

course and hypokalemia during the second. The patient was entered for a 3rd course of chemotherapy on 3rd June presenting with a pre-existing large right sided pleural effusion and had been coughing for the previous week although was not particularly breathless. At the start of this episode there were no cardiac problems and none had been observed. Cardiac failure developed on 7th June which was thought to be associated with a high fluid intake. Treatment was initiated with frumil, frusemide and vitamin K but on 9th June cardiac function deteriorated rapidly with severe heart failure unresponsive to treatment. The patient was transferred to intensive care for support but died the following day. Cause of death was intractable heart failure. In the investigators opinion it was highly unlikely that this was related to the study medication. It was noted that the chemotherapy administered during this treatment cycle was substantially different to that received during the previous 2 episodes and that there was a definite possibility that the chemotherapy regimen of busulphan and cyclophosphamide precipitated the cardiac problems and renal failure. It is highly unlikely that the deterioration was related to itraconazole as the patient had previously received the drug with no side effects.

#0811: 69 year old female with acute myeloid leukemia entered the study on 8th July 1994 and received itraconazole 2.5 mg/kg twice daily for 4 days. The patient developed pyrexia of unknown origin that was unresolved. Study medication was withdrawn and systemic antifungals introduced but the patient died of her underlying leukemia. No post-mortem was conducted.

#0910: 61 year old female with acute myeloid leukemia entered the study on 1st November 1993 and received itraconazole 2.5 mg/kg twice daily for 4 days. The patient was receiving post-induction chemotherapy. There was a significant disseminated intravascular coagulation resulting in severe thrombocytopenia and prolonged coagulation tests. The patient had a sudden loss of consciousness and rapidly developed fixed pupils and died on 7th November. The probable cause of death was an intracranial hemorrhage. Septicemia was also present due to gram negative rods.

#1101: 68 year old male with acute myeloid leukemia entered the study on 26th March 1993 and received itraconazole 2.5 mg/kg twice daily for 6 weeks. He was withdrawn from the study in the week commencing 7th May with pyrexia of unknown origin. The patient subsequently died on 14th May of septicemia caused by *Staphylococcus aureus*. This was thought not to be related to the study medication.

#1604: 72 year old female with acute myeloid leukemia entered the study on 9th March 1994 and received itraconazole 2.5 mg/kg twice daily for 7 weeks. The patient died of hypotension and sepsis on 22nd May with the post-mortem showing a probable underlying abdominal event, perforation of the large bowel. There was no evidence of fungal infection and the event was thought not to be related to the study medication.

#1609: 63 year old female with acute myeloid leukemia entered the study on the 4th August 1994 and received itraconazole 2.5 mg/kg twice daily for 13 days. She developed an elevated bilirubin and the study medication was stopped on 22nd August. The patient suffered progressive cardiac failure leading to death the same day. The investigator attributed the development of cardiac failure as either the underlying disease or to the toxicity of an anthracycline cytotoxic.

#1810: This patient received a second course of chemotherapy on the 17th May 11 days after being withdrawn from the study due to elevated bilirubin. The patient died 3 weeks after the last dose of itraconazole on 30th May. Cause of death given as probable infection.

ITR-INT-54:

Itraconazole (N = 18):

#149: 71-year-old male patient with AML entered the trial on 03OCT94. Treatment with itraconazole started on 05OCT94 until 19NOV94. The patient died 16 days after the end of treatment, on 05DEC94, because of sepsis (day 6 post-R/x with aplasia, severe; not drug-related). The patient discontinued the treatment prematurely after 45 days of treatment, on 19NOV94, because of SGPT increased (severe; possibly drug-related; adverse event still present) and SGOT increased (severe; possibly drug-related; adverse event still present).

The following important laboratory abnormalities were detected:

- ALT (pathological limits: 0-67.6 U/l): 183 U/l at Week 6; 153 U/l at Week 7; 298 U/l at Week 7
- AST (pathological limits: 0-78 U/l): 317 U/l at Week 6; 92 U/l at Week 7; 135 U/l at Week 7

Total bilirubin (pathological limits: 0-24 micromol/l): 28 micromol/l at Week 3; 29 micromol/l at Week 3; 48 micromol/l at Week 6; 229 micromol/l at Week 7; 273 micromol/l at Week 7; 229 micromol/l at End point

#155: 53-year-old female patient with lymphoma entered the trial on 25JAN95. Treatment with itraconazole started on 26JAN95 until 14FEB95. The patient died 6 days after the end of treatment, on 20FEB95, because of depression (2/8, severe; not drug-related), cardiac and respiratory failure (2/10, severe; not drug-related) and coughing (severe; not drug-related, cardiomyopathy is considered as a chemotherapy induced failure).

#157: 64-year-old female patient with AML entered the trial on 12OCT94. Treatment with itraconazole started on 13OCT94 until 18OCT94. The patient died 26 days after the end of treatment, on 13NOV94, because of leukemia (severe; not drug-related) and respiratory insufficiency. The patient discontinued

the treatment prematurely after 5 days of treatment, on 18OCT94, because of malaise (severe; not drug-related; adverse event resolved).

#420: 61-year-old female patient with lymphoma entered the trial on 26AUG95. Treatment with itraconazole started on 26AUG95 until 13SEP95. The patient died 2 days after the end of treatment, on 15SEP95, because of diarrhea (severe; possibly drug-related), circulatory failure (severe; not drug-related) and rash (day 18, severe; possibly drug-related). The patient discontinued the treatment prematurely after 18 days of treatment, on 13SEP95, because of rash (severe; possibly drug-related; patient died).

#503: 72-year-old male patient with AML entered the trial on 05MAY95. Treatment with itraconazole started on 06MAY95 until 17MAY95. The patient died 42 days after the end of treatment, on 28JUN95, because of fungal infection (day 33, severe; not drug-related) and respiratory disorder (day 35).

#571: 68-year-old female patient with myelodysplastic syndrome entered the trial on 24MAY95. Treatment with itraconazole started on 25MAY95 until 31MAY95. The patient died 58 days after the end of treatment, on 28JUL95, because of condition aggravated (severe; not drug-related). The patient discontinued the treatment prematurely after 6 days of treatment, on 31MAY95, because of diarrhea (moderate; possibly drug-related; adverse event resolved), nausea (moderate; possibly drug-related; adverse event resolved) and vomiting (moderate; possibly drug-related; adverse event resolved). Serious adverse events occurred 31 days after the end of treatment, on 01JUL95: moniliasis. Another serious adverse event: condition aggravated (severe; not drug-related; patient died) was reported but his start date was unknown.
[Patient was hospitalized early July with clinical symptoms of oral, vaginal and GI candidiasis.]

#590: 65-year-old male patient with AML entered the trial on 24MAY95. Treatment with itraconazole started on 24MAY95 until 31MAY95. The patient died 2 days after the end of treatment, on 02JUN95, because of pneumonia (day 7, therapy discontinued, severe; not drug-related), sepsis (severe; not drug-related) and circulatory failure (severe; not drug-related).

#644: 35-year-old male patient with AML entered the trial on 30JUN95. Treatment with itraconazole started on 30JUN95 until 08JUL95. The patient died 33 days after the end of treatment, on 10AUG95, because of encephalopathy (day 24, severe; not drug-related).

#682: 56-year-old female patient with lymphoma entered the trial on 03JUL95. Treatment with itraconazole started on 04JUL95 until 14JUL95. The patient died 66 days after the end of treatment, on 18SEP95, because of hematoma (severe; not drug-related). The patient discontinued the treatment prematurely after 10

days of treatment, on 14JUL95, because of nausea (moderate; possibly drug-related; adverse event still present).

#713: 40-year-old male patient with AML entered the trial on 20SEP95. Treatment with itraconazole started on 20SEP95 until 20OCT95. The patient died 14 days after the end of treatment, on 03NOV95, because of circulatory failure (severe; not drug-related). A serious adverse event occurred 7 days after the end of treatment, on 27OCT95 when the patient was hospitalized for bilateral pneumonia.

#726: 56-year-old male patient with CML entered the trial on 20OCT95. Treatment with itraconazole started on 20OCT95 until 07NOV95. The patient died 32 days after the end of treatment, on 09DEC95, because of fungal infection, skin hypertrophy and condition aggravated (severe; not drug-related).

#804: 33-year-old female patient with AML entered the trial on 23APR96. Treatment with itraconazole started on 24APR96 until 27MAY96. The patient died 14 days after the end of treatment, on 10JUN96, because of heart disorder (day 33, severe; not drug-related) and hepatocellular damage (day 33, severe; not drug-related).

The following important laboratory abnormalities were detected:

- ALT (pathological limits: 0-96.2 U/l): 250 U/l at Week 5
- AST (pathological limits: 0-91 U/l): 381 U/l at Week 5
- gGT (pathological limits: 0-78 U/l): 82 U/l at Week 1; 133 U/l at Week 2
- Total bilirubin (pathological limits: 0.1-1.4 mg/dl): 2.3 mg/dl at Week 4; 3.6 mg/dl at Week 4; 3.65 mg/dl at Week 5; 3.65 mg/dl at end point

#873: 28-year-old male patient with AML entered the trial on 07JUL96. Treatment with itraconazole started on 08JUL96 until 13JUL96. The patient died 17 days after the end of treatment, on 30JUL96, because of dyspnea (day 4, severe; not drug-related) and condition aggravated (not drug-related).

#886: 66-year-old male patient with AML entered the trial on 16FEB96. Treatment with itraconazole started on 16FEB96 until 28FEB96. The patient died after 12 days of treatment, on 28FEB96, because of circulatory failure (severe; not drug-related). Serious adverse events occurred after 11 days of treatment, on 27FEB96: hypotension, myalgia and circulatory failure (severe; not drug-related; patient died). Another serious adverse event: bacterial infection was reported but start date was unknown.

#924: 62-year-old male patient with AML entered the trial on 04APR96. Treatment with itraconazole started on 06APR96 until 10APR96. The patient died 1 day after the end of treatment, on 11APR96, because of cerebral hemorrhage (day 4, discontinued R/x, severe; not drug-related) and thrombocytopenia [related to acute myeloid leukemia and chemotherapy].

#957: 68-year-old male patient with AML entered the trial on 06MAY96. Treatment with itraconazole started on 08MAY96 until 21MAY96. The patient died 36 days after the end of treatment, on 26JUN96, because of periorbital cellulitis (severe; not drug-related) and sepsis. The patient discontinued the treatment prematurely after 13 days of treatment, on 21MAY96, because of gastro-intestinal hemorrhage (severe; possibly drug-related; adverse event resolved).

#1125: 52-year-old female patient with AML entered the trial on 05DEC95. Treatment with itraconazole started on 08DEC95 until 30DEC95. The patient died 14 days after the end of treatment, on 13JAN96, because of cellulitis and condition aggravated (severe; not drug-related), due to sepsis with *Pseudomonas aeruginosa*] and acute renal failure.

#1177: 46-year-old female patient with AML entered the trial on 07FEB96. Treatment with itraconazole started on 08FEB96 until 19FEB96. The patient died 9 days after the end of treatment, on 28FEB96, because of coma (day 11, severe; not drug-related) and infection (day 11, severe; not drug-related).

Amphotericin B (N = 23):

#160: 50-year-old male patient with myelodysplastic syndrome entered the trial on 08NOV94. Treatment with amphotericin B started on 08NOV94 until 12NOV94. The patient died 2 days after the end of treatment, on 14NOV94, because of abnormal renal function (moderate; not drug-related), cardiac failure (severe; not drug-related) and dyspnea (day 4, therapy discontinued, moderate; not drug-related), see also discontinuation.

#205: 53-year-old male patient with AML entered the trial on 03FEB95. Treatment with amphotericin B started on 03FEB95 until 02MAR95. The patient died 13 days after the end of treatment, on 15MAR95, because of cerebrovascular disorder (severe; not drug-related).

#247: 57-year-old male patient with refractory anemia entered the trial on 07JUN95. Treatment with amphotericin B started on 08JUN95 until 28JUN95. The patient died after 20 days of treatment, on 28JUN95, because of hypoxia (severe; not drug-related) and circulatory failure (day 12, severe; not drug-related). The patient had a septic shock syndrome and a multi-organ failure, due to *Streptococcus viridans* and *Staphylococcus* infection.

#479: 65-year-old male patient with AML entered the trial on 06APR95. Treatment with amphotericin B started on 06APR95 until 19APR95. The patient died after 13 days of treatment, on 19APR95, because of abnormal renal function (severe; not drug-related) and respiratory insufficiency (severe; not drug-related).

#520: 53-year-old male patient with AML entered the trial on 03FEB95. Treatment with amphotericin B started on 03FEB95 until 18FEB95. The patient died 8 days after the end of treatment, on 26FEB95, because of hypotension (severe; not drug-related), abnormal renal function (severe; not drug-related) and sepsis (day 13, severe; not drug-related).

#530: 59-year-old female patient with AML entered the trial on 02FEB95. Treatment with amphotericin B started on 03FEB95 until 22FEB95. The patient died 16 days after the end of treatment, on 10MAR95, because of cardiac arrest (severe; not drug-related). Serious adverse events occurred after 19 days of treatment, on 22FEB95: pleural effusion and respiratory disorder; 15 days after the end of treatment, on 09MAR95: dyspnea; 16 days after the end of treatment, on 10MAR95: CPK increased, SGOT increased and abscess. Patient was admitted to the ICU on 22FEB95 for respiratory distress with a clinical picture of invasive pulmonary aspergillosis and aplasia.

#541: 62-year-old male patient with AML entered the trial on 10MAR95. Treatment with amphotericin B started on 11MAR95 until 04APR95. The patient died 30 days after the end of treatment, on 04MAY95, because of condition aggravated (severe; not drug-related). [Death was directly related with second relapse of acute leukemia and due to pulmonary and cerebral leukostasis.

#546: 36-year-old female patient with AML entered the trial on 18FEB95. Treatment with amphotericin B started on 18FEB95 until 14MAR95. The patient died 4 days after the end of treatment, on 18MAR95, because of colitis (day 24, severe; possibly drug-related), diarrhea (severe; possibly drug-related), dysphagia (severe; possibly drug-related) and condition aggravated (severe; not drug-related).

#568: 33-year-old male patient with AML entered the trial on 03MAY95. Treatment with amphotericin B started on 03MAY95 until 14MAY95. The patient died 78 days after the end of treatment, on 31JUL95, because of hypokalemia (severe; not drug-related) and infection fungal (severe; not drug-related).

#570: 69-year-old female patient with AML entered the trial on 15MAY95. Treatment with amphotericin B started on 16MAY95 until 04JUN95. The patient died 9 days after the end of treatment, on 13JUN95, because of condition aggravated (severe; not drug-related) and respiratory disorder (severe). Serious adverse events occurred after 12 days of treatment, on 28MAY95: confusion and stupor; after 15 days of treatment, on 31MAY95: respiratory disorder (severe; patient died) and after 16 days of treatment, on 01JUN95: condition aggravated (severe; not drug-related; patient died).

#627: 82-year-old male patient with AML entered the trial on 24JUN95. Treatment with amphotericin B started on 24JUN95 until 01JUL95. The patient stopped the

oral solution because of nausea and vomiting (day 9, moderate; possibly drug-related; adverse event resolved).

The patient died 29 days after the end of treatment, on 30JUL95, because of respiratory disorder (severe; not drug-related) [due to refractory febrile pneumopathy].

#646: 73-year-old male patient with AML entered the trial on 17AUG95.

Treatment with amphotericin B started on 18AUG95 until 01SEP95. The patient died 30 days after the end of treatment, on 01OCT95, because of cerebrovascular disorder (severe; not drug-related) and somnolence (severe; not drug-related).

#719: 48-year-old male patient with AML entered the trial on 23NOV95.

Treatment with amphotericin B started on 25NOV95 until 15DEC95. The patient died after 20 days of treatment, on 15DEC95, because of hemorrhage not otherwise specified (severe; not drug-related).

#793: 28-year-old female patient with ALL entered the trial on 11OCT95.

Treatment with amphotericin B started on 12OCT95 until 23OCT95. The patient died 30 days after the end of treatment, on 22NOV95, because of fungal infection (day 22, severe; not drug-related) and respiratory insufficiency (severe; not drug-related). The patient was transferred to Intensive Care Unit with progressive respiratory insufficiency.

#849: 24-year-old female patient with AML entered the trial on 18JUL96.

Treatment with amphotericin B started on 18JUL96 until 28JUL96. The patient died 45 days after the end of treatment, on 11SEP96, because of pneumonia (severe) and condition aggravated (severe).

#880: 52-year-old female patient with AML entered the trial on 05MAR97.

Treatment with amphotericin B started on 06MAR97 until 24MAR97. The patient died 1 day after the end of treatment, on 25MAR97, because of gastro-intestinal hemorrhage (moderate; not drug-related) and diarrhea (mild; not drug-related). Serious adverse events occurred after 11 days of treatment, on 17MAR97: colitis and after 15 days of treatment, on 21MAR97: gastro-intestinal hemorrhage.

#887: 43-year-old female patient with AML entered the trial on 29MAR96.

Treatment with amphotericin B started on 29MAR96 until 10APR96. The patient died 4 days after the end of treatment, on 14APR96, because of gastro-intestinal hemorrhage (severe; not drug-related), colitis (day 9, severe; not drug-related), fever (day 9, severe; not drug-related) and sepsis.

#894: 24-year-old male patient with AML entered the trial on 02APR96.

Treatment with amphotericin B started on 03APR96 until 25APR96. The patient died 23 days after the end of treatment, on 18MAY96, because of cerebral hemorrhage and circulatory failure (severe; not drug-related).

#901: 82-year-old female patient with AML entered the trial on 31MAR96. Treatment with amphotericin B started on 02APR96 until 27APR96. The patient died 14 days after the end of treatment, on 11MAY96, because of gastro-intestinal hemorrhage, cardiac failure (severe; not drug-related), cerebral hemorrhage (severe; not drug-related), coma and thrombocytopenia.

#909: 51-year-old female patient with AML entered the trial on 04MAR96. Treatment with amphotericin B started on 04MAR96 until 28MAR96. The patient died 13 days after the end of treatment, on 10APR96, because of diarrhea (day 3 post-R/x, severe; possibly drug-related) and gastro-intestinal hemorrhage (day 3 post-R/x, severe; possibly drug-related).

#960: 66-year-old male patient with ALL entered the trial on 23JUL96. Treatment with amphotericin B started on 25JUL96 until 02AUG96. The patient died 3 days after the end of treatment, on 05AUG96, because of sepsis (severe; not drug-related) due to a gram-negative bacteria. The patient discontinued the treatment prematurely after 8 days of treatment, on 02AUG96, because of diarrhea (moderate; possibly drug-related; adverse event resolved).

#1061: 19-year-old female patient with ALL entered the trial on 29FEB96. Treatment with amphotericin B started on 01MAR96 until 29MAR96. The patient died 25 days after the end of treatment, on 23APR96, because of alkaline phosphatase increased (day 28, severe; possibly drug-related), bilirubinemia (day 28, severe; possibly drug-related), hepatic failure (day 28, severe; possibly drug-related) and respiratory insufficiency (day 28, severe; possibly drug-related).

#1194: 28-year-old male patient with AML entered the trial on 28FEB96. Treatment with amphotericin B started on 28FEB96 until 17MAR96. The patient died 22 days after the end of treatment, on 08APR96, because of condition aggravated (severe; not drug-related), diarrhea (severe; not drug-related) and abdominal pain (severe; not drug-related).

ITR-INT-18:

Itraconazole (N = 15):

#35: 45-year-old female with AML entered the trial on 24SEP94. Treatment with itraconazole started on 24SEP94 until 05OCT94. The patient died 34 days after the end of treatment on 08NOV94, because of systemic fungal infection (day 11, severe; not drug-related) and respiratory insufficiency (patient died following shock lung and respiratory failure).

#39: 54-year-old male with ALL entered the trial on 03SEP94. Treatment with itraconazole started on 03SEP94 until 14SEP94. The patient died after 11

days of treatment on 14SEP94, because of cardiac arrest (severe; not drug-related), sepsis (severe; not drug-related) and respiratory insufficiency (severe; not drug-related).

#52: 59-year-old male with AML entered the trial on 30NOV94. Treatment with itraconazole started on 30NOV94 until 16DEC94. The patient died after 16 days of treatment on 16DEC94, because of hypertension (day 13, severe; not drug-related), fungal infection (day 13, severe; not drug-related), hemiparesis (severe; not drug-related) and hypokalemia (day 16, mild; not drug-related).

#54: 45-year-old male with AML entered the trial on 12SEP95. Treatment with itraconazole started on 12SEP95 until 20SEP95. The patient died 13 days after the end of treatment on 03OCT95, because of acute renal failure (severe; not drug-related), hemorrhagic gastritis (moderate; not drug-related) and enterocolitis (severe; not drug-related).

#56: 44-year-old male with AML entered the trial on 31DEC95. Treatment with itraconazole started on 31DEC95 until 09JAN96. The patient died 13 days after the end of treatment on 22JAN96, because of acute renal failure (9 days after the EOT, severe; not drug-related), diarrhea (moderate; not drug-related), jaundice (1 day after the end of treatment on 10JAN96: severe; not drug-related) and melena (severe; not drug-related)

#59: 79-year-old female with AML entered the trial on 10MAY95. Treatment with itraconazole started on 10MAY95 until 13MAY95. The patient died 3 days after the end of treatment on 16MAY95, because of cardiac arrest (severe; not drug-related). Serious adverse events occurred after 3 days of treatment on 12MAY95: fungal infection (*Candida* esophagitis) and 3 days after the end of treatment on 16MAY95: cardiac arrest (severe; not drug-related; patient died).

#118: 43-year-old male with AML entered the trial on 10DEC94. Treatment with itraconazole started on 10DEC94 until 21DEC94. The patient died after 11 days of treatment on 21DEC94, because of coma (severe; not drug-related), hematemesis (severe; not drug-related) and melena (severe; not drug-related). The patient discontinued the treatment and the trial prematurely after 11 days of treatment on 21DEC94, because of cerebral hemorrhage (severe; not drug-related; adverse event still present) and coma (severe; not drug-related; patient died).

#121: 64-year-old male with AML entered the trial on 23JUL94. Treatment with itraconazole started on 23JUL94 until 27JUL94. The patient died after 4 days of treatment on 27JUL94, because of cardiac arrest (severe; not drug-related).

#140: 59-year-old male with MM entered the trial on 01JUN95. Treatment with itraconazole started on 02JUN95 until 19JUN95. The patient died after 17 days of treatment on 19JUN95, because of respiratory insufficiency (severe; not drug-related) and bilirubinemia (moderate; not drug-related).

#198: 52-year-old male with ALL entered the trial on 13JAN95. Treatment with itraconazole started on 13JAN95 until 27JAN95. The patient died after 14 days of treatment on 27JAN95, because of circulatory failure (severe; not drug-related). The patient discontinued the treatment and the trial prematurely after 14 days of treatment on 27JAN95, because of increased SGPT (mild; not drug-related; adverse event still present), bilirubinemia (moderate; not drug-related; adverse event still present), circulatory failure (severe; not drug-related; patient died) and because of serious adverse experience and death.

#290: 48-year-old male with ALL entered the trial on 05MAY95. Treatment with itraconazole started on 05MAY95 until 17MAY95. The patient died 23 days after the end of treatment on 09JUN95, because of hepato-renal syndrome: bilirubinemia (day 12, severe; not drug-related) and acute renal failure (day 18, severe; not drug-related).

#342: 61-year-old female with AML entered the trial on 29AUG95. Treatment with itraconazole started on 29AUG95 until 12SEP95. The patient died 20 days after the end of treatment on 02OCT95, because of fungal infection and sepsis. The patient discontinued the treatment prematurely after 14 days of treatment on 12SEP95, because of abdominal pain (severe; not drug-related; adverse event resolved), diarrhea (severe; not drug-related; adverse event resolved) and vomiting (severe; not drug-related; adverse event resolved). Serious adverse events that occurred: after 11 days of treatment on 09SEP95: fungal infection (patient died); after 12 days of treatment on 10SEP95: abdominal pain (severe; not drug-related; adverse event resolved), diarrhea (severe; not drug-related; adverse event resolved) and vomiting (severe; not drug-related; adverse event resolved). Trial assessments were continued until 10OCT95.

#360: 59-year-old male with AML entered the trial on 14OCT95. Treatment with itraconazole started on 14OCT95 until 30OCT95. The patient died after 16 days of treatment on 30OCT95, because of fever (severe; not drug-related), bacterial infection (*E.coli*) (severe; not drug-related) and sepsis (severe; not drug-related) (*see also serious adverse event*). Serious adverse events occurred after 11 days of treatment on 25OCT95: fever (severe; not drug-related; patient died) and sepsis (severe; not drug-related; patient died); 1 day after the end of treatment on 31OCT95: bacterial infection (severe; not drug-related; patient died).

#389: 57-year-old female with AML entered the trial on 23SEP95. Treatment with itraconazole started on 23SEP95 until 24SEP95. The patient died after 1 day of treatment on 24SEP95, because of cardiac failure (severe; not drug-related), increased CR., leukocytosis, pulmonary edema (severe; not drug-related) and acute renal failure (severe; not drug-related) (*see also serious adverse event*). Serious adverse events occurred: within the first day of treatment on 23SEP95: increased CREATININE (patient died) and leukocytosis (patient died); after 1 day of treatment on 24SEP95: cardiac failure (severe; not drug-related; patient died), pulmonary edema (severe; not drug-related; patient died) and acute renal failure (severe; not drug-related; patient died).

#417: 39-year-old male with AML entered the trial on 25JAN96. Treatment with itraconazole started on 25JAN96 until 21FEB96. The patient died 2 days after the end of treatment on 23FEB96, because of spleen disorder (acute rupture) (severe; not drug-related).

Placebo (N = 16 available case histories):

(As per the applicant, case histories on subjects 102 and 103 were not available because no AEs were reported on these subjects and the date of death was also not know).

#49: 18-year-old male with ALL entered the trial on 22JUN94. Treatment with placebo started on 22JUN94 until 08JUL94. The patient died 15 days after the end of treatment on 23JUL94, because of fungal infection. The patient discontinued the treatment prematurely after 16 days of treatment on 08JUL94, because of diarrhea (severe; possibly drug-related; adverse event resolved). Trial assessments were continued until 26JUL94.

#119: 51-year-old female with AML entered the trial on 16MAR95. Treatment with placebo started on 16MAR95 until 01APR95. The patient died 26 days after the end of treatment on 27APR95, because of circulatory failure (severe; not drug-related).

#124: 71-year-old male with AML entered the trial on 04JUL94. Treatment with placebo started on 04JUL94 until 25JUL94. The patient died after 21 days of treatment on 25JUL94, because of pneumonia (severe; not drug-related) and cardiac failure (severe; not drug-related).

#148: 27-year-old male with AML entered the trial on 11MAY95. Treatment with placebo started on 11MAY95 until 23MAY95. The patient died 5 days after the end of treatment on 28MAY95, because of abnormal renal function (severe; not drug-related) and sepsis (septic shock/*E.coli*) (severe; not drug-related).

#237: 74-year-old male with AML entered the trial on 08FEB95. Treatment with placebo started on 08FEB95 until 20FEB95. The patient died 2 days after the end of treatment on 22FEB95, because of respiratory insufficiency

(moderate; not drug-related), cardiac arrest, confusion (mild; not drug-related), dyspnea (moderate; not drug-related), pulmonary edema (severe; not drug-related), respiratory depression and urinary incontinence (severe; not drug-related).

#242: 58-year-old female with AML entered the trial on 03FEB95. Treatment with placebo started on 03FEB95 until 17FEB95. The patient died 18 days after the end of treatment on 07MAR95, because of pneumonia (severe; not drug-related).

#244: 52-year-old male with ALL entered the trial on 27MAR95. Treatment with placebo started on 27MAR95 until 07APR95. The patient died 3 days after the end of treatment on 10APR95, because of cerebral hemorrhage (severe; not drug-related). The patient discontinued the treatment prematurely after 11 days of treatment on 07APR95, because of nausea (severe; not drug-related; adverse event still present) and vomiting (severe; not drug-related; adverse event still present).

#297: 59-year-old female with refractory anemia entered the trial on 21JAN95. Treatment with placebo started on 21JAN95 until 30JAN95. The patient died 6 days after the end of treatment, on 05FEB95, because of infection (severe; not drug-related) and respiratory insufficiency (severe; not drug-related).

#301: 44-year-old female with AML entered the trial on 09FEB95. Treatment with placebo started on 09FEB95 until 23FEB95. The patient died 11 days after the end of treatment, on 06MAR95, because of dyspnea (severe; not drug-related).

#329: 28-year-old female with non-Hodgkin's lymphoma entered the trial on 14MAR95. Treatment with placebo started on 18MAR95 until 30MAR95. The patient died 29 days after the end of treatment on 12APR95, because of aggravated condition (severe; not drug-related) and respiratory insufficiency (severe; not drug-related).

#355: 54-year-old female with AML entered the trial on 07OCT95. Treatment with placebo started on 08OCT95 until 23OCT95. The patient died 1 day after the end of treatment on 24OCT95, because of cerebral hemorrhage (severe; not drug-related) and thrombocytopenia (severe, patient died).

#382: 49-year-old female with AML entered the trial on 22FEB96. Treatment with placebo started on 22FEB96 until 09MAR96. The patient died after 16 days of treatment on 09MAR96, because of cerebral hemorrhage (severe; not drug-related) and melena.

#410: 75-year-old male with AML entered the trial on 02DEC95. Treatment with placebo started on 02DEC95 until 22DEC95. The patient died 11 days after the end of treatment on 02JAN96, because of fungal infection.

#420: 37-year-old female with AML entered the trial on 26JAN96. Treatment with placebo started on 26JAN96 until 27JAN96. The patient died 1 day after the end of treatment on 28JAN96, because of hypophosphatemia, aggravated condition (severe; not drug-related), acute renal failure and coma.

#422: 34-year-old male with AML entered the trial on 14JAN96. Treatment with placebo started on 14JAN96 until 25JAN96. The patient died 5 days after the end of treatment on 30JAN96, because of bilirubinemia (severe; possibly drug-related), ileus and jaundice (severe; possibly drug-related). . The patient discontinued the treatment prematurely after 11 days of treatment on 25JAN96, because of diarrhea (severe; possibly drug-related; adverse event resolved), bilirubinemia (severe; possibly drug-related; patient died) and jaundice (severe; possibly drug-related; patient died).

#439: 71-year-old female with AML entered the trial on 31MAR96. Treatment with placebo started on 31MAR96 until 31MAR96. The patient died 14 days after the end of treatment on 14APR96, because of arrhythmia (moderate; not drug-related) and pulmonary edema (severe; not drug-related). The patient discontinued the treatment and the trial prematurely on the day of treatment on 31MAR96, because of nausea (severe; drug-related; adverse event still present), serious adverse experience and because of treatment deviation.

ITR-INT-60:

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

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

#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 hemorrhage, epistaxis, creatinine increased, hypomagnesemia, hypocalcemia, hypokalemia, ulcerative stomatitis, nausea, mild: edema, headache, dyspepsia, fluid overload, confusion, pulmonary edema, rash.)

#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).

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

#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).

02/5/01

APPENDIX B:**MOR of Oral Prophylaxis studies:**

As part of the safety dataset the applicant submitted study reports and supporting data from 5 prophylaxis studies where ITR oral solution was used. These studies are reviewed below:

ITR-BEL- 4:

Title: Prophylaxis of fungal infections in neutropenic patients. An open, randomized, comparative trial of the efficacy and safety of itraconazole oral solution versus a combination of oral amphotericin B and oral nystatin.

Study Dates: 2/28/90 – 12/2/93

Investigators:

- M. Boogaerts, M.D., Internist, A.Z. Gasthuisberg, Leuven
- R. De Bock, M.D., Internist, U.Z. Antwerp, Edegem
- G. Fillet, M.D., Internist, C.H.U. Sart Tilman, Liege
- M. Peetermans, M.D., Internist, U.Z. Antwerp, Edegem
- J. Schmit, M.D., Internist, U.C.L. Brussels, Brussels
- D. Selleslag, M.D., Internist, A.Z. St. Jan, Brugge
- A. Van Hoof, M.D., Internist, A.Z. St. Jan, Brugge
- B. Vandercam, M.D., Internist, U.C.L. Brussels, Brussels
- K. Vandewoude, M.D., Internist, U.Z. Gent, Gent
- P. Zachee, M.D., Internist, A.Z. Stuyvenberg, Antwerp

Study Synopsis: Phase II open, randomized, comparative, multicenter trial to evaluate the efficacy and safety of itraconazole oral solution in comparison with a combination of high-dose oral amphotericin B and nystatin in the prevention of fungal infections in neutropenic patients. Inclusion criteria specified patients with leukemia, aplastic anemia, or BMT. Excluded were subjects requiring hospitalization for < 7 days or who were receiving other antifungals. The start of the prophylactic therapy coincided or immediately (3 to 4 days) preceded the administration of chemotherapy and continued until the neutrophil count was restored to $> 1.0 \times 10^9/l$. 280 patients were recruited and 277 were randomized to treatment; 144 were assigned to itraconazole oral solution 10 mg/mL (100 mg BID immediately after a meal) and 133 to amphotericin B capsules 250 mg /nystatin oral suspension (500 mg TID/ 2 million units QID).

Medical Officer's Comment: *The itraconazole dose used in this study was the same as that used in trial 62 (200 mg PO BID). It should be noted that oral amphotericin B and nystatin are not absorbed.*

The median duration of treatment was 22 days in the itraconazole group and 20 days in the amphotericin B/nystatin group. Subjects were assessed on study days 0, 3, 5, and

then twice a week for 8 weeks. Safety assessments included BP, HR, temperature, monitoring for AEs, and clinical laboratory measurements.

There were more male subjects on the ITR arm and the ITR patients were slightly younger than the AMP B patients. As per the applicant "there was significant intergroup differences at baseline for sex ($p = 0.040$) and height ($p = 0.007$); marginally significant intergroup difference for weight ($p = 0.059$)." Similar numbers of patients discontinued therapy due to an AE or died.

Medical Officer's Comment: *The demographics of the subjects in this trial were similar to those in study 62.*

Table B1
Demographics and Discontinuations
As per the Applicant

Baseline characteristics - patient disposition	Itraconazole	Amphotericin B/Nystatin
Number of patients entered (M/F)	144 (88/56)	133 (64/69)
Age: median (min-max), yrs	46 (17-76)	51 (16-80)
Weight: median (min-max), kg	70 (46-144)	67 (40-115)
Height: median (min-max), cm	172 (150-199)	168 (147-194)
Underlying pathology, n (%):		
acute myeloid leukaemia ¹	88 (61%)	95 (71%)
bone marrow transplant ¹	15 (10%)	10 (8%)
First episode, n (%)	133 (92%)	123 (92%)
Patient treated under laminar air flow conditions, n (%)	61 (42%)	47 (35%)
Neutrophil count $< 0.5 \times 10^9/l$, median (min-max) No. Of days	11 (0-65)	12 (0-55)
Duration of treatment, median (min-max) No. Of days	22 (1-65)	20 (2-59)
Drop-outs - reason		
• abnormal laboratory values	1	
• adverse event	23	23
• death ²	8	7
• insufficient response ³	53	60
• ineligible	5	2
• investigator incapacitation	13	11
• lost to follow-up	1	2
• non-compliance	1	1
• patient's decision	3	1
• withdrew consent		1
Total No. of drop-outs	104	101

¹ with or without another disorder

² total number of patients who died: see adverse events section

³ includes also those patients who had developed a fungal infection (had completed the trial)

Medical Officer's Comment: A large number of patients (104/144 (72.2%) ITR and 103/133 (77.4%) comparator subjects discontinued the trial. Reasons for discontinuation were similar on both arms.

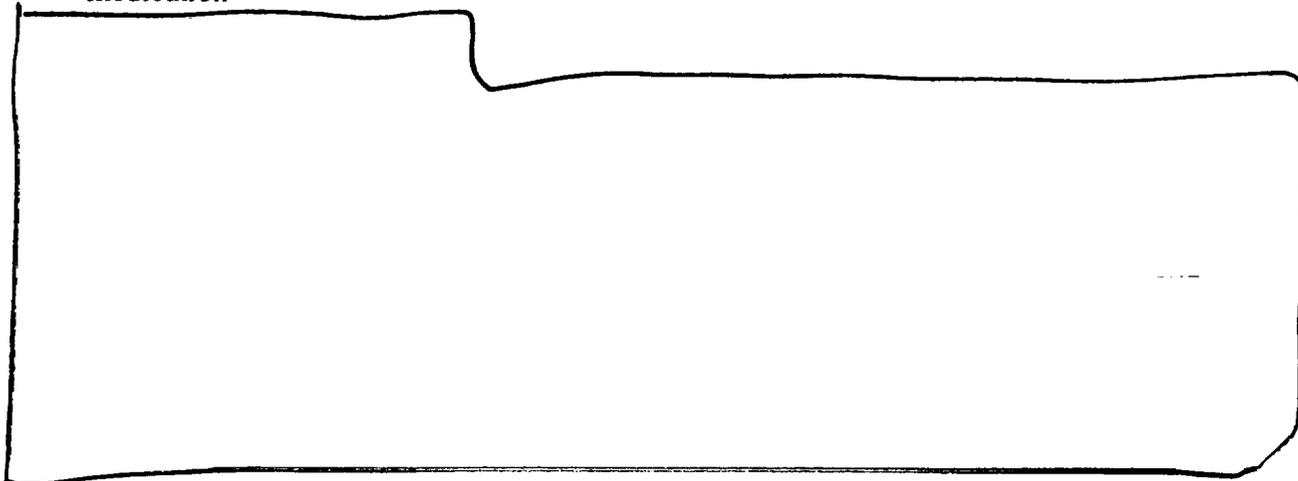
As per the applicant GI AEs were most common, followed by death when reported as an AE, and rash.

Table B2
Safety Assessment as per the Applicant

Safety (N = number of patients with data)	Itraconazole (N = 144)	Amphotericin B/Nystatin (N= 133)
Adverse events (AE) reported by at least five per cent of the patients in any group:		
• vomiting	14	12
• death ¹	13	9
• diarrhea	12	9
• nausea	5	12
• rash (including erythematous rash)	2	14
Total number of patients assessed	144	133
No. (%) with one or more AE	63 (44%)	61 (46%)
No. (%) with one or more severe AE	23 (16%)	26 (20%)
No. (%) with one or more serious AE	18 (13%)	18 (14%)
No. (%) treatment stopped due to AE	34 (24%)	33 (25%)
No. of patients who died ²	17 (12%)	17 (13%)
Clinical laboratory parameters	There were many important laboratory abnormalities, but considering the patient population, these could be accounted for.	

¹ in some patients, death was not recorded as an adverse event, but as the outcome of an adverse event (see: No. of patients who died)

² during the trial, including the period up to 30 days after the last intake of the trial medication



As per the MO: The safety database was compromised of 144 ITR and 133 AMP B/NYS patients. The primary underlying disease was AML (56% both arms). 23/144 (15.9%) of the ITR patients and 23/133 (17.3%) of the comparator patients discontinued study medication due to an AE. Additionally 8 deaths on the ITR arm and 7 on the comparator arm occurred during therapy and thus led to discontinuation.

63/144 (44%) of the ITR patients and 61/133 (46%) of the comparator patients sustained an AE. As can be seen in the following table, the most frequent AEs on both arms were from the GI tract. More deaths occurred during the treatment periods or within 30 days of the EOT on the ITR arm. These deaths were classified as AEs. Rash occurred more frequently on the comparator arm. Hepatic system abnormalities occurred more frequently on the ITR arm.

Table B3
All reported AEs by Treatment Arm

Adverse Event	ITR N = 144		AMP B/nystatin N = 133	
	n	%	n	%
Application Site Disorders				
Application site Reaction	1	0.7	-	-
Cellulitis	1	0.7	-	-
Injection Site Pain	-	-	1	0.8
Gastrointestinal System Disorders				
Diarrhea	12	8.3	9	6.8
Constipation	1	0.7	-	-
Nausea	5	3.5	12	9
Vomiting	14	9.7	12	9
Duodenal Ulcer Reactivated	1	0.7		
Abdominal Pain	3	2.1	1	0.8
GI Hemorrhage	-	-	1	0.8
Stomatitis (Ulcerative)	1	0.7	1	0.8
Gastroenteritis			1	0.8
Reflux	1	0.7	-	-
Gingivitis	-	-	1	0.8
Ileus	1	0.7	-	-
Mucositis	7	4.9	4	3
Toothache	-	-	1	0.8
Respiratory System Disorders				
Dyspnea	2	1.4	4	3
Pulmonary Edema	3	2.1	2	1.5
Bronchospasm	1	0.7	-	-
Pulmonary Hemorrhage	-	-	1	0.8
Pharyngitis	-	-	1	0.8
Pleural Pain	-	-	1	0.8
Pulmonary Infiltration	-	-	2	1.5

Pneumonia	1	0.7	3	2.3
Body as a Whole-General Disorders				
Asthenia	-	-	1	0.8
Condition Aggravated	2	1.4	-	-
Death	13	9	9	6.8
Fever	7	4.9	6	4.5
Generalized Edema	2	1.4	1	0.8
Pain	1	0.7	-	-
Rigors	-	-	2	1.5
Therapeutic Response Decreased	-	-	1	0.8
Unspecified	1	0.7	2	1.5
Central and Peripheral Nervous System Disorders				
Headache	1	0.7	2	1.5
Meningitis	-	-	1	0.8
Neuropathy	-	-	1	0.8
Paresthesia	-	-	1	0.8
Psychiatric Disorders				
Anorexia	1	0.7	2	1.5
Insomnia	1	.0	-	-
Resistance Mechanism Disorders				
Abscess	-	-	1	0.8
Herpes Simplex	-	-	1	0.8
Sepsis	3	2.1	2	1.5
Skin and Appendages Disorders				
Rash	2	1.4	13	9.8
Contact Dermatitis	1	0.7	1	0.8
Erythematous Rash	-	-	1	0.8
Skin Disorder	-	-	1	0.8
Pruritus	2	1.4	1	0.8
Metabolic and Nutritional System Disorders				
Diabetes	2	1.4	1	0.8
Gout	1	0.7	-	-
Cardiovascular Disorders Including Rhythm Disorders				
Cardiac Failure	1	0.7	-	-
Hypertension	1	0.7	1	0.8
Cardiac Arrest	-	-	1	0.8
Atrial Fibrillation	1	0.7	-	-
Vascular Disorders				
CVA	-	-	1	0.8
Intracranial Hemorrhage	-	-	1	0.8
Ocular Hemorrhage	1	0.7	-	-
DVT	1	0.7	-	-
Vein Disorder	-	-	2	1.5
Renal System Disorders				
Renal Function Abnormal	3	2.1	4	3

Liver and Biliary System Disorders				
Hepatocellular Damage	-	-	2	1.5
Bilirubinemia	3	2.1	-	-
Increased SGPT	1	0.7	-	-
Hepatitis	7	4.9	4	3
Hepatic Failure	2	1.4	2	1.5
Gall Bladder Disorder	1	0.7	-	-
Musculoskeletal System Disorders				
Arthralgia	1	0.7	-	-
Bursitis	-	-	1	0.8
Myalgia	1	0.7	2	1.5
Skeletal Pain	1	0.7	-	-
WBC Disorders				
Cervical Adenopathy	-	-	1	0.8
Coagulation Disorders				
DIC	2	1.5	1	0.8
Eye Disorders				
Conjunctivitis	-	-	1	0.8
Genital Tract Disorders				
Vaginal Hemorrhage	-	-	1	0.8
RBC Disorders				
Marrow Suppression	-	-	1	0.8
Collagen Disorders				
Immunologic Reaction	-	0	1	0.8
Pericardial and Valve Disorders				
Hemopericardium	1	0.7	-	-
Neoplasm				
Leukemia	1	0.7	-	-
Acute Leukemia	-	-	2	1.5
Lymphocytic Leukemia	1	0.7	-	-

38/144 (26.4%) ITR subjects as compared to 28/133 (21%) comparator subjects developed AEs judged to be possibly or definitely related to therapy. Of note 10 of the possibly related events on the itraconazole arm were determined to be "hepatitis" as compared to no such events on the comparator arm. Additionally, there were 2 events of bilirubinemia as well as 2 events of transaminase abnormalities on the ITR arm as compared to none on the comparator arm. Vomiting, nausea, and rash were the events most frequently attributed to therapy on the comparator arm.

Table B4
Definitely and Possibly-Drug-related Adverse Events

Adverse event (WHO preferred term)	No. of subjects	
	Itraconazole N = 144	Amphotericin B N = 133
Definitely Drug-related AEs		
General/Whole Body		
Taste Perversion	1 (0.7%)	-
GI System		
Nausea	-	3 (2.2%)
Vomiting	6 (4.2%)	2 (1.5%)
Regurgitation	1 (0.7%)	-
Total No. (%)	8 (5.5%)	5 (3.8%)
Possibly Drug-related AEs		
Body as a Whole/General		
Rigors	-	1 (0.8%)
Asthenia	-	1 (0.8%)
Anorexia	1 (0.7%)	1 (0.8%)
GI System		
Nausea	2 (1.4%)	5 (3.8%)
Diarrhea	4 (2.8%)	-
Vomiting	4 (2.8%)	8 (8%)
Abdominal Pain	1 (0.7%)	1 (0.8%)
Mucositis	1 (0.7%)	-
Abnormal Hepatic Function		
Bilirubinemia	2 (1.4%)	-
Abnormal Hepatic Function	1 (0.7%)	-
SGPT Increased	1 (0.7%)	-
Hepatitis	10 (6.9%)	-
Hepatic Toxicity	-	1 (0.8%)
Skin		
Rash	-	3 (2.3%)
Pruritus	-	1 (0.8%)
Cardiovascular		
Atrial Fibrillation	1 (0.7%)	-
CNS and Peripheral Nervous System		
Headache	1 (0.7%)	1 (0.8%)
Coagulation Disorders		
DIC	1 (0.7%)	-
Total No. (%)	30 (21%)	23 (17.3%)

Discontinuations due to AEs:

34/144 (23.6%) ITR patients and 33/133 (25%) AMP B patients discontinued therapy because of an AE. 32 and 30 of these patients per arm respectively also dropped out of the trial and no longer had assessments.

The following AEs led to withdrawal:

Table B5
AEs Leading to Withdrawal

Adverse Event	ITR N = 144		AMP B/nystatin N = 133	
	n	%	n	%
Gastrointestinal System Disorders				
Nausea	3	2.1	11	8.3
Vomiting	11	7.6	11	8.3
Abdominal Pain	-	-	1	0.8
Reflux	1	0.7	-	-
Mucositis	3	2.1	2	1.6
Respiratory System Disorders				
Dyspnea	1	0.7	1	0.8
Pulmonary Edema	2	1.4	2	1.6
Pulmonary Hemorrhage	-	-	1	0.8
Pulmonary Infiltration	-	-	2	1.6
Pneumonia	-	-	1	0.8
Body as a Whole-General Disorders				
Condition Aggravated	2	1.4	-	-
Death	4	2.8	4	3.2
Fever	3	2.1	1	0.8
Rigors	-	-	1	0.8
Central and Peripheral Nervous System Disorders				
Headache	1	0.7	1	0.8
Meningitis	-	-	1	0.8
Resistance Mechanism Disorders				
Sepsis	2	1.4	1	0.8
Skin and Appendages Disorders				
Rash	-	-	1	0.8
Cardiovascular Disorders Including Rhythm Disorders				
Cardiac Failure	1	0.7	-	-
Vascular Disorders				
CVA	-	-	1	0.8
Renal System Disorders				
Renal Function Abnormal	1	0.7	1	0.8
Liver and Biliary System Disorders				
Bilirubinemia	3	2.1	-	-
Hepatitis	4	2.7	1	0.8
Hepatic Failure	-	-	1	0.8

Pericardial and Valve Disorders				
Hemopericardium	1	0.7	-	-
Neoplasms				
Leukemia	1	0.7	-	-
Acute Leukemia	-	-	2	1.6
Lymphocytic Leukemia	1	0.7	-	-

Medical Officer's Comment: *The MO reviewed the case histories of the ITR patients who developed hepatitis and/or bilirubinemia that led to discontinuation of therapy (N = 7). Synopses of these cases are provided below. The MO determined that all cases reviewed below were attributable to the trial medication. Hepatic dysfunction usually appeared during the first 2 weeks of therapy and resolved within an additional 2 week period. Not all cases of transaminitis were associated with bilirubinemia and not all cases of bilirubinemia were associated with transaminitis. When reported, bilirubinemia in the absence of hepatic enzyme abnormalities appeared to resolve within 4 – 7 days. All patients were on multiple cytotoxic medications as well as broad-spectrum antimicrobials.*

- 46-year old, Caucasian male patient entered the trial on 06JUL90. The patient was diagnosed with acute lymphatic leukemia. Medical history showed iatrogenic pneumothorax. There was a discontinuation of the trial medication from 03AUG90 until 27AUG90 (discontinued); the patient stopped the intake of trial medication because of moderate hepatitis. The investigator considered the adverse event to be possibly drug-related. The patient recovered without residual effects.
- 17-year old, Caucasian female patient entered the trial on 28FEB91. The patient was diagnosed with acute lymphatic leukemia. No medical history was noted. Evidence of hepatitis developed on day 16 of therapy and resolved 5 weeks later (gGT: 373 U/l, Day 14, 287 U/l, Day 21, 472 U/l, Day 28 and 361 U/l, Day 35 (range below pathological grade 2: 0-130 U/l). Therapy was discontinued on study day 34 because of refractory lymphocytic leukemia and DIC.
- 17-year old, Caucasian male patient entered the trial on 04MAY91. The patient was diagnosed with acute lymphatic leukemia. No medical history was noted. The patient stopped the trial on 25MAY91, i.e. 21 days after randomization, because of moderate hepatitis (continuous). The investigator considered the adverse event to be possibly drug-related. The hepatitis resolved approximately 4 weeks later. The following important laboratory abnormalities were detected: ALT: 118 U/l, Day 14 and 875 U/l, Day 21 (range below pathological grade 2: 0-78 U/l); AST: 143 U/l, Day 21 (range below pathological grade 2: 0-78 U/l);
- 40-year old, Caucasian male patient entered the trial on 17AUG91. The patient was diagnosed with acute myeloid leukemia. No medical history was

noted. The patient stopped the trial on 06SEP91, i.e. 20 days after randomization, because of increased bilirubin. The investigator considered the adverse event to be possibly drug-related. The event resolved after 4 days (Total bilirubin: 8.3 mg/dl, Day 14 and 5.7 mg/dl, Day 21 (pathological limits: 0.1-1.4 mg/dl).

- 29-year old, Caucasian female patient entered the trial on 22NOV91. The patient was diagnosed with a myelodysplastic syndrome and had had a bone marrow transplant. Medical history showed surgery breast cancer. There was a discontinuation of the trial medication from 04DEC91 until 06DEC91 (discontinued), i.e., the patient permanently stopped the intake of the trial medication on 04DEC91, 12 days after randomization, and she stopped the trial on 06DEC91, 14 days after randomization, because of severe hepatitis (continuous). The investigator considered the adverse event to be possibly drug-related. In addition, the patient also had an abnormal renal function and bilirubin increased. Both adverse events were reported as serious. The following important laboratory abnormalities were detected: Total bilirubin: 30.8 mg/l, Day 7, 113 mg/l, Day 10, 192 mg/l, Day 14, and 24.8 mg/l, Day 21 (pathological limits: 0-14 mg/l);
- 32-year old, Caucasian female patient entered the trial on 03MAR92. The patient was diagnosed with acute myeloid leukemia. No medical history was noted. The patient stopped the trial on 19MAR92, i.e. 16 days after randomization, because of both inefficacy (fungal infection) and severe bilirubinemia (continuous). The investigator considered the adverse event to be possibly drug-related. The event resolved 4 days later. Total bilirubin: 3.4 mg/dl, Day 14 (pathological limits: 0.1-1.4 mg/dl);
- 33-year old, Caucasian female patient entered the trial on 09MAR93. The patient was diagnosed with acute myeloid leukemia. No medical history was noted. There was a discontinuation of the trial medication from 28MAR93 until 29MAR93 (discontinued); i.e. the patient permanently stopped the intake of the trial medication on 28MAR93, i.e. 19 days after randomization, because of both inefficacy (fungal infection possible) and abnormal laboratory values, i.e., severe, continuous bilirubinemia. The investigator considered the adverse event to be not drug-related. The patient stopped the trial one day later, i.e., on 29MAR93, because of the same reasons. Total bilirubin: 1.7 mg/dl, Day 14 (pathological limits: 0.1-1.4 mg/dl);

Deaths:

Medical Officer's Comment: 17 (11.8% ITR and 12.8% AMP B/NYS) patients on each treatment arm died during this trial (including the period up to 30 days after the last intake of trial medication). Death was reported as an adverse event in 13 itraconazole patients and 9 amphotericin B/nystatin patients and was the reason for trial discontinuation in 8 and 7 patients, respectively. AEs that occurred in the remaining 4 ITR patients included 1 each: aggravated condition, pulmonary edema, cardiac failure,

and sepsis. 2 patients had death reported as an AE associated with either dyspnea or fever. On the comparator arm, the remaining 8 patients who died had the following AEs: mucositis and ARF, pneumonia and BM suppression, pulmonary hemorrhage and edema with sepsis (2), intracranial hemorrhage, dyspnea and fever, CVA, pneumonia (2), DIC, cardiac arrest, and hepatitis. None of the deaths were reported related to study medication.

Synopses of all patient case histories associated with death are provided in appendix A to the MOR.

Serious AEs:

18 patients in each group were reported as sustaining a serious AE (12.5% ITR and 13.5% comparator). Other than “death” (13 ITR and 9 AMP B), the following adverse events were considered as serious in the ITR group:

Condition aggravated (1), cardiac failure (1), sepsis (1), hepatitis (2), pulmonary edema (1), and abnormal renal function (1).

In the comparator group the following SAEs were seen:

Fever (1), therapeutic response decreased (1), neuropathy (1), hematemesis (1), stomatitis (1), mucositis (1), cardiac arrest (1), abscess (1), sepsis (1), dyspnea (1), pneumonia (2), pulmonary infiltration (1), pulmonary hemorrhage (1), renal function abnormal (3), cerebrovascular disorder (1), intracranial hemorrhage (1), and vein disorder (1).

Severe AEs:

Severe AEs were reported in 23/144 (16%) ITR patients and 26/133 (19.5%) AMP B patients. Of those events that were seen in > 1 patient, the following were seen:

Fever: ITR (3), AMP B/NYS (3); Vomiting: ITR (9), AMP B/NYS (7); Pulmonary Edema: ITR (3), AMP B/NYS (2); Renal function abnormal: ITR (1), AMP B/NYS (2); and Hepatitis: ITR (1), AMP B/NYS (2).

Laboratory:

139/144 itraconazole patients and 125/133 amphotericin B/nystatin patients had laboratory data both at baseline and at least once during or at the end of treatment As per the applicant:

No consistent, clinically relevant changes in the mean values of biochemistry, hematology, or urinalysis were observed.

Biochemistry:

114/144 (79%) ITR and 99/133 (74%) comparator patients showed important abnormalities in biochemistry (except for liver function) tests or urinalysis at any time

point during the trial. Of these, 81 itraconazole patients and 77 amphotericin B/nystatin patients had a "code-4" or "code-5" important abnormality. These abnormalities included:

- Hypochloremia: 12 (8.3%) ITR and 3 (2.3%) comparator;
- Hypokalemia: 6 (4.2%) ITR and 8 (6%) comparator
- Hypoproteinemia: 32 (22.2%) ITR and 27 (20.3%) comparator
- Hyperglycemia: 33 (23%) ITR and 27 (20.3%) comparator
- Bilirubinemia: 25 (17.4%) ITR and 20 (15%) comparator
- Increased BUN: 17 (11.8%) ITR and 16 (12%) comparator
- Hypouricemia: 21 (14.6%) ITR and 14 (10.5%) comparator.

LFTs:

- 72/144 (50%) ITR and 55/133 (41%) comparator patients had important abnormalities in liver function tests at any time point during treatment, i.e., they had codes 1 to 5. Of these:
- 36 (25% ITR and 27% comparator) patients in each group had a "code-4" important abnormality for pathologic grade 1
- 20 (13.8%) and 17 (12.8%) respectively had a "code-4" important abnormality for pathologic grade 2
- 9 (6.3%) and 5 (3.8%) respectively had a "code-4" important abnormality for pathologic grade 3
- (1.4%) and 3 (2.3%) per arm respectively had a "code-4" important abnormality for pathologic grade 4.

Conclusions for ITR-BEL 4:

ITR BEL-4 was an open, randomized, comparative trial of ITR oral solution (200 mg PO BID) compared to oral AMP B and oral nystatin in the prophylaxis of FN patients. Median duration of treatment was 22 days on the ITR arm and 20 days on the comparator arm. Patient demographics were similar to those seen in trial 62 with most patients diagnosed with hematologic malignancies. AEs were reported in 63/144 (44%) of the ITR patients and 63/133 (46%) of the comparator. Most events were from the GI tract and included nausea, vomiting, and diarrhea. With the exception of vomiting, these events were more frequent on the comparator arm. Other frequently reported events included rash (13/133 (9.8%) AMP B/N vs. 2/144 (1.4%) ITR, and hepatitis (7/144 ITR (4.9%) vs. 4/133 (3%) AMP B/N. The overall number of events from the hepatobiliary system was higher on the ITR (14 events) arm as compared to the comparator (8 events).

Of the events attributable to treatment, more ITR patients had definitely related events (8, 5.5%) as compared to the comparator arm (5, 3.8%). This difference was due to a larger number of episodes of vomiting attributed to treatment on the ITR arm.

Similarly, more ITR events were determined to be possibly related to therapy 30 (21%) as compared to 23 (17.3%) on the comparator arm. Once again, GI events were frequent

however, 10 occurrences of hepatitis on the ITR arm were attributable to treatment as compared to none on the comparator arm.

34/144 (23.6%) ITR patients as compared to 33/133 (25%) comparator patients discontinued due to an AE and 17 patients on each arm (11.8% ITR, 12.8% AMP B/N) died during the trial. A review of the CRFs revealed that none of the deaths could be attributed to therapy.

18 patients in each group were reported as sustaining a serious AE (12.5% ITR and 13.5% AMP B). 2 of the SAEs on the ITR arm were classified as hepatitis.

Laboratory abnormalities occurred with similar frequency on both study arms. As expected, patients on ITR had more LFT and bilirubin abnormalities as compared to the comparators.

ITR-GBR-17

Title: A randomized study to compare itraconazole solution with fluconazole suspension as antifungal prophylaxis for patients undergoing treatment for hematological malignancy.

Study Dates: 11/1992 – 3/1995

Investigators: UK mycoses study group (multicenter)

- Child. A. FRCPLeeds
- Gray. A. MRCPath Swindon
- Green. S.E. MRCPath Swindon
- Hutchinson. M. FRCP Leicester
- Johnson. S.A.N. FRCPath Taunton
- Marcus. R.A. FRCP Cambridge
- Morgenstern. G., FRCPath Manchester
- Oscier. D.G. FRCPath Bournemouth
- Poynton.C. MRCPath Cardiff
- Prentice. H.G. FRCP London
- Prentice. A.G. FRCP Plymouth
- Ropner. J. FRCP Gloucester
- Samson. D. FRCP London
- Schey. S. FRCP London
- Smith. A.G. FRCP Southampton
- Smith. G J. MRCPath Bath
- Taylor. P.J. MRCPath Rotherham
- Winfield. D. FRCP Sheffield

Study Synopsis: Multicenter, open, randomized trial in adult patients undergoing chemotherapy or bone marrow transplant (BMT) for hematologic malignancies. Patients

were randomized to receive antifungal prophylaxis with either 2.5mg/kg BID itraconazole solution (ITR) or 100 mg fluconazole suspension (FLU). Prophylaxis was started prior to neutropenia and continued until neutrophil levels had recovered. Allowable duration of therapy ranged from 60 – 90 days in an episodic fashion. If fungal infection was suspected, study drug was stopped and normal treatment instituted. All cases were independently reviewed by raters unaware of the prophylaxis group. Inclusion criteria specified patients undergoing initial remission-induction, consolidation or re-induction after relapse for AML or ALL, or any malignancy, patients undergoing intensive chemotherapy for myelodysplastic syndrome, or patients undergoing allogeneic or autologous BMT for AML, ALL, chronic granulocytic leukemia, Hodgkin's disease, NHL, or myeloma who were expected to be significantly neutropenic, defined as $< 1 \times 10^9$ neutrophils/L expected for 7 days or more. The exclusion criteria were standard. Notable was the exclusion of patients with a previously proven and documented invasive fungal infection, patients receiving non-absorbable polyenes (amphotericin, nystatin), patients likely to exceed 90 days cumulative treatment in any one episode, and patients having received antifungal prophylaxis or treatment with either itraconazole or fluconazole, in the last 21 days (prior to randomization).

***Medical Officer's Comment:** The population studied, adults with hematologic malignancies, was similar to that studied in trial 62. Notable was the exclusion of patients who had received prior itraconazole or fluconazole. Regarding the dose, assuming a median weight of 60 – 65 kilograms, would have led to 150 – 200 mg PO BID, that may have been somewhat less than that received in trial 62.*

445 patients with 591 neutropenic episodes were enrolled. 581 episodes in 218 ITR patients (288 episodes) and 227 FLU patients (293 episodes) were deemed evaluable after excluding 10 episodes.

Patients were monitored for AEs daily during the initial episode and then weekly.

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**Table B6
Demographics and Discontinuations
As per the Applicant**

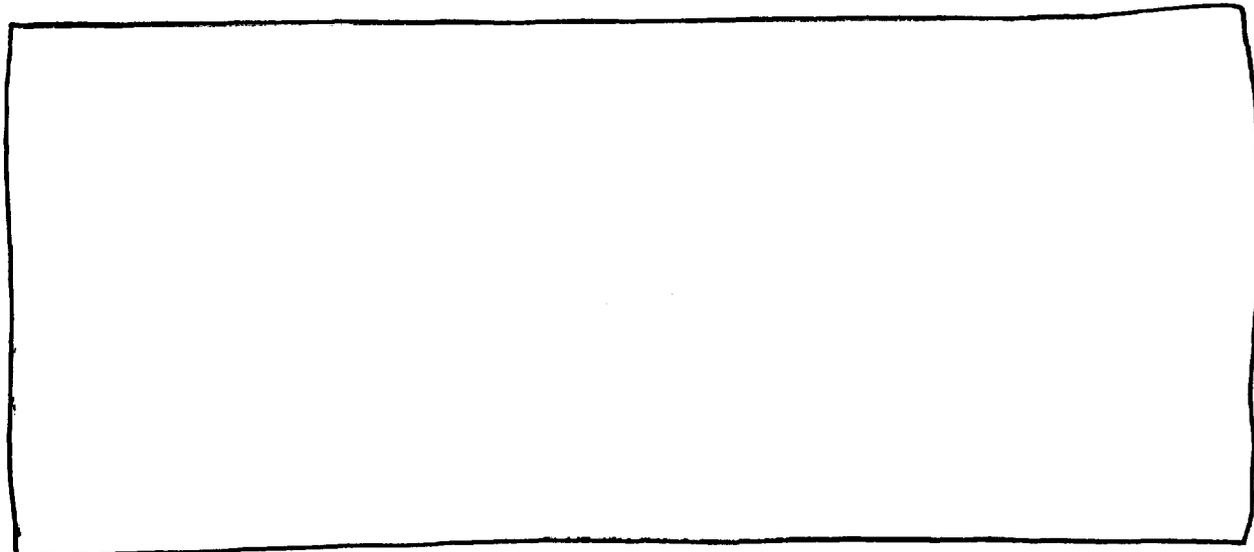
Baseline characteristics - patient disposition	Itraconazole N = 218	Fluconazole N = 227
Number of patients entered (M/F)	218 (135/83)	227 (140/87)
Age: median (min-max), yrs	46.5 (17 – 81)	46 (16 – 80)
Weight: median (min-max), kg	Not provided	Not provided
Height: median (min-max), cm	172 (124 – 193)	172 (132 – 255)
Underlying pathology, n (%):		
acute myeloid leukemia	152 (52.8%)	152 (51.8%)
bone marrow transplant	110 (37.6%)	120 (41%)
First episode, n (%)	76 (26.4%)	74 (25.3%)
Patient treated under laminar air flow conditions, n (%)	148 (51.4%)	156 (53.2%)
Duration of treatment, median (min-max) No. Of days		
Episodes Excluded from Analysis	8	2
Discontinuations (by episode)	Itraconazole N = 288	Fluconazole N = 293
Drop-outs - reason		
• adverse event	51 (17.7%)	13 (4.4%)
• death (non fungal)	3 (1%)	7 (2.4%)
• ineligible	17 (5.9%)	30 (10.2%)
• lost to follow-up	1 (0.3%)	3 (1%)
• non-compliance	11 (3.8%)	11 (3.8%)
• withdrew consent	19 (6.6%)	8 (2.7%)
Other	1 (0.3%)	-
Total No. of drop-outs	103 (35.8%)	72 (24.6%)

Demographics: The treatment groups were well-balanced with regards to sex (61% male, age, weight, underlying disease (60% AML), stage of disease, and type of therapy. 51/288 (17.7%) ITR patient episodes versus 13/293 (4.4%) FLU patients/episodes were discontinued due to an AE.

Medical Officer's Comment: A larger number of itraconazole-treated patients discontinued treatment and the trial due to an AE and were classified as failures.

Table B7
Safety Assessment as per the Applicant

Safety (N = number of patients with data)	Itraconazole (N = 296)	Fluconazole (N = 295)
Total number of patients assessed	296	295
No. (%) with one or more AE	280 (94.6%)	275 (93.2%)
No. (%) with one or more severe AE	100 (33.8%)	100 (33.9%)
No. (%) with one or more serious AE	35 (11.8%)	32 (10.5%)
No. (%) treatment stopped due to AE	123 (41.6%)	92 (31.2%)
No. of patients who failed due to an AE	51 (17.7%)	13 (4.4%)



AEs were reported in 280/296 (94.6%) ITR patients and 275/295 (93.2%) FLU patients. 1064 AEs were reported for ITR as compared to 1140 for FLU. Severe AEs were reported in 100 patients on each arm (33.8% ITR and 33.9% FLU) and serious AEs were reported from 35 (11.8%) ITR patients as compared to 32 (10.5%) FLU. Treatment was discontinued in 123 (41.6%) ITR patients as compared to 92 (31.2%) FLU patients because of an AE.

All AEs by body system can be seen below. Of note, AEs from the GI tract as well as from the hepatobiliary system were more frequent on the ITR arm.

Table B8
All AEs by Body system

Adverse Experience	Itraconazole	Fluconazole
None	16 (5.4%)	20 (6.8%)
Skin and appendages disorders	68 (23%)	92 (31.2%)
Musculo-skeletal system disorders	8 (2.7%)	14 (4.7%)
Central and peripheral nervous system disorders	36 (12.2%)	48 (16.3%)
Autonomic nervous system disorders	17 (5.7%)	23 (7.8%)
Vision disorders	8 (2.7%)	6 (2%)
Hearing and vestibular disorders	1 (0.3%)	1 (0.3%)
Special senses others disorders	1 (0.3%)	2 (0.7%)
Psychiatric disorders	35 (11.8%)	29 (9.8%)
Gastro-intestinal system disorders	233 (78.7%)	209 (70.8%)
Liver and biliary system disorders	19 (6.4%)	11 (3.7%)
Metabolic and nutritional disorders	86 (29.1%)	56 (19%)
Myo/endo/pericardial and valve disorders	0	1 (0.3%)
Heart rate and rhythm disorders	6 (2%)	8 (2.7%)
Vascular (extracardiac) disorders	5 (1.7%)	11 (3.7%)
Respiratory system disorders	47 (15.9%)	54 (18.3%)
Red blood cell disorders	1 (0.3%)	0
White cell and RES disorders	1 (0.3%)	2 (0.7%)
Platelet, bleeding and clotting disorders	24 (8.1%)	41 (13.9%)
Urinary system disorders	16 (5.4%)	17 (5.8%)
Reproductive disorders female	11 (3.7%)	10 (3.4%)
Neoplasms	0	1 (0.3%)
Body as whole general disorders	206 (69.6%)	230 (78%)
Application site disorders	3 (1%)	5 (1.7%)
Resistance mechanism disorders	51 (17.2%)	59 (20%)
Disease	55 (18.6%)	63 (21.4%)
Not classified	110 (37.2%)	127 (43.1%)
TOTAL	1064	1140

NOTE: the applicant did not provide a by system breakdown of all reported AEs.

Listed below are events determined to be definitely or possibly related to therapy. Nausea, vomiting and diarrhea were attributed more frequently to treatment on the ITR arm. Liver and biliary system events appeared to occur with similar frequency on both arms.

Table B9
Definitely and Possibly Drug-related adverse events

Adverse event (WHO preferred term)	No. of episodes	
	Itraconazole N = 296	Fluconazole N = 295
Definitely Drug-related AE		
General/Whole Body		
Fever	2 (0.7%)	1 (0.3%)
Hyperpyrexia	-	1 (0.3%)
GI System		
Nausea	11 (3.7%)	3 (0.9%)
Vomiting	12 (4%)	1 (0.3%)
Diarrhea	1 (0.4%)	-
Bloating	1 (0.4%)	-
Stomatitis	-	1 (0.3%)
Renal And Electrolyte		
Hypokalemia	-	1 (0.3%)
Hypoglycemia	-	1 (0.3%)
Respiratory		
Bronchospasm	-	2 (0.6%)
Immune System		
Sepsis	1 (0.4%)	-
Rash	1 (0.4%)	1 (0.3%)
Special Senses		
Taste Perversion	1 (0.4%)	-
Total No. (%)	30 (10%)	12 (4%)
Possibly Drug-related AE		
Body as a Whole/General		
Rigors	3 (1%)	1 (0.3%)
Ankle Edema	1 (0.4%)	-
Back Pain	-	1 (0.3%)
Fever	13 (4.4%)	8 (2.7%)
Chest Pain	-	1 (0.3%)
Malaise	1 (0.4%)	-
Fluid Retention	1 (0.4%)	-
GI System		
Nausea	60 (20.3%)	46 (15.6%)
Diarrhea	50 (16.9%)	23 (7.8%)
Vomiting	51 (17.2%)	32 (10.8%)
Abdominal Pain	13 (4.4%)	11 (3.7%)
Mucositis	1 (0.4%)	3 (0.9%)
Dyspepsia	9 (3%)	7 (2.4%)
Constipation	6 (2%)	6 (2%)
Dysphagia	-	1 (0.3%)

Flatus	-	1 (0.3%)
GI Hemorrhage	1 (0.4%)	-
Gingivitis	1 (0.4%)	1 (0.3%)
Stomatitis	3 (1%)	4 (1.3%)
Tongue Discoloration	1 (0.4%)	-
Tooth Discoloration	1 (0.4%)	-
Renal and Electrolyte		
Hypokalemia	7 (2.4%)	3 (0.9%)
Increased creatinine	-	1 (0.3%)
Abnormal Renal Function	1 (0.4%)	1 (0.3%)
Dehydration	1 (0.4%)	-
Hypocalcemia	-	1 (0.3%)
Hyperglycemia	1 (0.4%)	-
Fluid Overload	-	1 (0.3%)
BUN Increased	-	3 (0.9%)
Hematuria	1 (0.4%)	-
Decreased Output	1 (0.4%)	-
Increased Frequency	1 (0.4%)	-
Proteinuria	-	1 (0.3%)
Hyperglycemia	-	1 (0.3%)
Abnormal Hepatic Function		
Bilirubinemia	9 (3%)	3 (0.9%)
Jaundice	4 (1.6%)	1 (0.3%)
Enzyme Abnormality	16 (5.4%)	12 (4.1%)
Increased LDH	1 (0.4%)	-
Increased Alk. Phos.	-	2 (0.6%)
AST Increased	-	4 (1.3%)
ALT Increased	2 (0.8%)	9 (3%)
gGT Increased	4 (1.6%)	2 (0.6%)
Skin		
Rash	18 (6.1%)	17 (5.8%)
Erythematous Rash	3 (1%)	2 (0.6%)
Pruritus	2 (0.8%)	1 (0.3%)
Urticarial Rash	1 (0.4%)	1 (0.3%)
Acne	1 (0.4%)	-
Ulcer	-	1 (0.3%)
Folliculitis	-	2 (0.6%)
Cardiovascular		
Bradycardia	1 (0.4%)	-
Tachycardia	1 (0.4%)	3 (0.9%)
Eye		
Itchy eyes	1 (0.4%)	-
Dry eyes	-	1 (0.3%)
Infection		

Fungal Infection/col.	5 (1.7%)	8 (2.6%)
CNS and Peripheral Nervous System		
Headache	2 (0.8%)	3 (0.9%)
Vertigo	1 (0.4%)	-
Depression	1 (0.4%)	1 (0.3%)
Confusion	-	1 (0.3%)
Somnolence	-	1 (0.3%)
Anorexia	-	3 (0.9%)
Lightheadedness	1 (0.4%)	-
Respiratory		
Coughing	-	3 (0.9%)
Sinusitis	1 (0.4%)	-
Rhinitis	-	1 (0.3%)
Hemoptysis	-	1 (0.3%)
Musculoskeletal		
Neck Pain	-	1 (0.3%)
Arthralgia	-	1 (0.3%)
Myalgia	1 (0.4%)	1 (0.3%)
Coagulation Disorders		
Vaginal Bleeding	5 (1.7%)	-
Total No. of AEs	390	244

Deaths:

The total number of deaths by study arm was 22/218 (10%) ITR versus 27/227 (11.9%) FLU. No death was attributed to study drug. After an independent review of all deaths the MO concurred with the investigators' determinations. All 22 of the ITR deaths were classified as serious AEs as compared to 20 of the FLU deaths. The remaining 7 FLU deaths were due to fungal infection.

Medical Officer's Comment: The MO found a varying numbers of deaths in this trial depending on the source. In the ISS there were 25 ITR deaths as compared to 23 FLU deaths. As noted above the study report referred to 22 ITR deaths and 27 FLU deaths. In the SAEs, for ITR the MO found 23 ITR deaths and 20 FLU deaths. The remaining ITR death, # 1806, was located in the CRFs and synopsis below. Additionally, 1 (#222) of the 25 ITR deaths was misclassified, thus there were CRFs for 24 ITR deaths. An additional 3 FLU deaths (#911, #916, #226) were also located in the CRFs. The MO requested that the sponsor clarify the remaining reported 4 FLU deaths as well as provide an explanation as to the numerical discrepancies.

Synopses of all patient case histories associated with death are provided in appendix A to the MOR.

Adverse events leading to withdrawal:

64 (51/288 (17.8%) ITR vs. 13/293 (4.4%) FLU) patients withdrew due to adverse events. These were predominantly gastrointestinal (nausea and vomiting).

Serious and severe adverse events:

35/288 (12.1%) SAEs were reported in the ITR group, (from 34 patients) and 33/293 (11.2%) in FLU, (from 31 patients). Of these 22 in the itraconazole group and 18 in the fluconazole group died either during the study period or up to 30 days after. A further 2 patients in the fluconazole group died as a result of their serious adverse event after the 30 day post-study period. Other than deaths, other SAEs on the ITR arm included: vaginal hemorrhage x 2, hyperbilirubinemia x 4, elevated LFTs x 2, sepsis x 2, cellulitis x 1, paralytic ileus x 1, and ARF x 1. All recovered.

On the FLU arm, SAEs other than death included: MI x 1, increased LFTs x 4, sepsis x 3, appendicitis x 1, hypotension x 1, jaundice x 2. All patients in this listing recovered.

A review of the CRFs of patients (including deaths) with SAEs and liver or biliary abnormalities revealed the following:

ITR: In 2 cases of hyperbilirubinemia, the investigators attributed the AEs to other causes. In the remaining cases no causal attribution was made. However, in all cases ITR treatment was stopped at the time of the event with gradual recovery in the ensuing weeks.

FLU: Causal determinations were not reported. As on the ITR arm, gradual recovery usually occurred. More patients on FLU had LFT abnormalities as compare to ITR where hyperbilirubinemia was more common.

ITR (N = 7):

#0301: 23 year old female with acute myeloid leukemia entered the study on 26th November 1992 and received itraconazole 2.5 mg/kg twice daily for 18 days. She developed hyperbilirubinemia and the itraconazole was stopped. The bilirubin ranged from 40 to 300 (2 weeks later) and had returned to 47 three weeks later. There was no evidence of hepatic toxicity and the cause was attributed to reabsorption from the pleural/hemorrhagic effusion.

#0328: 39 year old high-risk male with acute myeloid leukemia entered the study on 19th August 1993 and received itraconazole 2.5 mg/kg twice daily for 15 days. He was withdrawn at this point as liver function tests had risen to greater than 5 times the upper limit of normal. No further details available.

#1453: 56 year old undergoing an autologous bone marrow transplant for non-Hodgkin's lymphoma entered the study on 13th May 1994 and received itraconazole 2.5 mg/kg twice daily for 12 days. The patient's bilirubin rose to over

5 times the upper limit of normal and was therefore withdrawn as per the protocol. The investigator did not feel this was attributable to the study medication as patient was also on multiple chemotherapy and other medications. The bilirubin settled spontaneously and the patient is well.

#1456: 48 year old male undergoing an autologous bone marrow transplant for non-Hodgkin's lymphoma entered the study on 26th June 1994 and received itraconazole 2.5 mg/kg twice daily for 9 days. The bilirubin rose to 50 mcml/l and was withdrawn from the study as per the protocol. The patient remained well throughout this event and fully recovered.

#1802: 24 year old female with acute lymphoblastic leukemia entered the study on 4th October 1993 and received itraconazole 2.5 mg/kg twice daily for 9 days. The patient developed elevated AST and ALT with a slight increase in bilirubin and therefore was withdrawn from the study. No further details available

#1810: 73 year old female with acute lymphoblastic leukemia entered the study on the 8th April 1994 and received itraconazole 2.5 mg/kg twice daily for 29 days. She developed an elevated bilirubin and was withdrawn from the study on 6th May. Bilirubin had normalized by 20th May.

#1609: 63 year old female with acute myeloid leukemia entered the study on the 4th August 1994 and received itraconazole 2.5 mg/kg twice daily for 13 days. She developed an elevated bilirubin and the study medication was stopped on 22nd August. The patient suffered progressive cardiac failure leading to death the same day. The investigator attributed the development of cardiac failure as either the underlying disease or to the toxicity of an anthracycline cytotoxic.

FLU (N = 10):

#0314: 18 year old high-risk male with acute lymphoblastic leukemia entered the study on 6th April 1993 and received fluconazole 100mg daily for 5 weeks. Study medication was stopped at this point because of severely elevated AST and ALT. Chemotherapy was also stopped. The patient subsequently recovered.

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

#0602: 80 year old female with acute myeloid leukemia entered the study on the 12th February 1993 and received fluconazole 100mg daily for 24 days. The patient developed a cellulitis of the left arm with a clinical neutropenic sepsis requiring intravenous antibiotics. The patient developed abnormal liver and

impaired renal function and subsequently died on 15th March. Clinical complications thought not to be related to the study medication.

#0663: 20 year old female with acute lymphoblastic leukemia entered the study on 17th January 1994 and received fluconazole 100mg daily for 6 weeks. She developed a febrile episode on 7th February with jaundice. The fever resolved with antibiotics and the bilirubin normalized by 25th February. She was clinically well but transaminases were persistently elevated. Therapy was continued but methotrexate was delayed. A liver biopsy on 30th March showed increased iron and minimal fibrosis with no clinically significant abnormality in the context of her leukemia or ongoing medication. The patient subsequently recovered.

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

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

#1231: 31 year old female with acute myeloid leukemia entered the study on 19th October 1993 and received fluconazole 100mg once daily for 8 days. On the 25th October her γ GT was elevated to 449 IU/L. The patient was withdrawn from the study, as this was greater than 5 times the upper limit of normal. The patient subsequently recovered

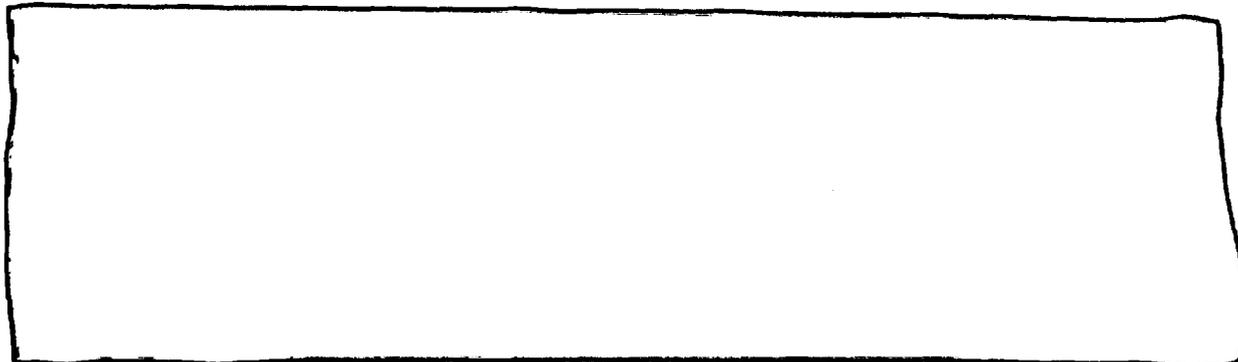
#1261: 31 year old male with acute lymphoblastic leukemia entered the study on 15th December 1993 and received fluconazole 100mg once daily for 27 days. The patient's SGPT was elevated on entry but continued to rise further. The patient was not withdrawn and by the end of the study had returned to normal.

#1819: 27 year old male with acute lymphoblastic leukemia entered the trial on 8th November 1994 and received fluconazole 100mg once daily for 5 weeks. On entry to the study ALT and bilirubin were elevated but within the range allowed for inclusion. Over the next few weeks the bilirubin continued to rise to greater than 50 μ mol/l but then remained stable and was not reported as a serious adverse event. On the 12th December the ALT was greater than 5 times the upper limit of normal and the patient was withdrawn. No further details available.

#1932: 35 year old male with a non-hematological malignancy entered the study on 14th March 1994 and received fluconazole 100mg once daily for 16 days. The

patient developed jaundice on March 28th and on March 30th had a bilirubin of 120. The patient was withdrawn from the study and subsequently recovered.

Laboratory:



A review of the tables provided revealed that similar numbers of subjects on both study arms developed LFT abnormalities including transaminase elevations and bilirubinemia as well as hypokalemia.

MO conclusion: *ITR and FLU were comparable with regard to the types of AEs that occurred in this trial. GI events were more frequent on the ITR arm. The reason for this discrepancy was not explained.*

ITR-CAN- 15:

Title: The assessment of itraconazole oral solution (5 mg/kg total daily) as primary prophylaxis for fungal infections in patients with hematological malignancy and profound neutropenia

Study Dates: June 30, 1994 – April 5, 1995

Investigator: M. Laverdière, M.D., Department of Microbiology and Infectious Diseases, Hôpital Maisonneuve-Rosemont, Montréal, Canada

Study Synopsis: Open-label, phase III clinical trial with the primary objective of establishing the efficacy and safety of itraconazole oral solution (10 mg/mL) as primary prophylaxis for fungal infections in severe neutropenic patients with hematological malignancies. Additional objectives included determining the use of intravenous amphotericin B as therapy for suspected fungal infections. The impact of itraconazole oral solution on the colonization by fungal pathogens was also evaluated. Safety was assessed through the reporting of adverse events and laboratory abnormalities throughout the trial. Itraconazole oral solution was administered on a 5 mg/kg body weight basis, divided evenly in a morning and evening dose (2.5 mg/mL) and administered without a meal. Prophylaxis was to start on the first day of chemotherapy and continue up to the end of neutropenia, or until predefined study endpoints of documented or suspected fungal infections. The trial plan included an inclusion visit, eight possible weekly visits

during the study treatment period and a post-prophylaxis visit four weeks after the end of neutropenia.

The inclusion criteria specified male or female patients ≥ 18 years of age with acute leukemia scheduled for remission/induction; or consolidation/re-induction chemotherapy; or autologous bone marrow transplantation involving chemotherapy but without total body irradiation and without autologous blood stem cell transplantation; or myelodysplastic syndrome scheduled to receive leukemia-like cytostatic therapy; or chemotherapy for the blast crisis of chronic myelogenous leukemia; or lymphoma or myeloma undergoing aggressive chemotherapy (e.g. melphalan or a combination of cyclophosphamide, adriamycin, vincristine, prednisone). The patients' neutrophil count was expected to be $< 500/\mu\text{L}$ during at least 14 days with no signs or symptoms of fungal infection (fungal colonization allowed) and with a life expectancy of at least 14 days.

Excluded were patients with proven or suspected deep fungal infection (including cases where mycological sampling was not performed) which was diagnosed during previous episodes of neutropenia, or who presented with chest X-ray suggestive of fungal infection, or with a fever of unknown origin ($> 38.5^\circ\text{C}$ rectal temperature, or $> 38.0^\circ\text{C}$ axillary/oral). Also excluded were patients expected to receive GM-CSF, M-CSF, IL3 or other growth factors except G-CSF which was allowed or who had received systemic antifungal therapy within two weeks before trial entry or topical intra-oral antifungal therapy within one week.

21 patients enrolled were evaluated for efficacy and safety (three patients were entered twice, so there were 18 unique patients). All the patients discontinued study medication before the end of the possible 8 week treatment period; only one patient (5%) discontinued because of an adverse event (increased ALT).

Patients were assessed at inclusion and on a weekly basis through week 8. A final visit was performed at week 12, 4 weeks after the discontinuation of ITR.

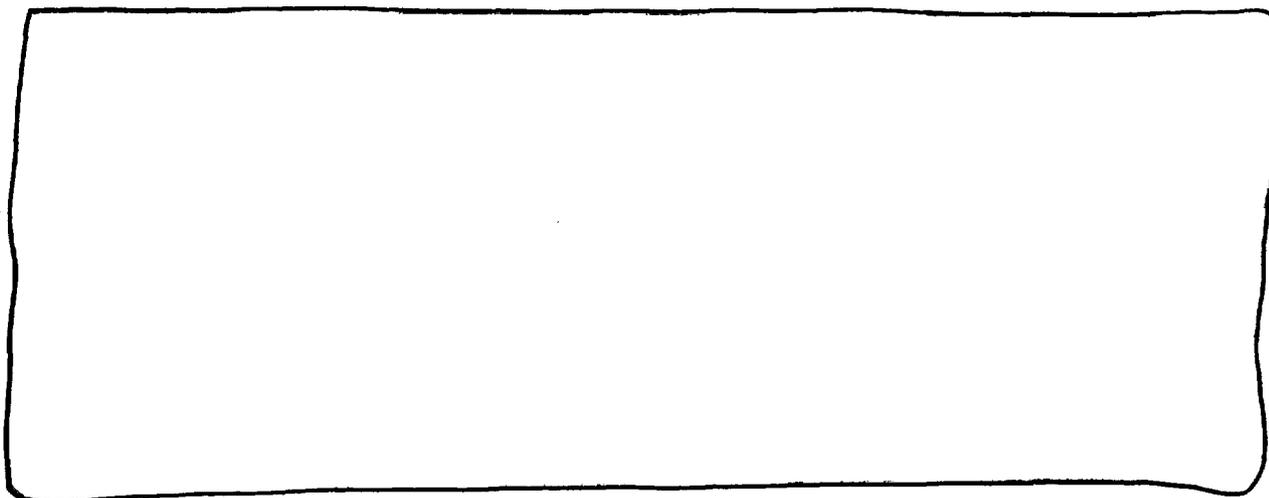


Table B10
Safety as per the applicant

Safety (n = number of patients with data)	Oral Itraconazole (n = 21)
Adverse events (AE) <ul style="list-style-type: none"> • nausea • abdominal pain • diarrhea • ALT increased • vomiting Total number of patients assessed No. (%) with one or more AE No. (%) with one or more severe AE No. (%) with one or more serious AE No. (%) treatment stopped due to AE	15 14 14 12 10 21 21 (100%) 5 (23.8%) 4 (19.0%) 1 (4.8%)
Clinical laboratory parameters	No consistent trend of important changes in laboratory parameters was noted during the study. One patient was withdrawn for a greater than four times increase in SGPT (ALT).

As per the MO:

18 subjects were enrolled, 10 men and 8 women. Three patients were enrolled twice and thus the demographics for the total population were 11 men and 10 women. Underlying diseases included AML (34%), lymphoma (38%), ALL (24%), and CML (5%). The current episode of neutropenia was the first in 67% of patients and 20/21 had no apparent risk factors other than the underlying disease process. The remaining patient had a history of DM. Mean age of the subjects was 41.2 and mean weight was 69.3 kg.

***Medical Officer's Comment:** As in previous studies the dosage of oral ITR used was approximately 350 mg QD, slightly less than that in study 62.*

The mean time on treatment was 17.9 days and the mean time in the trial was comparable at 18.2 days.

All 21 patient/episodes were discontinued before the 8 week endpoint. In 20 a study endpoint was attained and 1 discontinued because of abnormal laboratory values. 12 subjects remained febrile and neutropenic and were started on AMP B. An additional 2 were started on AMP B because of intolerance. 2 had documented fungal infections, 1 because he was moved to an isolation room, and 2 refused ITR. Information was not provided on 1 subject.

All patients were alive at the end of the first post-prophylaxis visit but 2 patients subsequently died, one as a result of lymphoma and 1 from a deep-seated fungal infection.

Patient #1 was a 56 year old male who received itraconazole prophylaxis for 15 days, and died 19 days after he stopped taking the study medication. The physician reported gradual deterioration secondary to lymphoma and indicated in the regular adverse event form that none of the adverse events associated with this patient were drug related.

Two serious adverse event forms were completed for patient #8, a 48 year old male. The first report indicated that the patient had received itraconazole prophylaxis for 20 days. A chest X-ray taken on the second day of study treatment showed a left pleural effusion that regressed four days later. The physician reported a relapse of a left hemorrhagic pleural effusion with severe dyspnea one day after the end of study treatment. The patient received a pleural tap and the adverse event was reported as on-going when the investigator completed the serious adverse event form six days after the end of antifungal prophylaxis. Three days after submitting the first serious adverse event form for this patient, the physician submitted a follow-up serious adverse event form to indicate that a progressive cardiac failure developed and the patient died nine days after the discontinuation of study medication. Again, none of the adverse events reported on the regular adverse event form for this patient were considered to be drug related.

The safety analysis included data from all 21 patient enrollments (18 unique patients with 3 patients enrolled on two separate occasions).

All 21 patients experienced adverse events during the study. There were a total of 403 adverse event reports, of which 299 were reported during the treatment period (on-study), and 284 of these were unique (the last or only event for a patient for a specific preferred term).

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Table B11
Kind and incidence of adverse events by body system

ADVERSE EVENT	Itraconazole N = 21 (100%) Number of patients reporting
GASTRO-INTESTINAL SYSTEM	20 (95.2%)
Diarrhea	14 (67%)
Nausea	15 (71.4%)
Vomiting	10 (47.6%)
Abdominal Pain	14 (66.7%)
Dyspepsia	7 (34%)
Ulcerative Stomatitis	3 (14.3%)
Constipation	3 (14.3%)
Mucositis NOS	1 (4.8%)
Dry Mouth	5 (23.8%)
Gingivitis	1 (4.8%)
Gum Hyperplasia	1 (4.8%)
Hemorrhoids	3 (14.3%)
Abdomen enlarged	1 (4.8%)
Anus disorder	2 (9.5%)
Hiccup	4 (19%)
BODY AS A WHOLE - GENERAL DISORDERS	14 (66.7%)
Rigors	3 (14.3%)
Asthenia	4 (19%)
Fever	2 (9.5%)
Leg Edema	5 (23.8%)
Edema Peripheral	3 (14.3%)
Back Pain	5 (23.8%)
Facial edema	5 (23.8%)
Hot Flushes	3 (14.3%)
Leg Pain	1 (4.8%)
Skeletal Pain	4 (19%)
METABOLIC AND NUTRITIONAL DISORDERS	8 (38.1%)
Hypokalemia	3 (14.3%)
Hyperkalemia	1 (4.8%)
Thirst	1 (4.8%)
Hyponatremia	1 (4.8%)
Hypocholesterolemia	1 (4.8%)
Hyperglycemia	2 (9.5%)
Hypocalcemia	2 (9.5%)

RESPIRATORY SYSTEM DISORDERS	11 (52.4%)
Dyspnea	7 (34%)
Coughing	8 (38.1%)
Pulmonary Edema	2 (9.5%)
Pneumonia	1 (4.8%)
Pulmonary Infiltration	4 (19%)
Rhinitis	1 (4.8%)
Hemoptysis	1 (4.8%)
Pharyngitis	4 (19%)
SKIN AND APPENDAGES DISORDERS	11 (52.4%)
Rash	5 (23.8%)
Rash Erythematous	7 (34%)
Pruritus	4 (19%)
Skin Ulceration	1 (4.8%)
URINARY SYSTEM DISORDERS	4 (19%)
Increased BUN	2 (9.5%)
Hematuria	1 (4.8%)
Dysuria	1 (4.8%)
PSYCHIATRIC DISORDERS	13 (61.9%)
Anxiety	9 (43%)
Nervousness	1 (4.8%)
Insomnia	7 (34%)
Depression	2 (9.5%)
LIVER AND BILIARY SYSTEM DISORDERS	12 (57.1%)
Bilirubinemia	2 (9.5%)
Hepatomegaly	1 (4.8%)
Jaundice	1 (4.8%)
SGPT Increased	12 (57.1%)
SGOT Increased	8 (38.1%)
gGT Increased	3 (14.3%)
CENTR & PERIPH NERVOUS SYSTEM DISORDERS	9 (42.9%)
Headache	8 (38%)
Dizziness	1 (4.8%)
Tremor	1 (4.8%)
Ataxia	1 (4.8%)
Hemiparesis	1 (4.8%)
Hypoaesthesia	3 (14.3%)
Paresthesia	1 (4.8%)
Speech disorder	2 (9.5%)
CARDIOVASCULAR DISORDERS,	9 (44.7%)

GENERAL	
Hypotension	6 (28.6%)
Postural Hypotension	1 (4.8%)
Hypertension	1 (4.8%)
Pericardial Effusion	1 (4.8%)
Cardiomyopathy	1 (4.8%)
PLATELET, BLEEDING & CLOTTING DISORDERS	2 (9.5%)
Epistaxis	1 (4.8%)
Coagulation disorder	1 (4.8%)
Hematoma	1 (4.8%)
Hemorrhage NOS	1 (4.8%)
RESISTANCE MECHANISM DISORDERS	7 (33.3%)
Infection	3 (14.3%)
Sepsis	3 (14.3%)
Herpes Simplex	1 (4.8%)
Fungal Infection	
HEART RATE AND RHYTHM DISORDERS	2 (9.5%)
Tachycardia	1 (4.8%)
Bradycardia	1 (4.8%)
VISION DISORDERS	7 (33.3%)
Conjunctivitis	3 (14.3%)
Abnormal Vision	4 (19%)
Eye Pain	1 (4.8%)
Photophobia	1 (4.8%)
Hearing/Vestibular	1 (4.8%)
Deafness	1 (4.8%)
APPLICATION SITE DISORDERS	2 (9.5%)
Cellulitis	2 (9.5%)
VASCULAR	2 (9.5%)
Ocular Hemorrhage	1 (4.8%)
Vascular disorder	1 (4.8%)
Musculoskeletal	4 (19%)
Skeletal Pain	4 (19%)
No. (%) with any AE	21 (100%)/299 events

Almost all of the patients (95.2%) reported the occurrence of gastrointestinal adverse events while on study medication; the most frequently reported were nausea (71.4%), abdominal pain (66.7%), diarrhea (66.7%), and vomiting (47.6%). Additionally, an increased SGPT (ALT) was reported for 12/21 (57.1%) of the patients.

Twelve (57.1%) of the patients had at least one adverse event during study treatment that was assessed as possibly related to the study drug (31 /299 events or 10.4%).

Table B12
AEs Attributed to Therapy

Adverse event (WHO preferred term)	No. of subjects Itraconazole N = 21
Definitely Drug-related AE	
Total No. (%)	0
Possibly Drug-related AE	
GI System	
Nausea	4
Vomiting	3
Abdominal Pain	4
Dyspepsia/Heartburn	2
Renal and Electrolyte	
Creatinine Increased	1
Abnormal Hepatic Function	
AST Increased	7
ALT Increased	9
Skin	
Pruritus	1
Total No. (%)	31 events

Discontinuation due to an AE:

1 patient (#102(15)) was listed as withdrawing from the trial due to an abnormal laboratory value (adverse event). This event was an increase of ALT to > 4x normal. The investigator determined that this event was possibly related to ITR but the patient was also treated with other hepatotoxic drugs including ranitidine IV, ondansetron, allopurinol, and chemotherapy. There were no clinical signs of hepatitis.

Serious AEs:

5 patient episodes (23.8%) had 10 AEs categorized as severe. 2 patients (4 reports) had evidence of increased ALT and AST. In only one instance was the AE determined to be drug-related. 1 patient reported hemiparesis, 1 reported diarrhea, and 1 had evidence of sepsis, hypotension, pulmonary edema, and cardiomyopathy. None of the latter were determined to be related to ITR.

Laboratory:

There were a total of 40 important laboratory abnormalities, determined by the occurrence of pathological values (values outside the normal range). Eleven of these were improvements from a pathological value at inclusion to a value within the normal range at the termination of the study. Eight of the values were pathological (high/low) at inclusion and remained pathological (remained high/remained low) at termination. Twenty-one values changed from not pathological at inclusion to pathological at