ITEM	GRADE 1 TOXICITY	GRADE 2 TOXICITY	GRADE 3 TOXICITY	GRADE 4 TOXICITY
CARDIAC DYSFUNCTION				
CARDIAC RHYTHM		asymptomatic, transient signs, no Rx required	recurrent/persistent; no Rx required	requires treatment
HYPERTENSION	transient increase > 20 mm; no Rx	recurrent, chronic, > 20 mm, Rx re.	requires acute therapy (outpatient)	requires hospitalization
HYPOTENSION	transient orthostatic hypotension; No Rx	symptoms correctable with oral fluid Rx	requires IV fluids no hosp. required	requires hospitalization
PERICARDITIS	minimal effusion	mild/mod asymp. effusion, no Rx	symptomatic effusion, pain, EKG changes	tamponade; pericardio-centesis or surgery re.
HEMORRHAGE, BLOOD LOSS	microscopic/occult	mild, no transfusion	gross blood loss; or 1-2 units transfused	massive blood loss, or > 3 units transfused
RESPIRATORY				
COUGH - for aerosol studies	transient - no Rx	treatment associated cough; local Rx	uncontrolled	
BRONCHOSPASM ACUTE	transient; no Rx; < 80% - > 70% FEV_1 (or peak flow)	re. Rx; normalizes with bronchodilator; or FEV_1 50% - 70% (or peak flow); retraction	no normalization w/ bronchodilator or FEV_1 25% - 50% (or peak flow); retraction	cyanosis or FEV_1 < 25% (or peak flow) or intubated
NEURO/NEUROMUSCULAR				
NEURO-CEREBELLAR	slight incoordination Dysdiadochokinesia	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
MOOD	mild anxiety or mild depression	therapy required and moderate anxiety or moderate depression	needs assistance for severe anxiety or severe depression or severe mania	acute psychosis or incapacitated or hospitalization
NEURO CONTROL (ADL = Activities of Daily Living)	no Rx., ADL unaffected and mild difficulty concentrating or mild confusion or mild agitation	some limitation of ADL; min. therapy and moderate confusion or moderate agitation	therapy required, assistance for ADL and severe confusion or severe agitation	toxic psychosis; hospitalization
MUSCLE STRENGTH	subjective weakness; no objective	mild objective signs, symptoms	objective weakness; function limited	paralysis
GASTROINTESTINAL				
STOMATITIS	mild discomfort, no limits on activity	some limits on eating/drinking	eating/talking very limited	requires IV fluids
NAUSEA	mild discomfort; maintains reasonable intake	mod. discomfort; intake decreased significantly; some activity limited	severe discomfort; no significant intake activities limited	minimal fluid intake
VOMITING	transient emesis	occ/moderate vomiting	orthostatic hypo-tension or IV fluid Rx re.	hypotensive shock or hospitalization re. for IV fluid therapy
CONSTIPATION	mild	moderate	severe	distension with vomiting
DIARRHEA	transient or 3 - 4 loose stools/day	5-7 loose stools/day or nocturnal loose stools	orthostatic hypo-tension or > 7 loose stools/day or IV fluid Rx re.	hypotensive shock or hospitalization re. for IV fluid Rx
OTHER PARAMETERS				
FEVER; oral, > 12 hours	37.7 - 38.5C or 100.0 - 101.5F	38.6 - 39.5C or 101.6 - 102.6F	39.6 - 40.5C or 103 - 105F	> 40.5C or > 105F
HEADACHE	mild, no Rx therapy	transient, mod.; Rx re.	severe, responds to initial narcotic therapy	intractable, re. repeated narcotic therapy
FATIGUE	no dec. in daily activities	normal activity dec. 25 - 50%	normal activity dec. > 50%; can't work	unable to care for self
ALLERGIC REACTION	pruritus w/o rash	localized urticaria	generalized urticaria angioedema	anaphylaxis
LOCAL REACTION	tenderness or erythema	induration < 10 cm or phlebitis or inflammation	induration > 10 cm or ulceration	necrosis
MUCOCUTANEOUS	erythema, pruritus	diffuse, maculo-papular rash, dry	vesiculation, moist	exfoliative dermatitis, mucous

ITEM	GRADE 1 TOXICITY	GRADE 2 TOXICITY	GRADE 3 TOXICITY	GRADE 4 TOXICITY
		desquamation	desquamation, or ulceration	membrane involvement, or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery

Results:
As per the applicant:

88% or 28/32 IV patients reported AEs. The most frequently reported events during this phase were application site reaction 4 events (12%), including 3 coded as reaction (9%) and 1 as edema (3%), 1 chest pain (3%), 1 abdominal pain (3%), 2 bilirubinemia (6%), 1 increased gGT (3%), 2 hyperglycemia (6%), 1 glycosuria (3%), 1 arthrosis (3%), 1 anemia (3%), 1 bone marrow suppression (3%), 1 rash (3%), 1 maculopapular rash (3%), 2 taste perversion (6%), 2 albuminuria (6%), 1 hematuria, 1 pyuria (3%), 1 vasculitis (3%), 2 granulocytopenia (6%), and 1 leucopenia (3%).

A similar number of patients in each treatment group reported AEs during the oral phases of the trial: 200 QD 14/16 (88%), and 200 BID 14/16 (88%). The most frequently reported events during the oral phase were diarrhea: 3/16 (20%) and 2/16 (15%) respectively, and granulocytopenia 1/16 (7%) and 4/16 (31%) respectively. Neither of these events occurred during the initial IV phase.

Events that occurred in at least 5% of the population throughout the trial were application site reaction, fever, headache, abdominal pain, diarrhea, taste perversion, granulocytopenia, nausea, and bilirubinemia.

Events considered definitely-related to the study drug were application site reaction, headache, bilirubinemia, jaundice, taste perversion, and granulocytopenia.

During the IV phase (7 days) there was a trend towards decreased WBC, RBC, and platelet counts which rebounded during the oral QD phase but not in the BID patients.

As per the MO:

Demographics:

32 patients were enrolled and evaluable for safety. 15 patients were white, 17 black, 5 female, and 27 male.

27 patients completed the study and there were 5 discontinuations (2 for an AE during the IV phase (6%) and 1 (3%) for an AE during the oral 200 mg BID phase). 2 patients discontinued for other reasons (withdrawn consent) during the IV phase.

112 AEs were reported, 86 possibly-related, 13 definitely-related, and the remainder had no relationship to the study drug. No deaths or serious AEs were reported. 13/112 (11%) of the reported events were of moderate severity.

There were 3 discontinuations due to AEs possibly or probably-related to the trial medications. These patients are summarized below:

> **Patient #3002**: 4 events recorded (all application site reaction). 36 YO male entered the trial on October 7, 1996 and discontinued the trial after 3 days of treatment due to phlebitis in the left hand, which started at the infusion site. This reaction was coded as moderately severe and definitely related. The patient was treated for 7 days with Keflex® and ibuprofen. The phlebitis resolved on October 28, 1996.
>
> **Patient #3013**: 4 events, (2 abdominal pain (moderate) during the open PO and post-trial phases and 2 pyuria (mild) during IV and PO phases). 47YO male entered the trial on December 2, 1996. Discontinued the trial after 13 days of treatment with itraconazole, at the request of his primary physician, when he developed right upper quadrant abdominal pain with mild LFT

(transaminases) elevations (3 x normal). The primary physician believed this event was possibly-related to the trial medication. This event of unknown etiology resolved spontaneously on December 26, 1996.

Patient #3045: 2 events of vasculitis during IV and post-IV trial phases (both events of moderate severity). 38 YO male, entered the trial on November 12, 1996. After 4 days of treatment, the patient discontinued the trial due to bilateral vasculitis in the antecubital fossae. This prevented intravenous access for administration of trial medication. This event was considered possibly-related to the trial medication even though it was infused in only one arm. The event resolved on January 28, 1997.

Additionally, there were 2 patients who discontinued for "other" reasons (#3008: 4 events of hyperglycemia and glycosuria of moderate severity, possibly-related during the IV phase and post trial and #3012 who had no AEs reported).

APPEARS THIS WAY
ON ORIGINAL

Table 9
All reported AEs by Study Arm and Total (As per the MO)

Adverse Event	IV Phase N = 32		Oral Phase 200 QD N = 16		Oral Phase 200 BID N = 16		Total N = 32	
# Reporting an AE	28 (88%)		14 (88%)		14 (88%)		28 (88%)	
	n	%	n	%	n	%	n	%
Gastrointestinal System Disorders								
Abdominal Pain	1	3.1	-	-	2	12.5	3	9.4
Diarrhea	-	-	3	18.7	2	12.5	5	15.6
Nausea	-	-	1	6.3	1	6.3	2	6.3
Vomiting	-	-	1	6.3	-	-	1	3.1
Pharyngitis	-	-	1	6.3	-	-	1	3.1
Body as a Whole-General Disorders								
Fever	-	-	2	12.6	1	6.3	3	9.4
Chest Pain	1	3.1	-	-	-	-	1	3.1
Edema	-	-	1	6.3	-	-	1	3.1
Arthritis/Arthrosis	1	3.1	-	-	1	6.3	2	6.3
Earache	-	-	1	6.3	-	-	1	3.1
Lymphadenopathy	-	-	-	-	1	6.3	1	3.1
Liver and Biliary System Disorders								
Liver Function Abnormalities	3	9.4	1	6.3	2	12.5	6	18.7
Bilirubinemia/Jaundice	2	6.3	-	-	1	6.3	3	9.4
Skin and Appendages Disorders								
Rash/Maculopapular	1	3.1	1	6.3	-	-	2	6.3
Dry Skin	1	3.1	-	-	-	-	1	3.1
Vascular Disorders								
Application Site Reaction	4	12.5	-	-	-	-	4	12.5
Vasculitis	1	3.1	-	-	-	-	1	3.1
Respiratory System Disorders								
Cough	-	-	1	6.3	-	-	1	3.1
URI/Rhinitis	-	-	1	6.3	1	6.3	2	6.3
Urinary System Disorders								
Albuminuria	2	6.3	-	-	-	-	2	6.3
Glycosuria	1	3.1	1	6.3	-	-	2	6.3
Pyuria	1	3.1	-	-	-	-	1	3.1
Hematuria	1	3.1	-	-	-	-	1	3.1
Central and Peripheral Nervous System Disorders								
Taste Perversion	2	6.3	1	6.3	-	-	3	9.4
Headache	1	3.1	1	6.3	1	12.5	3	3.1
Insomnia	-	-	-	-	1	6.3	1	3.1
WBC Disorders								
Bone Marrow Suppression	3	9.4	1	6.3	4	25	8	25
Granulocytopenia	2	6.3	1	6.3	4	25	6	18.7
Leucopenia	1	3.1	-	-	-	-	1	3.1
RBC Disorders								
Anemia	1	3.1	1	6.3	-	-	2	6.3

Laboratory Abnormalities:

The MO ascertained that 1 patient, #3052 had an abnormal SGPT at baseline, which decreased after IV therapy and which normalized after the EOT. A similar course occurred with the gGT in patient #3005. No BUN/Creatinine abnormalities of clinical significance were found.

One patient #3008, developed hyperglycemia (glucose to 381) after 3 days R/x

Uncertain significance: thrombocytopenia was not evident in any patients at the start of the trial but developed in 2 patients (6.2%) by week 6. This subsequently resolved and no explanation was provided. Granulocytopenia developed *de novo* in 6 patients and anemia in 2.

As per the MO: The following events occurred in > 7% of the total population studied during the trial (IV and PO): application site reaction, taste perversion, bilirubinemia, granulocytopenia, abdominal pain, diarrhea, fever, liver function abnormalities, rash, nausea, fever, anemia, URI, and bone marrow suppression.

None of the events that occurred were unexpected. For a determination of relatedness refer to the overall conclusion.

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

Study Dates: July 24, 1995 – November 10, 1995

Study Sites and Investigators: Michael Goldman, MD
Infectious Diseases Research clinic
Indiana University Medical Center
350 North University Boulevard
Indianapolis, IN 46202

Robert Anderson, MD
Novum
5900 Penn Ave.
Pittsburgh, PA 15206

This trial was designed in a similar fashion to trial 127. There were no significant differences between the trials both in design as well as in populations studied.

Study Synopsis: Trial 113 was a phase I, multicenter, randomized, open-label comparative study with primary objective to demonstrate a dosing regimen for intravenous itraconazole that produced a plasma concentration range comparable to that obtained after approved oral dosages of itraconazole capsules. The secondary objective was to monitor safety. 30 patients were enrolled to receive IV itraconazole 200 mg BID for 2 days, and then 200 mg IV QD for 5 days. The patients subsequently and after randomization at study entry were switched over to one of two PO itraconazole regimens (200 mg QD or 200 mg BID) for 28 days. Both clinical and laboratory were performed in a similar fashion to study 127. Pharmacokinetic parameters were also evaluated in a similar manner.

31 patients were randomized to treatment, 16 to the IV → 200 mg PO QD phase and 15 to the IV → 200 mg PO BID phase. One patient, #0212 assigned to the IV → 200 mg PO QD arm did not receive any study medication. Therefore the dataset contained information on only the 30 enrolled and treated patients.

Safety Analysis as per the applicant:

AEs occurred in 24 of the 30 (80%) patients at any time during the trial. AEs of any severity reported in > 5% and possibly-related to the study drug were: application site reaction 12 (40%), nausea 7 (23%), vein disorder 9 (30%), headache 3 (10%), diarrhea 3 (10%), abdominal pain 2 (7%), and rash 2 (7%).

The applicant concluded that "itraconazole administered by the parenteral formulation and route, is associated with irritation at the infusion site both in this study as in previous trials. The clinical laboratory finding of concern, was that of decreased platelet count. No conclusions however

could be drawn with regard to this issue given the patients baseline illness and their small number".

"Most events were mild, none required special treatment."

As per the MO: The MO performed an analysis of the dataset utilizing the electronic search tool provided by the applicant. Additionally the MO independently verified the accurate transfer of data from the CRFs.

Results:

Demographics: 30 male patients were enrolled in the trial. 22 of the patients were white, 6 black, and 2 Hispanic.

Deaths and Discontinuations: There were no deaths and 3 patients withdrew from the trial because of an AE. All of the discontinuations were on the IV→ 200 mg PO BID arm. These events are described below:

> **Patient #0105**: 31 YO white male left the research unit upon completion of the IV phase of the protocol and attempted suicide. The patient recovered and followed-up 2 weeks later. This event was not considered related to the study drug.
>
> **Patient#0209:** 35 YO white male with oral candidiasis developed a maculopapular rash on study day 9. He continued on the study drug for an additional 3 days. The rash resolved 3 days after the study drug was discontinued and while on antihistamines.
>
> **Patient #0106**: 41 YO white male was discontinued from the study on day 35 when he presented to the ER for overall weakness and loss of motor function in the lower extremities. PML was diagnosed and determined to be unrelated to the study drug.

Serious AEs: 3 patients had serious or severe AEs. Patients #0105 and #0106 listed above (suicide attempt and encephalopathy respectively, unrelated to study drug) and patient #0207 on the 200 mg PO QD arm who had severe nausea during the IV phase and which resolved with symptomatic therapy.

Overall: There were 30 patients with 119 events. 57 events in the IV phase and the remainder in the oral phases. 5 events were severe (2 suicide attempt reports, same patient, encephalopathy and hypokinesia, same patient, and 1 case of nausea which was possibly-related to therapy).

9 events were of moderate severity (4 application site reactions definitely-related to therapy, 1 application site reaction possibly-related to therapy and 1 each headache, nausea, granulocytopenia, and back pain which were coded as not related to therapy). All patients recovered from their AE.

Table 10
All reported AEs by Study Arm and Total (As per the MO)

Adverse Event	IV Phase N = 30		IV 200 →Oral Phase 200 QD N = 15		Oral Phase 200 BID N = 14		Total N = 30	
# Reporting an AE	24 (80%)		8 (53.4%)		8 (57%)		24 (80%)	
	n	%	n	%	n	%	n	%
Gastrointestinal System Disorders								
Nausea	4	13.4	3	20	-	-	7	23.4
Diarrhea	3	10	2	13.4	2	14.2	4	13.4
Abdominal Pain	2	6.7	2	13.4	1	7.1	3	10
Constipation	-	-	1	6.7	-	-	1	3.4
Dyspepsia	-	-	1	6.7	-	-	1	3.4
Body as a Whole-General Disorders								
Back Pain	1	3.4	-	-	1	7.1	1	3.4
Pruritus	1	3.4	1	6.7	-	-	1	3.4
Fever	-	-	-	-	1	7.1	1	3.4
Ear Disorder	-	-	-	-	1	7.1	1	3.4
Fatigue	-	-	-	-	1	7.1	1	3.4
Liver and Biliary System Disorders								
Increased gGT	-	-	1	6.7	-	-	1	3.4
Liver Function Abnormalities	-	-	1	6.7	1	7.1	1	3.4
Skin and Appendages Disorders								
Rash/Maculopapular	1	3.4	2	13.4	2	14.2	3	10
Vascular Disorders								
Application Site Reaction	12	40	8	53.4	4	30	12	40
Vein Disorder	9	30	5	34	4	30	9	30
Implantation Site Complication	1	3.4	-	-	1	7.1	1	3.4
Respiratory System Disorders								
Sinusitis	2	6.7	2	13.4	1	7.1	3	10
Urinary System Disorders								
Urinary Incontinence	-	-	-	-	1	7.1	1	3.4
Central and Peripheral Nervous System Disorders								
Headache/Migraine	4	13.4	3	20	2	14.2	5	16.7
Increased Sweating	1	3.4	1	6.7	-	-	1	3.4
Syncope	1	3.4	1	6.7	-	-	1	3.4
Encephalopathy	-	-	-	-	1	7.1	1	3.4
Hypokinesia	-	-	-	-	1	7.1	1	3.4
Psychiatric Disorders								
Suicide Attempt	1	3.4	-	-	1	7.1	1	3.4
Insomnia	-	-	1	6.7	-	-	1	3.4
WBC Disorders								
Granulocytopenia	2	6.7	1	6.7	1	7.1	2	6.7
RBC Disorders								
Anemia	-	-	-	-	1	7.1	1	3.4
Eye Disorders								
Conjunctivitis	-	-	-	-	1	7.1	1	3.4

Laboratory Abnormalities:

One patient (#0110) developed an increased creatinine to > 2 x normal at week six of therapy. Baseline was reported as 1.2. On day 5 the creatinine was 1.5 (0.7 – 1.4). At week 6 it was reported as 3.3. This resolved after the completion of therapy. There was no concomitant elevation of BUN.

3 patients were found to have elevations of gGT to > 3 x normal (#0105, #0107, and #0205). Specifically: in patients #0105 and #0205 this parameter was elevated at baseline and changed minimally. In patient #0107 all LFTs were normal at baseline and increased during therapy (oral). All parameters returned to normal at the conclusion of therapy.

As in the previous study, approximately 4/30 (13.4%) of the patients entered the study with some degree of anemia. This increased to approximately 15/30 (50% during the study, although the degree of decrease in hemoglobin was not clinically significant. A similar pattern occurred with the platelet count. Specifically, 6 (20%) patients entered the study with thrombocytopenia whereas 13 (44%) patients had evidence of thrombocytopenia during the study. 8 patients (26.8%) entered the study with granulocytopenia and 18 (60%) had this abnormality by the end of the first week.

All abnormalities normalized or returned to baseline at the conclusion of the study. One patient (#0220) was found to have granulocytopenia at the end of week 6. This resolved without therapy.

The MO found no abnormalities of clinical significance. The most consistent abnormality found was that of thrombocytopenia. Although the MO agreed with the applicant that a baseline thrombocytopenia is expected in this group of patients, the decrease from a normal baseline in 24 % is unexpected and unexplained. It should be noted that a similar event occurred in #127 although in only 2/32 (6.3%) patients.

MO Conclusion: The most common AE during the IV phase of the trial was application site reaction. The degree of reaction varied from verbatim terms of simple burning or tingling to the development of pain, hardness and erythema. This event occurred in 40% of the population studied (12/30) and the AE of vein disorder developed in 30% or 9/30. Other events that developed in > 7% of the population studied and that may have had a causal relationship to the study drug were headache 5/30 (16.7%), diarrhea 4/30 (13.4%), rash 3/30 (6%), and nausea 7/30 (23.4%). Sinusitis developed in 3 patients but the clinical significance of this is unknown.

From the standpoint of the laboratory abnormalities, the only events of unclear significance were thrombocytopenia, anemia, and granulocytopenia. Minor LFT abnormalities developed in 2 patients. No significant disturbances in renal function were noted.

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

Study Dates: January 11, 1994 – April 25, 1995

Investigator: F. Colardyn, MD
Intensive Care Unit
U.Z. Gent. Belgium

Study Synopsis: Study 58 was a single center, phase II, open trial of IV itraconazole in ICU patients. The patients received itraconazole 200 mg IV at 0, 8, 24 and 32 hours and then 200 mg IV QD from days 3 – 7. Subsequently the patients were randomized to itraconazole oral solution 200 mg QD or BID for 2 weeks. The study objectives were to assess the tolerability and safety and to describe the itraconazole, hydroxy-itraconazole, and hydpoxy-propoyl-cyclodextrin plasma levels after the infusions and after the oral phase. 16 patients were studied. The inclusion criteria were standard. Enrolled were patients who required antifungal prophylaxis and who had no signs of fungal infection. The exclusion criteria were similar to

those previously described. Laboratory safety monitoring consisted of standard hematology, chemistry and urine panels performed at baseline, 24, 48, and 96 hours, and 7, 14, and 21 days after the first infusion. Creatinine clearance was determined in days 0, 7, and 14. AEs and a determination of causality were recorded on the CRF and in the event or serious AE reported to the clinical monitor.

Results as per the applicant:

16 patients were recruited and 7 were assigned to the IV itraconazole 200 mg QD/PO itraconazole and 9 to the IV itraconazole/200 BID PO itraconazole arm. 3 patients dropped out of the trial during the IV phase, 1 from the IV-QD arm because he withdrew consent and 2 from the IV-BID arm because of death. 2 additional patients dropped out of the oral phase, both from the IV-BID arm, one because of death and one because of an AE. The most common AE was diarrhea attributed by the applicant to the cyclodextrin molecule. Diarrhea was severe enough in 1 patient to lead to study termination and of moderate severity in an additional 2. The applicant determined that there appeared to be a dose-related incidence of GI AEs during oral treatment More severe laboratory abnormalities were noted during the IV phase of the trial. None of the laboratory abnormalities noted were deemed clinically significant.

As per the MO: The MOs analyses were performed using the laptop search tool provided by the applicant, the line listings and the CRFs of those patients who dies or who had a severe AE or death.

Demographics: 16 patients were enrolled, 8 male and 8 female. All patients were Caucasian with the exception of 1 Oriental male. Underlying disease processes were varied but consistent with those expected of patients in an ICU setting.

Deaths and Discontinuations: 3 patients died and 5 patients discontinued therapy (including those who died), 4 males and 1 female. These 5 patients accounted for a total of 20 events. All deaths and discontinuations are described below:

> **Patient #0012:** AEs: cardiac failure, respiratory insufficiency, and pneumothorax (all coded as no relationship to study drug). 53 YO female undergoing treatment for aspiration pneumonia due to hypoglycemia-induced coma. Her history included Addison's disease, insulin-dependent diabetes, and ischemic cardiomyopathy. In the intensive care unit, the patient developed supraventricular tachycardia and was treated with digoxin. Three days later she suddenly developed bradycardia, then cardiac arrest. She was resuscitated. An electrocardiogram revealed diminished left ventricular function and she was started on epinephrine continuous infusion. Volume-controlled ventilation was changed to pressure-controlled ventilation. The next day the patient's hemodynamic and pulmonary status was stable but vasodepressor-dependent, and she developed renal insufficiency, possibly due to cardiac failure, and acute tubular necrosis. Five days after admission the patient was started on itraconazole injection. On the same day, she developed hypoxia, hypotension, and cardiac arrest. She then developed cardiogenic shock and left-sided pneumothorax due to ventilator-associated barotrauma. She died the next day from refractory hypoxia and shock.
>
> **Patient #0013:** AEs: circulatory failure, sepsis, and dyspnea (all coded as no relation to study drug). 52 YO male, admitted to the intensive care unit for treatment of burns. Medical history included alcoholism. Physical examination showed full sedation, hypertension, burns over 60% of the body, respiratory burns and respiratory insufficiency, bronchopneumonia, intraventricular conduction abnormality, paralytic ileus, and curarization. He discontinued therapy 7 days after beginning treatment with itraconazole injection when he developed dyspnea, sepsis, and circulatory failure, which led to his death.
>
> **Patient #0015:** AEs: hypotension x3, respiratory suppression, and dyspnea (all coded as no relation to study drug). 39 YO male, PMH included insulin-dependent diabetes mellitus, nosocomial sinusitis, subarachnoidal bleeding, and ventilator-associated pneumonia. Physical examination showed full sedation, sinusoidal tachycardia, paralytic ileus due to sedation, curarization, and external ventricular drainage. He was mechanically ventilated. The patient completed 7 days of itraconazole injection followed by 14 days of the oral solution. During this

time, he developed respiratory depression, respiratory insufficiency, and hypotension; was accidentally extubated; and was reintubated with difficulty. A tracheotomy was performed and the patient stabilized. He subsequently died as a result of ARDS and multi-organ failure.

Patient #0017: AEs: diabetes insipidus (mild), abdominal pain (severe), nausea (severe), diarrhea (severe), and anxiety (mild). All GI-events were possibly-related to the study drug and occurred during the PO BID phase of the trial. The patient, a 26 YO male, had a history of burns and respiratory compromise secondary to burns. After 8 days of treatment, he developed abdominal pain, diarrhea, and nausea. He discontinued from the trial 4 days later for those reasons.

Patient #0004: AE: pain (no relation to study drug). 40 YO male with a history of pancreatitis and bilateral pleuritis, experienced pain during infusion and withdrew consent during the IV phase of the trial. The pain was of mild severity.

Overall, 16 patients accounted for 60 events. All events were coded as mild or moderate with the exception of the 6 severe events noted above in patient #0017 as well as the following 4 severe events in 2 patients.

#0011: diarrhea during the oral phase, possibly related, patient recovered and #0014: diarrhea x 2 and albuminuria, all possible related. The diarrhea occurred during the oral phase and the albuminuria during the IV phase.

Table 11
All reported AEs by Study Arm and Total (As per the MO)

Adverse Event	IV Phase N = 16		IV 200 →Oral Phase 200 QD N = 6		IV 200 →Oral Phase 200 BID N = 7		Total N = 16	
# Reporting an AE	11 (69%)		4 (66.7%)		6 (85.7%)		16 (100%)	
	n	%	n	%	n	%	n	%
Gastrointestinal System Disorders								
Diarrhea	1	9.1	1	16.7	5	71.4	7	43.7
GI disorders	1	9.1	-	-	-	-	1	6.3
Abdominal Pain	-	-	-	-	1	14.3	1	6.3
Vomiting	-	-	1	16.7	-	-	1	6.3
Dyspepsia	-	-	-	-	1	14.3	1	6.3
Nausea	-	-	-	-	1	14.3	1	6.3
Body as a Whole-General Disorders								
Pain	2	18.2	1	16.7	1	14.3	4	25
Injury	2	18.2	-	-	-	-	2	12.2
Fever	1	9.1	1	16.7	-	-	2	12.2
Fluid Overload	1	9.1	-	-	-	-	1	6.3
Cardiovascular Disorders								
Hypotension	2	18.2	-	-	-	-	2	12.2
Hypertension	1	9.1	1	16.7	-	-	2	12.2
Cardiac failure	1	9.1	-	-	-	-	1	6.3
Circulatory failure	1	9.1	-	-	-	-	1	6.3
Skin and Appendages Disorders								
Rash/Maculopapular	1	9.1	-	-	-	-	1	6.3
Urticaria	-	-	1	16.7	-	-	1	6.3
Respiratory System Disorders								
Dyspnea	1	9.1	-	-	1	14.3	2	12.2
Pneumothorax	1	9.1	-	-	-	-	1	6.3
Respiratory Depression	1	9.1	-	-	-	-	1	6.3
Respiratory Insufficiency	1	9.1	-	-	-	-	1	6.3
Rhinitis	1	9.1	-	-	-	-	1	6.3
Urinary System Disorders								
Albuminuria	1	9.1	-	-	-	-	1	6.3
Metabolic and Nutritional System Disorders								
Diabetes Insipidus	1	9.1	-	-	-	-	1	6.3
Hyperglycemia	-	-	1	16.7	-	-	1	6.3
Resistance Mechanism Disorders								
Sepsis	2	18.2	-	-	-	-	2	12.2

Laboratory Abnormalities: As per the applicant, during the trial all 16 patients exhibited important laboratory abnormalities. 14/16 patients treated with IV itraconazole exhibited abnormalities as compared to 3/6 oral QD patients and 5/7 oral BID patients. Most abnormalities were pre-existing prior to itraconazole infusion and worsened possibly due to the underlying disease processes. A direct causal relationship could not be established.

As per the MO:

The following lab values were associated with significant changes from normal baselines during the course of therapy:

ALT: 2/16 (12.5%) developed a mild increase to > 2 x normal during the IV phase of therapy.
AST: 1/16 (6.3%) developed a mild increase to > 2 x normal during the IV phase of therapy.
Albumin: 8/16 (50%) developed a decrease to < 2 x normal during the IV phase of therapy.
Calcium: 3/16 (18.8%) developed a clinically significant decrease during the IV phase of therapy.
Chloride: 2/16 (12.5%) developed a clinically significant increase during the IV phase of therapy.
Creatinine: 2/16 (12.5%) developed mild increases during the IV phase of therapy.
gGT: 1/16 (6.3%) developed a mild increase to > 2 x normal during the IV phase of therapy.
Glucose: 1/16 (6.3%) developed a clinically significant increase during the IV phase of therapy.
Hematocrit: 1/16 (6.3%) developed a mild decrease during the IV phase of therapy.
Hemoglobin: 1/16 (6.3%) developed a mild decrease during the IV phase of therapy.
Phosphorus: 1/16 (6.3%) developed a clinically significant decrease during the IV phase of therapy.
1/16 (6.3%) developed a clinically significant increase during the IV phase of therapy.
Platelet count: 2/16 (12.5%) developed a clinically significant decrease during the IV phase of therapy.
Potassium: 3/16 (18.8%) developed a clinically significant decrease during the IV phase of therapy.
Total Bilirubin: 3/16 (18.8%) developed a mild increase during the IV phase of therapy.
Total Protein: 2/16 (12.5%) developed a clinically significant decrease during the IV phase of therapy.
WBC: 1/16 (6.3%) had an initial WBC that was wnl and which decreased to below the lower limit of normal during the IV phase.

During the PO-QD phase the following significant changes were noted:

ALT: 1/16 (6.3%) developed an increase to > 3 x normal.
Glucose: developed a clinically significant increase.

During the PO-BID phase, the following were noted:

ALT: 1/7 (14.3%) developed an increase to > 2 x normal.
Albumin: 1/7 (14.3%) developed a clinically significant decrease on day 14.
Chloride: 1/7 (14.3%) developed a mild decrease.
gGT: 1/7 (14.3%) developed an increase to > 3 x normal.
Glucose: 1/7 (14.3%) developed a clinically significant increase.
Platelet Count: 1/7 (14.3%) developed a clinically significant decrease.
Potassium: 1/7 (14.3%) developed a clinically significant increase.
Triglycerides: 2/7 (28.6%) developed a mild increase.
Urea: 1/7 (14.3%) developed a clinically significant increase.

Although multiple abnormalities existed during the IV phase, a review of the CRFs revealed that none were unexpected and that in most cases the abnormalities were pre-existing. Mild abnormalities of renal and hepatic function developed in 2 patients respectively. The MO did not detect any trends with regard to the development of myelosuppression as was noted in the US-PK studies. Thrombocytopenia was not striking in this study as in previously reviewed studies.

MO Conclusion: The use of IV itraconazole followed by PO itraconazole in this population of critically ill ICU patients was unaccompanied by any significant AEs that were unexpected. The most frequent AE was diarrhea from the GI tract on the 200 mg BID arm (5/7 (71.4%) and one episode each on the IV and PO-QD arms for a total of 7/16 (43.7%). Other GI events were noted but were not seen in more than 1 patient per arm.

From a laboratory standpoint, no significant trends were noted, Most events could be explained on the basis of the patients' underlying diseases. No trend towards general myelosuppression was noted, although 2 patients had a mild thrombocytopenia and 1 patient had a mild anemia. One additional patient had leucopenia. Mild renal dysfunction was noted in 2 patients and mild LFT elevations in 2 patients.

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

Study 59 was in all ways similar to study 58 with the exception that the patient population was compromised of patients with underlying leukemia.

Study Dates: January 20, 1995 – April 28, 1995

Investigators: M Boogaerts, MD
Dept. of Hematology
UZ Gasthuisberg
Leuven, Belgium

A Bosly, MD
Dept. of Hematology
Cliniques Universitaires St. Luc
Mont Godinne, Belgium

JL Michaux, MD
Dept. of Hematology
Cliniques Universitaires St. Luc
Bruxelles, Belgium

A Van Hoof, MD
Dept. of Hematology
AZ St. Jan
Brugge, Belgium

As per the applicant: 18 patients were recruited of whom 17 were randomized, 6 to IV itraconazole →PO QD and 11 to IV itraconazole → PO BID. 53% of the patients were male, all Caucasian except one Oriental and the median ages for the 2 treatment groups were 46 and 35 years of age. 1 patient died in the post-study period (2 weeks after discontinuing IV therapy) and 9 patients discontinued treatment because of an AE. 3 of these patients had AEs determined to be serious (9, 11, 18).

Adverse events, primarily related to the GI system, were reported by 13/17 (77%) of IV patients, by all 6/6 PO QD patients and by 8/9 (89%) of the PO BID patients. The most frequently reported AEs were constipation (7 IV and 1 QD), fever (6 IV, 3 QD, and 3 BID), diarrhea (1 IV, 1 QD, and 3 BID), and bacterial infection (3 IV and 2 BID).

All patients had significant laboratory abnormalities during the trial. During the IV treatment, 16/17 had an important abnormality and 5/17 had a clinically significant abnormality. During the oral QD phase, 5/6 patients with paired data had an important abnormality and 1 had a clinically significant abnormality. During the PO BID phase 4/5 patients had an important abnormality and none had a clinically significant abnormality. None of the parameters were consistently changed and all could be accounted for by the underlying disease processes.

The results of this trial indicated that IV and oral itraconazole were well tolerated and safe.

As per the MO: 17 patients were enrolled and randomized to treatment and accounted for 98 AEs.

Demographics: 9 male and 8 female. All were Caucasian with the exception of one male Oriental patient. 15 patients had leukemia as the underlying disease process. One patient had multiple myeloma and 1 had lymphoma.

Deaths and Discontinuations: 9 patients discontinued therapy (3 patients because of diarrhea coded as mild occurring during the oral phase and possibly-related to the study drug (#0007 ,#0008, and #0017), 2 patients because of the development of pneumonitis unrelated to the study drug (#009 and #0011), and 3 patients because of the development of fever of moderate severity unrelated to the study drug), and accounted for 42 events. None of the patients died during active treatment but #0018 died 2 weeks after terminating the IV phase from pneumonia. This patient's death occurred after completion of the dataset and was not included in the electronic portion of the submission. Reviewed below is the patient who died:

> **Patient #0018**: AEs: pain, constipation: mild, hypertension: moderate, and fever, pneumonia: severe. 29 YO male, with acute myeloid leukemia discontinued the trial 5 days after beginning treatment when he developed bilateral lung infiltration and respiratory failure and was started on mechanical ventilation. The patient also experienced mild pain from the Hickman catheter, mild constipation, and moderate hypotension. All events were assessed as unrelated to the study drug.

Severe events: #0007: arthritis, unrelated and patient, #0001 d severe constipation coded as unrelated to the study drug.

MO Comment: In summary, 2 patients (#0018, #0013) discontinued therapy while on the IV phase of the trial, 2 patients (#0007, #0008) while on the PO-QD phase, and 5 patients discontinued while on the PO-BID phase (#0017, #0016, #0009, #0011, and #0012).
Additionally, 1 death occurred (#0018), 2 weeks after concluding the trial from pneumonitis.

Table 12
All reported AEs by Study Arm and Total (as per the MO)

Adverse Event	IV Phase N = 17		IV 200 →Oral Phase 200 QD N = 6		IV 200 →Oral Phase 200 BID N = 9		Total N = 17	
# Reporting an AE	13 (76.5%)		6 (100%)		8 (88.9%)		17 (100%)	
	n	%	n	%	n	%	n	%
Gastrointestinal System Disorders								
Constipation	7	41.2	1	16.7	-	-	8	47
Diarrhea	1	5.9	1	16.7	3	34	5	29.4
Abdominal Pain	-	-	-	-	1	11.2	1	5.9
Vomiting	2	11.8	-	-	-	-	2	11.8
Nausea	1	5.9	-	-	-	-	1	5.9
Dyspepsia	-	-	-	-	1	11.2	1	5.9
Colitis	-	-	1	16.7	-	-	1	5.9
Gingivitis	1	5.9	-	-	-	-	1	5.9
Body as a Whole-General Disorders								
Fever	6	35.3	3	50	3	34	11	64.7
Allergic Reaction	1	5.9	1		1		3	17.6
Arthritis	1	5.9	-	-	-	-	1	5.9
Lymphadenopathy	1	5.9	-	-	1		2	11.8
Pain	1	5.9	-	-	-	-	1	5.9
Condition Aggravated	-	-	1	16.7	-	-	1	5.9
Rigors	-	-	1	16.7	1	11.2	2	11.8
Central and Peripheral Nervous System Disorders								
Headache	1	5.9	-	-	-	-	1	5.9
Extrapyramidal disorder	1	5.9	-	-	-	-	1	5.9
Increased Sweating	1	5.9	-	-	-	-	1	5.9
Convulsions	-	-	-	-	1	11.2	1	5.9
Cardiovascular Disorders								
Hypotension	1	5.9	-	-	-	-	1	5.9
Chest Pain	-	-	1	16.7	-	-	1	5.9

Substernal Chest Pain	-	-	-	-	1	11.2	1	5.9
Skin and Appendages Disorders								
Rash	-	-	1	16.7			1	5.9
Respiratory System Disorders								
Pneumonitis	1	5.9	-	-	2		3	17.6
Urinary System Disorders								
Albuminuria	1	5.9	-	-	-	-	1	5.9
Glycosuria	1	5.9	-	-	-	-	1	5.9
Metabolic and Nutritional System Disorders								
Hyperglycemia	2	11.8	-	-	-	-	2	11.8
Resistance Mechanism Disorders								
Bacterial Infection	3	17.6	-	-	2	23	5	29.4
HSV	1	5.9	-	-	2	23	3	17.6
Folliculitis	1	5.9	-	-	-	-	1	5.9
Fungal Infection	-	-	2	34	-	-	2	11.8
Vascular Disorders								
Application site reaction	1	5.9	-	-	-	-	1	5.9
Genital Tract Disorders								
Vaginitis	1	5.9	-	-	-	-	1	5.9
Vaginal Hemorrhage	1	5.9	-	-	-	-	1	5.9
Psychiatric Disorders								
Anxiety	2	11.8	-	-	-	-	2	11.8
Depression	1	5.9	-	-	-	-	1	5.9

MO Comment: The MO was unable to complete the above table utilizing the database alone because discrepancies were found between the electronic portion of the submission and the paper line listings. Specifically the MO found an increase in the number of total episodes of fever and constipation by 1 each.

Laboratory:
The MO assessed the laboratory abnormalities via the line listings and CRFs only. The electronic portion of the submission did not provide the ability to query with regard to patients with a normal baseline and subsequent deterioration.

The following lab values were associated with significant changes from normal baselines during the course of therapy:

ALT: 2/17 (11.8%) developed an increase to > 3 x normal during the IV phase of therapy.
AST: 1/17 (5.9%) developed an increase to > 3 x normal during the IV phase of therapy.
Albumin: 1/17 (5.9%) developed a decrease to < 2 x normal during the IV phase of therapy.
Calcium: 6/17 (35.3%) developed a clinically significant decrease during the IV phase of therapy.
Chloride: 3/17 (17.6%) developed a clinically significant increase during the IV phase of therapy.
gGT: 3/17 (17.6%) developed an increase to > 3 x normal during the IV phase of therapy.
Glucose: 3/17 (17.6%) developed a clinically significant increase during the IV phase of therapy.
Hematocrit: 3/17 (17.6%) developed a clinically significant decrease during the IV phase of therapy.
Hemoglobin: 3/17 (17.6%) developed a clinically significant decrease during the IV phase of therapy.
Phosphorus: 3/17 (17.6%) developed a clinically significant decrease during the IV phase of therapy.
Platelet count: 2/17 (11.8%) developed a clinically significant decrease during the IV phase of therapy.
Total Bilirubin: 1/17 (5.9%) developed a clinically significant increase during the IV phase of therapy.
Total Protein: 4/17 (23.5%) developed a clinically significant decrease during the IV phase of therapy.
Urea: 3/17 (17.6%) developed a clinically significant increase during the IV phase of therapy.
1/17 (5.9%) developed a clinically significant decrease during the IV phase of therapy.
WBC: 8/17 (47%) had initial WBCs that were grossly elevated and which decreased to below the lower limit of normal during the IV phase.

During the PO-QD phase the following significant changes were noted:

ALT: 1/6 (16.7%) developed an increase to > 3 x normal
Albumin: 1/6 (16.7%) developed a decrease to < 2 x normal
Calcium: 1/6 (16.7%) developed a clinically significant decrease
Chloride: 1/16 (16.7%) developed a clinically significant increase
Hemoglobin: 1/6 (16.7%) developed a clinically significant decrease
Phosphorus: 2/6 (34%) developed a clinically significant decrease
Platelet count: 2/6 (34%) developed a clinically significant decrease
Potassium: 1/6 (16.7%) developed a clinically significant decrease
WBC: 3/6 (50%) had initial WBCs that were normal and which decreased to below the lower limit of normal.

During the PO-BID phase, the following were noted:
Calcium: 1/9 (11.2%) developed a clinically significant decrease.
Glucose: 2/9 (23%) developed a clinically significant increase.
Potassium: 1/9 (11.2%) developed a clinically significant decrease.
Total Bilirubin: 2/9 (23%) developed a clinically significant increase.
Triglycerides: 1/9 (11.2%) developed a clinically significant increase.
Urea: 1/9 (11.2%) developed a clinically significant increase.

MO Conclusion: The most frequently seen AEs in trial 59 were associated with the GI tract. The most common event was constipation seen in 7/17 (41.7%) of patients receiving IV itraconazole or 8/17 (47%) of all patients. Diarrhea was most frequently seen in patients on the oral-BID arm of the trial 3/9 (34%), total 5/17 (29.4%). Fever was also seen frequently on all arms of this trial with 6/17 (35.3%) of the IV patients experiencing temperature elevations as compared to 3/6 (50%) of the PO-QD patients and 3/9 (34%) of the PO-BID patients. The total number of febrile events for the trial was 11/17 (64.7%). The MO questions the significance of this event given the population under study.

From a laboratory standpoint, the MO detected no significant trends in this trial. Although 3/17 (17.6%) of patients developed a decrease in hemoglobin during the IV phase, the MO was unsure of the clinical significance of this event. The same was true for the decrease in WBC noted in 8/17 (47%) of the patients. All of the baseline WBCs were markedly abnormal and the decrease in individual values represented a trend towards normalization. 2/17 (11.8%) of patients developed a clinically significant decrease in platelet count during the IV phase as compared to the PO arms. This event may be of significance given the similar events noted in previously reviewed trials.

No significant disturbances of renal or hepatic function were noted.

Clinical Studies:

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

Study Dates: April 11, 1996 – April 27, 1997*
*Please note that at the time of submission, this trial was incomplete. The data search tool provided by the applicant contained information on 23 patients (data collection endpoint May 31, 1997). The paper submission endpoint was September 30, 1997 and included additional withdrawal and serious AE information. This study was completed by May 1, 1998 and in the 4 month safety update the applicant updated the dataset with information on an additional 8 patients (not included in this section of the MOR).

Investigators (N = 12):

Canada: G. Garber, MD: 2 subjects
General Hospital Infectious Diseases
501 Smyth St.
Ottawa, Canada

A McGeer, MD: 3 subjects
Princess Margaret Hospital
690 – 500 Sherbourne St.
Toronto, Canada

F. Small, MD: 1 subject
Dept. of Microbiology and Infectious Diseases
McMaster Univ. Medical Center
1200 Main St.
Hamilton, Canada

France: D. Caillot, MD: 1 subject
Faculty if Medicine
Univ. of Dijon
Dijon, France

B. Coronel, MD: 2 subjects
Internal Medicine, Univ. Hospital
Lyon, France

J. Harousseau, MD: 7 subjects
Centre Hospitalier, Dept. Hematology
Nantes, France

Great Britain: H. Prentice, MD: 1 subject
Royal Free Hospital
NW3 Pondstreet
London, Great Britain

S. Rule, MD: 1 subject
Musgrove Par Hospital
Taunton, Great Britain

S. Schey, MD: 1 subject
Guy's Hospital
Lambeth Place Road

London, Great Britain

Greece: H. Bassaris, MD: 1 subject
School of Medicine
Univ. of Patras
Patras, Greece

A. Fassas, MD: 2 subjects
George Papanicolaou General Hospital
57010 Exokhi
Thessaloniki, Greece

G. Pettrikos, MD: 1 subject
Laiko General Hospital
17 Agiou Thomma
11527 Athens, Greece

Countries in which study performed: Canada, Greece, France, and Great Britain.

Study Synopsis: This study was a phase III, open, uncontrolled, multicenter trial of IV itraconazole 200 mg BID x 2 days followed by 200 mg IV QD x 12 days in 30 patients with proven pulmonary or disseminated aspergillosis. Subsequent to the IV phase, patients received itraconazole capsules 200 mg PO QD (2 100 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 submission. The primary objective was to study the efficacy and safety of IV itraconazole followed by itraconazole capsules in 30 patients with aspergillosis. Additionally, plasma levels of itraconazole were monitored. The inclusion criteria stipulated patients of either sex with histologically proven aspergillosis who provided informed consent. The exclusion criteria were standard. Patients with LFTs > 5 x normal or with a creatinine clearance > 3 x normal were excluded. Copied below is the applicant's reference to safety monitoring:

Evaluation of safety

Evaluation of laboratory safety

Before entry into the trial (at recruitment), after 2 days, and 7 and 14 days after the first itraconazole administration, and at the end of trial samples for hematology, biochemistry and urinalysis will be taken

The following tests will be performed:

Hematology

Hemoglobin, Hematocrit, RBC, WBC, leukocyte differential count and platelet count.

Blood biochemistry

Sodium, potassium, chloride, calcium, inorganic phosphorus, total protein, albumin, glucose, total cholesterol, triglycerides, blood urea nitrogen (BUN), creatinine (twice weekly), uric acid, total bilirubin, alkaline phosphatase, ASAT (SGOT), ALAT (SGPT), gGT and LDH.

Urinalysis

pH, RBC, WBC, albumin, glucose, urobilinogen, bilirubin, acetone, bacteria, epithelial cells, crystals, sperms, casts, mucin, fungi, fat droplets and occult blood.

Creatinine clearance

Creatinine clearance will be calculated on day 0, 4, 7, 11 and 14 or at the end of the IV administration.

Changes in liver function

Patients should be told that they should immediately contact the investigator or his/her designee for side effects suggestive for liver function abnormalities, especially dark urine, jaundice, or persistent nausea and vomiting. Similarly, the investigator must remain alert.

Patients with marked liver function abnormalities as described in exclusion criterion 5 must discontinue treatment immediately. The abnormal tests should be repeated within 48 hours, and thereafter at 3 to 7 day intervals until they resolve. Additional evaluation of patients with marked abnormalities that persist after study drug treatment is discontinued should be arranged. The additional evaluation may include GI consultation and additional laboratory tests (e.g., HBV, HAV or CMV serology; CPK; reticulocyte count).

Adverse experiences

Type and incidence of all adverse events will be tabulated per phase (IV phase and oral phase).

Laboratory safety parameters

Descriptive statistics will be calculated for all biochemistry and hematology data and urine data. Additionally, cross tabulations versus baseline will be produced, with categories for within, above and below normal ranges.

Important abnormalities (above or below pathological limits) will be reported in a separate table.

Study Report as per the applicant: 23 patients were enrolled. 16 of the patients had an unspecified underlying disease, 1 had AIDS, 1 chronic granulomatous disease, 4 hematologic malignancies with transplant. 4 patients terminated the study during the IV phase because of an AE and 4 during the PO phase because of an AE. A total of 18 patients entered the oral phase of the study. 1 additional patient terminated during the IV phase for "other".

"During the IV itraconazole treatment, over 20% of subjects reported AEs for dyspnea, fever, and pulmonary edema. These AEs can be accounted for when the underlying medical status is taken into consideration. During the subsequent treatment with oral itraconazole, over 20% of subjects reported AEs for nausea alone. "

As per the MO: 23 subjects (16 male and 7 female) were enrolled and randomized. 8 patients discontinued therapy because of an AE and 4 patients died. The 23 subjects reported 265 events. 153 of these events were reported during the IV phase. 38 events from 23 patients were reported as severe, the remainder were mild to moderate in severity.

Of the 38 severe events, 4 were reported as definitely-related to the study drug. 1 of these events from patient #3019 was reported as rigors and the remaining 3 were reported from patient #3043. All 3 events in this patient were rash which resolved. 8 events were reported as possibly-related to therapy including events from patient #3018: hepatic function abnormalities, #3019: abnormal gait and hemoptysis, #3031: dyspnea x 2 and respiratory disorder, and #3071: increased creatinine x 2. All other severe events were considered unrelated to therapy.

Deaths (N = 4):

As stated previously, 4 patients died during the study and are listed below:

Patient #3049: 32 YO Oriental female received 11 days of treatment before she experienced worsening of her underlying condition. After 43 days she developed a fungal infection. She discontinued therapy 45 days after beginning treatment because of the fungal infection and mucositis. She developed convulsions and became comatose. She died 7 days after discontinuing therapy. (AEs: severe: condition aggravated, edema, mucositis, moderate: syncope, leg pain, headache, pleural effusion, pleural pain, fungal infection, bacterial infection, vaginal hemorraghe, epistaxis, creatinine increased, hypomagnesemia, hypocalcemia, hypokalemia, ulcerative stomatitis, nausea, mild: edema, headache, dyspepsia, fluid overload, confusion, pulmonary edema, rash.)

Patient #3060: 36 YO male received therapy for 86 days, at which time his condition worsened and treatment was discontinued. The patient died 8 days later (AEs: severe: condition aggravated x 2, moderate: nausea).

Patient #3067: 58 YO female died 10 days after beginning treatment when she developed a fungal infection and a gastrointestinal hemorrhage (AEs: severe: GI hemorraghe, fungal infection, moderate: diarrhea, renal function abnormality.)

Patient #3069: 78 YO male died 10 days after beginning treatment. Death was attributed to a bacterial infection that began before initiation of treatment with itraconazole, dyspnea that began 4 days after beginning treatment, and a myocardial infarction that occurred 5 days after beginning treatment (AEs severe: bacterial infection, MI, dyspnea).

MO Comment: None of the deaths were attributable to the study medication and all were due to complications of the underlying diseases.

Discontinuations (N = 8):
In addition to the 4 patients that died, 4 patients discontinued therapy because of an AE: Of these patients, one (#3018) developed severe LFT abnormalitles after 4 weeks of therapy and 1 patient (#3031 developed renal dysfunction. Case synopses on both of these patients are provided below because of the seriousness of the AEs.

Patient #3018:AEs: 33 YO female developed a maculopapular rash after 23 days of treatment. After 24 days she developed abnormal hepatic function, and after 26 days she developed xerophthalmia. She discontinued therapy 29 days after beginning treatment because of abnormal hepatic function. Her liver function test results at Day 14 were SGOT: 63 U/L; SGPT: 115 U/L; gGT: 84 U/L; alkaline phosphatase: 168 U/L; total bilirubin: 20 umol/L; and urea: 4.1 mmol/L. The abnormal results continued to rise to the following levels at Week 14: SGOT: 213 U/L; SGPT: 543 U/L; gGT: 525 U/L; alkaline phosphatase: 755 U/L; total bilirubin: 73 umol/L; and urea: 11.3 mmol/L. No additional information was available.

Patient #3031:69 YO male discontinued therapy 4 days after beginning treatment because of a decrease in his creatinine clearance. Relevant laboratory abnormalities were:

- creatinine: 1.7 mg/dL at baseline; 2.1 mg/dL at Day 3
  (normal limits: 0.9-1.6 mg/dL)
- BUN/urea: 67 mg/dL at baseline; 57 mg/dL at Day 3
  (normal limits: 15-54 mg/dL)

He had also experienced dyspnea and a respiratory disorder. The symptoms were still present at the end of the trial.

The remaining 2 patients who discontinued therapy did so because of worsening of their underlying disease processes (#3071: neutropenia, #3019, hemoptysis). Both events were serious but expected.

Serious AEs: An additional 6 patients other than those previously listed (3018, 3019, 3047, 3065, 3067, and 3069) developed serious AEs (#3015 developed pneumonia after 86 days of therapy, unrelated to study drug, #3021 developed a rash after 28 days of study drug, #3041 experienced nausea and vomiting while receiving trial medication (IV phase) as well as fever and rigors after 61 days of treatment which subsequently resolved without discontinuation and 3 patients developed worsening of their underlying pulmonary pathology (#3076, #3072, and #3074).

MO Comment: The MO determined that none of the serious pulmonary events were related to therapy. The nausea experienced by #3041 appeared to be related to the IV study drug.

Table 13

All reported AEs by Treatment Arm (As per the MO)

Adverse Event	IV Phase N = 23		PO Phase N = 18		Total N = 23	
	n	%	n	%	n	%
Gastrointestinal System Disorders						
Diarrhea	4	17.4	3	16.7	6	26.1
Constipation	3	13	2	11.2	4	17.4
Nausea	2	8.7	5	55	5	21.7
Vomiting	2	8.7	3	16.7	4	17.4
Dyspepsia	2	8.7	-	-	2	8.7
Abdominal Pain	1	4.4	2	11.2	3	13
GI Hemorrhage	1	4.4	-	-	1	4.4
Stomatitis (Ulcerative)	1	4.4	1	5.6	1	4.4
Respiratory System Disorders						
Dyspnea	6	26.1	1	5.6	7	30.4
Pulmonary Edema	5	21.7	1	5.6	5	21.7
Coughing	4	17.4	3	16.7	4	17.4
Respiratory Disorder	3	13	2	11.2	3	13
Bronchospasm	3	13	1	5.6	3	13
Hypoxia	2	8.7	1	5.6	2	8.7
Hemoptysis	2	8.7	1	5.6	3	13
Stridor	2	8.7	-	-	2	8.7
Pleurisy	1	4.4	1	5.6	1	4.4
Abnormal CxR	1	4.4	1	5.6	1	4.4
Pleural effusion	-	-	1	5.6	1	4.4
Rhinitis	-	-	1	5.6	1	4.4
URI	-	-	1	5.6	1	4.4
Pneumonia	-	-	2	11.2	2	8.7
Sinusitis	-	-	2	11.2	2	8.7
Body as a Whole-General Disorders						
Fever	5	21.7	4	23	8	34.8
Condition Aggravated	2	8.7	3	16.7	3	13
Edema	2	8.7	1	5.6	2	8.7
Fluid Overload	2	8.7	-	-	2	8.7
Temperature changed	1	4.4	-	-	1	4.4
Allergic Reaction	1	4.4	-	-	1	4.4
Dysphonia	1	4.4	1	5.6	1	4.4
Myalgia	1	4.4	-	-	1	4.4
Lab Values Abnormal	1	4.4	1	5.6	1	4.4
Rigors	1	4.4	1	5.6	2	8.7

Leg Pain	-	-	1	5.6	1	4.4
Enlarged Abdomen	-	-	1	5.6	1	4.4
Peripheral Edema	-	-	1	5.6	1	4.4
Fatigue	-	-	1	5.6	1	4.4
Injury	-	-	1	5.6	1	4.4
Central and Peripheral Nervous System Disorders						
Headache	2	8.7	4	23	2	8.7
Syncope	2	8.7	-	-	2	8.7
Confusion	2	8.7	1	5.6	2	8.7
Dizziness	1	4.4	-	-	1	4.4
Convulsions	1	4.4	1	5.6	2	8.7
Hypertonia	1	4.4	-	-	1	4.4
Stupor	1	4.4	-	-	1	4.4
Abnormal Gait	-	-	1	5.6	1	4.4
Coma	-	-	1	5.6	1	4.4
Resistance Mechanism Disorders						
Infection	-	-	1	5.6	1	4.4
Herpes simplex	1	4.4	3	16.7	3	13
Bacterial Infection	2	8.7	2	11.2	3	13
Sepsis	1	4.4	1	5.6	1	4.4
Cellulitis	1	4.4	1	5.6	1	4.4
Fungal Infection	1	4.4	3	16.7	4	17.4
Mucositis	1	4.4	1	5.6	1	4.4
Skin and Appendages Disorders						
Rash	4	17.4	3	16.7	5	21.7
Metabolic and Nutritional System Disorders						
Hypokalemia	2	8.7	1	5.6	2	8.7
Hyponatremia	-	-	1	5.6	1	4.4
Creatinine Increased	2	8.7	1	5.6	2	8.7
CrCl Decreased	1	4.4	-	-	1	4.4
Acidosis	1	4.4	1	5.6	1	4.4
Hypocalcemia	1	4.4	1	5.6	1	4.4
Hypochloremia	1	4.4	1	5.6	1	4.4
Hypomagnesemia	1	4.4	1	5.6	1	4.4
Hyperglycemia	-	-	1	5.6	1	4.4
Cardiovascular Disorders						
Hypotension	1	4.4	-	-	1	4.4
MI	1	4.4	-	-	1	4.4
Hypertension	-	-	1	5.6	1	4.4
Urinary System Disorders						
Cystitis	-	-	1	5.6	1	4.4
UTI	-	-	1	5.6	1	4.4
Renal System Disorders						
Renal function Abnormal	1	4.4	-	-	1	4.4
Liver and Biliary System Disorders						
Hepatocellular Damage	1	4.4	1	5.6	1	4.4
Abnormal Hepatic Function	-	-	1	5.6	1	4.4
Increased LDH	-	-	1	5.6	1	4.4
WBC Disorders						
Granulocytopenia	-	-	1	5.6	1	4.4
Coagulation Disorders						
Epistaxis	2	8.7	1	5.6	2	8.7
Thrombophlebitis	-	-	1	5.6	1	4.4

Eye Disorders						
Eye Abnormality	1	4.4	-	-	1	4.4
Xeropthalmia	-	-	1	5.6	1	4.4
Genital Tract Disorders						
Vaginal Hemorrhage	1	4.4	1	5.6	1	4.4
RBC Disorders						
Hyperhemogobinemia	-	-	1	5.6	1	4.4

Laboratory:
The MO assessed the laboratory abnormalities via the line listings and CRFs only. The electronic portion of the submission did not provide the ability to query with regard to patients with a normal baseline and subsequent deterioration.

The following lab values were associated with significant changes from normal baselines during the course of therapy:

Chloride: 2 patients developed values significantly below normal during the first 3 days of therapy.
LDH: 1patients developed a clinically significant increase from a baseline increased value of 588 U/L to 2439U/L by day 7.
RBC: 1 patient developed a clinically significant decrease during the first week of therapy.
Total bilirubin: 1 patient developed a clinically significant increase over the 14 weeks of therapy.
Total Protein: 1 patient each developed a clinically significant increase and decrease during the 14 weeks of therapy.
Triglycerides: 3 patients developed clinically significant increase, 2 during the first 2 weeks of IV therapy and 1 by week 14.
BUN: 2 patients developed clinically significant increase by week 14 of therapy.
WBC: 3patients developed increased WBC counts during the first 2 weeks of therapy. 1patient became neutropenic during the fist 14 days of therapy and remained so through week 14.
Alk. Phos.: 2 patients developed clinically significant increase during the first 2 weeks of therapy.
ALT and AST: 1 patient developed a clinically significant increase of both parameters during the first 2 weeks of therapy.
Calcium: 4 patients developed significant decreases during the first 2 weeks of therapy.
Creatinine: 3 patients developed increased values during the first 2 weeks of therapy.
gGT: 4 patients developed increased values during the first 2 weeks of therapy.
Hemoglobin: 3 patients developed decreased values during the first 2 weeks of therapy.
Neutrophils: 1 patient became neutropenic during the first 2 weeks and remained so through week 14.
Platelets: 1 patient became thrombocytopenic during the first 2 weeks with incomplete recovery by week 14.
Sodium: 2 patients became hyponatremic during the first week of therapy with recovery during the oral phase.

MO Comment: Most of the clinically significant laboratory abnormalities occurred in patients who discontinued therapy within the first 1 –2 weeks because of death.

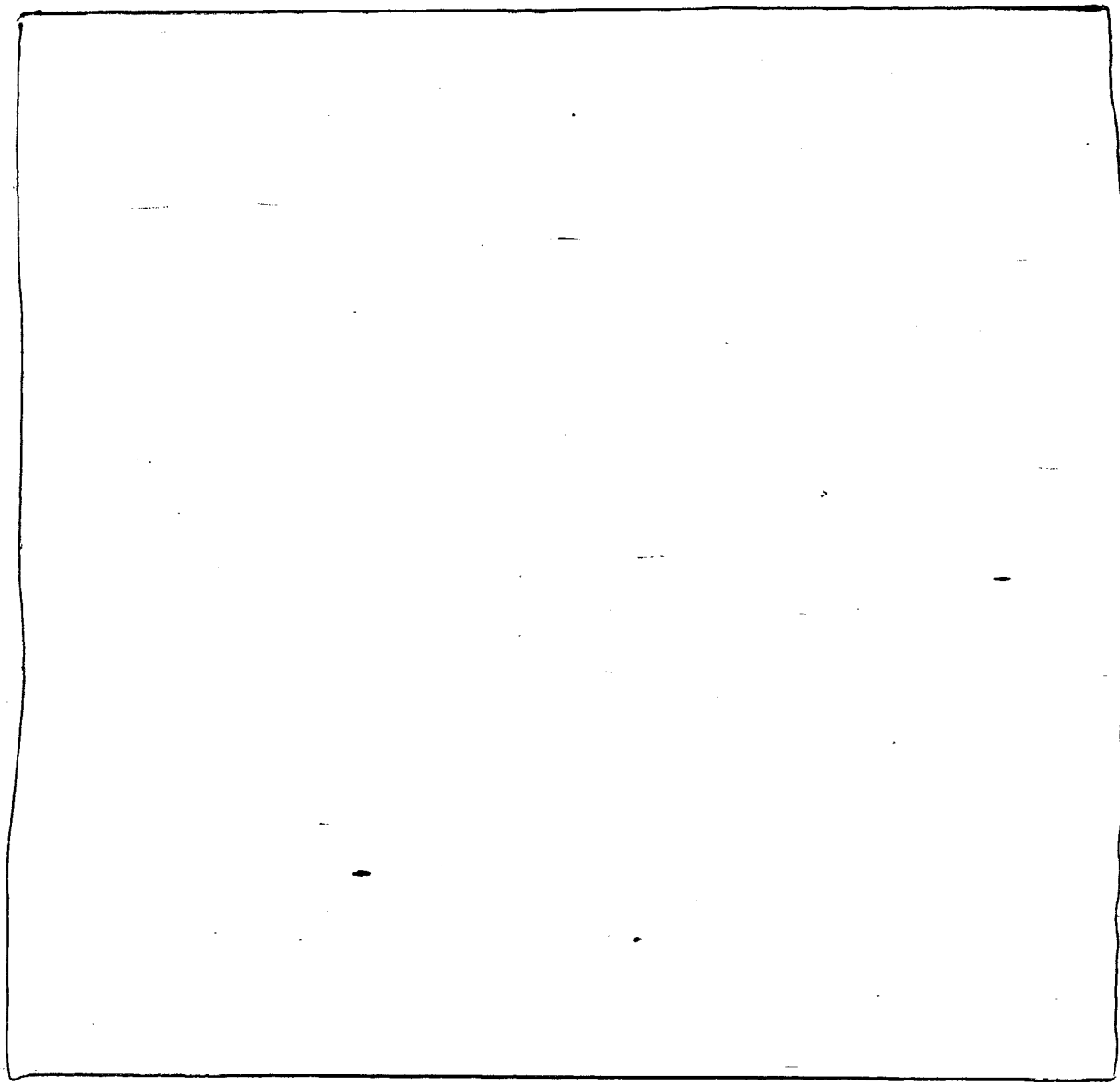
MO Conclusion: During the IV phase of the trial, of the events considered definitely or possibly-related to therapy, only diarrhea was seen in 3/23 or 13% of the patients. All other events with the exception of rash and rigors were seen in < 5% and included hyponatremia, hypochloremia, hypocalcemia, hypomagnesemia, dyspnea, edema, acidosis, respiratory disorder, syncope, abnormal renal function, myalgia, hypertonia, hepatocellular damage, decreased renal function, and temperature change. There were 2 events each of rash and rigors or 8.7%.

During the oral phase, the following definitely or possibly-related events were seen in > than 5% of the patients: nausea 3/18 (16.7%), fungal infection 2/18 (11.2%), and rash 2/18 (11.2%).

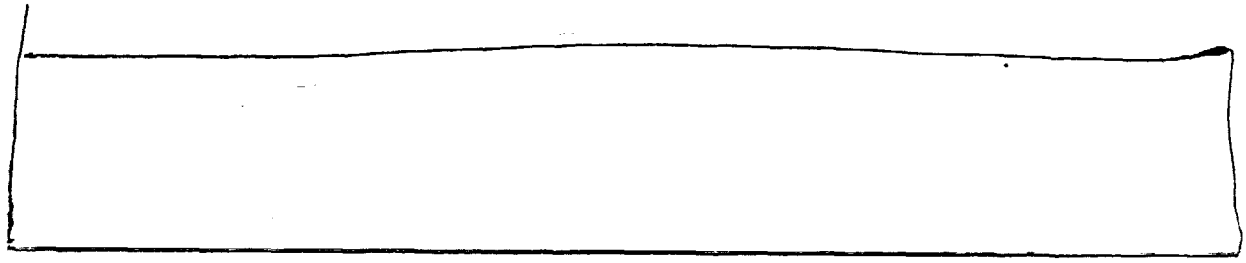
Overall, during the IV phase, 5/23 patients had fever, 6/23 had dyspnea, and 4/23 had diarrhea. Other events noted in > 5% of the subjects included: nausea, pulmonary edema, rash, bronchospasm, constipation, coughing, vomiting, aggravated condition, hemoptysis, headache, respiratory disorder, acidosis, dyspepsia, epistaxis, fluid overload, hypoxia, increased BUN, edema, stridor, and syncope. During the oral phase, the following were noted in > 5% of the subjects irrespective of causality: fever, diarrhea, nausea, rash, fungal infection, abdominal pain, vomiting, herpes simplex, bacterial infection, and edema.

The MO agreed with the applicant's determination that most of the AEs were justified by the patients underlying conditions. Only rash and diarrhea appeared to have a definite causal relationship to the intravenous study drug.

From the standpoint of laboratory abnormalities, mild renal dysfunction developed in 2 patients who also developed death or significant medical problems. No overall trends were noted.



This page of the document contains confidential information that will not be included in the redacted portion of the document for the public to obtain.



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

Study Dates: March 28, 1996 – ongoing
(The electronic portion of the submission contained data on patients enrolled through May 20, 1997. The paper potion of the submission contained additional information on those patients as well as information on patients enrolled between May and September 1997. The additional patient information was not provided electronically or in the line listings.)

# of Investigators: 47

 # Of Subjects Entered: 196

 # Of Subjects Randomized: 191 (Itraconazole: 95, Amphotericin B: 96)

Study Summary: Trial INT-62 was an open, randomized, parallel group, comparative trial to assess the efficacy and safety of a 7- to 14-day intravenous regimen of itraconazole followed by a 400 mg daily itraconazole oral solution with 0.7 to 1.0 mg/kg of intravenous amphotericin B in 390 neutropenic patients with hematological malignancy and fever > 38°C for 3 to 7 days under broad-spectrum antibiotic therapy with or without signs and symptoms potentially attributable to deep fungal infection. The trial is being conducted at 30 sites (US, Canada, Europe and Australia). Patients were stratified for the signs and symptoms potentially attributable to deep-seated fungal infections and for underlying therapy (marrow transplant or chemotherapy).

The objective of the trial was to compare the efficacy and safety of intravenous itraconazole followed by oral itraconazole with intravenous amphotericin B as empiric therapy in 390 neutropenic patients with hematological malignancy. Patients remaining febrile after 3 to 7 days of empiric antimicrobial treatment and still severely granulocytopenic without microbiologically documented infection i.e. those with no clinically significant pathogens but with clinically documented (site of infection known) or possible (FUO) infection. In addition plasma levels of itraconazole were followed.

In addition to the standard for antifungal trials inclusion and exclusion criteria, excluded were:

Subjects with liver disease defined as liver enzymes (SGPT or SGOT) ≥ 5 times the upper normal limit or bilirubin ≥ 50 mmol/liter at trial entry and

Subjects with renal insufficiency defined as a calculated creatinine clearance < 30 ml/minute

Evaluation of laboratory safety:

Before entry to the trial (at recruitment), after 2 days and 7, 14 and 21 days after the first administration, and at the end of trial, samples for hematology, biochemistry, and urinalysis were obtained.

The following tests were performed:

Hematology:

Hemoglobin, hematocrit, RBC, WBC, leukocyte differential count and platelet count.

(WBC and differential count performed daily).
Blood biochemistry:

Sodium, potassium, chloride, calcium, inorganic phosphorus, total protein, albumin, glucose, total cholesterol, triglycerides, urea, creatinine (twice weekly), uric acid, total bilirubin, alkaline phosphatase, ASAT (SGOT), ALAT (SGPT), gGT, and LDH.
Urinalysis:

pH, RBC, WBC, albumin, glucose, epithelial cells.

Creatinine clearance:

Creatinine clearance was calculated on days 0, 3, 8, 11, 15, 18, 22, and 24 or at the end of the study drug administration.
Changes in liver function:

Patients were told that they should immediately contact the investigator or his/her designee for side effects suggestive for liver function abnormalities, especially dark urine, jaundice, or persistent nausea and vomiting. Patients with marked liver function abnormalities were withdrawn from the study. The abnormal tests were repeated within 48 hours, and thereafter at 3 to 7 day intervals until they resolved. Additional evaluation of patients with marked abnormalities that persist after study drug treatment is discontinued was arranged. The additional evaluation included GI consultation and additional laboratory tests (e.g., antiHAV IgM, antigen HBs, antiHBc IgM, antiCMV IgM, EBV VCA, EBV EA, MNI test).

Adverse events were monitored for continuously.

Patients received 200 mg itraconazole IV BID for the first 2 days followed by 200 mg IV QD for 5 days. This could be continued for an additional 7 days. Subsequently at 7 or 14 days they were switched to oral itraconazole solution 200 mg PO BID onward. Patients on the amphotericin B arm received 0.5 – 1.0 mg/kg/day IV amphotericin. Treatment continued for a maximum of 30 days or until the end of neutropenia defined as one neutrophil count superior to 500 cells/mm'3 or up to a maximum of 2 days with a neutrophil count of > 1000 cells/mm'3.

As per the Applicant:

95 patients (63 males and 32 females) were enrolled on the itraconazole arm and 96 (56 males and 40 females) on the comparator arm.

59 and 54 patients per arm respectively had AML, 8 and 6 ALL, 18 and 19 CML, 4 and 5 lymphoma, and other 1 and 7. The median duration of neutropenia was 8 days on both arms and the median duration of fever was 5 days.

21 patients on the itraconazole arm as compared to 35 on the comparator arm terminated because of an AE. 21 on itraconazole versus 7 on the comparator terminated because of insufficient response. Additionally 6 itraconazole and 13 comparator patients terminated for a variety of other reasons including ineligibility or withdrawn consent.

Results as per the Applicant:

On the itraconazole arm reported in at least 5% of the patients were: nausea (34%), diarrhea (28%), vomiting (25%), rigors (10%), hypokalemia (18%), increased BUN (6%), coughing (18%), abdominal pain (11%), dyspnea (8%), rash (15%), bilirubinemia (12%), stomatitis (12%), pulmonary infiltration (11\%), application site reaction (6%), dizziness (6%), edema (6%), pulmonary edema (6%), fever (7%), epistaxis (6%), headache '6%), fluid overload (7%), chest pain (10%), generalized edema (6%), pneumonia (7%), erythematous rash (8%), hematuria (6%)constipation (6%), and respiratory disorder (8%).

On the comparator arm reported in at least 5% of patients were: nausea (30%), diarrhea (32%), vomiting (30%), rigors (39%), hypokalemia (27%), increased BUN (25%), coughing (8%), abdominal pain (14%),

dyspnea (15%), rash (8%), hypotension (9%), renal function abnormal (10%), hypomagnesemia (8%), application site reaction (5%), dizziness (5%), mucositis (7%), tachycardia (75), edema (5%), pulmonary edema (5%), fever (12%), epistaxis (12%), hypertension (6%), headache (12%), fluid overload (9%), chest pain (6%), generalized edema (9%), pneumonia (8%), erythematous rash (6%), hematuria (6%), constipation (6%), respiratory disorder (6%), abnormal hepatic function (5%), and hyperglycemia (5%).

As per the study report, there were 7 deaths on the itraconazole arm and 8 on the comparator arm.

Applicant's Conclusion: " In the laboratory safety analysis many important abnormalities were documented. Over 20% of subjects in both groups reported diarrhea, nausea, and vomiting. On the comparator arm, over 20% of subjects reported rigors, an increase in BUN and hypokalemia, whereas in the itraconazole group arm increased occurrence of pulmonary infiltration (11%) was noted. In view of the underlying subject medical status and relevant treatments these deviations are not considered significant."

As per the MO:

Deaths: 13 itraconazole and 18 amphotericin patients died during the trial. The electronic dataset contained information on 9 itraconazole deaths/patients and 9 amphotericin deaths/patients. Information on 4 itraconazole and 9 amphotericin patients was found only in the ISS and not in the electronic dataset or the line listings. Case histories are provided below. Where available, the AEs sustained by each patient and their severity have been listed in order to illustrate the severe degree of illness in the population under study.

Itraconazole (N = 13)

Patient #3255 (not included in dataset): 50 YO died after receiving trial medication for 15 days. Cause of death was multi-organ failure secondary to chemotoxicity and radiotoxicity.

Patient #3019: 67 YO male died 1 day after the end of treatment due to pneumonia (AEs: severe: injury, circulatory failure, hypotension, pneumonia, pulmonary infiltration, moderate: edema, pain, cyanosis, hypotension, hypoxia, pneumonia, respiratory disorder, mild: purpura, rhinitis).

Patient #3033: 65 YO male died 1 day after the end of treatment due to multi-organ failure (AEs: severe: condition aggravated, bilirubinemia, hypoxia, CVA, mydriasis).

Patient #3065: 20 YO female died 19 days after the end of treatment due to sepsis (AEs: severe: allergy, moderate: application site reaction, dysmenorrhea, menorraghia, sepsis, conjunctivitis, mild: hypotension, diarrhea, nausea, stomatitis, vomiting, coughing).

Patient #3092: 74 YO male discontinued trial medication after 16 days of treatment due to nausea. His condition continued to deteriorate, and he died 20 days after the end of treatment from complications of his underlying disease (AEs: severe: asthenia, moderate: chest pain, condition aggravated, fever, rigors, hypotension, syncope, abdominal pain, diarrhea, mucositis, nausea, bilirubinemia, generalized edema, pleural effusion, pneumonia, pulmonary infiltration, mild: malaise, coagulation disorder, thrombocytopenia, confusion, herpes simplex, bacterial infection, bronchospasm, pulmonary edema, CVA, abnormal vision).

Patient #3143 (not included in dataset): 55YO received 6 days of treatment when he died due to pulmonary aspergillosis. A culture taken after mini alveolar lavage revealed *Aspergillosis fumigatus*. In addition, a scan of the thorax revealed pleuropneumopathy of the middle and superior lobes of the right lung. Death was attributed to severe pulmonary aspergillosis.

Patient #3150: 47 YO male died 20 days after the end of treatment due to hemoptysis (AEs: severe: hemoptysis, moderate: rash x 2).

Patient #3198 (not included in dataset): 45YO received 7 days treatment with itraconazole. Because he continued febrile on itraconazole, he was switched to amphotericin B. One day later, he died. Follow-up indicates that the possible cause of death was an intracerebral event, but this was not confirmed since no autopsy was performed.

Patient #3365: 56 YO male died 9 days after the end of treatment. Causes of death were enterocolitis, pulmonary edema, and respiratory insufficiency (AEs: severe: enterocolitis, respiratory insufficiency, moderate: pulmonary edema, GI distress, peripheral edema, mild: mac/pap rash, hypomagnesemia, vomiting).
Patient #3437: 67 YO female died 26 days after the end of treatment due to pneumonia (AEs: moderate: injury, fluid overload, atelectasis, pneumonia, mild: hypomagnesemia, increased BUN).

Patient #3444: 32 YO male died 1 day after the end of treatment due to cardiac failure and respiratory insufficiency (AEs: severe: cardiac failure, nausea, respiratory insufficiency).

Patient #3465: 28 YO male discontinued treatment after 2 days due to pneumonia. He died 23 days later for the same reason (AEs: severe: hepatitis, pneumonia, moderate: fever, rigors, abdominal pain, hepatitis, coughing, pneumonia, mild: agitation, abdominal pain, nausea, vomiting, rigors).

Patient #3532 (not included in dataset): 71 YO discontinued treatment after 1 day when her fever failed to subside. She was switched to amphotericin B treatment but died 3 days later. Death was attributed to her preexisting pulmonary interstitial fibrosis in the setting of neutropenic sepsis.

MO Comment: The MO determined that none of the deaths in the itraconazole-treated patients appeared related to the study drug but rather were due to complications of the patients underlying disease processes.

Amphotericin (N = 18)

Patient #3238: 54 YO male died 6 days after the end of treatment due to multi-organ failure (AEs: severe: dyspnea, pneumonia, CVA, moderate: fecal incontinence, fluid overload, pulmonary hemorraghe, respiratory disorder, urinary incontinence, mild: hypotension, skin discoloration).

Patient #3379 (not included in dataset): 51 YO received 2 days treatment when she was found unresponsive and in asystole on a monitor. CPR was initiated, but the patient did not respond to resuscitative measures. Autopsy revealed the cause of death to be extensive pulmonary hemorrhage.

Patient #3391: 46 YO male discontinued treatment after 1 day when his overall condition deteriorated. He died 1 day after the end of treatment due to *Klebsiella* sepsis and multi-organ failure (AEs: severe: hypotension, tachycardia, somnolence, sepsis, respiratory disorder, abdomen enlarged).

Patient #3011: 63 YO male discontinued treatment after 8 days when he developed dyspnea, fever, hypotension, hypoxia, and pneumonia. He died 1 day later (AEs: severe: dyspnea, hypoxia, pneumonia, hypotension, diarrhea, moderate: rigors, mild: GI distress, respiratory disorder).

Patient #3013: 42 YO male died 14 days after the end of treatment due to progression of his underlying disease, hyperkalemia, oliguria, and acute renal failure (AEs: severe: condition aggravated, pain, GI hemorraghe, melena, pneumonia, moderate: granulocytopenia, acute renal failure, oliguria, albuminuria, dyspnea, infection, infection bacterial, generalized edema, hypokalemia, hyperkalemia, tachycardia, dysphagia, fever, mild: hypotension, diarrhea, tachycardia).

Patient #3034: 51 YO male died 8 days after the end of treatment due to multi-organ failure (AEs: severe: death, injury, leukemia, hemorraghe, bacterial infection, moderate: UTI, pain, diarrhea, generalized edema, mild: pneumonia, rash).

Patient #3066: 75 YO male discontinued treatment after 2 days due to nephrotoxicity. He died 21 days later due to fungal sepsis (AEs: severe: severe: toxic nephropathy, moderate: rigors, hypertension, nausea, vomiting, tachycardia, fungal infection, bronchospasm, mild: abnormal vision).

Patient #3112: 19 YO male died 22 days after completing treatment due to complications of his underlying disease (AEs: severe: asthenia, aggravated condition, moderate: pain, rigors, headache, diarrhea, nausea, vomiting, increased sweating, mild: edema.

Patient #3119: 72 YO female died 4 days after the end of treatment due to complications of her underlying disease (AEs: moderate: application site reaction, aggravated condition, rigors, hypertension, melena, nausea, vomiting, tachycardia, mild: abnormal labs, dizziness, abdominal pain, hypotension, bilirubinemia, abnormal hepatic function, acidosis, increased BUN, fluid overload, hyperglycemia, hypoglycemia, hypokalemia, hypocalcemia, hypomagnesemia, hyponatremia, hypophosphatemia, hypoprotenemia, increased Alk. Phos, epistaxis, purpura, dyspnea, skin discoloration, urinary incontinence, abnormal WBC).

Patient #3217: 58 YO female discontinued treatment after 5 days due to deterioration of his underlying condition. She died 4 days after discontinuation due to complications of the underlying condition and respiratory insufficiency (AEs: severe: aggravated condition, respiratory insufficiency, dependent edema).

Patient #3310 (not included in dataset): 45 YO died after 3 days of treatment. Prior to his death, he had a deteriorating course marked by hypoxia, confusion, a convulsion, and a subarachnoid hemorrhage diagnosed by CT scan.

Patient #3361 (not included in dataset): 50 YO discontinued trial medication after 25 days of treatment due to development of positive cultures for enterobactericeae from blood, peritoneal fluid, and tracheal aspirate. Her condition continued to deteriorate and she died 5 days later of sepsis.

Patient #3460 (not included in dataset): 55 YO discontinued treatment after 1 day when he experienced respiratory failure. His condition deteriorated rapidly and he died two days later.

Patient #3480 (not included in dataset): 62 YO discontinued treatment after 4 days due to the development of septic shock and pneumonia. He was treated with epinephrine and nitroglycerin, but died 6 days after discontinuing trial medication.

Patient #3514 (not included in dataset): 73 YO male discontinued after 5 days of treatment when his condition deteriorated. He died 2 days later due to febrile neutropenia secondary to acute myelogenous leukemia.

Patient #3565 (not included in dataset): 52 YO male discontinued treatment after 7 days. A blood culture from the first day of treatment was positive for *Candida albicans*. His neurological and general condition continued to deteriorate after discontinuing trial medication. He died 4 days later due to *Candida albicans* septicemia.

Patient #3574 (not included in dataset): 55 YO male received 6 days of treatment. He died 22 days after the end of treatment due to end stage lymphoma.

Patient #3592 (not included in dataset): 53 YO female received 7 days of treatment. On the day after the end of treatment, she developed renal insufficiency, cardiopulmonary insufficiency, and progression of hematological disease. She died 19 days later due to cardiac failure.

MO Comment: As in the itraconazole-treated patients, all deaths appeared to be related to complications of the underlying disease process and not to the study drug.

Discontinuations: 23 itraconazole patients and 23 amphotericin patients discontinued therapy because of an AE. These patients are list below with the exception of itraconazole patients #3019, #3033, #3092,

#3444, and #3465 and amphotericin patients #3238, #3391, #3011, #3034, #3066, and #3217 who are listed in deaths above:

MO Comment: 5 of the itraconazole-treated patients listed below discontinued because of nausea and/or vomiting, 3 because of a rash, 5 because of the development of LFT abnormalities and/or renal dysfunction and the remainder due to hypoxia with or without pulmonary infiltrates. Due to the severe nature of the patients underlying disease processes, the definite attribution of these AEs to itraconazole was difficult but certainly may have contributed to their development.

The above should be compared to the amphotericin B patients listed below of whom 21 discontinued therapy because of renal toxicity and 4 because of rigors. Additionally, 1 patient discontinued because of decreased tolerance, 1 because of nausea, 1 because of thrombophlebitis, 1 because of bronchospasm and 1 due to increasing edema. The MO determined that the pattern of discontinuations on the amphotericin arm illustrates the very toxic effects of that agent.

Itraconazole (N = 18)
Patient #3367: 39 YO female discontinued treatment after 15 days due to nausea and vomiting.
Patient #3384: 30 YO female discontinued treatment after 16 days due to vomiting. She had become afebrile and her counts were improving so no further antifungal therapy was required.
Patient #3389: 35 YO female discontinued treatment after 8 days due to a rash.
Patient #3002: 70 YO male discontinued treatment after 4 days due to bilirubinemia, jaundice, and pulmonary infiltration.
Patient #3014: 59 YO male discontinued treatment after 16 days due to nausea and vomiting.
Patient #3016: 27 YO female discontinued treatment after 3 days due to dyspnea, fever, hypoxia, and pneumonia.
Patient #3018: 72 YO male discontinued treatment after 10 days due to an unspecified gastrointestinal disorder and nausea.
Patient #3087: 29 YO female discontinued treatment after 6 days due to pulmonary infiltrates.
Patient #3102: 49 YO male discontinued treatment after 2 days due to increasing SGOT and SGPT.
Patient #3114: 34 YO female discontinued treatment after 11 days due to nausea.
Patient #3116: 47 YO female discontinued treatment after 3 days due to a rash.
Patient #3137: 48 YO male discontinued treatment after 3 days due to jaundice.
Patient #3161: 33YO male discontinued treatment after 10 days due to a rash.
Patient #3194: 39 YO male discontinued treatment after 6 days due to hypoxia.
Patient #3218: 55 YO male discontinued treatment after 4 days due to dyspnea.
Patient #3274: 19 YO male discontinued treatment after 4 days due to bilirubinemia and increased hepatic enzymes.
Patient #3331: 54 YO female discontinued treatment after 3 days due to the development of a malignant skin neoplasm.
Patient #3434 (not included in dataset): 37YO neutropenic female with a hematological malignancy and fever of unknown origin, discontinued itraconazole treatment prematurely after 15 days because of increased creatinine, BUN/urea, SGOT, and SGPT. Relevant laboratory abnormalities were:
creatinine: 50 µmol/L at baseline; 47 µmol/L at Day 3; 51 µmol/L at Day 8; 189 µmol/L at Day 15 (normal limits: 50- 110 µmol/L)
BUN/urea: 1.8 µmol/L at baseline; 1.3 µmol/L at Day 3; 3.5 µmol/L at Day 8; 11.9 µmol/L at Day 15 (normal limits: 3- 6.5 µmol/L)

Amphotericin (N = 30)

Patient #3243: 32 YO female discontinued treatment after 1 day due to bronchospasm, fever, and rigors.
Patient #3373: 50 YO female discontinued treatment after 4 days due to increased creatinine.
Patient #3068: 72 YO male discontinued treatment after 2 days due to rigors.
Patient #3088: 65 YO male discontinued treatment after 4 days due to increased creatinine.
Patient #3104: 65YO male discontinued treatment after 22 days due to increased blood urea nitrogen, gGT, and creatinine.
Patient #3106: 22 YO female discontinued treatment after 5 days due to an increase in creatinine.

Patient #3107: 52 YO male discontinued treatment after 4 days due to edema.
Patient #3110: 69 YO male discontinued treatment after 3 days due to drug-related renal toxicity.
Patient #3115: 67 YO male discontinued treatment after 8 days due to rigors.
Patient #3133: 45 YO female discontinued treatment after 16 days due to encephalopathy and renal toxicity.
Patient #3138: 53 YO male discontinued treatment after 8 days due to renal toxicity and sepsis.
Patient #3152: 61 YO female discontinued treatment after 2 days due to renal toxicity.
Patient #3155: 38 YO female discontinued treatment after 7 days due to renal toxicity.
Patient #3179: 65 YO male developed bronchospasm at the end of Day 1 and discontinued treatment after 2 days due to continuing bronchospasm.
Patient #3195: 35 YO female discontinued treatment after 13 days due to renal toxicity.
Patient #3202: 31 YO male discontinued treatment after 3 days due to increased creatinine.
Patient #3219: 56 YO male discontinued treatment after 7 days due to acute renal failure.
Patient #3223: 28 YO male discontinued treatment after 8 days due to increased creatinine.
Patient #3233: 60 YO male discontinued treatment after 19 days due to acute renal failure.
Patient #3245: 25 YO male discontinued treatment after 3 days due to interstitial nephritis.
Patient #3246: 56 YO male discontinued treatment after 2 days due to acute renal failure.
Patient #3266: 46 YO female discontinued treatment after 4 days due to acute renal failure.
Patient #3267: 29 YO female discontinued treatment after 3 days due to hematuria and acute renal failure.
Patient #3279: 26 YO female discontinued treatment after 9 days due to thrombophlebitis.
Patient #3443: 57 YO male discontinued treatment after 1 day due to fever and rigors.
Patient #3451: 39 YO male discontinued treatment after 6 days due to nausea.
Patient #3458: 67 YO male discontinued treatment after 3 days due to hypokalemia and increased creatinine.
Patient #3461: 49 YO female discontinued treatment after 17 days due to worsening renal function.
Patient #3462: 39 YO female discontinued treatment after 7 days due to increased creatinine.
Patient #3466: 27 YO male discontinued treatment after 11 days due to decreased tolerance.

Serious AEs:
26 itraconazole patients (see #3255, #3002, #3029, #3033, #3067, #3085, #3092, #3102, #3143, #3150, #3198, #3218, #3274, #3365, #3434, #3437, #3444, #3465, #3532 above) and 38 amphotericin B patients (see #3238, #3379, #3391, #3011, 33013, #3034, #3066, #3106, #3112, #3119, #3133, #3138, #3179, #3195, #3202, #3217, #3266, #3267, #3279, #3310, #3361, #3460, #3461, #3480, #3514, #3565, #3574, #3592) experienced serious AEs. Information on 7 itraconazole patients and 15 amphotericin B patients was not provided in the database and could only be accessed in the ISS.

Of the 6 itraconazole-treated patients not listed above, 4 (#3239, #3059, #3328, #3329) developed respiratory compromise accompanied by pulmonary infiltrates necessitating hospitalization, 1(#3197) developed mental status changes due to hypoxia and a combination of medications (cyclizine and acyclovir) and possibly due to diamorphine withdrawal, and 1 (#3191) experienced elevated liver enzymes (greater than five times the upper normal limit) after 2 days of treatment.

Of the 10 amphotericin B patients not listed above, 5 developed septic phenomena (#3553, #3055, #3149, #3517, #3563), 1 each (#3056) experienced a cardiac arrest, (#3073) hemoptysis, (#3128) CVA, (#3189) abnormal renal function and (#3281) Sweet's syndrome.

Table 15

All reported AEs by Treatment Arm (As per the MO)

Adverse Event	IV Itraconazole N = 95		PO Itraconazole N = 42		Amphotericin B N = 96	
	n	%	n	%	n	%
Gastrointestinal System Disorders						
Nausea	25	26.3	8	19	29	32
Diarrhea	21	22.1	6	14.3	31	32.3
Vomiting	21	22.1	5	11.9	29	30.2

Stomatitis	11	11.6	-	-	3	3.1
Abdominal Pain	9	9.5	1	2.4	13	13.5
Constipation	6	6.3	-	-	7	7.3
Mucositis	4	4.2	-	-	7	7.3
Pharyngitis	3	3.2	-	-	3	3.1
Tooth Ache	2	2.1	-	-	-	-
Melena	2	2.1	-	-	4	4.2
Oral Hemorrhage	2	2.1	-	-	1	1
Enterocolitis	1	1.1	-	-	3	3.1
Anal Disorder	1	1.1	-	-	-	-
Anal fissure	1	1.1	-	-	-	-
GI Hemorrhage	1	1.1	-	-	2	2.1
Ulcerative Stomatitis	1	1.1	1	2.4	2	2.1
Eructation	1	1.1	-	-	-	-
GI Disorders	1	1.1	2	4.8	1	1
Dry Mouth	1	1.1	-	-	2	2.1
Gastroesophageal Reflux	1	1.1	-	-	1	1
Increased Saliva	1	1.1	-	-	1	1
Colitis	1	1.1	-	-	-	-
Tongue Ulceration	1	1.1	-	-	-	-
Salivary Gland Enlargement	1	1.1	-	-	-	-
Rectal Hemorrhage	1	1.1	-	-	-	-
Glossitis	1	1.1	-	-	-	-
Taste Perversion	1	1.1	-	-	-	-
Diarrhea *C. difficile*	-	-	1	2.4	-	-
Dysphagia	-	-	-	-	4	4.2
Anal Ulcer	-	-	2	2.4	-	-
Dyspepsia	-	-	-	-	4	4.2
Hemorrhoids	-	-	2	4.8	4	4.2
Gingivitis	-	-	-	-	2	2.1
Hematemesis	-	-	1	2.4	1	1
Esophagitis	-	-	-	-	2	2.1
Change in Bowel Habits	-	-	-	-	1	1
Gastroenteritis	-	-	-	-	1	1
Tongue Disorder	-	-	-	-	1	1
Tooth Disorder	-	-	-	-	1	1
Hiccup	-	-	-	-	1	1
Taste Loss	-	-	-	-	1	1
Body as a Whole-General Disorders						
Rigors	9	9.5	-	-	37	38.5
Fever	7	7.4	-	-	11	11.5
Fluid Overload	6	6.3	1	2.4	9	9.4
Generalized Edema	6	6.3	-	-	9	9.4
Edema	5	5.3	1	2.4	5	5.2
Peripheral Edema	4	4.2	1	2.4	5	5.2
Anaphylactoid Reaction	3	3.2	1	2.1	-	-
Back Pain	3	3.2	1	2.4	-	-
Injury	3	3.2	-	-	2	2.1
Pruritus	3	3.2	-	-	3	3.1
Pain	3	3.2	-	-	6	6.3
Malaise	2	2.1	-	-	4	4.2
Enlarged Abdomen	2	2.1	-	-	2	2.1
Fatigue	2	2.1	-	-	4	4.2

Hematoma	2	2.1	1	2.4	-	-
Asthenia	2	2.1	-	-	1	1
Syncope	2	2.1	-	-	1	1
Genital Pruritus	1	1.1	-	-	-	-
Leg Pain	1	1.1	1	2.4	-	-
Allergy	1	1.1	-	-	-	-
Ascites	1	1.1	-	-	-	-
Withdrawal Syndrome	1	1.1	-	-	-	-
Hot Flushes	1	1.1	-	-	-	-
Medication Error	1	1.1	-	-	-	-
Skeletal Pain	1	1.1	-	-	1	1
Facial Edema	1	1.1	-	-	1	1
Leg Pain	1	1.1	1	2.4	-	-
Allergy	1	1.1	-	-	-	-
Ascites	1	1.1	-	-	-	-
Allergic Reaction	1	1.1	1	2.4	1	1
Condition Aggravated	1	1.1	-	-	3	3.1
Death	-	-	-	-	1	1
Hypothermia	-	-	-	-	1	1
Temp. change sensation	-	-	-	-	1	1
Tolerance Decreased	-	-	-	-	1	1
Fall	-	-	1	2.4	-	-
Myalgia	-	-	-	-	2	2.1
Hemorrhage	-	-	-	-	3	3.1
Lab Values Abnormal	-	-	-	-	2	2.1
Lymphadenopathy	-	-	1	2.4	1	1
Ear Ache	-	-	-	-	1	1
Tinnitus	-	-	-	-	1	1
Central and Peripheral Nervous System Disorders						
Headache	6	6.3	-	-	11	11.5
Tremor	4	4.2	1	2.1	1	1
Dizziness	3	3.2	3	7.1	5	5.2
Hypoaesthesia	1	1.1	-	-	-	-
Fecal Incontinence	1	1.1	-	-	2	2.1
Ataxia	1	1.1	-	-	-	-
Leg Cramps	1	1.1	-	-	-	-
Vertigo	1	1.1	-	-	-	-
Visual Field Defect	-	-	-	-	1	1
Paresthesia	-	-	-	-	2	2.1
Encephalopathy	-	-	-	-	1	1
Cardiovascular Disorders						
Chest Pain	8	8.4	1	2.4	6	6.3
Cardiac Failure	4	4.2	1	2.4	-	-
Hypotension	3	3.2	2	4.2	9	9.4
Tachycardia	2	2.1	-	-	7	7.3
Bradycardia	1	1.1	-	-	-	-
Hypertension	1	1.1	-	-	6	6.3
Dependent Edema	1	1.1	-	-	2	2.1
Heart Murmur	1	1.1	-	-	1	1
Cyanosis	1	1.1	-	-	-	-
Circulatory Failure	1	1.1	-	-	-	-
Anemia	1	1,1	-	-	-	-
Palpitation	1	1.1	-	-	-	-

Arrythmia	1	1.1	-	-	1	1
Cardiac Arrest	-	-	-	-	1	1
Heart Disorder	-	-	-	-	1	1
Aggravated Hypertension	-	-	-	-	1	1
Postural Hypotension	-	-	1	2.4	-	-
Skin and Appendages Disorders						
Rash	12	12.6	2	4.8	8	8.3
Erythematous Rash	8	8.4	1	2.1	6	6.3
Increased Sweating	8	8.4	-	-	2	2.1
Application Site Reaction	5	5.3	1	2.4	5	5.2
Skin Disorder	1	1.1	-	-	-	-
Skin Ulceration	1	1.1	-	-	-	-
Dry Skin	1	1.1	-	-	2	2.1
Urticaria	1	1.1	-	-	1	1
Skin Exfoliation	1	1.1	-	-	-	-
Rash Mac/Pap	1	1.1	-	-	-	-
Cellulitis	1	1.1	-	-	-	-
Skin Neoplasm	1	1.1	-	-	-	-
Skin Discoloration	-	-	-	-	2	2.1
Eczema	-	-	-	-	1	1
Respiratory System Disorders						
Hypoxia	5	5.3	-	-	1	1
Coughing	15	15.8	3	7.1	8	8.3
Pulmonary Infiltration	9	9.5	1	2.4	2	2.1
Dyspnea	8	8.4	-	-	14	14.6
Pneumonia	6	6.3	1	2.4	8	8.3
Respiratory Disorder	4	4.2	-	-	6	6.3
Pulmonary Edema	4	4.2	-	-	6	6.3
Pleural Effusion	3	3.2	-	-	4	4.2
Respiratory Insufficiency	2	2.1	-	-	1	1
Rhinitis	2	2.1	-	-	1	1
Atelectasis	2	2.1	-	-	-	-
Bronchospasm	2	2.1	-	-	4	4.2
Hemoptysis	1	1,1	-	-	5	5.2
Abnormal CxR	1	1.1	-	-	1	1
Lobar Pneumonia	1	1.1	-	-	-	-
Pulmonary Hemorrhage	-	-	-	-	1	1
Respiratory Depression	-	-	-	-	1	1
Sinusitis	-	-	-	-	4	4.2
Pulmonitis	-	-	1	2.4	-	-
Pleural Pain	-	-	-	-	3	3.1
Airway Obstruction	-	-	-	-	1	1
Decreased Breath Sounds	-	-	-	-	1	1
Urinary System Disorders						
Abnormal Urine	5	5.3	-	-	1	1
Urinary Incontinence	4	4.2	1	2.4	3	3.1
Hematuria	3	3.2	3	7.1	6	6.3
Albuminuria	2	2.1	1	2.4	1	1
Oliguria	-	-	-	-	2	2.1
Micturition Disorder	-	-	-	-	2	2.1
Interstitial Nephritis	-	-	-	-	1	1
Pyelonephritis	-	-	-	-	1	1
Glomerulonephritis	-	-	-	-	1	1

Urethral Disorder	-	-	-	-	1	1
UTI	-	-	-	-	1	1
Metabolic and Nutritional System Disorders						
Hypokalemia	16	16.8	2	4.8	26	27.1
Hypomagnesemia	4	4.2	-	-	8	8.3
Hypocalcemia	2	2.1	-	-	4	4.2
Acidosis	2	2.1	-	-	2	2.1
Increased Alk. Phos.	2	2.1	2	4.8	3	3.1
Hyperglycemia	2	2.1	-	-	5	5.2
Hypophosphatemia	2	2.1	-	-	2	2.1
Weight Increase	1	1.1	-	-	-	-
Hyperuricemia	1	1,1	-	-	-	-
Hyperchloremia	1	1.1	-	-	2	2.1
Hypoproteinemia	1	1.1	-	-	1	1
Weight Decrease	1	1.1	-	-	1	1
Respiratory Acidosis	1	1.1	-	-	1	1
Increased CPK	1	1.1	-	-	-	-
Ketosis	1	1.1	-	-	-	-
Hypoglycemia	-	-	-	-	1	1
Hyperkalemia	-	-	-	-	1	1
Hyponatremia	-	-	-	-	1	1
Leg Edema	-	-	-	-	1	1
Liver and Biliary System Disorders						
Bilirubinemia	10	10.5	1	2.4	5	5.2
Jaundice	4	4.2	-	-	1	1
SGPT Increased	4	4.2	1	2.1	2	2.1
SGOT Increased	3	3.2	1	2.4	1	1
Hepatic Function Abnormal	2	2.1	-	-	5	5.2
Hepatitis	2	2.1	-	-	-	-
Hepatitis Cholestatic	1	1.1	-	-	1	1
Bilirubinuria	1	1.1	-	-	-	-
Increased Hepatic Enzymes	1	1.1	-	-	-	-
Increased LDH	1	1.1	3	7.1	-	-
Cholelithiasis	-	-	-	-	1	1
Increased gGT	-	-	1	2.1	2	2.1
Aggravated Bilirubinemia	-	-	-	-	1	1
Gallbladder Disorder	-	-	-	-	1	1
Hepatomegaly	-	-	2	4.8	1	1
Renal Disorders						
Increased Creatinine	4	4.2	2	4.8	24	25
Acidosis	2	2.1	-	-	2	2.1
BUN Increased	2	2.1	1	2.4	11	11.5
Abnormal Renal Function	2	2.1	1	2.4	10	10.4
CrCl Decreased	-	-	1	2.4	1	1
Acute Renal Failure	-	-	-	-	3	3.1
Toxic Nephropathy	-	-	-	-	3	3.1
Resistance Mechanism Disorders						
Herpes Simplex	4	4.2	-	-	-	-
Bacterial Infection	3	3.2	-	-	2	2.1
Moniliasis	2	2.1	-	-	-	-
Infection	1	1.1	-	-	3	3.1
Herpes Zoster	1	1.1	-	-	-	-
Infection Fungal	-	-	-	-	1	1

Sepsis	-	-	1	2.4	3	3.1
Coagualtion and Vascular Disorders						
Epistaxis	5	5.3	1	2.1	11	11.5
Purpura	3	3.2	-	-	5	5.3
Flushing	2	2.1	-	-	3	3.1
Coagulation Disorder	1	1.1	-	-	2	2.1
Cerebrovascular Disorder	1	1.1	-	-	1	1
Cerebral Hemorrhage	1	1.1	-	-	-	-
Gingival Bleeding	1	1.1	1	2.4	1	1
Thrombocytopenia	1	1.1	-	-	-	-
Thrombophlebitis	-	-	-	-	1	1
Decreased PT	-	-	-	-	2	2.1
Genital Tract Disorders						
Dysmenorrhea	1	1.1	-	-	-	-
Menorraghia	1	1.1	-	-	-	-
Perineal Pain Female	1	-	-	-	1	1
Penis Disorder	-	-	-	-	1	1
Testicular Pain	-	-	-	-	1	1
Testis Disorder	-	-	-	-	1	1
Vaginal Hemorrhage	-	-	2	4.2	-	-
Psychiatric Disorders						
Confusion	4	4.2	-	-	-	-
Hallucination	4	4.2	1	2.4	2	2.1
Sleep Disorder	4	4.2	-	-	3	3.1
Somnolence	4	4.2	-	-	3	3.1
Insomnia	3	3.2	-	-	5	5.2
Anorexia	3	3.2	-	-	1	1
Anxiety	2	2.1	-	-	5	5.2
Agitation	2	2.1	-	-	-	-
Depression	1	1.1	-	-	-	-
Delirium	1	.1	-	-	1	1
Apathy	-	-	-	-	1	1
Nervousness	-	-	-	-	1	1
Amnesia	-	-	-	-	1	1
Eye Disorders						
Abnormal Vision	3	3.2	-	-	1	1
Mydriasis	2	2.1	-	-	-	-
Retinal Hemorrhage	2	2.1	-	-	1	1
Conjunctivits	-	-	1	2.4	5	5.2
Diplopia	-	-	-	-	1	1
Eye Abnormality	-	-	1	2.4	-	-
Eye Infection	-	-	-	-	1	1
Photophobia	-	-	-	-	1	1
Uveitis	-	-	-	-	1	1
WBC Disorders						
Granulocytopenia	2	2.1	-	-	1	1
WBC Abnormal	-	-	-	-	1	1
Leukemia	-	-	-	-	1	1

Relatedness of AEs to Study Drugs:

Seen in table 16 are the # of AEs considered possibly or definitely-related to the study drugs by the investigators. The MO concurred with these determinations.

Table 16
AEs Related to Study Drugs (As per the Investigators/Table per MO)

Event	Itraconazole IV		Itraconazole PO		Amphotericin B	
Relatedness	Possibly	Definitely	Possibly	Definitely	Possibly	Definitely
Gastrointestinal System						
Nausea	11	1	4	1	18	3
Diarrhea	10	-	5	-	11	1
Vomiting	8	-	2	-	13	1
Abdominal Pain	4	-	1	-	5	-
Constipation	3	-	-	-	1	-
GI Disorders	-	-	-	1	-	-
Melena	-	-	-	-	1	-
Dyspepsia	-	-	-	-	1	-
Taste Perversion	1	-	-	-	-	-
Taste Loss	-	-	-	-	1	-
Body as a Whole-General Disorders						
Rigors	1	-	-	-	9	22
Fever	-	-	-	-	1	4
Peripheral Edema	-	-	1	-	2	-
Pain	-	-	-	-	1	-
Fatigue	1	-	-	-	1	-
Malaise	-	-	-	-	2	-
Syncope	1	-	-	-	-	-
Abnormal Lab Values	-	-	-	-	1	-
Temp. Change Sensation	-	-	-	-	-	1
Decreased Tolerance	-	-	-	-	1	-
Flushing	1	-	-	-	1	2
Abnormal WBC	-	-	-	-	1	-
Medication Error	1	-	-	-	-	-
Metabolic and Nutritional Disorders						
Hypokalemia	11	-	1	-	11	12
Increased Creatinine	3	-	1	-	7	15
Fluid Overload	1	-	-	-	3	-
Generalized Edema	1	-	-	-	1	-
Increased BUN	2	-	-	-	5	3
Hypomagnesemia	1	-	-	-	6	-
Hyperglycemia	1	-	-	-	1	-
Increased Alk. Phos.	2	-	-	-	2	-
Hypocalcemia	-	-	-	-	1	1
Acidosis	1	-	-	-	2	-
Hypophosphatemia	1	-	-	-	1	-
Increased LDH	1	-	2	-	-	-
Hyperchloremia	1	-	-	-	-	-
Hypoproteinemia	-	-	-	-	1	-
Hyperuricemia	1	-	-	-	-	-
Hypoglycemia	-	-	-	-	1	-
Hyponatremia	-	-	-	-	1	-

Respiratory Disorders						
Coughing	1	-	-	-	-	-
Dyspnea	1	-	-	-	1	1
Pulmonary Infiltration	1	-	-	-	-	-
Pulmonary Edema	-	-	1	-	1	-
Respiratory Disorder	-	-	-	-	1	-
Pleural Effusion	1	-	-	-	1	-
Bronchospasm	-	-	-	-	1	2
Sinusitis	-	-	-	-	1	-
Skin and Appendages Disorders						
Rash	2	-	1	-	4	-
Erythematous Rash	2	-	-	-	-	-
Increased Sweating	2	-	-	-	-	-
Pruritus	-	-	-	-	2	-
Dry Skin	-	-	-	-	1	-
Urticaria	-	-	-	-	1	-
Skin Neoplasm	1	-	-	-	-	-
Renal and Urinary Disorders						
Abnormal Renal Function	-	-	-	-	4	6
Hematuria	1	-	-	-	-	-
Abnormal Urine	1	-	-	-	-	-
Albuminuria	-	-	1	-	-	-
Toxic Nephropathy	-	-	-	-	-	3
ARF	-	-	-	-	2	-
Decreased CrCl	-	-	1	-	-	1
Micturition Disorder	-	-	-	-	1	-
Interstitial Nephritis	-	-	-	-	-	1
Glomerulonephritis	-	-	-	-	-	1
Psychiatric Disorders						
Anxiety	-	-	-	-	1	-
Anorexia	-	-	-	-	1	-
Apathy	-	-	-	-	1	-
Nervousness	-	-	-	-	-	1
Central and Peripheral Nervous Systems Disorders						
Headache	1	-	-	-	2	-
Dizziness	1	-	-	-	2	-
Tremor	1	-	1	-	-	-
Fecal Incontinence	-	-	-	-	1	-
Paresthesia	-	-	-	-	1	-
Ataxia	1	-	-	-	-	-
Hypoaesthesia	1	-	-	-	-	-
Liver and Biliary Disorders						
Bilirubinemia	8	-	1	-	4	-
Abnormal Hepatic Function	2	-	-	-	3	-
Increased SGPT	4	-	1	-	2	-
Jaundice	4	-	-	-	1	-
Increased SG0T	3	-	1	-	-	1
Increased gGT	-	-	1	-	1	-
Hepatomegaly	-	-	2	-	1	-
Hepatitis	1	-	-	-	-	-
Cholestatic Hepatitis	1	-	-	-	-	-
Bilirubinuria	1	-	-	-	-	-
Aggravated Bilirubinemia	-	-	-	-	1	-

Increased Hepatic Enzymes	1	-	-	-	-	-
Cardiovascular Disorders						
Hypotension	-	-	-	-	1	-
Hypertension	-	-	-	-	3	1
Dependent Edema	-	-	-	-	1	-
Aggravated Hypertension	-	-	-	-	1	-
Tachycardia	1	-	-	-	2	1
Arrythmia	-	-	-	-	1	-
Eye Disorders						
Conjunctivitis	-	-	-	-	1	-
Abnormal vision	1	-	-	-	1	-
Mydriasis	1	-	-	-	-	-

MO Comment: From the above the MO noted that GI-related AEs were frequently graded as possibly or definitely-related to the study drugs on both IV arms. Additionally patients on oral itraconazole had GI-related AEs thought to be related to the study drug.

Rigors and fever were frequently possibly or definitely-associated with amphotericin B administration and rarely seen with itraconazole.

Although hypokalemia was possibly-related to study drug in 11 instances on both the itraconazole IV and the amphotericin B regimens, it was definitely-associated with amphotericin B in 15 instances. Additionally a decrease in creatinine clearance was possibly-related to IV itraconazole in 3 instances but possibly-related in 7 amphotericin B cases and definitely in 15. Multiple electrolyte abnormalities associated with renal dysfunction were more frequently found and possibly or definitely-associated with study drug administration on the amphotericin B arm.

Rash and allergic phenomena were associated with drug administration on both arms of the study.

Overt toxic nephropathy, interstitial nephritis, glomerulonephritis and ARF were seen predominantly on the amphotericin B arm.

Hepatic dysfunction in the form of LFT abnormalities or jaundice was seen on both arms however bilirubinemia and jaundice were possibly-associated with study drug more frequently on the itraconazole arm.

Laboratory:

The MO assessed the laboratory abnormalities via the line listings and the CRFs. As this study is ongoing, information on all patients included in the deaths and discontinuations was not available. Additionally, the electronic dataset did not provide the ability to query with regards to patients with normal baseline and subsequent deterioration. The following significant abnormalities were noted:

Itraconazole:

Albumin: 9 patients developed clinically significant hypoalbuminemia.
Alkaline Phosphatase: 3 patients developed clinically significant elevations.
ALT: 3 patients developed clinically significant elevations.
AST: 2 patients developed clinically significant elevations.
Calcium: 16 patients developed hypocalcemia.
Chloride: 3 patients developed hyperchloremia.
gGT: 5 patients developed clinically significant elevations.