0.6)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory Disorder	1 (0.3)	1 (0.4)	0 (0.0)	2 (1.0)	0 (0.0)
Hypoxia	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinitis	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Abnormal CxR	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Respiratory Insufficiency	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Sinusitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Cyanosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Vascular (extracardiac) Disorders	**12 (3.4)**	**2 (0.7)**	**0 (0.0)**	**6 (3.0)**	**10 (10.5)**
Flushing	1 (0.3)	1 (0.4)	0 (0.0)	3 (1.5)	0 (0.0)
Phlebitis	1 (0.3)	1 (0.4)	0 (0.0)	3 (1.50	0 (0.0)
Vein Disorder	9 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	9 (9.5)

Body system/ Adverse event	Total ITR n=360	Clinical (Controlled and Uncontrolled) ITR n=265	FLU n=32	AMB n= 202	PK ITR n=95
Thrombosis	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Application Site Disorders	**17 (4.7)**	**2 (0.9)**	**0 (0.0)**	**1 (0.5)**	**15 (15.8)**
Application Site Reaction	17 (4.7)	2 (0.9)	0 (0.0)	0 (0.0)	15 (15.8)
Application Site Edema	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site Inflammation	1 (0.3)	1 (0.4)	0 (0.0)	1 (0.5)	0 (0.0)
Special Senses other, Disorders	**3 (0.9)**	**1 (0.4)**	**0 (0.0)**	**2 (1.0)**	**2 (2.1)**
Taste Perversion	1 (0.3)	1 (0.4)	0 (0.0)	1 (0.5)	2 (2.1)
Other	1 (0.3)	1 (0.4)	0 (0.0)	1 (0.5)	0 (0.0)
Medication Error	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Injury	2 (0.6)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Increased Drug Level	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Increased Therapeutic Response	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal Lab	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)

Body system/ Adverse event	Total ITR n=360	Clinical (Controlled and Uncontrolled) ITR n=265	FLU n=32	AMB n= 202	PK ITR n=95
Vision	**2 (0.6)**	**2 (0.7)**	**0 (0.0)**	**2 (1.0)**	**0 (0.0)**
Abnormal vision	2 (0.6)	2 (0.7)	0 (0.0)	1 (0.5)	0 (0.0)
Mydriasis	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal	**3 (0.90**	**2 (0.7)**	**1 (3.1)**	**0 (0.0)**	**1 (3.2)**
Hypertonia	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	1 (3.2)
Tremor	2 (0.6)	2 (0.7)	0 (0.0)	1 (0.5)	0 (0.0)
Myalgia	2 (0.6)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal Gait	2 (0.6)	2 (0.7)	0 (0.0)		
Paresthesia	1 (0.3)	1 (0.4)	0 (0.0)	1 (0.0)	0 (0.0)
Involuntary Muscle contraction	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Hypoaesthesia	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Dystonia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
RBC Disorders	**2 (0.6)**	**1 (0.4)**	**0 (0.0)**	**2 (1.0)**	**0 (0.0)**
Increased Hemoglobin	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Anemia	2 (0.6)	2 (0.7)	0 (0.0)	2 (1.0)	0 (0.0)
WBC and Resistance Disorders	**2 (0.6)**	**1 (0.4)**	**0 (0.0)**	**3 (1.5)**	**0 (0.0)**
Infection	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
URI	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Granulocytopenia	7 (2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fungal Infection	3 (0.9)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Leucopenia	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sepsis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Decreased tolerance	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Abnormal WBC	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Neoplasm	**1 (0.3)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Psychiatric	**4 (1.2)**	**4 (1.6)**	**0 (0.0)**	**10 (5.0)**	**0 (0.0)**
Hallucination	1 (0.3)	1 (0.4)	0 (0.0)	1 (0.5)	0 (0.0)
Sleep Disorder	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Somnolence	1 (0.3)	1 (0.4)	0 (0.0)	2 (1.0)	0 (0.0)
Sensation of Temp. change	1 (0.3)	1 (0.4)	0 (0.0)	1 (0.0)	0 (0.0)
Aggressive Reaction	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Insomnia	2 (0.6)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Anorexia	1 (0.3)	1 (0.4)	0 (0.0)	3 (1.5)	0 (0.0)
Weight Gain	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Confusion	1 (0.3)	1 (0.4)	0 (0.0)	3 (1.5()	0 (0.0)
Anxiety	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Apathy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Nervousness	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)

MO Comment: As expected, the most frequent AEs were from the GI tract with nausea, vomiting, and diarrhea the predominant complaints. There was no major difference in the frequency of these events between the amphotericin-B-treated population and the itraconazole-treated population. GI events were infrequent in the fluconazole-treated population although the validity of this finding is unclear given the small sample size.

A larger number of itraconazole-treated patients developed liver and biliary disorders as compared to the amphotericin B treated patients. Interestingly, bilirubinemia was seen with the highest frequency in the fluconazole-treated population.

Hypokalemia and disturbances of renal function were seen predominantly in the amphotericin-B-treated population. However, hypokalemia was the most frequent metabolic abnormality in the itraconazole-treated group. This is consistent with the previously known AE profile of this agent.

Rash was seen relatively symmetrically between all groups and application site reactions remained the most common skin event in the itraconazole-treated patients.

Laboratory Abnormalities:

No major differences were noted in the incidence of previously seen abnormalities between the original database and the 6-month update.

Specifically, anemia, leucopenia, ad thrombocytopenia were seen frequently due to the high proportion of patients with underlying hematologic malignancies. The addition of 97 itraconazole-treated patients to the NDA database did not change the incidence of Grade 2 or 3 anemia. There was a slightly higher incidence of Grade 2, and particularly Grade 3, thrombocytopenia observed between the NDA database and the six-month safety update database (Grade 2: 13.6% (18 /132) versus 15.9% (22/138), respectively and Grade 3: 15.2%(21/138) versus 20.5% (31/151), respectively). There was also a slightly higher incidence of leucopenia in itraconazole-treated patients in the six-month update compared with the NDA (31.8% (27/85) versus 37.3% (38/102), respectively). Increases, however, were also noted in amphotericin-treated patients (58.3% (7/12) versus 75% (18/24). The incidences of these hematologic changes are not markedly different from the NDA database and are consistent with the underlying hematologic malignancies in the ITR-INT-62 patient population.

Hypocalcemia was slightly less frequent in the 6-month update as compare to the original database (11.7% (27/230) versus 10.7 % (34/319). The overall incidence of grade II hypocalcemia was unchanged at 22% and the incidence of Grade III hypocalcemia increased slightly compared with the original database (6-month 19/327 (5.8%) versus original 10/239 (4.2%). The above are compared to the amphotericn arm where grade 3 hypocalcemia was found in 27/162 (16.7%) at the 6-month update.

Hypokalemia, a known AE of both itraconazole and amphotericn B continued to be observed in the 6-month update with a higher incidence in the amphotericin B-treated patients. Specifically the downward potassium shift for itraconazole-treated patients was observed in the six-month database compared with the NDA database (14.0% (48/342) versus 12.2% (30/245), respectively) and for amphotericin B (25.3% (45/178) versus 22.9% (22/96), respectively).

Hyperglycemia was noted in the analysis of the original NDA database as well as in the 6-month update There was a slight decrease in the incidence of Grade II and III hyperglycemia at the 6-month update (original grade II 30/194 (15.5%) versus 6-month 40/273 (14.7%) and Grade III: original 12/217 (5.5%) versus 16/310 (5.2%). At the 6-month update the incidence of hyperglycemia Grade II on the amphotericin B arm was 37/142 (26.1%) and grade III was 16/160 (10%).

Elevations of BUN and creatinine were seen in the analysis of the original database and there were no substantial changes noted in the six-month database in shift from within to above normal values or in NIH Grade 2 and 3 toxicities (original 20/243m(8.2%) versus 6-month 27/335 (8.1%). With the exception of NIH Grade 3 toxicity, which was low across all treatment groups, the incidences of increased values remained highest in the amphotericin B-treated patients (74/170 (43.5%).

The incidence of increased creatinine remained unchanged at 5.3% for the itraconazole-treated patients.

LFTs: Bilirubin:

The incidence of increased bilirubin laboratory values and NIH Grade 2 and 3 toxicity in itraconazole-treated patients was slightly higher in the six-month safety database than in the NDA database (original 30/224 (13.4%) versus 6-month 45/311 (14.5%) versus 6-month amphotericn 18/163 (11%). At the 6-month update, 15.5 5 of itraconazole-treated patients (45/291) versus 15.55 of amphotericn B-treated patients (23/148) had Grade II toxicity and 9% (29/332) versus 6.1% (10/163) per arm respectively had Grade III toxicity.

Liver enzymes

No significant differences were noted in the incidence of liver enzyme abnormalities between the NDA and six-month safety databases. In general the laboratory value changes for itraconazole were similar or slightly lower in the six-month update compared with the original NDA.

Premature discontinuations due to laboratory abnormalities of liver function

Five itraconazole injection-treated patients summarized in the original NDA discontinued therapy with abnormalities of liver function that appeared related to itraconazole. One patient is summarized in this six-month safety update that discontinued therapy with an adverse event reported as an abnormality of liver function that the investigator determined may have been related to itraconazole injection. No discontinuations or serious adverse events for liver abnormalities that appeared related to itraconazole were reported in the four-month update.

Six-month safety update
Discontinuation for adverse event
Patient #03191: 34 YO male received itraconazole on September 6, 1997 to September 7, 1997. His medical history included hematologic malignancy, nasal congestion, and heartburn. On the first day of treatment with intravenous itraconazole the patient experienced a rise in liver enzymes. The enzymes were reported to be more than five times the upper limits of normal. Results of a liver ultrasound done on September 19, 997 were normal. Itraconazole was discontinued because of severe abnormal hepatic function. The abnormal liver function was reported to be possibly drug-related. Relevant laboratory abnormalities included:
Total bilirubin: 15 µmol/l at baseline; 20 µmol/l on Day 3 (normal limits: 5-7 µmol/l)
Alkaline phosphatase: 93 U/L at baseline; 197 U/L on Day 3 (normal limits: 0-110 U/L)
GGT: 73 U/L at baseline; 232 U/L on Day 3 (normal limits: 10-48 U/L)
AST (SGOT): 92 U/L at baseline; 551 U/L on Day 3 (normal limits: 5-40 U/L)
ALT (SGPT): 166 U/L at baseline; 1254 U/L on Day 3 (normal limits: 5-40 U/L)

Applicant's Discussion and Conclusions

The six-month safety update to NDA #20-966 (SPORANOX® Injection) provides additional safety information from 97 itraconazole-treated patients participating in ITR-INT-62, an open randomized trial comparing the efficacy and safety of intravenous followed by oral itraconazole with intravenous amphotericin B for empiric therapy in neutropenic patients with hematological malignancy. The complete databases for ITR-INT-62 and ITR-INT-60 (reported in the four-month safety update) have been combined with the data from the 255 itraconazole-treated patients reported in the original NDA to provide a new database of 360 itraconazole injection-treated patients. The six-month safety update also provides, in narrative summaries, a description of all patients who died or had other serious adverse events in trials [redacted] ITR-INT-61 and ITR-INT-62 during the reporting period from 1 May 1998 through 1 September 1998. Summaries for all patients who discontinued for an adverse event from ITR-INT-62 during the reporting period from 1 May 1998 through 1 September 1998 are also presented.

The adverse events summarized in the six-month safety update are consistent with the type and severity of adverse events summarized in the NDA and the four-month safety update to the NDA. In general, the adverse events reflect the severity of disease of the patient population under investigation. No new or unexpected adverse events were reported for itraconazole.

Reviewer's Discussion and Conclusions:

As noted in the introduction, the original database contained safety information on 255 patients who received IV itraconazole. 95 of these patients received less than 14 days of itraconazole and were studied within the context of PK trials. Subsequent to the original submission, the applicant submitted a 4-month and a 6-month safety update containing safety data on patients from 2 ongoing clinical trials. The final total number of itraconazole recipients was 360, with 265 receiving a 14-day course of therapy. 234 of the patients received itraconazole within the context of a comparative clinical trial.

Overall the MO agreed with the applicant's determination of safety. Additionally, no new AEs were described with the addition of 97 patients to the safety database.

The MO continues to recommend approval for IV itraconazole and proposes that a table (see below) of all investigator-determined, treatment-related AEs reported by ≥ 1% of patients be added to the label. The MO agreed with the current formatting of the table by the applicant in which the total itraconazole population as well as the comparative clinical trials populations are represented. Further labeling recommendations can be found below.

Consideration should be given to a Phase IV commitment to assess for the effect of the IV formulation in patients with renal insufficiency (GFR < 30 mL/min.). It is possible that patients with this degree of renal insufficiency msay benefit from the use of IV itraconazole, however, dosing recommendations cannot be made for this population based on the patients studied in this NDA.

Consideration should be given to the modification of the dosing recommendations to reflect that the use of a loading dose pertains to patients with life-threatening infections.

SUMMARY OF POSSIBLY OR DEFINITELY DRUG-RELATED ADVERSE EVENTS REPORTED BY ≥1% OF SPORANOX® INJECTION PATIENTS (TOTAL)				
ADVERSE EVENT	**IV Itraconazole (N = 360) %**	**Comparative Trials**		
		IV Itraconazole (N = 234) %	**IV Fluconazole (N = 32) %**	**Amphotericin B (N = 202) %**
Gastrointestinal System Disorders				
Nausea	8	9	0	15
Diarrhea	6	6	3	9
Vomiting	4	6	0	10
Constipation	1	1	3	0.5
Abdominal Pain	2	2	0	3
Liver and Biliary System Disorders				
Bilirubinemia	4	6	9	3
SGPT (ALT) Increased	3	3	3	1
SGOT (AST) Increased	1	2	0	1
Jaundice	1	2	0	1
Hepatic Function Abnormal	1	2	0	2
Metabolic and Nutritional Disorders				
Hypokalemia	5	8	0	29
Increased Creatinine	2	2	3	26
Increased Alkaline Phosphatase	1	2	3	2
Hypomagnesemia	1	1	0	5
Body as a Whole				
Pain	1	1.5	0	0.5
Edema	1	1.1	0	6.9
Central and Peripheral Nervous System Disorder				
Dizziness	1	2	0	1
Headache	2	2	0	3
Urinary System Disorders				
Albuminuria	1	0	0	0
Renal Function Abnormal	1	1	0	11
Skin and Appendages Disorders				
Rash	3	2	3	3
Increased Sweating	1	2	0	1
Application Site Disorder				
Application site Disorder	4	0	0	0
Vascular (Extracardiac Disorders)				
Vein Disorder	3	0	0	0

The following adverse events also occurred in less than 1% of patients in clinical trials of Sporanox® injection: constipation, hyperglycemia, hepatitis, fever, rigors, dyspnea, and hypotension.

RECOMMENDED REGULATORY ACTION AND LABELING RECOMMENDATIONS:

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

The MO continues to propose that the following changes be incorporated into the applicant's proposed labeling:

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

   should be modified to:

   [redacted]

   The sentence "There are limited data on the use of SPORANOX® Injection for periods longer than fourteen days"

   should be modified to:

   [redacted]

   The sentences "Treatment should be continued for a minimum of three months and until clinical parameters and laboratory tests indicate that the active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection"

   [redacted]

2) Under **ADVERSE REACTIONS** the applicant's table and text (see MOR page 30 and MOR addendum II page 21) should be modified to include AEs related to therapy reported by ≥ 1% of itraconazole-treated patients and incorporated into the label.

   The section pertaining to events that occurred in 5% of patients where causality is uncertain should be deleted as it is not in accordance with labeling regulations that state that only AEs with a causal relationship to treatment should be included in product labeling.

[redacted]

/S/

Regina Alivisatos, MD
DSPIDP, HFD-590

Cc:
Orig. NDA 50-762
HFD-590
HFD-520
HFD-590/DIVDir/MGoldberger
HFD-590/DepDIVDir/RAlbrecht
HFD-590/MTL/BLeissa BL 6/4/99
HFD-590/Biopharm/PColangelo
HFD-590/Chem/Holbert
HFD-590/Pharm/McMaster
HFD-590/CSO/Kimzey
HFD-725/Biostat/Shen
3/19/99

APPEARS THIS WAY
ON ORIGINAL

APPENDIX I:
DEATHS:
Included in the database were all deaths that occurred between 1 May 1998 and 1 September 1998. Specifically, a total of 8 deaths in the itraconazole-treated population ([redacted]62), 9 in the fluconazole-treated population [redacted] and 2 in the amphotericn-B population (trial 62). A brief description of each patient follows:

Itraconazole (N = 8):

Patient #0152: 58 YO male received itraconazole from March 30, 1998 to April 19, 1998. The patient died from multi-organ failure on April 19, 1998. Autopsy indicated death was due to diffuse lung parenchymal damage. The kidneys showed mild arterionephrosclerosis and isometric vacuolization consistent with, but not specific for, cyclosporine toxicity. The investigator reported that the event was not related to study drug.

Patient #0167: 36 YO male received itraconazole from July 16, 1998 until his death on August 1, 1998. The patient had a history of acute myelogenous leukemia and received an allogeneic bone marrow transplant. On July 16, 1998 neutropenia was noted. Intravenous imipenem was administered and cultures were drawn. He developed mucositis and his liver function began to deteriorate as evidenced by increasing abnormal liver function tests. Blood cultures grew *Enterococcus* spp. He received vancomycin. A liver biopsy revealed no necrosis but the culture grew *Enterococcus* spp. In addition, he developed acute renal failure necessitating dialysis and he died on August 1, 1998. The investigator reported that this death was not related to study drug.

Patient #0506: 42 YO female started itraconazole on May 7,1998. On June 5, 1998 study drug was temporarily held following complications from a second bone marrow transplant. Itraconazole was restarted on June 7, 1998. The patient experienced complications following her bone marrow transplant including venous occlusive disease, ascites, and liver and renal failure ultimately causing respiratory failure leading to her death on June 20, 1998. The investigator reported that the cause of death was not related to study drug.

Patient #0217: 66 YO female started itraconazole on May 14, 1998. She discontinued on May 16, 1998 due to a worsening of her underlying candidemia. Fluconazole was given on May 16,1998 and subsequently changed to amphotericin B with no improvement. The patient died on May 19, 1998 due to *Candida* septicemia, hepatic failure, acute renal failure, and small bowel obstruction. Death was reported as not related to study drug.

Patient # 3552: 57 YO female received itraconazole from September 15, 1997 to September 28, 1997. The patient had acute myelogenous leukemia. A bronchoscopy confirmed the presence of *Aspergillus* pneumonia. The patient developed left-sided hemiparesis and a computer-assisted tomography confirmed a fungal process in the brain. The patient continued on antibiotics including amphotericin B, however she died on September 30, 1997. It was reported that in the opinion of the investigator the death was not related to study drug.

Patient #3625: 67 YO female received itraconazole from November 11, 1997 to November 20, 1997. The patient's medical history included lymphoma, hypertension, cataracts, asthma, and mild renal insufficiency. Itraconazole was stopped after ten days of treatment because of moderately abnormal renal function, reported as not drug related. Subsequently the patient developed adult respiratory distress syndrome, atrial fibrillation, and multi-organ failure and died on December 9, 1997. The death was reported as not related to study drug according to the investigator.

Patient #3626: 65 YO male began itraconazole on September 22, 1997 and discontinued prematurely two days later due to respiratory insufficiency. The patient's medical history included bypass surgery for coronary artery disease, non-insulin dependent diabetes, and alcoholic liver disease. On September 27,

1997, the patient was admitted to the ICU for a diagnostic bronchoscopy. During the procedure, the patient's condition deteriorated suddenly and he required intubation. He died of respiratory failure reported as doubtfully related to study drug.

Patient # 3423: 61 YO male received study drug from September 12, 1997 to September 21, 1997. The subject died on September 29, 1997 of pneumonia and complications of acute myelogenous leukemia not related to study drug.

MO Comment: None of the deaths in the itraconazole-treated patients appeared related to therapy but rather to the patients' serious underlying conditions.

Fluconazole Patients (N = 9):

Patient #0142: 55 YO male began fluconazole on January 27, 1998. He had chronic lymphoid leukemia. His post-transplant course was complicated by congestive heart failure, veno-occlusive disease, elevated bilirubin levels, acute renal failure, neutropenia, fevers and atrial fibrillation due to pericarditis. He died on February 10, 1998 secondary to heart failure and veno-occlusive disease. The investigator reported that the death was unrelated to study drug.

Patient #0149:45 YO male received fluconazole from March 10, 1998 to May 15, 1998. Amphotericin B lipid complex was begun on May 16, 1998. The patient died June 4, 1998 due to liver failure secondary to graft-versus-host-disease. No autopsy was performed. The investigator reported the death was unrelated to study drug.

Patient #0153: 51 YO female received fluconazole from April 13, 1998 until July 22, 1998. The patient was hospitalized on July 12, 1998 for a relapse of acute lymphocytic leukemia. She developed sepsis and adult respiratory distress syndrome requiring intubation on July 28, 1998. Despite supportive therapy, the patient died on July 30, 1998. The investigator reported the death as unrelated to study drug.

Patient #0156: 53 YO male received fluconazole from May 4,1998 to July 16, 1998. The patient had a medical history of myelodysplastic syndrome and received an allogeneic bone marrow transplant on May 5, 1998. Complications developed post-transplantation. He developed acute renal failure, graft-versus-host-disease, and *Aspergillus* pneumonia. The patient died on July 19, 1998. The investigator considered this death unrelated to study drug.

Patient #0158: 48 YO female began study medication on May 19, 1998 to June 21, 1998. This patient had a history of chronic myelogenous leukemia and diabetes. Her bone marrow transplant was complicated by graft-versus-host-disease with skin and liver involvement and difficulty controlling her hyperglycemia. On June 18, 1998, she required mechanical ventilation and dialysis. Despite supportive therapy the patient died on June 21, 1998. The cause of death was multiple organ failure secondary to chronic myelogenous leukemia. The investigator considered this death unrelated to study drug.

Patient #0163: 56 YO male received fluconazole from June 23, 1998 to July 15, 1998. This patient had a history of Hodgkin's disease and a cardiac transplant. He developed acute myelogenous leukemia and was treated with an allogeneic bone marrow transplant on June 24, 1998. He developed multiple complications following his bone marrow transplant and died on July 15, 1998 of sepsis, respiratory and multi-organ failure. The investigator reported that this death was unrelated to study drug.

Patient #0312: 49 YO male began fluconazole on March 27, 1998. He was hospitalized on July 22, 1998 for relapsed acute myelogenous leukemia. The patient's myeloblast count continued to increase while the graft-versus-host-disorder involving the gastrointestinal system continued to worsen. Cyclosporin and methylprednisolone treatment which had previously been discontinued was reinitiated. Endoscopy revealed Grade 3 acute graft-versus-host-disease on July 27, 1998. The investigator considered the patient to have uncontrollable graft-versus-host-disease of the gastrointestinal tract on July 28, 1998. The patient died on July 31, 1998. The investigator reported that this death was unrelated to study drug.

Patient #0518: 57 YO female received fluconazole from June 20, 1998 to June 23, 1998. While in hospice care, on August 24, 1998, the patient died secondary to malnutrition and failure to thrive. The investigator reported the death as not related to study drug.

Patient #0519: 74 YO female received fluconazole on June 17, 1998. The patient developed sepsis and multi-system organ failure, and died on June 18, 1998. Death was reported as not related to study drug.

Amphotericin B (N = 2):

Patient #3524: 81 YO male received amphotericin B from August 18, 1997 to August 21, 1997. The patient died of pneumonia on September 3, 1997. This death was reported unrelated to study drug.

Patient #3640: 41 YO female received trial medication from October 10, 1997 to October 21, 1997. On November 12, 997, 22 days after completing study medication, the patient died of his underlying hematologic malignancy. This death was reported as unrelated to study drug.

MO Comment: All reported deaths on the fluconazole and amphotericin B treatment arms were unrelated to study drug.

Premature Discontinuations due to AEs:

There were a total of 10 discontinuations in the itraconazole-treated patients ([redacted]62) and 1 discontinuation in the fluconazole-treated patients. There were no premature discontinuations due to an AE on the amphotericn-B arm. Listed below are the patients.

Itraconazole (N = 10):

Patient #0423: 20 YO male received itraconazole from July 16, 1998 to July 29, 1998. This patient had a history of idiopathic aplastic anemia and underwent an allogeneic bone marrow transplant on July 16, 1998. He developed sepsis and respiratory distress on July 26, 1998. He was transferred to the intensive care unit diagnosed with chemotherapy toxicity and required mechanical ventilation. During an infusion of itraconazole the patient experienced a hypotensive episode. Dopamine was administered and the patient was withdrawn from the study as a precaution. The investigator felt that the hypotension was possibly related to study drug while all other events were considered to be unrelated. On August 2, 1998 he died following a left middle cerebral artery infarct with uncal and conal brain herniation

Patient #3380: 65 YO female received itraconazole on August 25, 1997 to September 2, 1997. Her medical history included hysterectomy and hematologic malignancy. The patient was discontinued from intravenous itraconazole after nine days of treatment on because of a rash. The rash was reported to be possibly drug-related.

Patient #3381: 38 YO female received itraconazole on October 9, 1997 to October 30, 1997. Her medical history included caesarian section, Grade 2/3 systolic ejection murmur, mucositis, and hematologic malignancy. The patient discontinued itraconazole treatment because of a bacterial infection. The bacterial infection was reported to be not drug-related.

Patient #3188: 68 YO male received itraconazole on October 28, 1997 to October 29, 1997. His medical history included peptic ulcer disease, arthritis, chronic obstructive pulmonary disease, severe thrush of the hard palate, and nausea. Itraconazole was discontinued because of fever. The fever was reported to be not drug-related.

Patient #3191: 34 YO male received itraconazole on September 6, 1997 to September 7, 1997. His medical history included hematologic malignancy, nasal congestion, and heartburn. On the first day of treatment with intravenous itraconazole the patient experienced a rise in liver enzymes. The enzymes were reported to be more than five times the upper limits of normal. Results of a liver ultrasound done on

September 9, 1997 were normal. Itraconazole was discontinued because of severe abnormal hepatic function. The abnormal liver function was reported to be possibly drug-related.

Patient #3197: 46 YO male received itraconazole on June 5, 1997 to June 6, 1997. His medical history included diabetes and cutaneous T-cell lymphoma. On June 6, 1997, within 45 minutes of drug administration, the patient experienced hypoxia, confusion, hallucinations, and aggressive behavioral changes. The adverse events resolved within one hour. Itraconazole was discontinued and these events were reported to be possibly related to itraconazole and a combination of medications and diamorphine withdrawal.

Patient #3528: 61 YO female Th received itraconazole on September 3, 1997 to September 4, 1997. Her medical history included hematologic malignancy, anaphylactic allergy to etoposide, and mucositis. The patient was discontinued from itraconazole treatment because of bilirubinemia. The bilirubinemia was reported to be not drug-related.

Patient #3627: 46 YO male received itraconazole on October 6, 1997 to October 24, 1997. His medical history included hematologic malignancy and hypertension. The patient was discontinued from itraconazole treatment after 19 days on October 24, 1997 because of nausea. The nausea was reported to be possibly drug-related.

Patient #3635: 48 YO female received itraconazole on October 14, 1997 to October 19, 1997. Medical history included hematologic malignancy. The patient was discontinued from itraconazole treatment because of edema of the mouth, periorbital edema, and rash. These events were reported to be possibly drug-related.

Patient #3643: 44 YO male received itraconazole on November 7, 1997 to November 9, 1997. His medical history included hematologic malignancy, fatigue, and muscle aches. The patient was discontinued from itraconazole treatment because of bronchospasm, dyspnea and tachycardia. These events were considered possibly drug-related.

Fluconazole (N = 1):

Patient #0419: 29 YO female began fluconazole on April 21, 1998. She discontinued from fluconazole on June 13, 1998 and received amphotericin B because of severe pulmonary consolidation in the left upper and left lower lobe. She was diagnosed with community acquired pneumonia. Her condition worsened and she was intubated. Nitropaste was administered to stabilize blood pressure fluctuations. Her pulmonary condition improved and she was extubated. She was diagnosed with left lung empyema and a left thoracotomy was performed on 30 June 1998.

Serious AEs:

There were a two serious AEs reported in itraconazole-treated patients. One patient (#0313) developed TTP considered unrelated to the study drug. The other patient (#0416), developed GVHD also considered unrelated to study drug.

No serious AEs were reported for amphotericn-B-treated patients.

There were 4 reported serious AEs on the fluconazole-treated patients. 1 patient (#0406) experienced a seizure thought to be related to a high cyclosporine level, a second (#0422) developed increased LFTs which resolved on therapy, a third, (#0616) develop occlusion of the femoral artery, and the fourth (#0218), developed syncope. All of the above were considered unrelated to the study drug.