

termination. There were no values that went from pathological low (high) at inclusion to pathological high (low) at termination.

The most common abnormalities that developed from a normal baseline were bilirubinemia in 6 subjects, hypocalcemia in 4 subjects, and increase in ALT in 3 subjects. The bilirubinemia occurred in different patients from the ALT increases. Increases ranged from 3 – 5 x ULN.

Additionally 2 subjects developed hypokalemia and 2 had an increase in gGT.

Medical Officer's Conclusion: *The safety profile of ITR in this small study did not differ from that previously seen. Most commonly AEs were from the GI tract. Hepatic and biliary disorders also occurred in 12 (57.1%) of subjects. In only 1 case of LFT abnormalities was the AE attributed to ITR. Overall compliance was poor after the first week of treatment, therefore conclusions regarding long term use of ITR oral solution cannot be drawn.*

ITR-INT-54:

Title: A double-blind trial comparing itraconazole oral solution with oral amphotericin B capsules for primary prophylaxis of fungal infections in subjects with hematological malignancy and profound neutropenia.

Study Dates: July 4, 1994 – April 16, 1997

Investigators: 78 investigators from Austria, Belgium, France, Greece, Portugal, Spain, and The Netherlands

Study Synopsis:

Phase III, randomized, double-blind, double-dummy trial to compare the efficacy of itraconazole oral solution with oral amphotericin B in the prevention of deep fungal infections, to compare the incidence of other fungal infections, the frequency of and the time to initiation of intravenous amphotericin B and the evolution of colonization in hematological malignancy and profound neutropenia. Prophylactic treatment was started on the first day of chemotherapy and was continued until the end of neutropenia or up to a maximum of 3 days following the end of neutropenia, unless a trial end point was reached earlier, with a maximum of 8 weeks. 559 subjects were entered, 557 were randomized to treatment: 281 were assigned to itraconazole (2.5 mg/kg BID) and 276 to amphotericin B (2 capsules QID). Because of the double blind, double-dummy nature of the trial, subjects received either active itraconazole solution together with placebo capsules or active amphotericin B capsules together with placebo solution. Noteworthy inclusion criteria specified adult patients of either sex who had acute leukemia scheduled for remission/induction or consolidation/re-induction chemotherapy, autologous bone marrow transplantation, or subject with myelodysplastic syndrome scheduled to receive leukemia-like cytostatic therapy or chemotherapy for the blast crisis of chronic

myelogenous leukemia, or lymphoma, or myeloma undergoing aggressive chemotherapy. These subjects were expected to have a neutrophil count $<500/\mu\text{l}$ during at least 14 days and could not have had any signs or symptoms of fungal infection (fungal colonization was allowed). Excluded were patients with proven or suspected deep fungal infection (including all cases without mycological sampling) diagnosed during previous episodes of neutropenia, patients presenting with a chest X-ray suggestive of fungal infection, patients presenting with a fever of unknown origin ($>38.5^{\circ}\text{C}$, rectal temperature), or patients expected to receive GMCSF, MCSF, IL3 or other growth factors, except for GCSF.

Other noteworthy exclusion criteria included the exclusion of patients who had received systemic antifungal therapy within two weeks before trial entry or topical intra-oral antifungal therapy within one week, or patients who had evidence of liver disease defined as liver enzymes (SGPT or SGOT) ≥ 4 times the upper normal limit at trial entry.

Safety assessments if the form of clinic visits were performed on a weekly basis and included blood analyses.

59 % of ITR patients and 55% of AMP B patients had AML. The median duration of neutropenia (neutrophil count $< 0.5 \times 10^9/\text{l}$) was 18 days in the itraconazole group and 20 days in the amphotericin B group. The median duration of treatment was 19 days in the itraconazole group and 18 days in the amphotericin B group. Baseline characteristics were similar in the two groups.

As per the applicant:

Adverse events, mainly gastro-intestinal system disorders, were reported in 222 (79%) itraconazole subjects and in 205 (74%) amphotericin B subjects. The most frequently reported adverse events were diarrhea (78 itraconazole subjects and 75 amphotericin B subjects), nausea (56 and 60 subjects) and vomiting (49 and 43 subjects). Severe adverse events, mainly nausea, diarrhea, vomiting and mucositis, were reported in 94 (34%) itraconazole subjects and 69 (25%) amphotericin B subjects. Overall, serious adverse events were reported in 26 (9%) itraconazole subjects and 32 (12%) amphotericin B subjects. Eighteen (6.4%) itraconazole subjects and 23 (8.3%) amphotericin B subjects died during the trial (including the period up to 30 days after the last intake of the trial medication). Seventy-five (27%) itraconazole subjects and 78 (28%) amphotericin B subjects permanently stopped the intake of the trial medication because of adverse events or death.

Changes in biochemical laboratory parameters were comparable in the two groups; there were many important laboratory abnormalities but considering this subject population, these could be accounted for.

In conclusion, the trial medication was well tolerated and safe.

Table B13
Safety Summary as per the Applicant

Safety (n = number of subjects with data)	Itraconazole N = 281	Amphotericin B N = 276
Adverse events (AE) (> 5%)		
Most frequently reported AE:		
• Abdominal pain	31 (11)	29 (11)
• Bilirubinemia	18 (6)	15 (5)
• Diarrhoea	78 (28)	75 (27)
• Fever	27 (10)	18 (7)
• Headache	11 (4)	17 (6)
• Herpes simplex	14 (5)	12 (4)
• Hypokalemia	30 (11)	19 (7)
• Mucositis NOS	20 (7)	16 (6)
• Nausea	56 (20)	60 (22)
• Rash	48 (17)	37 (13)
• Sepsis	19 (7)	16 (6)
• Vomiting	49 (17)	43 (16)
No. (%) with one or more AE	222 (79)	205 (74)
No. (%) with one or more serious AE	26 (9)	32 (12)
No. (%) of deaths	18 (6.4)	23 (8.3)
No. (%) with one or more other serious AE ¹	12 (4)	17 (6)
No. (%) treatment stopped due to AE	75 (27)	78 (28)
• Clinical laboratory parameters	Overall, there was a tendency towards a decrease in total cholesterol, and an increase in total bilirubin, gGT, and ALT; these changes were observed in the two groups. There were many important laboratory abnormalities but considering this subject population, these could be accounted for.	

¹includes also some subjects who died, but in whom serious adverse events were reported without outcome died

As per the MO:

281 ITR subjects (167 males and 114 females) were randomized as compared to 276 (147 males and 129 females) AMP B subjects. The median age was 48 and 49.5 years per study arm respectively. All subjects were diagnosed with hematologic malignancies and median duration of treatment was 19 and 18 days per arm respectively. Overall the profile of subjects was similar to that in study 62. Patients were assessed on a weekly basis.

In the table below are all AEs that occurred. As expected most AEs on both arms occurred from the GI tract including nausea, vomiting, and diarrhea. Fever was common on both study arms and possibly attributable to the patients underlying disease processes. Hypokalemia was also seen on both study arms. Although hypokalemia is associated with IV AMP B, it is not a frequent phenomenon attributable to the PO, non-absorbable formulation. Hypokalemia is associated with ITR. LFT abnormalities including hyperbilirubinemia were seen on both arms but with greater frequency on the ITR arm. Rash and erythematous rash were reported with similar frequency.

Table B14
All Adverse events ITT Population

ADVERSE EVENT	Itraconazole N = 281 (100%)	Amphotericin B N = 276 (100%)
GASTRO-INTESTINAL SYSTEM		
Diarrhea	78 (27.8%)	75 (27.2%)
Bloody diarrhea	1(0.4%)	-
Duodenal Ulcer	1(0.4%)	-
Dyspepsia	11 (3.9%)	8 (2.9%)
Dysphagia	4 (1.4%)	1 (0.4%)
Enteritis	1 (0.4%)	1(0.4%)
Nausea	56 (19.9%)	60 (21.7%)
Vomiting	49 (17.4%)	43 (15.6%)
Abdominal Pain	31 (11%)	29 (10.5%)
Stomatitis	3 (1.1%)	1 (0.4%)
Constipation	5 (1.8%)	5 (1.8%)
Mucositis NOS	20 (7.1%)	16 (5.8%)
Stomatitis Aphous	2 (0.7%)	-
Esophagitis	-	1(0.4%)
Pancreatitis	2 (0.7%)	1 (0.4%)
Hemorrhoids	3 (1.1%)	4 (1.4%)
GI Disorder NOS	1 (0.4%)	-
Gastroenteritis	1 (0.4%)	-
GI Hemorrhage	3(1.1%)	4 (1.4%)
Hematemesis	2 (0.7%)	-
Colitis	-	6 (2.2%)
Flatulence	-	1(0.4%)
Gastritis	-	1(0.4%)



Hyperglycemia	-	2 (0.7%)
Hypocalcemia	2 (0.7%)	1 (0.4%)
Alkaline Phosphatase Increased	1 (0.4%)	5 (1.8%)
Hyponatremia	1 (0.4%)	-
LDH Increased	-	1 (0.4%)
Hypercholesterolemia	-	1 (0.4%)
RESPIRATORY SYSTEM DISORDERS		
Dyspnea	4 (1.4%)	5 (1.8%)
Coughing	5 (1.8%)	5 (1.8%)
Pneumonia	3 (1.1%)	1 (0.4%)
Pulmonary Infiltration	2 (0.7%)	-
Respiratory Disorder	4 (1.4%)	7 (2.5%)
Pleural Effusion	-	1 (0.4%)
Pneumonitis	-	1 (0.4%)
Pneumothorax	-	1(0.4%)
Bronchospasm	1 (0.4%)	-
CxR Abnormal	1 (0.4%)	-
Respiratory Insufficiency	2 (0.7%)	3 (1.1%)
Hypoxia	1 (0.4%)	1 (0.4%)
Pharyngitis	1 (0.4%)	4 (1.4%)
Rhinitis	1 (0.4%)	1 (0.4%)
Sinusitis	2 (0.7%)	2 (0.7%)
SKIN AND APPENDAGES DISORDERS		
Rash	30 (10.7%)	22 (8%)
Rash Erythematous	16 (5.7%)	15 (5.4%)
Maculopapular Rash	1 (0.4%)	-
Purpuric Rash	1 (0.4%)	-
Bullous Eruption	1 (0.4%)	-
Dermatitis	4 (1.4%)	6 (2.2%)
Folliculitis	4 (1.4%)	3 (1.1%)
Pruritus	6 (2.15)	8 (2.95)
Skin Disorder	1 (0.4%)	2 (0.7%)
Urticaria	-	1 (0.4%)
Alopecia	2 (0.7%)	4 (1.4%)
URINARY SYSTEM DISORDERS		
Renal Function Abnormal	5 (1.8%)	10 (3.6%)
Hematuria	-	2 (0.7%)
Pyelonephritis	1 (0.4%)	-
ARF	1 (0.4%)	-
UTI	3 (1.1%)	4 (1.4%)
PSYCHIATRIC DISORDERS		
Confusion	1 (0.4%)	3 (1.1%)
Anxiety	1 (0.4%)	1 (0.4%)
Somnolence	-	1 (0.4%)

Insomnia	2 (0.7%)	-
Sleep disorder	2 (0.7%)	1 (0.4%)
Anorexia	2 (0.7%)	1 (0.4%)
Depression	4 (1.4%)	1 (0.4%)
Amnesia	-	1 (0.4%)
Neurosis	1 (0.4%)	-
Psychosis	1 (0.4%)	-
LIVER AND BILIARY SYSTEM DISORDERS		
Bilirubinemia	18 (6.4%)	15 (5.4%)
Cholecystitis	-	1 (0.4%)
gGT Increased	4 (1.4%)	11 (45)
Hepatic Enzymes Increased	5 (1.8%)	4 (1.4%)
Hepatic Failure	-	1 (0.4%)
Hepatic Function Abnormal	7 (2.5%)	8 (2.9%)
Hepatitis	3 (1.1%)	2 (0.7%)
Cholestatic Hepatitis	6 (2.1%)	2 (0.7%)
Hepatocellular Damage	5 (1.8%)	10 (3.6%)
Jaundice	4 (1.4%)	4 (1.4%)
SGPT Increased	6 (2.1%)	8 (2.9%)
SGOT Increased	3 (1.1%)	4 (1.4%)
Venoocclusive Liver Disease	1 (0.4%)	-
CENTR & PERIPH NERVOUS SYSTEM DISORDERS		
Headache	11 (3.9%)	17 (6.2%)
Dizziness	3 (1.1%)	2 (0.7%)
Neuropathy	1 (0.4%)	1 (0.4%)
Encephalopathy	1 (0.4%)	-
Cerebellar disorder	1 (0.4%)	-
Coma	1 (0.4%)	1 (0.4%)
Convulsions	2 (0.7%)	1 (0.4%)
Paresthesia	1 (0.4%)	2 (0.7%)
Paresis	-	1 (0.4%)
Stupor	-	1 (0.4%)
Tremor	-	1 (0.4%)
Vertigo	1 (0.4%)	-
CARDIOVASCULAR DISORDERS, GENERAL		
Hypotension	1 (0.4%)	5 (1.8%)
Hypertension	6 (2.1%)	1 (0.4%)
Cardiac Failure	6 (2.1%)	4 (1.4%)
Left Cardiac Failure	1 (0.4%)	-
Circulatory Failure	5 (1.8%)	6 (2.2%)
Heart disorder	1 (0.4%)	-
Postural Hypotension	-	1 (0.4%)
MYO-, ENDO-, PERI- and VALVE DISORDERS		
Angina	1 (0.4%)	-

Cardiomyopathy	1 (0.4%)	-
Pericarditis	-	1 (0.4%)
PLATELET, BLEEDING & CLOTTING DISORDERS		
Epistaxis	7 (2.5%)	3 (1.1%)
Purpura	2 (0.7%)	1 (0.4%)
Coagulation disorder	1 (0.4%)	-
Coagulation disorder Increased	1 (0.4%)	-
Decreased Fibrinogen	1 (0.4%)	-
Hematoma	2 (0.7%)	-
Hemorrhage	2 (0.7%)	1 (0.4%)
Thrombocytopenia	1 (0.4%)	1 (0.4%)
Thrombosis	2 (0.7%)	1 (0.4%)
Arm Venous thrombosis	-	1 (0.4%)
RESISTANCE MECHANISM DISORDERS		
Abscess	2 (0.7%)	4 (1.4%)
Infection	5 (1.8%)	3 (1.1%)
Bacterial Infection	5 (1.8%)	7 (2.5%)
Sepsis	19 (5.8%)	16 (5.8%)
Herpes Simplex	14 (5%)	12 (4.3%)
Fungal Infection	3 (1.1%)	6 (2.2%)
Viral Infection	2 (0.7%)	1 (0.4%)
Moniliasis	2 (0.7%)	4 (1.4%)
PCP	-	1 (0.4%)
HEART RATE AND RHYTHM DISORDERS		
Tachycardia	1 (0.4%)	1 (0.4%)
Bradycardia	1 (0.4%)	1 (0.4%)
Arrhythmia	-	3 (1.1%)
Cardiac Arrest	-	1 (0.4%)
Atrial fibrillation	1 (0.4%)	1 (0.4%)
VISION DISORDERS		
Conjunctivitis	6 (2.1%)	2 (0.7%)
Corneal Deposits	-	1 (0.4%)
Abnormal Vision	1 (0.4%)	2 (0.7%)
Hemorrhage	-	1 (0.4%)
Eye Pain	1 (0.4%)	-
HEARING and VESTIBULAR DISORDERS		
Earache	-	2 (0.7%)
APPLICATION SITE DISORDERS		
Application Site reaction	6 (2.1%)	5 (1.8%)
Injection Site Inflammation	1 (0.4%)	3 (1.15)
Cellulitis	2 (0.7%)	-
Skin Nodule	-	1 (0.4%)
MUSCULOSKELETAL DISORDERS		
Myalgia	2 (0.7%)	-

Osteomyelitis	1 (0.4%)	-
VASCULAR		
Cerebral Hemorrhage	1 (0.4%)	2 (0.7%)
CVA	-	3 (1.1%)
Thrombophlebitis	1 (0.4%)	-
Vasculitis	1 (0.4%)	-
NEOPLASMS		
Leukemia	1 (0.4%)	-
Skin Hypertrophy	1 (0.4%)	-
WHITE CELL DISORDERS		
Lymphadenopathy	1 (0.4%)	-
RBC DISORDERS		
Aplasia	-	1 (0.4%)
Hemolysis	1 (0.4%)	1 (0.4%)
Pancytopenia	-	1 (0.4%)
ENDOCRINE DISORDERS		
Panniculitis	1 (0.4%)	-
FETAL DISORDERS		
Abortion	-	1 (0.4%)
REPRODUCTIVE DISORDERS		
Menstrual Disorder	2 (0.7%)	2 (0.7%)
Male Perineal Pain	1 (0.4%)	-
No. (%) with any AE	222 (79%)	205 (74.3%)

Of the 281 ITR patients, 13 (4.6%) had AEs (15 events) reported as definitely related to therapy and 133 (47.3%) had events reported as possibly related. The respective numbers on the AMP B arm were 13/275 (4.7%/20 events) and 113/275 (41%).

The most frequently reported definitely drug-related adverse events were application site reaction (five subjects in each group, nausea (2 itraconazole subjects and 7 amphotericin B subjects) and vomiting (3 and 6 subjects, respectively).

Medical Officer's Comment: *As expected GI events were the most common on both study arms. The relatedness of the application site reactions to oral therapy remains unclear and is of doubtful significance.*

Table B15
AEs Definitely-Related to Therapy

ADVERSE EVENT	Itraconazole N = 281 (100%)	Amphotericin B N = 276 (100%)
Total AEs Definitely Related	15 (5.4%)	20 (7.2%)
Total subjects with an AE	13 (4.6%)	13 (4.7%)
GASTRO-INTESTINAL SYSTEM		
Nausea	2 (0.7%)	7 (2.5%)
Vomiting	3 (1.1%)	6 (2.2%)
Abdominal Pain	1 (0.3%)	2 (0.7%)
Pancreatitis	1 (0.3%)	-
BODY AS A WHOLE – GENERAL DISORDERS		
Fever	1 (0.3%)	-
Pain	1 (0.3%)	-
PLATELET, BLEEDING & CLOTTING DISORDERS		
Coagulation disorder Increased	1 (0.3%)	-
Decreased Fibrinogen	1 (0.3%)	-
APPLICATION SITE DISORDERS		
Application site reaction	5 (1.8%)	5 (1.8%)

The most frequently reported possibly drug-related adverse events were diarrhea (54 itraconazole subjects and 48 amphotericin B subjects), nausea (45 and 42 subjects, respectively) and vomiting (34 and 29 subjects). Of note, LFT abnormalities possibly attributable to treatment occurred with relatively equal frequency on both study arms. Hypokalemia and rash also occurred with marginally greater frequency on the ITR arm.

Table B16
AEs Possibly-Related to Therapy

ADVERSE EVENT	Itraconazole N = 281 (100%)	Amphotericin B N = 276 (100%)
Total subjects with an AE	133 (47.3%)	113 (41.1%)
GASTRO-INTESTINAL SYSTEM		
Diarrhea	54 (19.2%)	48 (17.4%)
Bloody diarrhea	1(0.3%)	-
Duodenal Ulcer	1(0.3%)	-
Dyspepsia	10 (3.5%)	6 (2.2%)
Dysphagia	2 (0.7%)	1 (0.3%)
Nausea	45 (16%)	42 (15.2%)
Vomiting	34 (12.1%)	29 (10.5%)
Abdominal Pain	18 (6.4%)	15 (5.4%)
Stomatitis	-	1 (0.3%)
Constipation	2 (0.7%)	2 (0.7%)
Mucositis NOS	1(0.3%)	2 (0.7%)

Pancreatitis	-	1 (0.3%)
GI disorder NOS	1(0.3%)	-
Gastroenteritis	1(0.3%)	
GI Hemorrhage	2 (0.7%)	1 (0.3%)
Hematemesis	2 (0.7%)	-
Colitis	-	1 (0.3%)
Flatulence	-	1 (0.3%)
Ileus	1(0.3%)	-
Tongue disorder	2 (0.7%)	-
BODY AS A WHOLE - GENERAL DISORDERS		
Fever	1(0.3%)	1 (0.3%)
Edema	-	1 (0.3%)
Syncope	-	1 (0.3%)
Allergic Reaction	1(0.3%)	2 (0.7%)
Pain	2 (0.7%)	1 (0.3%)
Fatigue	1(0.3%)	1 (0.3%)
Malaise	1 (0.3%)	1 (0.3%)
Asthenia	-	1 (0.3%)
Unspecified	-	1 (0.3%)
METABOLIC AND NUTRITIONAL DISORDERS		
Hypokalemia	13 (4.6%)	10 (3.6%)
Hyperkalemia	1(0.3%)	3 (1.1%)
Hyperglycemia	-	1 (0.3%)
Alkaline Phosphatase Increased	1(0.3%)	3 (1.1%)
LDH Increased	-	1 (0.3%)
Hypocholesterolemia	2 (0.7%)	-
RESPIRATORY SYSTEM DISORDERS	2 (0.7%)	
Coughing	2 (0.7%)	-
Respiratory Insufficiency	-	1 (0.3%)
Pharyngitis	-	1 (0.3%)
SKIN AND APPENDAGES DISORDERS		
Rash	12 (4.3%)	7 (2.5%)
Rash Erythematous	6 (2.1%)	5 (1.8%)
Purpuric Rash	1(0.3%)	-
Dermatitis	1(0.3%)	1 (0.3%)
Folliculitis	1(0.3%)	-
Pruritus	1(0.3%)	3 (1.15)
Skin Disorder	-	1 (0.3%)
Alopecia	-	1 (0.3%)
URINARY SYSTEM DISORDERS		

Renal Function Abnormal	-	1 (0.3%)
PSYCHIATRIC DISORDERS		
Anorexia	2 (0.7%)	1 (0.3%)
Psychosis	1(0.3%)	-
LIVER AND BILIARY SYSTEM DISORDERS		
Bilirubinemia	12 (4.3%)	6 (2.2%)
gGT Increased	2 (0.7%)	7 (2.5%)
Hepatic Enzymes Increased	5 (1.8%)	4 (1.4%)
Hepatic Failure	-	1 (0.3%)
Hepatic Function Abnormal	4 (1.4%)	5 (1.8%)
Hepatitis	2 (0.7%)	2 (0.7%)
Cholestatic Hepatitis	4 (1.4%)	1 (0.3%)
Hepatocellular Damage	-	4 (1.4%)
Jaundice	1(0.3%)	2 (0.7%)
SGPT Increased	4 (1.4%)	7 (2.5%)
SGOT Increased	2 (0.7%)	3 (1.1%)
Venoocclusive Liver Disease	1(0.3%)	-
CENTR & PERIPH NERVOUS SYSTEM DISORDERS		
Headache	3 (1.1%)	7 (2.5%)
Dizziness	1(0.3%)	1 (0.3%)
Neuropathy	-	1 (0.3%)
Convulsions	-	1 (0.3%)
Paresthesia	-	1 (0.3%)
Tremor	-	1 (0.3%)
CARDIOVASCULAR DISORDERS, GENERAL		
Hypotension	-	1 (0.3%)
Hypertension	1(0.3%)	1 (0.3%)
Cardiac Failure	1(0.3%)	-
PLATELET, BLEEDING & CLOTTING DISORDERS		
Epistaxis	1(0.3%)	-
Purpura	-	1 (0.3%)
VISION DISORDERS		
Abnormal Vision	1(0.3%)	1 (0.3%)
HEARING and VESTIBULAR DISORDERS		
Earache	-	1 (0.3%)

Severe AEs:

Severe adverse events were reported in 94/281 (34%) ITR subjects and in 69/276 (25%) AMP B subjects. The most frequently reported severe adverse events were nausea (11 (3.9%) itraconazole subjects and 9 (3.3%) amphotericin B subjects), diarrhea (12(4.3%) and 7 (2.5%) subjects), vomiting (9 (3.2%) and 8 (2.9%) subjects) and mucositis not otherwise specified (9 (3.2%) and 7 (2.5%) subjects).

2 (0.7%) of the hyperbilirubinemia episodes on the ITR arm as compared to 4 (1.4%) of episodes on the AMP B arm were classified as severe. Similar numbers were obtained for “hepatic enzymes increased” and “hepatocellular damage” on both arms.

Serious AEs including Deaths:

Serious adverse events were reported in 26/281 (9%) itraconazole subjects and 32/276 (12%) amphotericin B subjects. 18 (6.4%) events on the ITR arm and 23(8.3%) on the AMP B arm were deaths that occurred within 30 days of the last medication day. The most frequently reported adverse events with death as outcome were aggravated underlying condition (4 itraconazole subjects and 5 amphotericin B subjects), circulatory failure (4 and 2 subjects, respectively), sepsis (3 subjects in each group), diarrhea (1 itraconazole subject and 4 amphotericin B subjects), gastro-intestinal hemorrhage (4 amphotericin B subjects), fungal infection (2 subjects in each group), and respiratory insufficiency (1 itraconazole subject and 3 amphotericin B subjects). 1 episode of hepatocellular damage on the ITR arm and 1 episode of hyperbilirubinemia with increased alkaline phosphatase on the AMP B arm were classified as serious events in patients who died. 1 itraconazole death due to diarrhea was classified as related to study drug as opposed to none on the AMP B arm.

Premature discontinuation due to death was reported in 4 subjects, 1 ITR (#886, circulatory failure) and 3 AMP B (#479, RF and respiratory insufficiency, #719, hemorrhage, and #247, circulatory failure, hypoxia)

Apart from adverse events leading to death, other serious adverse events were reported in 12 (4%) itraconazole subjects and 17 (6%) amphotericin B subjects. Other serious adverse events were circulatory failure (1 itraconazole subject and 3 amphotericin B subjects), hepatic function abnormal, confusion and sepsis (each noted in 3 amphotericin B subjects), hypokalemia and pulmonary infiltration (each noted in 2 itraconazole subjects), and hypotension, bacterial infection and moniliasis (each noted in 1 subject in each group).

Detailed descriptions of the subjects who died and the events reported can be found in Appendix A to the MOR.

Premature Discontinuations:

75/281 (27%) itraconazole subjects and 78/276 (28%) amphotericin B subjects permanently stopped the intake of the trial medication because of adverse events or death. Of these, 68 and 60 subjects, respectively, also dropped out of the trial (i.e., both stopped the treatment and had no assessments any longer) because of adverse events or death.

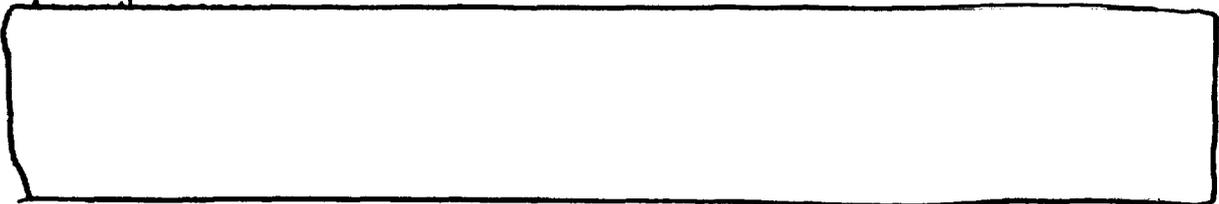
The most frequently reported adverse events leading to withdrawal were nausea (24 itraconazole subjects and 29 amphotericin B subjects), vomiting (22 and 19 subjects) and diarrhea (6 itraconazole and 8 amphotericin B subjects). Interestingly, application site reactions accounted for 5 withdrawals on each arm despite the fact that both study drugs were PO.

8 itraconazole patients who withdrew had a hepatic event, including hyperbilirubinemia (1), as compared to 13 amphotericin B patients 2 of whom had hyperbilirubinemia.

Rash and erythematous rash were reported in 3 itraconazole subjects respectively.

Laboratory:

Clinical laboratory data were available for 279 ITR and 274 AMP B subjects. Of these, 274/279 itraconazole subjects and 274/274 amphotericin B subjects had laboratory data both at baseline and at least once during or at the end of treatment.



166/274 (61%) ITR subjects and 153/274 (55.8%) AMP B subjects had 'code-4' important laboratory abnormalities, i.e., reference value is not pathological, but at least two values - or the last one - during the observation period are pathological. Specifically:

Hypocalcemia: 72/274 (26.3%) ITR, 61/274 (22.3%) AMP B
Hypokalemia: 47/274 (17.1%) ITR, 31/274 (11.3%) AMP B
Hyponatremia: 5/274 (1.8%) ITR, 4/274 (1.5%) AMP B
Hypocholesterolemia: 36/274 (13.1%) ITR, 21/274 (7.6%) AMP B
Bilirubinemia: 74/274 (27%) ITR, 63/274 (23%) AMP B
Increased BUN: 22/274 (8%) ITR, 24/274 (8.8%) AMP B
Increased Cr.: 2/274 (0.7%) ITR, 6/274 (2.2%) AMP B
Hyperuricemia: 15/274 (5.5%) ITR, 10/274 (3.6%) AMP B

Medical Officer's Comment: The type of laboratory abnormalities recorded was consistent primarily with the patients' underlying diseases. Observed electrolyte

abnormalities on both study arms were primarily due to the underlying processes and treatments of them. As oral AMP B is NOT absorbed, the incidence rate of these events on the AMP B arm provided a background rate and as expected certain abnormalities such as hypokalemia, hypocalcemia, hyperuricemia, and bilirubinemia were observed more frequently in the ITR-treated population.

LFT abnormalities:

For pathological grade 1, 182/268 (68%) itraconazole subjects and 191/266 (72%) amphotericin B subjects who had data at baseline and at least once thereafter showed important abnormalities in liver function tests at some time point during treatment, i.e., they had codes 1 to 5. Of these, 110/268 (41%) itraconazole subjects and 125/266 (47%) amphotericin B subjects had a 'code-4' important abnormality.

For pathological grade 2, important abnormalities were noted in 90/268 (34%) itraconazole subjects and in 92/266 (35%) amphotericin B subjects. Of these, 'code-4' important abnormalities were noted in 52/268 (19%) and 53/266 (20%) subjects, respectively.

For pathological grade 3, the number of subjects with important abnormalities was 29/268 (11%) in the itraconazole group and 32/266 (12%) in the amphotericin B group. Of these, 17/268 (6%) and 20/266 (8%) subjects had 'code-4' important abnormalities. For pathological grade 4, 9/268 (3%) itraconazole subjects and 7/266 (3%) amphotericin B subjects showed important abnormalities. Of these, 2/268 (1%) and 5/266 (2%) subjects had a 'code-4' important abnormality.

Medical Officer's Comment: *As noted above the rate of observed abnormalities on the AMP B arm served as background. A review of the CRFs revealed no new or unusual findings regarding the incidence of LFT abnormalities associated with ITR treatment.*

Safety conclusions from ITR-INT-54: AEs were reported in 222/281 (79%) of ITR subjects as compared to 205/279 (74%) of AMP B subjects. AEs were primarily from the GI tract on both study arms. Serious AEs were reported in 94/281 (34%) ITR subjects and 69/274 (25%) AMP B subjects. 18 (6.4%) of ITR subjects and 23 (8.3%) of AMP B subjects died during the trial. LFT abnormalities were seen with a moderate increased frequency on the ITR arm. This was expected given the known AE profile of ITR and the lack of absorption of oral AMP B. Similarly expected were the minor differences in rates of hypokalemia, hypouricemia, and hypocalcemia.

In conclusion, ITR and oral AMP B appeared to be tolerated equally as well.

ITR-INT-18:

Title: Antifungal prophylaxis in hematological malignancy with profound neutropenia: a double-blind trial to compare itraconazole oral solution with placebo.

Study Dates: June 20, 1994 – May 30, 1996

Investigators: A. Del Favero, M.D., Oncologist, Perugia, Italy, primary investigator with 39 sub-investigators in Italy.

Study Synopsis:

Phase III, multicenter, randomized, double-blind, parallel group, placebo-controlled trial of antifungal prophylaxis in hematological malignancy subjects with profound neutropenia to compare the prophylactic efficacy of itraconazole oral solution with placebo, to compare the incidence of suspected and proven deep fungal infections and the incidence of superficial candidal infections, and to compare the frequency of IV amphotericin B initiation. Subjects received itraconazole oral solution (10 mg/mL, 0.25 ml/kg BID) or placebo.

In the chemotherapy group, treatment was started together with chemotherapy; in the bone marrow transplant group, treatment was started in the period between 7 days prior to and 3 days after re-infusion of marrow. All subjects also received both ciprofloxacin (500 mg BID) and nystatin (500,000 IU QID).

Treatment continued until recovery of neutrophils $> 1000/\mu\text{l}$ or until another trial end point was reached, with a maximum of 8 weeks and a total trial duration of 12 weeks.

The inclusion criteria specified adult subjects undergoing initial remission-induction, consolidation or re-induction treatment after relapse for acute myeloid leukemia (AML), or lymphoblastic leukemia (ALL), or myelodysplastic syndrome in subjects undergoing intensive chemotherapy or undergoing autologous bone marrow transplantation for AML, ALL, chronic granulocytic leukemia, Hodgkin's disease, non-Hodgkin lymphoma, or myeloma expected to become neutropenic, defined as $< 1.0 \times 10^9$ neutrophils/liter, expected to last for at least 10 days who had no signs or symptoms of fungal infection and life expectancy of at least 14 days. Excluded were subjects unable to take oral medication or who had received systemic antifungal therapy within two weeks before entry into the trial, or topical intra-oral antifungal therapy within one week. Additionally excluded were subjects with liver disease, (defined as liver enzymes (SGPT or SGOT) ≥ 4 times the upper normal limit or a total plasma bilirubin level > 2.5 mg/dl within one month prior to entry into the trial), subjects with FUO, or subjects with proven deep fungal infection diagnosed during a previous episode of neutropenia.

Medical Officer's Comment: *As in the previous oral solution prophylaxis trials the population studied and the dose and duration of ITR treatment were similar to those of trial 62.*

201 patients were randomized to ITR and 204 to placebo. Approximately 65% of patients on each arm (122 ITR and 123 AMP B) had AML. Median duration of treatment was 19 days (1, 56) on both arms.

Results as per the sponsor:

Table B17
Safety Trial 18 as per the Applicant

Safety (n = number of subjects with data)	Itraconazole (N=201)	Placebo (N=204)
Adverse events (AE)		
Most frequently reported AE:		
Abdominal pain	23 (11%)	21 (10%)
Bilirubinemia	35 (17%)	33 (16%)
Diarrhea	57 (28%)	57 (28%)
Fever	7 (4%)	12 (6%)
Hepatic enzymes increased	16 (8%)	14 (7%)
Hypokalemia	18 (9%)	10 (5%)
Mucositis	9 (5%)	15 (7%)
Nausea	31 (15%)	38 (19%)
Rash	14 (7%)	13 (6%)
Rash erythematous	10 (5%)	11 (5%)
SGPT increased	19 (10%)	16 (8%)
Vomiting	40 (20%)	35 (17%)
No. (%) with one or more AE	155 (77%)	153 (75%)
No. (%) with one or more serious AE	20 (10%)	21 (10%)
No. (%) of deaths ¹	15 (7.5%)	18 (8.8%)
No. (%) with one or more other serious AE ²	9 (4%)	9 (4%)
No. (%) treatment stopped due to AE	58 (29%)	46 (23%)
Clinical laboratory parameters	There were many important laboratory abnormalities but considering this subject population, these could be accounted for	

¹ including two placebo subjects, #102 and #103, for whom the exact date of death is not known and for whom no adverse events were reported; these subjects are included as deaths because they died with a proven deep fungal infection soon after they were discharged from the hospital (about 14 days after the last intake of the trial medication) in a severe general condition

² includes also some subjects who died, but in whom serious adverse events were reported without outcome died

Sponsor conclusions:

Adverse events, mainly gastro-intestinal system disorders and liver and biliary system disorders were reported in 155 (77%) itraconazole subjects and in 153 (75%) placebo subjects. The most frequently reported adverse events were diarrhea (57 subjects in each group) and

vomiting (40 itraconazole subjects and 35 placebo subjects). Severe adverse events, mainly diarrhea, were reported in 51 (25%) itraconazole subjects and 52 (26%) placebo subjects. Serious adverse events were reported in 20 (10%) itraconazole subjects and in 21 (10%) placebo subjects; 15 (7.5%) itraconazole subjects and 18 (8.8%) placebo subjects died. Fifty-eight (29%) itraconazole subjects and 46 (23%) placebo subjects permanently stopped the intake of the trial medication because of adverse events or death.

Changes in biochemical laboratory parameters were comparable in the two groups, and the hematological changes that were observed were inherent to the studied patient population.

In conclusion, the trial medication was well tolerated and safe.

As per the Reviewer:

155/201 ITR patients (77.1%) as compared to 153/204 (75%) placebo subjects reported AEs. Most AEs on both arms occurred from the GI tract including nausea, vomiting, and diarrhea. Fever was common on both study arms and most likely attributable to the patients underlying disease processes. Hypokalemia was also seen on both study arms. LFT abnormalities including hyperbilirubinemia were seen on both arms. Rash and erythematous rash were reported with similar frequency.

Medical Officer's Comment: Notable was the overall similarity in the frequency of most AEs. This indicates that most AEs were due to the underlying condition of the subjects and provided a background rate. A notable difference between the ITR and placebo arms was noted for hypokalemia 18/201 (9%) ITR versus 10/204 (4.9%) placebo. Minor differences were noted for hypocalcemia and LFT abnormalities.

Table B18
All Adverse Events ITT Population

ADVERSE EVENT	Itraconazole N = 201 (100%)	Placebo N = 204 (100%)
GASTRO-INTESTINAL SYSTEM		
Diarrhea	57 (28.4%)	57 (27.9%)
Diarrhea, C difficile	2 (1%)	1 (0.5%)
Duodenitis	1 (0.5%)	-
Dyspepsia	9 (4.5%)	3 (1.5%)
Dysphagia	-	2 (1%)

Enterocolitis	1 (0.5%)	-
Nausea	31 (15.4%)	38 (18.6%)
Vomiting	40 (19.9%)	35 (17.2%)
Abdominal Pain	23 (11.4%)	21 (10.3%)
Stomatitis	6 (3%)	2 (1%)
Constipation	2 (1%)	2 (1%)
Mucositis NOS	9 (4.5%)	15 (7.4%)
Stomatitis Aphthous	1 (0.5%)	-
Hemorrhoids	1 (0.5%)	-
Gastritis Hemorrhagic	1 (0.5%)	-
GI Hemorrhage	-	1 (0.5%)
Hematemesis	1 (0.5%)	-
Gingivitis	1 (0.5%)	1 (0.5%)
Gum Hyperplasia	-	1 (0.5%)
Rectal Hemorrhage	-	2 (1%)
Ileus	3 (1.5%)	1 (0.5%)
Intestinal Ulceration	-	1 (0.5%)
Intestinal Obstruction	1 (0.5%)	-
Hiccup	3 (1.5%)	1 (0.5%)
Melena	7 (3.5%)	3 (1.5%)
Anus Disorder	-	2 (1%)
Oral Hemorrhage	1 (0.5%)	-
Dry Mouth	-	1 (0.5%)
BODY AS A WHOLE - GENERAL DISORDERS		
Rigors	-	2 (1%)
Fever	7 (3.5%)	12 (5.9%)
Chest Pain	-	1 (0.5%)
Substernal Chest Pain	-	1 (0.5%)
Edema Generalized	2 (1%)	1 (0.5%)
Back Pain	1 (0.5%)	1 (0.5%)
Syncope	1 (0.5%)	3 (1.5%)
Allergic Reaction	3 (1.5%)	3 (1.5%)
Pain	1 (0.5%)	2 (1%)
Condition Aggravated	-	2 (1%)
Leg Pain	-	1 (0.5%)
Asthenia	1 (0.5%)	1 (0.5%)
Hot Flushes	-	1 (0.5%)
METABOLIC AND NUTRITIONAL DISORDERS		
Hypokalemia	18 (9%)	10 (4.9%)
Hypophosphatemia	-	1 (0.5%)
CREATININE Increased	2 (1%)	5 (2.5%)
BUN Increased	2 (1%)	4 (2%)
Electrolyte abnormality	-	1 (0.5%)
Leg edema	3 (1.5%)	1 (0.5%)

Hypoproteinemia	1 (0.5%)	-
Gout	-	1 (0.5%)
Hyperuricemia	4 (2%)	1 (0.5%)
Hyperglycemia	-	2 (1%)
Hypocalcemia	6 (3%)	2 (1%)
Hypochloremia	2 (1%)	-
Hypoglycemia	-	1 (0.5%)
Alkaline Phosphatase Increased	4 (2%)	9 (4.4%)
Hyponatremia	2 (1%)	2 (1%)
Weight Increased	2 (1%)	-
Hypercholesterolemia	1 (0.5%)	3 (1.5%)
RESPIRATORY SYSTEM DISORDERS		
Dyspnea	-	4 (2%)
Coughing	3 (1.5%)	2 (1%)
Pneumonia	1 (0.5%)	3 (1.5%)
Pulmonary edema	2 (1%)	2 (1%)
Respiratory Depression	-	1 (0.5%)
Respiratory Insufficiency	3 (1.5%)	4 (2%)
SKIN AND APPENDAGES DISORDERS		
Rash	14 (7%)	13 (6.4%)
Rash Erythematous	10 (5%)	11 (5.4%)
Maculopapular Rash	1 (0.5%)	-
Pustular Rash	-	1 (0.5%)
Dermatitis	2 (1%)	3 (1.5%)
Folliculitis	-	1 (0.5%)
Pruritus	3 (1.5%)	4 (2%)
Skin Disorder	-	3 (1.5%)
Urticaria	3 (1.5%)	6 (2.9%)
Increased sweating	1 (0.5%)	-
URINARY SYSTEM DISORDERS		
Renal Function Abnormal	-	1 (0.5%)
Incontinence	-	1 (0.5%)
ARF	4 (2%)	2 (1%)
Renal Pain	-	1 (0.5%)
Dysuria	2 (1%)	1 (0.5%)
Facial Edema	-	1 (0.5%)
Hematuria	1 (0.5%)	-
Oliguria	1 (0.5%)	-
Polyuria	1 (0.5%)	1 (0.5%)
PSYCHIATRIC DISORDERS		
Confusion	1 (0.5%)	2 (1%)
Agitation	1 (0.5%)	1 (0.5%)
Insomnia	1 (0.5%)	-
Depression	1 (0.5%)	-

LIVER AND BILIARY SYSTEM DISORDERS		
Bilirubinemia	35 (17.4%)	33 (16.2%)
Cholecystitis	1 (0.5%)	1 (0.5%)
Hepatic Enzymes Increased	16 (8%)	14 (6.9%)
Hepatic Function Abnormal	1 (0.5%)	-
Hepatitis	1 (0.5%)	-
Hepatocellular Damage	1 (0.5%)	1 (0.5%)
Jaundice	4 (2%)	3 (1.5%)
SGPT Increased	19 (9.5%)	16 (7.8%)
SGOT Increased	9 (4.5%)	8 (3.9%)
CENTR & PERIPH NERVOUS SYSTEM DISORDERS		
Headache	9 (4.5%)	2 (1%)
EEG Abnormal	1 (0.5%)	-
Neuropathy	1 (0.5%)	-
Neuralgia	1 (0.5%)	-
Coma	1 (0.5%)	2 (1%)
Convulsions	1 (0.5%)	2 (1%)
Convulsions Grand Mal	-	1 (0.5%)
Convulsions Local	-	1 (0.5%)
Hemiparesis	1 (0.5%)	1 (0.5%)
Hyperkinesia	1 (0.5%)	-
Vertigo	-	1 (0.5%)
PLATELET, BLEEDING & CLOTTING DISORDERS		
Epistaxis	-	4 (2%)
Purpura	5 (2.5%)	3 (1.5%)
Gingival Bleeding	-	1 (0.5%)
Decreased Fibrinogen	-	1 (0.5%)
Hemorrhage NOS	1 (0.5%)	2 (1%)
Thrombocytopenia	5 (2.5%)	3 (1.5)
Thrombosis	2 (1%)	-
Arm Venous thrombosis	1 (0.5%)	-
RESISTANCE MECHANISM DISORDERS		
Abscess	-	2 (1%)
Infection	-	1 (0.5%)
Bacterial Infection	2 (1%)	2 (1%)
Sepsis	3 (1.5%)	2 (1%)
Herpes Simplex	8 (45)	4 (2%)
Herpes Zoster	-	1 (0.5%)
Fungal Infection	4 (2%)	2 (1%)
Viral Infection	-	1 (0.5%)
Moniliasis	-	1 (0.5%)
HEART RATE AND RHYTHM DISORDERS		
AV Block	1 (0.5%)	-
Bradycardia	1 (0.5%)	-

Arrythmia	1 (0.5%)	1 (0.5%)
Cardiac Arrest	3 (1.5%)	2 (1%)
Atrial fibrillation	1 (0.5%)	-
Extrasystoles	1 (0.5%)	-
VISION DISORDERS		
Blepharitis	-	1 (0.5%)
Blindness	1 (0.5%)	-
Photophobia	-	1 (0.5%)
HEARING and VESTIBULAR DISORDERS		
Decreased Hearing	-	1 (0.5%)
APPLICATION SITE DISORDERS		
Application Site reaction	5 (2.5%)	3 (1.5%)
Cellulitis	1 (0.5%)	-
MUSCULOSKELETAL DISORDERS		
Myalgia	2 (1%)	1 (0.5%)
Skeletal Pain	1 (0.5%)	-
VASCULAR		
Cerebral Hemorrhage	2 (1%)	3 (1.5%)
CVA	1 (0.5%)	-
Thrombophlebitis Arm	-	1 (0.5%)
Thrombophlebitis Cerebral Vein	-	1 (0.5%)
Phlebitis	1 (0.5%)	-
WHITE CELL DISORDERS		
Lymphadenopathy	1 (0.5%)	-
Granulocytopenia	-	1 (0.5%)
Leucocytosis	1 (0.5%)	-
RBC DISORDERS		
Spleen disorder	1 (0.5%)	-
REPRODUCTIVE DISORDERS		
Menstrual Disorder	-	1 (0.5%)
Menorrhagia	1 (0.5%)	-
Vaginal Hemorrhage	-	1 (0.5%)

Of the 201 ITR patients, 22 (10.9%) had AEs (32 events) reported as definitely related to therapy and 34 (16.9%) had events reported as possibly related. The respective numbers on the placebo arm were 18/204 (8.9%/31 events) and 24/204 (11.8%).

The most frequently reported drug-related adverse events were nausea (10 itraconazole subjects and 12 placebo subjects) and vomiting (9 and 7 subjects, respectively).

Table B19
AEs Definitely-Related to Therapy

ADVERSE EVENT	Itraconazole N = 201 (100%)	Placebo N = 204 (100%)
GASTRO-INTESTINAL SYSTEM		
Nausea	10 (5%)	12 (5.9%)
Vomiting	9 (4.3%)	7 (3.4%)
Abdominal Pain	2 (1%)	2 (1%)
Dyspepsia	4 (2%)	1 (0.5%)
Dysphagia	-	1 (0.5%)
BODY AS A WHOLE – GENERAL DISORDERS		
Allergic Reaction	1 (0.5%)	-
LIVER and BILIARY SYSTEM DISORDERS		
Hepatitis	1 (0.5%)	-
SKIN and APPENDAGES DISORDERS		
Pruritus	1 (0.5%)	-
Rash	2 (1%)	-
CENTRAL and PERIPHERAL NERVOUS SYSTEM		
Headache	-	1 (0.5%)
Vertigo	-	1 (0.5%)

The most frequently reported possibly drug-related adverse events were diarrhea (33 itraconazole subjects and 22 placebo subjects), nausea (12 and 12 subjects, respectively) and vomiting (17 and 13 subjects).

Medical Officer's Comment: AEs on the ITR arm that exceeded the background rate on the placebo arm included diarrhea, hypokalemia, and the generic "hepatic enzymes increased". Subjects on both arms had a similar number of reports of hyperbilirubinemia.

Table B20
AEs Possibly Related to Treatment

ADVERSE EVENT	Itraconazole N = 201 (100%)	Placebo N = 204 (100%)
GASTRO-INTESTINAL SYSTEM		
Diarrhea	33 (16.4%)	22 (10.8%)
Dyspepsia	2 (1%)	1 (0.5%)
Nausea	12 (6%)	12 (5.9%)
Vomiting	17 (8.4%)	13 (6.4%)
Abdominal Pain	8 (4%)	10 (4.9%)
Stomatitis	1 (0.5%)	-
Constipation	1 (0.5%)	-
Hiccup	1 (0.5%)	-
Dry Mouth	-	1 (0.5%)
BODY AS A WHOLE - GENERAL DISORDERS		
Fever	1 (0.5%)	1 (0.5%)
METABOLIC AND NUTRITIONAL DISORDERS		
Hypokalemia	5 (2.5%)	1 (0.5%)
Hypocalcemia	2 (1%)	1 (0.5%)
Hyponatremia	-	1 (0.5%)
Alkaline Phosphatase Increased	1 (0.5%)	-
Electrolyte Abnormality	-	1 (0.5%)
Leg Edema	1 (0.5%)	-
RESPIRATORY SYSTEM DISORDERS		
Coughing	-	1 (0.5%)
SKIN AND APPENDAGES DISORDERS		
Rash	4 (2%)	5 (2.4%)
Rash Erythematous	2 (1%)	4 (2%)
Maculopapular Rash	1 (0.5%)	-
Dermatitis	1 (0.5%)	1 (0.5%)
Pruritus	-	2 (1%)
Increased Sweating	1 (0.5%)	-
Urticaria	1 (0.5%)	-
LIVER AND BILIARY SYSTEM DISORDERS		
Bilirubinemia	17 (8.4%)	17 (8.4%)
Hepatic Enzymes Increased	11 (5.5%)	4 (2%)
Hepatocellular Damage	1 (0.5%)	1 (0.5%)
Jaundice	2 (1%)	1 (0.5%)
SGPT Increased	11 (5.5%)	10 (4.9%)
SGOT Increased	3 (1.5%)	5 (2.4%)
CENTR & PERIPH NERVOUS SYSTEM DISORDERS		
Headache	4 (2%)	-

CARDIOVASCULAR DISORDERS, GENERAL		
Hypertension	-	1 (0.5%)
Circulatory Failure	-	1 (0.5%)
PLATELET, BLEEDING & CLOTTING DISORDERS		
Fibrinogen decreased	-	1 (0.5%)
Purpura	1 (0.5%)	-
MUSCULOSKELETAL SYSTEM DISORDERS		
Myalgia	-	1 (0.5%)
HEART RATE and RHYTHM DISORDERS		
Bradycardia	1 (0.5%)	-

Severe AEs:

Severe adverse events were reported in 51/201 (25.4%) ITR subjects and in 52/204 (25.6%) placebo subjects. The most frequently reported severe adverse events were nausea in 8 (4%) itraconazole subjects and 8 (3.9%) placebo subjects, diarrhea in 12 (6%) ITR subjects and 8 (3.9%) placebo subjects, vomiting in 7 ITR (3.5%) and 6 (3%) placebo subjects, and abdominal pain in 5 ITR (2.5%) and 2 (1%) placebo subjects.

5 (2.5%) of the hyperbilirubinemia episodes on the ITR arm as compared to 3 (1.5%) of episodes on the placebo arm were classified as severe. Similar numbers were obtained for "hepatic enzymes increased" and "hepatocellular damage" on both arms.

ARF was also reported in 4 (2.1) ITR subjects and 0 placebo.

Serious AEs including Deaths:

Serious adverse events were reported in 20/201 (10%) itraconazole subjects and 21/204 (10.3%) placebo subjects. 15/201 (7.5%) serious events on the ITR arm and 18/204 (8.8%) on the placebo arm were deaths that occurred within 30 days of the last medication day. The most frequently reported adverse events with death as outcome were respiratory insufficiency (three subjects in each group), acute renal failure (four itraconazole subjects and one placebo subject), fungal infection (three and two subjects) and sepsis and cardiac arrest (each noted in three and one subjects). Additionally there were 2 cases of hyperbilirubinemia on the ITR arm versus 1 on the placebo arm.

Death was the reason for premature discontinuation of the treatment in six itraconazole subjects (#39, #121, #140, #198, #360 and #389) and in three placebo subjects (#124, #355 and #382).

Other serious AEs were reported in 9 subjects from each treatment group. These events included diarrhea (one itraconazole subject and two placebo subjects), thrombocytopenia (two ITR and one placebo subject), hepatic enzymes increased (1 itraconazole), and hepatitis (1 itraconazole). Only 1 event of hepatocellular damage was reported on the placebo arm. (Synopses of deaths can be found in appendix A to the MOR)

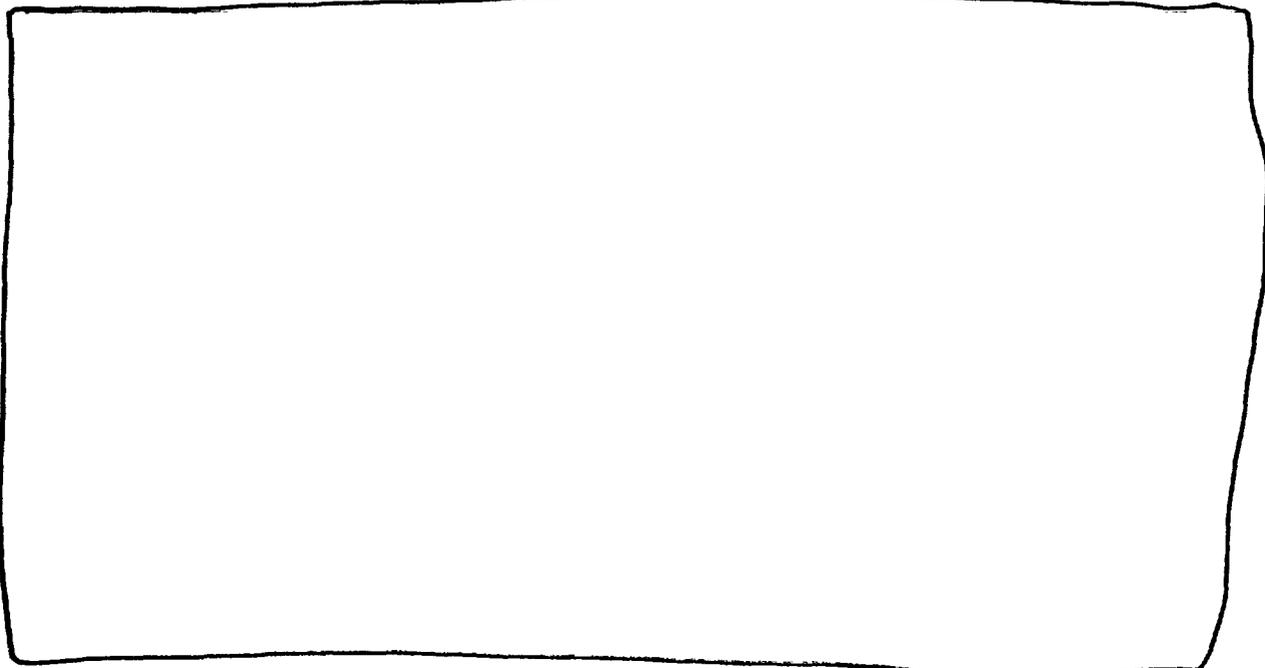
Premature Discontinuations:

58/201 (29%) itraconazole subjects and 46/204 (23%) placebo subjects permanently stopped the trial medication because of adverse events or death. 57 and 41 subjects, respectively, also dropped out of the trial (i.e., both stopped the treatment and had no assessments any longer) because of adverse events or death. As noted above, death was the reason for dropout or premature discontinuation in 6/201 (3%) ITR subjects and 3/204 (1.5%) placebo subjects.

The most frequently reported adverse events leading to withdrawal were from the GI tract and included vomiting in 19/201 (9.4%) itraconazole subjects and 15/204 (7.3%) placebo subjects), nausea in 15/201 (7.5%) ITR and 14/204 (6.9%) placebo subjects, diarrhea in 6/201 (3%) ITR and 9/204 (4.4%) placebo subjects, dyspepsia in 5/210 (2.5%) ITR and 1 placebo), and abdominal pain (7 and 4 subjects). Other events were fever (3 itraconazole and 1/204 (0.5%) placebo subjects, headache in 2/201 (1%) ITR and 0 placebo subjects, cardiac arrest in 2/201 (1%) ITR subjects and 1/204 (0.5%) placebo subjects, hyperbilirubinemia in 3/201 (1.5%) ITR subjects and 2/204 (1%) placebo subjects, infection (bacterial 2 (1%) each arm, fungal 2 (1%) ITR arm), respiratory insufficiency (2 (1%) each arm), rash (2/201 (1%) itraconazole), erythematous rash (2 (1%) each arm), and ARF in 2/201 (1%) ITR subjects.

Laboratory:

Clinical laboratory data were available for all 201 ITR and 204 placebo subjects. Of these, 185/201 (92%) itraconazole subjects and 191/204 (93.6%) placebo subjects had laboratory data both at baseline and at least once during or at the end of treatment.



151/185 (81.6%) ITR subjects and 150/191 (78.5%) placebo subjects had important abnormalities at some point, of these, 108/185 (58.4%) ITR and 89/191 (46.6%) placebo subjects 'code-4' important laboratory abnormalities, i.e., reference value is not pathological, but at least two values - or the last one - during the observation period are pathological. Specifically, the following were noted during a review of line listings:

Hypocalcemia: 27/185 (14.6%) ITR, 24/191 (12.5%) placebo
Hypokalemia: 34/185(18.4%) ITR, 30/191 (15.7%) placebo
Hyponatremia: 0 ITR, 3/191 (1.6%) placebo
Hypocholesterolemia: 15/185 (8.1%) ITR, 7/191 (3.6%) placebo
Bilirubinemia: 36/185 (19.4%) ITR, 30/191 (15.7%) placebo
Increased BUN: 5/185 (2.7%) ITR, 9/191 (4.7%) placebo
Increased Cr.: 2/185 (1.1%) ITR, 2/191 (1%) placebo
Hyperuricemia: 13/185 (7%) ITR, 13/191 (6.8%) placebo

Medical Officer's Comment: *The type of laboratory abnormalities that occurred was consistent with the underlying disease status of the subjects on both study arms. As expected, hypokalemia, hypocholesterolemia, and increased bilirubin were seen with an increased frequency on the itraconazole arm.*

Medical Officer's Conclusion regarding safety for ITR-ITA-18: *AEs, primarily from the GI tract were reported from 155/201 (77%) ITR subjects and 153/204 (75%) placebo subjects. AEs attributable to treatment were seen in 22 (11%) ITR subjects and 18/204 (9%) placebo subjects. Events possible attributable to treatment were seen in 34/201 (17%) ITR and 24/191 (12%) placebo subjects. The difference in rates of AEs attributable to therapy was due to the increased incidence of diarrhea, and increased hepatic enzymes on the ITR arm. Severe AEs occurred with similar frequency on both study arms and death rates were also similar with 15/201 (7.5%) on the ITR arm as compared to 18/204 8.8%) on the placebo arm. No death appeared attributable to treatment. Laboratory abnormalities occurred in approximately 75% of subjects on both study arms with the rate on the placebo arm providing a background rate. Hypokalemia, increased bilirubin, and hypocholesterolemia were seen more frequently on the ITR arm. Overall there were no unexpected AEs or laboratory abnormalities.*

2/5/01

**Amendment I to MOR of SNDA 20 - 966 (S-004) and 20 – 657 (S-005)
Empiric Therapy of Febrile Neutropenia
4 Month Safety Update**

1.1 SNDA 20-966 (S-004): Itraconazole Injection 200 mgm/vial and 10 mg/mL solution

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

1.3 Submission Review Dates: Date of Submissions: September 22, 2000
CDER Stamp Dates: September 22, 2000
Date Received by MO: September 26, 2000
Date Review Begun: September 26, 2000
Date Review Completed: September 30, 2000

1.4 Drug Identification: Generic Name: Itraconazole
Trade Name: Sporanox®

1.5 Pharmacologic Category: Antifungal

1.6 Dosage Form: Injection and oral solution

1.7 Route of Administration: Intravenous and per os

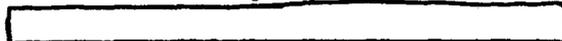
1.8 Strengths: 10 mg/mL

1.9 Chemical Name: (±)-1-[(RS)-sec-butyl]-4-[p-[[2R,4S)-2-2[2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]-Δ²-1,2,4-triazolin-5-one

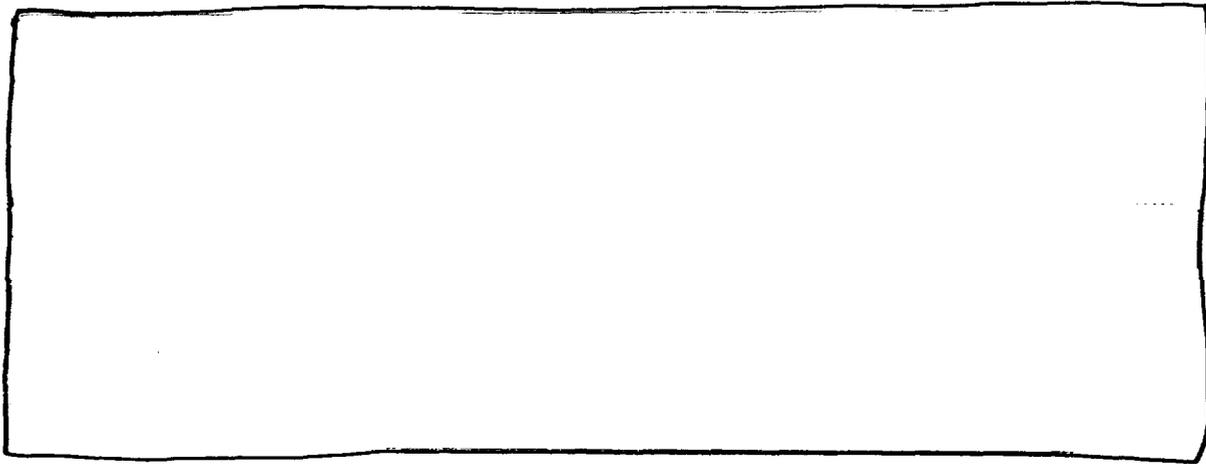
1.10 Proposed Indication and Usage section (as per the proposed label):
“SPORANOX® (itraconazole) is also indicated for the empiric therapy of suspected fungal infections in febrile neutropenic patients.”

1.11 Proposed Dosage and Administration: 200 mg IV BID (2 one-hour infusions) for 2 days, followed by 200 mg IV QD (one one-hour infusion) for 3 – 7 days. Itraconazole IV could be continued up to a total of 14 days or itraconazole oral solution 20 ml BID (200 mg PO BID) could be started on day 8 or day 15 through day 28

1.12 Related INDs and NDAs: NDA 20–966 (Itraconazole injection 10 mg/mL)
NDA 20–657 (Itraconazole oral solution 10 mg/mL for oropharyngeal candidiasis)



9 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.



Regina Alivisatos, MD
DSPIDP, HFD-590

Concurrence only:
HFD-590/DIVDir/MGoldberger

Cc:
Orig. NDA 20-966, NDA 20-657
HFD-590
HFD-590/ActDIVDir/RAIbrecht
HFD-590/MTL/BLeissa
HFD-590/CSO/KimeyR
HFD-725/Biostat/DaviR
HFD-520/Biopharm/McMasterO
2/6/00