

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**20-966/S-001, S-003, S-004**

**20-657/S-004, S-005**

**MEDICAL REVIEW**

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ON ORIGINAL**

**EXECUTIVE SUMMARY**  
**ITRACONAZOLE SNDA 20-966 (S-004) and SNDA 20-657 (S-005)**

**Background:**

Janssen submitted 2 supplemental new drug applications (SNDA) 20-966 (S-004) and 20-657 (S-005) for the use of the intravenous and oral solution formulations of itraconazole in the empiric therapy of febrile neutropenia. The proposed dose is 200 mg IV BID (2 one-hour infusions) for 2 days, followed by 200 mg IV QD (one one-hour infusion) for 3 – 7 days. Itraconazole IV can be continued up to a total of 14 days. Treatment should be continued with SPORANOX® Oral Solution 200 mg (20 mL) BID until resolution of the clinically significant neutropenia or 28 days. The indication as it appears in the proposed label is as follows:

“SPORANOX® (itraconazole) is also indicated for the empiric therapy of suspected fungal infections in febrile neutropenic patients.”

**Clinical Studies:**

The clinical data in the applicant’s NDA submission were derived from 1 multicenter, open-label, comparative, randomized clinical trial of itraconazole versus amphotericin B in febrile neutropenic patients with hematologic malignancies. There were a total of 60 investigators at 30 centers in Europe, Canada, Australia, and the US. 384 patients were enrolled, 192 per study arm. A determination of success (response) required (a) patient survival with resolution of fever and neutropenia within 28 days of treatment, (b) absence of emergent fungal infections, (c) no discontinuation of therapy due to toxicity or lack of efficacy, and (d) treatment for three or more days.

The primary population assessed by the MO was the ITT, comprised of all randomized patients who met the inclusion/exclusion criteria and who had received at least one dose of study drug. The applicant-derived response rate using an intent-to-treat analysis was 47% in the itraconazole group and 38% in the amphotericin B group and itraconazole was non-inferior to amphotericin B in the overall population.

**Overview of Efficacy**

<b>Efficacy Parameters</b>	<b>ITR N = 179</b>	<b>AMP B N = 181</b>	<b>95% CI (FDA)</b>
<b>Success Rate ITT</b>	84/179 (47%)	68/181 (38%)	- 1.4%, 20%, $\Delta = \pm 15$
<b>Fever Resolution</b>	131/179 (73%)	127/181 (70%)	- 6.8%, 12.9%, $\Delta = \pm 15$
<b>Without EFI</b>	169/179 (94%)	172/181 (95%)	- 5.8%, 4.5%, $\Delta = \pm 15$
<b>Survival</b>	161/179 (90%)	156/181 (86%)	- 3.5%, 11%, $\Delta = \pm 5$
<b>No premature discontinuation due to toxicity</b>	144/179 (80%)	111/181 (61%)	- 9.4%, 28.8%, $\Delta = \pm 15$

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

A larger number of itraconazole subjects (itraconazole 59/179 (33%) versus 32/181 (18%) of the amphotericin B patients) were assessed as failures due to lack of efficacy (including insufficient response, persistent fever, change in therapy due to fever, emergent fungal infections, deterioration of signs and symptoms, or death). However, a larger number of amphotericin B-treated subjects were assessed as failures due to toxicity (12/179 (7%) itraconazole versus 38/181 (21%) amphotericin B).

<b>Outcome</b>		
	<b>ITR N = 179</b>	<b>AMP B N = 181</b>
<b>Success</b>	84 (47%)	68 (38%)
<b>Failure because unevaluable</b>	24 (13%)	43 (24%)
<b>Failure due to intolerance</b>	12 (7%)	37 (20%)
<b>Failure due to lack of efficacy</b>	59 (33%)	32 (18%)

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

<b>Efficacy in the ITT Transplant and Non-Transplant Populations</b>			
<b>Transplant Status</b>	<b>Itraconazole</b>	<b>Amphotericin B</b>	<b>95% CI (<math>\Delta = \pm 15\%</math>)</b>
<b>Success Rate with transplant</b>	29/62 (47%)	28/58 (48%)	- 21%, 18%
<b>Success Rate without transplant</b>	55/117 (47%)	40/123 (33%)	1.4%, 27.6%

If response was assessed by use of previous antifungal prophylaxis (primarily azole derivatives), itraconazole was non-inferior to AMP B in those subjects who had received prophylaxis but NOT in those who had not received it.

#### **Success by Antifungal Prophylaxis ITT Population**

<b>Antifungal Prophylaxis</b>	<b>Itraconazole</b>	<b>Amphotericin B</b>	<b>95% CI (<math>\Delta = \pm 15\%</math>)</b>
<b>YES</b>	63/132 (48%)	48/139 (35%)	- 2%, 25%
<b>NO</b>	21/47 (45%)	20/42 (48%)	- 26%, 20%

The total number of deaths during trial 62 was 19/187 (9.9%) on the itraconazole arm and 25/192 (12.7 %) on the amphotericin B arm. 16 of the itraconazole deaths and 23 of the amphotericin B deaths occurred during the treatment period. In the ITT population as defined by the MO, there were 18 ITR deaths and 25 AMP B deaths. After review of the case report forms the MO concluded that none of the deaths on either study arm were related to study drug. NOTE: Information was provided in the safety update regarding 2 additional deaths post study on the AMP B arm.

A finding of concern was the more prolonged duration of neutropenia observed in the itraconazole-treated subjects as compared to the amphotericin B subjects. Specifically 48 (29%) of the ITR subjects had neutropenia for > 14 days as compared to 28 (17%) of the AMP B subjects despite baseline comparability between the treatment groups for this factor. The significance of this finding is unknown.

Additional analyses by Dr. Shen to assess the strength of the data including evaluation of success and response rates based on patient populations, site, and underlying diagnosis, aided in the confirmation that the data submitted appeared to be robust, and supported the applicant's claim of efficacy for itraconazole for the requested indication.

Microbiologic data was not submitted with these supplements. 10 subjects on the ITR arm and 9 on the AMP B arm developed emergent fungal infections primarily due to *Candida* or *Aspergillus* spp.

**EFIs  
As per the MO**

Body Site	ITR N = 179	AMP B N = 181
<b>Blood</b>	2	2
<b>Lung</b>	2	4
<b>Venous Catheter</b>	1	-
<b>Unknown (pending)</b>	5	3
<b>Total</b>	10 (6%)	9 (5%)

#### Safety:

The applicant submitted an ISS primarily consisting of an ITR IV to PO safety database of 318 subjects (group 1), 192 from trial 62 and 126 from previously reviewed PK trials. The subjects from trial 62 were diagnosed with hematologic malignancies and were febrile and neutropenic at the time of enrollment. The PK study subjects were immunocompromised for a variety of reasons including invasive aspergillosis, AIDS, and ICU care. In all group 1 studies, subjects received the proposed for the indication of empiric therapy of febrile neutropenia regimen.

The applicant also submitted data from 868 subjects treated with oral solution alone. Although these subjects had similar underlying conditions as those in group 1 (hematologic malignancies with resultant neutropenia), the MO elected not to include

these subjects in the ISS and recommendations because of variability in dosing and duration of treatment regimens between the trials and their lack of comparability to the proposed IV to PO ITR regimen. Additionally, the MO found numerous discrepancies in the applicant's analyses of this group including omissions of whole studies in calculations of serious adverse events or deaths. The MO determined that the group 1 database of 318 subjects was adequate in order to update the labels of both the IV and oral solution for the proposed indication.

AEs were reported from 90% itraconazole patients and 94% amphotericin B patients. AEs on both arms were primarily from the GI tract or the body-as-a-whole.

The most remarkable differences between the two groups were noted for rigors in 10% itraconazole subjects versus 40% amphotericin B subjects ( $p= 0.001$ ) and for metabolic and nutritional disorders in general in 36% itraconazole versus 61% amphotericin B recipients ( $p = 0,001$ ). Additionally creatinine was increased in 4% itraconazole versus 26% amphotericin B subjects ( $p= 0.001$ ).

The investigators considered one or more adverse events to be definitely drug-related in 5% of itraconazole subjects and 54% of amphotericin B subjects ( $p = 0.001$ ) and possibly related in 43% of itraconazole subjects versus 55% of amphotericin B subjects. GI events including nausea, vomiting, and diarrhea were the most frequent events possibly related to therapy on both study arms. Additionally, hypokalemia was found in 8.8% of itraconazole subjects versus 15.1% of amphotericin B subjects. Other events possibly associated with treatment on the amphotericin B arm included rigors, increased creatinine, and abnormal renal function. On the itraconazole arm, bilirubinemia was seen in 5.7% of patients as compared to 2.6% on the amphotericin B arm. Additionally, there were more reports of transaminase elevations, hepatitis, hepatomegaly, and cholestatic hepatitis on the itraconazole arm.

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

### **Special Populations:**

#### **Efficacy:**

There were no differences observed in the efficacy rates between the treatment groups with respect to gender, age, or ethnic group.

#### **Safety:**

There were no differences observed in the incidence of adverse events or laboratory abnormalities with respect to race or gender. More adverse events were observed in

subjects 65 years of age or greater on both study arms. There was a statistically significant difference in the incidence of hypokalemia, renal function abnormalities, hyperglycemia, and fluid overload between the age groups on the itraconazole arm. This difference did not exist in the AMP B treated patients. It should be noted however, that the denominator in this analysis was too small to allow for valid conclusions.

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

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

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

**Recommendations:**

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

The medical officer recommendation for the itraconazole intravenous and oral solution formulation regarding the indication of empiric therapy of febrile neutropenia is:

**Approval** for the indication of empiric therapy of febrile neutropenia in febrile neutropenic patients with suspected fungal infections.

Due to concerns regarding the large differences between the treatment arms regarding reasons for discontinuation or failure the MO recommends revision of the **Indications and Usage** section of the labeling as well as the **Clinical Studies** section submitted by the applicant to reflect these concerns.

**APPEARS THIS WAY  
ON ORIGINAL**

**Medical Officer's Review of SNDAs 20 - 966 (S-004) and 20-657 (S-005)  
Empiric Therapy of Febrile Neutropenia**

**1.1 SNDA 20-966 (S-004):** Itraconazole Injection 200 mg/vial  
**SNDA 20-657 (S-005):** Itraconazole 10 mg/mL solution

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

**1.3 Submission Review Dates:** Date of Submissions: April 28, 2000  
CDER Stamp Dates: May 1, 2000  
Date Received by MO: May 28, 2000  
Date Review Begun: June 1, 2000  
Date Review Completed: February 1, 2001

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

**1.5 Pharmacologic Category:** Antifungal

**1.6 Dosage Form:** Injection and oral solution

**1.7 Route of Administration:** Intravenous and per os

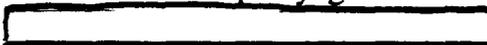
**1.8 Strengths:** 10 mg/mL

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

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

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

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



**1.13 List of Currently Approved Indications:** SPORANOX® (itraconazole) Injection is indicated for the treatment of the following fungal infections in immunocompromised and non-immunocompromised patients:

1. Blastomycosis, pulmonary and extrapulmonary;
2. Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis; and
3. Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to Amphotericin B therapy.

Additionally the oral solution is currently approved for the treatment of oropharyngeal candidiasis.

***Medical Officer's Comment:*** Imperative in the support of an empiric therapy indication is that the applicant provide evidence of antifungal activity of the compound under study in documented infections. Itraconazole has demonstrated antifungal activity in the treatment of histoplasmosis and blastomycosis and received an approval as first-line therapy for those indications. Additionally, itraconazole is approved as second-line therapy in patients with aspergillosis. It is widely understood that aspergillosis is more common in febrile neutropenia as opposed to histoplasmosis and blastomycosis. The approval for the aspergillosis indication was received in 1994 after review of NDA 20-083 (S-004). The applicant's submission consisted of 3 open-label, non-concurrent control studies of approximately 250 patients with pulmonary or disseminated aspergillosis who were intolerant or failing conventional amphotericin B therapy. Efficacy ranged from 41- 50%. The reviewing MO recommended approval as second line therapy due to the absence of a controlled pivotal trial.

**1.14 Abbreviations used in this document:**

IIR = Itraconazole  
FLU = Fluconazole  
AMP B = Amphotericin B  
AE = Adverse Event  
ETFN = Empiric Therapy of Febrile Neutropenia

**1.15 Materials Reviewed:** SNDA 20-966 (S-004) vols. 1 - 55, electronic case report tabulations, multiple submissions submitted to [REDACTED] from 9/15/99 – 2/15/00, electronic search tool, submitted 3/15/00.

***The original study report as well as data listings for study 62, the pivotal study for the ETFN indication, were submitted to the IND in 9/99. Additionally, over a 6 month***

*period the remaining study reports and data listings for the safety database were submitted for review. Subsequently and prior to the submission of the SNDAs, investigator fraud was discovered on the part of a S. African investigator, (Dr. W. Bezwoda). The applicant re-performed all of the efficacy analyses after excluding the subjects enrolled by this investigator (N = 10, 5 ITR and 5 AMP B). The safety database remained unchanged.*

**MO Comment:** *Where the MO copied portions of the applicant's text, the font Arial 12 was utilized.*

**1.16 Regulatory Background as it pertains to the indication of ETFN and to the choice of the comparator:** Empiric antifungal therapy with amphotericin B, in the presence of continued fever after 3 –5 days of antimicrobial therapy was the clinical standard of care at the time this study was initiated. Amphotericin B is not specifically approved for this indication however; it was generally accepted as an appropriate active control arm for the study of an empiric therapy indication. Subsequently Ambisome® received the indication of empiric therapy of febrile neutropenia.

In 1994 and 1995, 2 public meetings were held to discuss the issue of study design for a number of antifungal liposomal amphotericin B preparations that were seeking the ETFN indication. There was consensus at both meetings that amphotericin B is an adequate comparator and that an equivalence study design should be used. For the indication, the 1995 committee endorsed the FDA proposition that in order to attain an approval a submission should consist of at least 1 treatment study of any fungal indication that can demonstrate efficacy plus at least one adequate well-controlled empiric trial.

The issue of trial design for the ETFN indication was extensively discussed at an open workshop conducted by the FDA on 4/20/1994 (Clinical Trial Design Issues of Liposomal Antifungal Agents). This workshop dealt with the issue of the need for as well as the design of trials for antifungal agents for the ETFN indication. Main points were that:

- A study must assure that reduced toxicity is not the result of giving less drug.
- A high level of certainty is important since resolution of fever, rather than proven infection is used as a determinate of sample size. Thus in order to demonstrate equivalence a sample size sufficiently large to detect response differences of 10% between arms is necessary.

The issue of sample size and predictive study design was again discussed at an FDA AC on 4/3/1995 (Clinical Trial Design and Regulatory Issues with Liposomal Antifungal Agents). The study groups agreed to the following study design for the evaluation of the ETFN indication: An equivalency trial with power to detect differences and response rates of 10% between study groups or 660 evaluable patients, 330 per arm. It was considered imperative that a study have the power:

- to predict differences in proven fungal infections documented histologically or by culture,
- to detect differences in mortality due to fungal infections,
- to detect differences in fever within a 10% CI, and
- to detect differences in safety.

1997 (4/14) FDA AC: Overview of empiric antifungal therapy in FN by Dr. Alan Sugar: “Empiric or presumptive therapy is given to patients because some will actually need it. However, others will not, that is they are treated unnecessarily. At issue is the diagnosis of invasive of fungal infection and the difficulties associated with it. The window of opportunity to start ET is small, 3 –5 days. Also at issue is the degree of neutropenia. What level places the patient at higher risk? Overall consensus is that patients with an ANC < 100 are at highest risk. The duration of the neutropenia also contributes to risk”.

“*Candida* spp. and *Aspergillus* spp. are the main fungal pathogens however, *Fusarium* spp. and *Trichosporon* spp. are increasing in significance”.

“Ideally an antifungal approved for this indication should be efficacious against most commonly encountered fungi; it should have low toxicity, good PK, low cost, and few interactions”.

“Amphotericin B has been in use since the 1950s and remains the gold standard of antifungal therapy. It has a broad spectrum but also a formidable list of toxicities including systemic reactions and nephrotoxicity”.

**CONCLUSIONS of 1997 AC:** Continued endorsement of the aforementioned trial design and of the composite endpoint made up of defervescence, sustained survival, and EFI rate.

### **1.17 Antifungal agents with the indication of empiric therapy of febrile neutropenia:**

**Ambisome®:** Ambisome® was studied in 3 randomized, controlled trials comparing the efficacy and safety of Ambisome® to amphotericin B in empiric therapy. 2 studies were conducted in Europe and were not blinded; however, the largest study was conducted in the US and was double-blinded. This larger study (94-0-002) was viewed as pivotal and evaluated the efficacy of Ambisome® (1.5-6.0 mg/kg/day) compared with Amphotericin B (0.3-1.2 mg/kg/day) in the empirical treatment of 687 adult and pediatric neutropenic patients who were febrile despite having received at least 96 hours of broad spectrum antibacterial therapy.

The US study 94-0-002 was considered by the 1997 Antiviral AC as the best study of empirical therapy completed to date. Strengths included double-blind administration of treatment, clear and precise definitions for fungal infection, clear protocols for timing and measurement of fever, and adequate sample size for the composite endpoint. Success was defined as survival 7 days after discontinuation of fever, fever resolution, baseline infection cured, no new fungal infection, and no severe toxicity. Delta utilized was  $\pm 10$ .

The overall therapeutic success rates for Ambisome® and amphotericin B were equivalent. Results are summarized in the following tables from the Ambisome® label. Note: The categories presented below are not mutually exclusive.

**Table 1**  
**Empirical Therapy in Febrile Neutropenic Patients:**  
**Randomized, Double-Blind Study in 687 Patients**

	<b>Ambisome®</b>	<b>Amphotericin B</b>
Number of Patients receiving at least one dose of study drug	343	344
Overall Success	171 (49.9%)	169 (49.1%)
Fever resolution during neutropenic period	199 (58.0%)	200 (58.1%)
No treatment emergent fungal infection	300 (87.5%)	301 (87.7%)
Survival through 7 days post study drug	318 (92.7%)	308 (89.5%)
Study drug not prematurely discontinued due to toxicity or lack of efficacy	294 (85.7%)	280 (81.4%)
* 8 and 10 patients, respectively, were treated as failures due to premature discontinuation alone.		

This therapeutic equivalence had no apparent relationship to the use of pre-study antifungal prophylaxis or concomitant granulocytic colony stimulating factors. The incidence of mycologically confirmed and clinically diagnosed, emergent fungal infections are presented in the following table. Ambisome® and amphotericin B were found to be equivalent with respect to the total number of emergent fungal infections.

**Table 2**  
**Empirical Therapy in Febrile Neutropenic Patients:**  
**Emergent Fungal Infections**

	<b>Ambisome®</b>	<b>Amphotericin B</b>
Number of Patients receiving at least one dose of study drug	343	344
Mycologically confirmed fungal infection	11 (3.2%)	27 (7.8%)
Clinically diagnosed fungal infection	32 (9.3%)	16 (4.7%)
Total emergent fungal infections	43 (12.5%)	43 (12.5%)

Mycologically confirmed fungal infections at study entry were cured in 8 of 11 patients in the Ambisome® group and 7 of 10 in the amphotericin B group.

Two supportive prospective randomized, open label, comparative multi-center studies examined the efficacy of two dosages of Ambisome® (1 and 3 mg/kg/day) compared to amphotericin B (1 mg/kg/day) in the treatment of neutropenic patients with presumed fungal infections. These patients were undergoing chemotherapy as part of a bone marrow transplant or had hematological disease. Study 104-10 enrolled adult patients

(n=134). Study 104-14 enrolled pediatric patients (n=214). Both studies supported the efficacy equivalence of Ambisome® and amphotericin B as empirical therapy in febrile neutropenic patients.

***Medical Officer's Comment:*** *Of note in the Ambisome® application was the utilization of a  $\Delta$  of  $\pm 10\%$  as compared to the under review SNDAs where a  $\Delta$  of  $\pm 15\%$  was specified in the original protocol. Extensive research by the MO into all communications between the applicant and the FDA at the time of the protocol submission revealed no comments about this issue.*

### **1.18 Antifungal agents not receiving an approval for the empiric therapy indication:**

**Amphotec®:** Presented to the AC in 1997. At the time of the submission, Amphotec® was approved as a second line agent in the treatment of aspergillosis. The basis for the original approval consisted of the submission of 80 patients from 5 non-comparative studies. 1 study, 7-26 was submitted as a supplement in support of the ETFN indication. This study was a double blind, randomized pilot study with a total enrollment of 213. Issues discussed in the AC meeting and that ultimately led to a non-approval were those of study design. Specifically the study was designed to compare the nephrotoxicity of Amphotec® versus amphotericin B and the sample size was powered to detect a decrease of 35% in renal toxicity in the Amphotec® group assuming that 50% was the rate in the amphotericin B group. The original goal was 60 evaluable patients per arm. Efficacy endpoints were not included in the sample size calculation and only 1 endpoint defervescence was included in the original protocol as a secondary objective. 80% of patients both arms had received fluconazole prophylaxis. This led to a decrease in the number of patients enrolled who actually required antifungal therapy. Other issues included the lack of uniformity in the diagnostic workup leading to the diagnosis of fungal infections. A composite endpoint was utilized however it was defined retrospectively and included survival, defervescence, and lack of toxicity. Ultimately the application was turned down and concurrence was obtained from the AC because of poor study design, retrospective assessment of endpoints, and toxicity issues.

### **1.19 Regulatory Background as it pertains to the current submission:**

Itraconazole is available in 3 formulations; the intravenous formulation of itraconazole where a cyclodextrin solubilizing agent is utilized was approved in 4/99, the oral solution approved in 3/96, and the capsules approved in 9/92. These formulations do not share common indications and the applicant's overall intent is to minimize this discrepancy and to add the indication of empiric therapy in febrile neutropenia to the indications of the solution and the intravenous formulations. In order to achieve this, the applicant submitted the currently under review SNDAs 20-966 (S-004) and 20-657 (S-005) filed to the oral solution NDA 20-657 as a labeling supplement to provide similar labeling changes to those provided for the IV to PO formulations.

This submission contains efficacy data from a single open-label, comparative trial of itraconazole IV/oral solution compared to IV amphotericin B for the empiric therapy of febrile neutropenic patients (ITR-INT-62).

The safety database is comprised of safety data from ITR-INT-62, ITR-INT-60, 4 pharmacokinetic trials, and 5 prophylaxis studies. These studies provide a database of 318 subjects who received the IV formulation and 1186 subjects who received the oral solution.

The safety data from trials ITR-INT-62, ITR-INT-60, and the 4 IV PK trials evaluated the safety of itraconazole primarily during the IV phase. This data was reviewed in full by the MO for NDA 20-966 and can be found in the MOR of that NDA as well as in the MORs of the 4 and 8 month safety updates.

The safety data from the oral solution periods of the aforementioned studies with the safety from the 5 prophylaxis studies that were performed with the oral solution evaluated the safety of that itraconazole formulation.

Additionally in the ISS are post-marketing experience data with the oral solution and serious AEs from the ongoing clinical studies through 7/31/99.

Despite the 4/99 approval, the injectable formulation was only recently distributed in the US and internationally.

The trials included in the safety database are listed below:

- 1 completed international open-label, active-controlled trial:
  - ITR-INT-62: A randomized, comparative, multicenter trial of itraconazole injection followed by itraconazole oral solution versus intravenous amphotericin B for the treatment of febrile neutropenic patients with hematologic malignancy.
- One completed international open-label uncontrolled trial:
  - ITR-INT-60: An efficacy and safety trial of itraconazole injection followed by oral itraconazole capsules in the treatment of hematologic, transplantation, acquired immunodeficiency syndrome, and chronic granulomatous disease patients with invasive pulmonary or disseminated aspergillosis.
- Two completed US open-label pharmacokinetic trials:
  - ITR-USA-113: A pharmacokinetic trial of itraconazole injection followed by oral itraconazole capsules in patients with advanced human immunodeficiency virus infection.

- ITR-USA-127: A pharmacokinetic trial of itraconazole injection followed by oral itraconazole solution in patients with advanced human immunodeficiency virus infection.
  - Two completed international open-label pharmacokinetic trials:
- ITR-INT-58: A pharmacokinetic trial of itraconazole injection followed by oral itraconazole solution in intensive care unit patients.
- INT-INT-59: A pharmacokinetic trial of itraconazole injection followed by oral itraconazole solution in patients with hematologic malignancy.
- 5 completed international prophylaxis trials:
  - ITR-BEL-4: 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 nystatin.
  - ITR-INT-18: Antifungal prophylaxis in hematologic malignancy with profound neutropenia: a double blind trial to compare itraconazole oral solution with placebo.
  - ITR-INT-54: A double blind trial comparing itraconazole oral solution with oral amphotericin B capsules for primary prophylaxis of fungal infections in subjects with hematological malignancy and profound neutropenia.
  - ITR-GBR-17: A randomized study to compare itraconazole oral solution with fluconazole suspension as antifungal prophylaxis for patients undergoing treatment for hematological malignancy.
  - ITR-CAN-15: The assessment of itraconazole oral solution (5 mg/kg total daily) as primary prophylaxis in patients with hematological malignancy and profound neutropenia.

Itraconazole was administered intravenously for at least 1 week in all of the IV to PO trials. The dosing regimen was the same, 200 mg BID for 2 days followed by 200 mg QD but the total duration (7 – 14 days) varied from trial to trial.

***Medical Officer's Comment:*** *The MO elected to briefly present the previously reviewed safety data from the PK trials and the already reviewed data from study 62 separately and then in the ISS. The MOR of safety data from the oral prophylaxis trials can be found in Appendix 2 to this document. The MO elected not to include the safety data from these trials in the ISS because of the incompatibility of the treatment regimens to that pertinent to the indication of ETFN and because of the variability of the regimens in those trials.*

<p align="center"><b>Table 3</b>  <b>SNDA 20-966 :Itraconazole injection and oral solution</b>  <b>Summary of clinical safety experience submitted with SNDA</b></p>						
	<b>Study number</b>	<b>Study population</b>	<b>Itraconazole Dosing*</b>	<b>Comparator</b>	<b>Itraconazole 200 mg IV recipients</b>	<b>Itraconazole Oral solution Recipients</b>
<b>Pharmacokinetic trials</b>	USA 113	HIV	14d IV	Non-comparative	30	-
	USA 127	HIV	14d IV	Non-comparative	32	-
	INT 58	ICU	14d IV	Non-comparative	16	-
	INT 59	Hematologic Malignancy	14d IV	Non-comparative	17	-
<b>Clinical Efficacy trials</b>	INT 60	Pulmonary & Disseminated Aspergillosis	14d IV → PO caps	Non-comparative	31	-
	INT 62	Febrile Neutropenia	14d IV → PO susp	Amphotericin B IV → PO Fluconazole	192	-
<b>Prophylaxis Trials</b>	BEL 4	Neutropenia	PO solution	Amphotericin B PO and PO nystatin	0	144
	ITA 18	Hematologic Malignancy/ Febrile Neutropenia	PO Solution	Placebo	0	201
	INT 54	Hematologic Malignancy	PO Solution	Amphotericin B capsules	0	281
	GBR 17	Hematologic Malignancy	PO Solution	PO Fluconazole	0	288
	CAN 15	Hematologic Malignancy/ Febrile Neutropenia	PO Solution	Non-comparative	0	21

\*200 mg IV BID x 2 days followed by 200 mg IV QD until the end of IV therapy  
 200 mg PO BID for 7 – 21 days

**Medical Officer's Comment:** *At the request of the reviewer, the applicant submitted minutes from 3 teleconferences held between Janssen and the FDA to discuss the content of the submission. The initial contact was in 8/95. Janssen received verbal approval as to the extent of the safety database (150 – 200 patients) from the FDA and was informed that a single study would probably be enough to support an indication of ETFN or*

prophylaxis in a febrile neutropenic population. This comment was reconfirmed in a teleconference on 2/27/96 with the qualifier that such a study would have to be statistically sound to support a claim.

**1.20 Microbiology:** No new information has been submitted. Briefly, itraconazole is an antifungal agent that inhibits the P-450-dependent synthesis of ergosterol, a component of fungal cell membranes. This agent exhibits *in vivo* activity against *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Histoplasma dudosii*, *Aspergillus flavus*, *Aspergillus fumigatus*, *Candida albicans*, and *Cryptococcus neoformans*. *In vitro* activity has been exhibited versus a number of other fungi however; correlation between *in vitro* activity and clinical outcome has not been shown.

**1.21 Human Pharmacokinetics:** Subsequent to administration, itraconazole is hepatically metabolized to the bioactive metabolite hydroxyitraconazole. The activity of this metabolite versus *Histoplasma capsulatum* and *Blastomyces dermatitidis* has not been evaluated.

PK studies were performed for the injectable formulation at a dose of 200 mg IV BID for 2 days and then 200 mg IV QD for 5 days. This regimen was followed by 200 mg PO for an unspecified period. These PK studies were performed in patients with advanced HIV infection (USA 113 and USA 127). Steady state plasma concentrations were reached on day 3 for itraconazole and day 6 for [redacted] PK parameters for itraconazole and hydroxyitraconazole are presented in below:

**Table 4**  
**PK Parameters (as per the applicant)**

Parameter	Injection 200 mg BID x 2 days → 200 QD Day 7 N = 29	Capsule 200 mg BID Day 36 N = 12
	Itraconazole	Itraconazole
<b>C max (ng/mL)</b>	2856 ± 866	2010 ± 1420
<b>T max (hr)</b>	1.08 ± 0.14	3.92 ± 1.83
<b>AUC 0 – 12 (ng-h/mL)</b>	-	18768 ± 13933
<b>AUC 0 – 24 (ng-h/mL)</b>	30605 ± 8961	-

As per the applicant "most patients had nondetectable plasma concentrations of [redacted] by 24 hours after IV administration. Approximately 93 – 101% of the [redacted] was excreted unchanged in the urine within 12 hours after dosing."

"The elimination half-life was not established in the previous study. Based on previous data, the mean elimination half-life for itraconazole at steady state after oral administration of 100 – 400 mg was 30 – 40 hours. Plasma protein binding

is 99.8% for itraconazole and 99.5% for the biometabolite. The volume of distribution averaged  $796 \pm 185$  L.”

“3 – 18% of the dose is excreted via the fecal route and less than 0.03% of the parent compound is found in the urine. 80 – 90% of the [redacted] [redacted] is eliminated via the kidneys.”

“In patients with mild to moderate renal insufficiency, the itraconazole plasma concentrations are similar to those obtained in healthy subjects. The same is true for patients receiving hemodialysis. Additionally, the majority of the cyclodextrin is eliminated within 120 hours in the above patient groups. In subjects however with severe renal impairment, the clearance of the cyclodextrin is reduced six-fold and therefore the injectable formulation of itraconazole is not indicated for patients with a Creatinine clearance less than 30 mL/min”.

“The effect of hepatic insufficiency on plasma concentrations of itraconazole is unknown and therefore patients need to be monitored carefully.”

**Potential Safety Issues:** Based on the known metabolism of the oral formulations of itraconazole (that is the CYP3A4-mediated route) and the well-established safety profile of the oral formulations, it is expected that the predominant number of AEs would be from the GI tract (nausea, vomiting, and diarrhea), as well as the liver (LFT elevations). Additionally, rash, hypokalemia, and edema are amongst the more serious AEs encountered with the capsule. These events are usually reversible upon discontinuation. It has been well established, that the metabolism of other CYP3A4 dependent drugs such as midazolam, astemizole, cisapride, nifedipine, [redacted] triazolam, diazepam, and vincristine can be inhibited by therapeutic concentrations of itraconazole and its metabolites, thereby leading to elevated plasma concentrations and exaggerated pharmacological effects of the affected agents.

A difference that exists for the injectable form of itraconazole (as opposed to the capsule) is the use of a cyclodextrin-solubilizing agent. This oligosaccharide is able to form inclusion complexes with different compounds and therefore is used as a host molecule for parenteral, oral, and local delivery of poorly soluble or unstable drugs. Once administered intravenously, this molecule is distributed in the extracellular fluids, and mainly eliminated via the kidney. Because excretion is primarily renal, there existed in the pre-clinical and early phases of human drug development, concerns with regard to the use of this agent in patients with pre-existing renal dysfunction. PK studies in the severely renally impaired population revealed that there was a 6-fold decrease in clearance and a 6-fold increase in half-life. Therefore it is recommended that this formulation not be used in this group of patients. Other issues that are significant relative to the long-term use of the cyclodextrin molecule are its carcinogenic effects. This issue is not applicable to the current NDA given the short duration of therapy requested.

**Efficacy:****Study ITR-INT-62:**

**Title:** An open, randomized trial comparing the efficacy and safety of intravenous followed by oral itraconazole with intravenous amphotericin B for empirical therapy in neutropenic subjects with hematological malignancy.

***Medical Officer's Comment:*** The ITR-INT-62 clinical research report was amended from that originally reviewed and submitted to [redacted] on September 10, 1999, to exclude 10 subjects (5 receiving itraconazole; 5 receiving amphotericin B). These subjects were enrolled in a study site in South Africa. The investigator (Dr. W. Bezwoda) admitted to clinical misconduct in a non-Janssen clinical trial. Therefore, the efficacy data were reanalyzed and these subjects censured. The revised results are bolded in this document.

**Countries:** Australia, Austria, Belgium, Canada, France, Germany, Great Britain, The Netherlands, South Africa, and USA.

**Study Dates:** March 22, 1996 – December 4, 1997

**Study Objectives:**

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

**Investigator List and Study Sites and number of subjects randomized**

Country	Main Investigator	Site Location	Specialty	ITR	AMP B	ALL
<b>Australia</b>	Arthur	St. Leonards	Hematologist	2	2	4
	Schwarer	Melbourne, Victoria	Hematologist	10	10	20
<b>Austria</b>	Lechner	Wien	Hematologist	1	1	2
	Linkesch	Grax	Hematologist	1	1	2
	Waldner	Wien	Internist	3	2	5
<b>Belgium</b>	Boogaerts	Leuven	Hematologist	6	5	11
	Bosly	Yvoir	Hematologist	3	3	6
	Crokaert	Brussel	Immunologist	2	2	4
	Michaux	Brussel	Internist	-	2	2
	Noens	Gent	Internist	1	1	2
	Schroyens	Edegem	Hematologist	2	4	6

	Van Hoof	Brugge	Hematologist	1	-	1
<b>Canada</b>	Bow	Winnipeg	Hematologist	9	8	17
	Fong	Toronto	Infectious Disease	-	2	2
	Garber	Ottawa	Immunologist	14	13	27
	Keating	Toronto	Hematologist	4	4	8
	LaVerdiere	Montreal	Infectious Disease	4	5	9
	McGeer	Toronto	Immunologist	7	6	13
	Nantel	Vancouver	Hematologist	2	1	3
	Rotstein	Hamilton	Immunologist	1	5	6
	Schlech	Halifax	Immunologist	6	5	11
	Smaill	Hamilton	Immunologist	2	1	3
<b>France</b>	Casassus	Bobigny	Hematologist	-	2	2
	Fenau	Lille	Hematologist	4	2	6
	Francois	Angers	Hematologist	2	-	2
	Herbrecht	Strasbourg	Hematologist	3	2	5
	Ifrac	Angers	Hematologist	1	-	1
	Le Prise	Rennes	Hematologist	2	1	3
	Mounier	Saint-Priest en Jarez	Hematologist	1	-	1
	Nedellec	Clamart	Hematologist	2	2	4
	Oriol	Saint-Priest en Jarez	Hematologist	-	2	2
	Rieux	Creteil	Hematologist	1	-	1
	Stamatoullas	Rouen	Hematologist	6	7	13
	Vernant	Creteil	Hematologist	1	1	2
	Witz	Vandoeuvre les Nancy	Hematologist	5	5	10
<b>Germany</b>	Boehme	Frankfurt	Hematologist	2	4	6
	Goldschmidt	Heidelberg	Hematologist	1	2	3
	Pfreunds Schuh	Homburg/Saar	Internist	2	2	4
	Schuler	Dresden	Internist	4	6	10
<b>Great Britain</b>	Blundell	Cheltenham	Hematologist	1	1	2
	Milligan	Birmingham	Hematologist	3	2	5
	Morgenstern	Manchester	Hematologist	2	1	3
	Pagluica	London	Hematologist	1	1	2
	Prentice	London	Hematologist	3	1	4
	Rule	Taunton	Hematologist	2	3	5
	Schey	London	Hematologist	2	4	6
<b>Netherlands</b>	Daenen	Groningen	Internist	1	1	2
	Dekker	Utrecht	Internist	2	3	5
	Kramer	Amersfoort	Internist	1	2	3
	Van Marwijk Kooy	Zwolle	Hematologist	-	1	1
<b>S. Africa</b>	Bezwoda*	Johannesburg	Oncologist	5	5	10
	Novitzky	Cape Town	Internist	5	5	10
<b>USA</b>	Anaissie	Little Rock	Hematologist	1	1	2
	Arnow	Chicago	Immunologist	1	3	4
	Blumer	Cleveland	Immunologist	5	6	11

	Martin	Portland	Infectious Disease	-	1	1
	Reboli	Camden	Infectious Disease	11	10	21
	Territo	Los Angeles	Hematologist	1	-	1
	Wingard	Gainesville	Hematologist	1	1	2
	Winston	Los Angeles	Infectious Disease	12	21	43

**\*In this amendment to the clinical research report, the subject and efficacy analyses have been reanalyzed excluding the data from Dr. Bezwoda's 10 subjects.**

### **Trial Design:**

This was an open, randomized, parallel group trial conducted by 60 investigators at 30 centers in Europe, Canada, Australia, and the US. Balancing was performed at each center in order to ensure that each treatment group was allocated an equal number of subjects. Randomization was performed centrally for each center by a CRO and subjects were stratified for the presence of signs and symptoms potentially attributable to deep fungal infection and for the underlying therapy (marrow transplant including peripheral stem cell infusion or chemotherapy only).

***Medical Officer's Comment:*** *As per the applicant given the toxicity profile of amphotericin B, it was impossible to perform a blinded trial. It should be noted that the open nature of the trial could have affected investigator decisions with regards to patient management, AE reporting, and outcome assessment. The overall distribution of patients was relatively equal between countries.*

### **Protocol Amendments:**

#### **Protocol amendment 1: 10/4/95 (before the start of the trial)**

- Modification of stratification factors to prestratify patients for the presence of signs and symptoms potentially attributable to deep fungal infection and for the underlying therapy (marrow transplant including peripheral stem cell infusion or chemotherapy only).
- Modification of inclusion criterion 2 to include only patients with hematologic malignancies treated by myelosuppressive therapy and/or hematopoietic stem cell support (except allogeneic bone marrow transplant).
- Modification of inclusion criterion 3 was changed from 'neutrophil count <1000/mm<sup>3</sup> (or <1.0 x 10<sup>9</sup>/l)' into 'neutrophil count <500/mm<sup>3</sup> (or < 0.5 x 10<sup>9</sup>/l) expected to last for at least 7 days.
- Modification of inclusion criterion 4 to include subjects with fever plus signs and symptoms potentially attributable to deep fungal infection (subjects had fever (>38°C\* and not considered related to blood products transfusion or drug fever) that is not responding to a total of 3 to 7 days of broad spectrum Gram positive plus Gram negative antibiotic therapy with or without signs and symptoms potentially

attributable to deep fungal infection. \*38°C = 38°C orally or rectally or 38.5 °C axillary).

***Medical Officer's Comment:*** *The applicant sought to ensure that only patients who were moderately to severely ill were enrolled. Febrile neutropenic patients with the highest morbidity and mortality are those with an ANC of < 100/mm<sup>3</sup>.*

- Modification of exclusion criterion 3 to allow for the use of oral itraconazole or fluconazole in the pre-study period as an investigational agent.

***Medical Officer's Comment:*** *The allowance of oral azoles in the pre-study period introduced the potential of an absence of true need for IV antifungal therapy or the potential for the development of resistance.*

- Modification of exclusion criterion 4 to exclude patients with a known fungal infection during previous neutropenic episodes.
  - Modification of exclusion criterion 7 to the exclude HIV-positive subjects and subjects with aplastic anemia, myelodysplastic syndrome, and allogeneic transplants
  - Modification of exclusion criterion 12 to exclude subjects with previous hypersensitivity to azole antifungals.
  - Modification of the duration of therapy to allow for continuation until the end of neutropenia defined by one neutrophil count higher than  $0.5 \times 10^9/l$  or up to a maximum of 2 days with a neutrophil count  $>1.0 \times 10^9/l$ .
  - Modifications were also made to the manner of study drug administration: Specifically, the duration of amphotericin B infusion was restricted to between 4 and 6 hours, the use in Intrapid™ together with amphotericin B was not allowed and hydrocortisone with a maximum of 50 mg per day was only allowed in case of amphotericin B-related adverse events.
  - Possible interactions between itraconazole and vincristine were added.
  - Modifications were made to the criteria to define response where response was defined as not having failed or not being unevaluable. Subjects who had received 10 days of study medication and remained afebrile for 3 consecutive days were included in the 'response' category and additionally after 7 days of therapy, the presence or absence of fever  $> 38^\circ\text{C}$  was scored and evaluated as a criterion of early response
- Failure and unevaluable categories were defined into the following categories:

**Failure:**

- documented deep fungal infection or CT scan highly suggestive for deep fungal infection
- clinically and microbiologically documented bacterial or viral infection responsible for the fever
- death (any cause) after > 3 days of study medication
- persistent fever at the end of neutropenia or at day 28
- deterioration of the signs and symptoms potentially attributable to deep fungal infection whether the fever had disappeared or not at the end of neutropenia or at day 28
- fever requiring a change in the empirical antifungal regimen
- discontinuation of study medication due to poor tolerance

**Unevaluable:**

- treatment duration  $\leq$  3 days
- any infection documented after the initiation of the empirical antifungal regimen resulting from investigations performed before its initiation.

**Protocol amendment 2: 1/12/96 (before the start of the trial)**

- Modifications to the statistical analysis plan based on FDA comments.

**Protocol amendment 3: 5/3/96**

- Modifications to the 'Interactions for itraconazole' section.

**Protocol amendment 4: 11/25/96**

- Minor revisions to the exclusion criteria were made.

**Protocol amendment 5: 5/26/97**

- In the statistical section of the protocol the definition of the number of subjects to be included in the ISS was modified. Instead of the first 100 subjects, all subjects entered before 1 May 1997 (201) were to be included in the ISS. This decision was based on the end-of-Phase II meeting with the FDA on 3 November 1995 and the follow-up meeting on 18 December 1995.

**Sample size:**

A total of 390 subjects were to be randomized.

**Inclusion criteria:**

Pertinent inclusion criteria specified subjects of either sex with an underlying hematologic malignancy undergoing chemotherapy or BMT (excluding allogeneic) who had a baseline ANC of  $< 500$  cells/mm<sup>3</sup> expected to last at least 7 days and a fever of  $> 38$  C not responding to 3 – 7 days of appropriate antimicrobial therapy.

**Exclusion criteria:**

Pertinent exclusion criteria specified the exclusion of subjects

- receiving an investigational drug unless it concerns anticancer regimens or open studies and compassionate clearance with itraconazole or fluconazole oral formulations
- proven or suspected deep fungal infection (including all cases without mycological sampling) diagnosed during previous episodes of neutropenia, and still present
- liver disease defined as liver enzymes (SGPT or SGOT)  $> 5$  times the upper normal limit or bilirubin  $> 50$  mol/liter at trial entry
- proven deep fungal infection at trial entry defined as either a positive culture from a normally sterile site (except for urine), a positive histopathology from any site or a highly suggestive CT-scan
- proven systemic bacterial or viral infection at trial entry or a superficial bacterial or viral infection responsible for the fever

Subjects could be withdrawn from the trial if:

- a serious adverse event occurred
- the investigator considered it, for safety reasons, in the best interest of the subject that he/she be withdrawn
- the subject withdrew his/her consent
- an exclusion criterion was met during the trial
- lack of efficacy
- a proven infection with a fungal species not considered susceptible to itraconazole was documented (*Fusarium* spp., *Mucor* spp.)

**Duration of Treatment:**

Study medication was continued until the end of neutropenia defined by one neutrophil count higher than  $0.5 \times 10^9$ /L or up to a maximum of 2 days with a neutrophil count  $> 1.0 \times 10^9$ /L but not to exceed 28 days.

***Medical Officer's Comment:*** *It should be noted that the continuation of study medication until at least one ANC of  $> 500$ /mm<sup>3</sup> is very near to the inclusion criterion specifying the inclusion of patients with ANCs  $< 500$ /mm<sup>3</sup>. This could potentially have allowed the inclusion of subjects with ANCs in the  $490$ /mm<sup>3</sup> range that quickly resolved (within 3 days to be considered evaluable) and were considered successes.*

**Dosing:****Itraconazole: IV Phase:**

For the first 4 doses, 200 mg itraconazole was administered twice daily. For the following 5 days, 200 mg itraconazole was administered once daily at the same time as the initial dose. If required by the clinical condition of the subject, this 200 mg QD dosing was continued for another week.

**Itraconazole oral solution (follow-up to IV phase):**

Itraconazole oral solution was administered without a meal. The oral solution was administered as a 20 ml (200 mg) dose each morning and evening from day 8 or day 15 onwards.

**Amphotericin B:**

A total daily dose of  $\geq 0.7$  mg/kg body weight had to be reached within 48 hours post study entry and the daily dose of amphotericin B was not to exceed 1 mg/kg daily during the entire study period. In case of minor side effects, the daily administration of amphotericin B was lowered up to 0.5 mg/kg without withdrawing the subject for intolerance. Amphotericin B was administered intravenously in glucose 5% as a slow infusion recommended to last 4 to 6 hours. The use of Intralipid<sup>®</sup> and all liposomal formulations of amphotericin B were not allowed. Renal function was monitored at least twice weekly. Reasons for all amphotericin B dosage changes were to be recorded in the CRF. The use of hydrocortisone was not recommended since it interferes with the evaluation of fever.

***Medical Officer's Comment:** Of note was the absence of pre-specified definitions of renal toxicity associated with AMP B use. This allowed each investigator to independently determine when to discontinue AMP B patients and to be categorized as failures.*

**Randomization:**

Subjects admitted to the trial were randomly allocated to one of the two treatment groups. At each center, balancing ensured that each treatment group was allocated an equal number of subjects. Central randomization was done by the Contract Research Organization ID<sup>2</sup> on a per center basis and subjects were stratified for the presence of signs and symptoms potentially attributable to deep fungal infection and for the underlying therapy (marrow transplant including peripheral stem cell infusion or chemotherapy only). Major inclusion and exclusion criteria were checked through telephone randomization.

***Medical Officer's Comment:*** *The applicant's randomization procedures appeared to ensure that differences between study groups were minimized.*

**Concomitant therapy:**

**Antifungal prophylaxis:**

All systemic antifungal prophylaxis was stopped at study entry. Oral and topical agents (skin and vaginals) were allowed if not absorbed. No other antifungal therapy was allowed during the trial period.

***Medical Officer's Comment:*** *As noted previously, pre-trial prophylaxis with itraconazole or fluconazole was allowed. The effect of this on the selection of patients who could have had a fungal infection that resolved is unknown.*

**Antibiotics and antivirals:**

Antibacterial and antiviral treatments administered either prophylactically or as treatment were allowed.

**Compliance:**

All trial drug administration was recorded on a daily basis.

**Assessments:**

**Pre-trial examination**

At randomization, the investigator made a complete clinical evaluation of the subject's condition and relevant medical and surgical history. Possible predisposing factors for deep fungal infection were described. Concomitant drug use was recorded, and the use of antifungal prophylaxis was specified in detail.

Body temperature (3 measurements daily), white blood cell count, and neutrophil count were recorded and all symptoms possibly related to fungal infection (cough, dyspnea, headache, pain, confusion, and increased respiratory rate) were scored as absent or present. When the subject was treated under laminar air flow conditions (LAF), this was specified.

All subjects had a CxR within the 24 hours before randomization. Subjects with pulmonary abnormalities underwent a CT-scan of the chest if possible. All radiological data and scans were kept available for examination and evaluation by an independent radiologist.

Subjects with pulmonary abnormalities had a bronchoscopy within 24 hours of randomization if possible. Bronchoalveolar lavage (BAL) and biopsies were performed if indicated. Results of biopsies, CT-scans, and fundoscopy were recorded when available.

Fungal, bacterial, and, if needed, viral cultures from blood, urine and other suspected sites had to be performed before trial initiation. All results (including routinely performed fungal surveillance) obtained since initiation of fever were reported.

**Pharmacokinetics:**

Blood samples of 10 ml each for drug analysis (itraconazole, [redacted]) were taken before the start of the treatment, before the fifth itraconazole infusion on day 3, before the IV or the first oral administration on day 8 and before the oral administration on days 15, 22 and 28. If the intravenous treatment was stopped between day 8 and 15, an extra sample was taken just before the first oral administration. If the treatment was stopped before day 28, a last blood sample was taken either 24 hours after the last intravenous administration or 12 hours after the last oral administration. Blood samples were drawn from the arm opposite to the one with the infusion line or from a central line. The exact times of blood samplings were recorded in the Case Report Form.

**Efficacy Assessments:**

**Examinations during the trial period**

Clinical data were collected daily during treatment up to the end of neutropenia. A global evaluation was made in case of premature discontinuation, at the end of neutropenia, and at day 8 (fever only).

Body temperature (three measurements daily), white blood cell count, neutrophil count and signs and symptoms possibly attributable to fungal infection were recorded daily. If body temperature was related to drug fever or blood product administration it was shown on the CRF.

All major clinical events during the trial period were recorded. This included new infections and/or intensive care treatment.

A CxR was obtained at least once weekly. The results were compared to baseline in terms of: still normal, normalized, improved, unchanged (if abnormal at baseline), or

deteriorated. In case a scan showing abnormalities was available at study entry, the CT-scan or other scan showing abnormalities was to be repeated. Additionally, CT-scan, other scan, and fundoscopy results in relation to fungal infection were described whenever they had been carried out. To obtain further evidence of fungal infection, biopsies from any relevant site were carried out when possible.

All catheter changes were recorded. Upon removal the catheter was examined for bacterial and fungal colonization.

Fungal, bacterial and if needed viral surveillance cultures were taken at least once weekly for the sites mentioned under pre-trial examination as well as for suspected sites of fungal infection. Isolated organisms were identified up to the species level. All results including routine fungal and bacterial surveillance were reported.

### **Outcome Assessments:**

At the time of discontinuation, a global evaluation was made according to the criteria described below (failure; unevaluable; response). The results of empirical antifungal therapy were classified according to the following criteria (primary efficacy parameter):

#### **Response:**

- was defined as not being classified into the failure or unevaluable criteria.

Subjects who had received 10 days of study medication and remained afebrile for 3 consecutive days were included in the "response" category.

#### **Additional early evaluation.**

- After 7 days of therapy, the presence or absence of fever > 38C was scored and evaluated as a criterion of early response.

#### **Failure or Unevaluable: (see definitions on MOR page 21)**

***Medical Officer's Comment:** The MO determined that the applicant's analysis plan was not dependent only upon the presence or absence of fever and that a composite endpoint was utilized to determine response. This plan led to difficulties in discriminating true efficacy between the treatment arms because of the large number of subjects that discontinued AMP B due to toxicity and who were either unevaluable or failures in the applicant's analyses.*

#### **Safety:**

##### **Adverse events:**

All AEs occurring during the trial were noted in the CRF by the investigator. A determination of severity and causality was also made. Outcomes were provided if known.

**Laboratory Safety Tests:**

Standard hematology and biochemistry tests and urinalyses were performed at entry into the trial, after 2 days, on study days 7, 14, and 21, and at the end of the trial. Creatinine clearance was calculated on days 0, 3, 8, 11, 15, 18, 22, and 24 or at the end of the study drug administration. If performed more frequently, results were to be recorded in the CRF.

If subjects developed a liver function test abnormality, they were withdrawn from the study and lab tests were re-performed after 48 hours and at 3 – 7 day intervals thereafter until normalization occurred.

**Determination of sample size:**

Based on an equivalence hypothesis at an estimated 65% response rate and a maximum allowable lower response rate of 15% of itraconazole versus amphotericin B and a statistical power of 90% with a significance level of 5% (one-sided), 174 evaluable subjects were required in each group (on protocol population). This sample size warranted an equivalence test at 0.05 level (two-sided) and 80% power.

As the estimated number of drop-outs was expected to be 10%, 390 subjects were entered into the trial.

**Statistical methods:****Populations for analysis:**

Three populations were considered in the analysis:

**Intent-to-treat population (ITT):**

The ITT analysis population included all randomized subjects who satisfied the inclusion criteria 2, 3 and 4 and exclusion criteria 4 and 8. This was the primary population for the efficacy analysis.

**On-protocol population**

All randomized subjects with at least one drug administration who satisfied inclusion criteria 2, 3 and 4 and exclusion criteria 4 and 8.

**All-treated (all subjects) population**

All randomized subjects with at least one drug administration. This was the primary population for the safety analysis.

All statistical tests were interpreted at the 5% significance level.

Since the subjects were stratified at randomization, the analysis was also stratified:

For the primary efficacy parameter, subgroup analyses were conducted for the stratification parameters, duration of neutropenia (=neutrophil count  $< 0.5 \times 10^9/L$ ), duration of non-response to antibiotic therapy (3-4 days and 5-7 days), use of growth factors, type of growth factor and the occurrence of proven fungal, viral and bacterial infections. It was recognized that the power to test equivalence of the 2 treatments within particular subgroups might be limited owing to the small number of subjects in the subgroup.

Descriptive statistics and between-group comparison (analysis of variance model with factors treatment and the stratification variables for continuous parameters; Cochran-Mantel-Haenszel test controlling for the stratification variables for categorical parameters) were presented to investigate the comparability of the treatment groups. If there was any baseline imbalance, the effect on the primary efficacy parameter was investigated.

The distribution of the stratification variables was tabulated.

#### **Efficacy Analyses:**

For subjects who do not have any data after baseline, the following strategies were used in the primary analysis (primary efficacy parameter), i) they were excluded from the analysis, ii) they were treated as failure, iii) they were treated as failure in the itraconazole group and as success in the control group. If the equivalence held in the case of iii), no more sensitivity analysis was performed. Otherwise, the equivalence tests were repeated by applying the assumed response rates among the subjects who had no data post-baseline.

The primary efficacy parameter was response at the end of treatment.

The response rate was defined as :

$$\text{Response}$$


---


$$\text{response} + \text{failure} + \text{unevaluable}$$

Other efficacy parameters were the duration of hospitalization, the number of febrile (>38 C) days, number of documented deep fungal infections, time to response and success which was defined as :

$$\text{Response}$$


---


$$\text{response} + \text{failure}$$

To analyze the equivalence between itraconazole and amphotericin B for the response and success rates, the Mantel-Haenszel-Type test was applied controlling for the stratification factors.

To analyze equivalence between treatment groups, the primary analysis was to construct 95% two-sided confidence intervals on the difference using the method in [redacted]. The p-value is calculated as the maximum of the two one-sided tests following the approach of [redacted] in the unstratified setting. Note that this is an approximation to the p-value under the correct null hypothesis. Moreover, 95% confidence intervals were calculated rather than 90% confidence intervals, explaining why the decisions based on the confidence intervals are more stringent. As a secondary analysis, the method of [redacted] was also performed. The stratification factors (presence of the signs and symptoms and underlying therapy) were adjusted in both methods.

To examine individual investigator effect, minimally, response rates within each center were summarized by descriptive statistics and confidence

intervals, and comparisons across centers were performed using graphics.

Early response defined as the absence of fever was also analyzed using the same statistical test after 7 days of therapy.

Body temperature, neutrophil count and changes in symptoms were descriptively analyzed. A tabulation of the fungal and bacterial colonization during the entire trial period was also performed.

Time to response was graphically presented using the Kaplan-Meier Product Limit Estimate and compared between the treatments using the  test. Influence of the stratification variables on the time to response was investigated using Cox proportional hazards model.

**Additional Analyses performed:**

- All planned analyses were performed. In addition, a factor analysis (exploratory analysis) was done. Data handling was as follows.
- A factor analysis addressed the relationship between a number of baseline subject and disease characteristics or trial-related factors to detect possible influences on the effect of the treatment. The efficacy parameter in this analysis was the global evaluation, categorized into a response and non-response (unevaluable and failure) class. The population used in this analysis was the intent-to-treat population, as defined in 3.6.2.1. The factors taken into account were:
  - treatment group: itraconazole, amphotericin B
  - presence of signs and symptoms at baseline potentially attributable to deep fungal infection (stratification factor)
  - underlying therapy: marrow transplant including peripheral stem cell infusion or chemotherapy only (stratification factor)
  - country
  - days of chemotherapy before the start of the treatment

- days of neutropenia before the start of the treatment
- number of previous febrile days
- race
- sex
- underlying disease: AML, ALL, lymphoma, myeloma, other
- age
- height
- weight
- duration of neutropenia:  $<7$  /  $\geq 7$  consecutive days
- duration of non-response (=fever) to antibiotic therapy:  $\leq 4$  /  $\geq 5$  consecutive days
- status of the underlying disease: first treatment yes/no. Yes if first treatment category, no if relapse + refractory, other or missing category
- use of growth factors :yes/no (G-CSF : Granulocyte-colony stimulating factor en GM-CSF Granulocyte-macrophage-colony stimulating factor)

The statistical methods for the factor analysis were as follows.

The logistic regression model was used to examine the effect of the different factors on the global evaluation. The effect was estimated on the basis of the Odds Ratio (OR). The interpretation of the OR for a factor with two levels is as follows:

*OR=1: no difference between the two levels*

*OR>1: higher relative chance of response in level 1*

*OR<1: lower relative chance of response in level 2*

The factors treatment group, presence of signs and symptoms at baseline potentially attributable to deep fungal infection and underlying therapy (transplant yes/no) were always included in the model.

Each of the other factors were first tested in a single-factor model.

Subsequently, all factors were included in one model, which was then reduced by dropping the factors with significance > 0.10 (stepwise backward regression).

***Medical Officer's Comment:*** *The FDA review team disagreed with the applicant's proposed patient populations and elected to utilize only those analyses generated from the ITT population. The rationale was that the ITT (subjects randomized who conformed to the inclusion and exclusion criteria and who received study drug) was more consistent with what occurs in the clinical setting. The applicant's intent to analyze success after the exclusion of the unevaluable subjects did not appear reasonable for the stated reasons. The on-protocol population proposed by the sponsor was virtually the same as the ITT and there did not appear to be any value in reiterating all the analyses performed.*

*Additionally, the MO elected to assess response (success) in the ITT population, as those subjects who had at least 1 dose of study medication with follow-up who defervesced, did not have an EFI, had resolution of their neutropenia, and who survived to the EOT (28 days). Assessed as failures were those ITT subjects who either received < 3 days of study drug, or who were true failures due to lack of efficacy. Subjects who received concomitant antifungals were in this category as were subjects lost to follow-up.*

### **Study Results:**

#### **Patient Disposition:**

60 investigators enrolled 394 subjects (197 itraconazole, 197 amphotericin B). 15 subjects on each arm either did not receive any trial medication or were not randomized. Therefore 384 subjects (192 each arm) were included in the all subjects population (safety database, all randomized subjects who received at least one dose of the study drug).

As per the applicant, the primary population for efficacy analysis was the ITT population (subjects who were randomized and satisfied the inclusion criteria and exclusion criteria). 374 subjects were included, 187 each in the itraconazole group and the amphotericin B group

**After the exclusion of the S. African site, 360 subjects were included in the ITT population (179 ITR and 181 AMP B).**

***Medical Officer's Comment:*** During an initial review of the data, the MO was unable to reconcile the numbers of patients in the results section of the line listings with statements made by the applicant with regards to the populations utilized. Specifically, the MO determined that although the applicant stated that the ITT population utilized for efficacy calculations was compromised of 187 patients on each arm, only 184 and 186 ITR and AMP B arms respectively were actually included. The MO requested that the applicant provide an explanation for the discrepancies. A reanalysis found that the efficacy analyses were performed utilizing strict statistical definitions that were not always the same as those used in the research report. The MO determined that these minor discrepancies were not of major significance.

**Table 5**  
**Patient Disposition**

	<b>Total</b>	<b>Itraconazole</b>	<b>Amphotericin B</b>
<b>Total recruited</b>	<b>394</b>	<b>197</b>	<b>197</b>
Not randomized or treated	2	-	2
<b>Total randomized and eligible for ITT</b>	<b>392</b>	<b>197</b>	<b>195</b>
Randomized but not treated	8	5	3
<b>Primary population for safety analysis</b>	<b>384</b>	<b>192</b>	<b>192</b>
Patients excluded from ITT because inclusion/exclusion criteria not met	14	8	6
<b>Patient Population used for efficacy analyses (original)</b>	<b>370</b>	<b>184</b>	<b>186</b>
Excluded South African subjects	10	5	5
<b>FINAL ITT</b>	<b>360</b>	<b>179</b>	<b>181</b>

104/192 (54%) of the randomized to itraconazole subjects (80/192 (41.7%) IV and 24/65 (36.9%) PO) and 119/192 (62%) of the randomized to amphotericin B subjects (all subjects population) discontinued therapy before completion (before the end of neutropenia, defined as one neutrophil count  $> 0.5 \times 10^9/l$ , or before a maximum of 2 days with a neutrophil count  $> 1.0 \times 10^9/l$ ). As can be seen in the table below, 36 (19%) of the itraconazole subjects discontinued due to an AE as compared to 74 (39%) of the amphotericin B subjects. A larger number of itraconazole treated subjects 46 (24%) discontinued due to an insufficient response as compared to 16 (8.3%) of the amphotericin B subjects. Classified in the other category of patients were those whose neutrophil counts recovered within 1 – 2 days of the start of the trial, those who never received medication because of unavailability, or because of physician error.

**Table 6**  
**Reasons for Discontinuation**  
**All Subjects Population**

<b>Reason for Discontinuation</b>	<b>Itraconazole</b>	<b>Amphotericin B</b>
Total Number of subjects	192	192
Adverse Event	36 (19%)	74 (39%)
Insufficient Response	46 (24%)	16 (8%)
Asymptomatic/Cured	2 (1%)	0
Ineligible	11 (6%)	15 (8%)
Withdrew Consent	2 (1%)	3 (2%)
Other	7 (4%)	11 (6%)
<b>Total Discontinued</b>	<b>104 (54%)</b>	<b>119 (62%)</b>

Major protocol deviations were noted in 18/187 (10%) itraconazole subjects and 14/187 (8%) amphotericin B subjects. The major protocol deviations were selection criteria not met (10 itraconazole subjects and 11 amphotericin B subjects), intercurrent therapy (5 and 3 subjects), and not randomized to treatment (3 itraconazole subjects).

**Demographics:**

Of the 384 subjects included in the all subjects population, 60% were male, and the median ages in the two groups were 46.5 years (ITR) and 50 years (AMP B). 89% of the subjects were Caucasian, and the median weight was 71 kg in the itraconazole group and 76 kg in the amphotericin B group. There was a significant intergroup difference in age ( $p = 0.020$ ) and a marginally significant intergroup difference in weight ( $p = 0.080$ ).

The primary underlying disease was AML (107 (56%) itraconazole subjects and 109 (57%) amphotericin B subjects). The start of chemotherapy was 13 days (median) before the start of treatment in the itraconazole group and 14 days before the start of treatment in the amphotericin B group, and the start of neutropenia was 7 days before the start of treatment in each group. The median number of previous febrile days was 5 days in the itraconazole group and 4 days in the amphotericin B group. Baseline disease characteristics were evenly distributed between the two groups.

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**Table 7**  
**Demographic data and Baseline Disease Characteristics**  
**All Subjects Population (Original Dataset)**

Parameter	Itraconazole		Amphotericin B		p value
	N	%	N	%	
<b>Total # of subjects</b>	192	100	192	100	
<b>SEX</b>					
Female	73	38	82	42.7	
Male	119	62	110	57.3	0.330
<b>AGE, YEARS</b>					
16 - <21	8	4.2	8	4.2	
21 - <65	161	83.9	151	78.6	
65 - HIGHER	23	12	33	17.2	
MEAN (SE)	45.6 (1.06)		49.2 (1.1)		
MEDIAN(MIN;MAX)	46.5 (47/67)		50(18/81)		0.020
<b>RACE</b>					
Black	8	4.2	15	7.8	
Caucasian	172	89.6	169	88	
Hispanic	4	2.1	3	1.6	
Oriental	2	1	0	0	
Other	6	3.1	5	2.6	0.379
<b>WEIGHT, KG</b>					
Mean (SE)	73.1 (1.138)		76 (1.208)		
Median (Min:Max)	71 (42 ; 134)		75.5(37,13)		0.080
<b>HEIGHT, CM</b>					
	N = 191	100	N = 189	100	
Mean (SE)	171 (0.72)		170.7 (0.76)		
Median (Min:Max)	171 (148, 193)		170 (132,194)		0.727
<b>UNDERLYING DSIEASE</b>					
Acute PML	2	1	1	0.5	
ALL	15	7.9	11	5.8	
AML	107	56	108	56.5	
AML-ALL	0	-	1	0.5	
Anemia/Neutropenia	1	0.5	0	-	
Breast CA	1	0.5	5	2.6	
CLL	0	-	1	0.5	
CML	6	3.1	5	2.6	
Extra-gon. Germ Cell	0	-	1	0.5	
Lymphoma	49	25.7	36	18.8	
MDS	1	0.5	0	-	
MDS-RAEB	0	-	4	2.1	
Myeloma	9	4.7	16	8.4	
Thrombocytopenia	0	-	1	0.5	

Tumor Germ Cell	0	-	1	0.5	
<b>CHEMOTHERAPY, Days before start R/x</b>					
0 - 7	17	8.9	11		
8 - 14	99	51.6	99		
> 14	76	39.6	82		
Mean (SE)	15.5 (1.93)		14.3 (0.43)		
Median (Min:Max)	13 (4, 376)		14 (0, 60)		0.468
<b>NEUTROPENIA, Days before start r/x</b>					
	N = 180		N = 187		
Before	2	1.1	1		
0 - 7	92	51.1	98		
8 - 14	56	31.1	58		
> 14	30	16.7	30		
Mean (SE)	8.9 (0.46)		9 (0.44)		
Median (Min:Max)	7 (-2, 34)		7 (-5, 39)		0.913
<b>NO. OF PREVIOUS FEBRILE DAYS</b>					
	N = 191		N = 192		
0 - 2	20		26		
3 - 7	171		166		
Mean (SE)	4.6 (0.13)		4.3 (0.12)		
Median (Min:Max)	5 (0,7)		4 (1,7)		0.084
<b>SIGNS AND SYMPTOMS</b>					
No	165	85.9	160	84	
Yes	27	14.1	32	16	
<b>TRANSPLANT</b>					
No	124	64.6	126	65.6	
Yes	68	35.4	66	34.4	
<b>STRATIFICATION GROUP</b>					
Signs No/Transplant No	108	56.3	108	56.3	
Signs No/Transplant yes	57	29.7	52	27.1	
Signs yes/Transplant no	16	8.3	18	9.4	
Signs yes/Transplant yes	11	5.7	14	7.3	

**Medical Officer's Comment:** The applicant was queried as to the inclusion of patients without hematologic malignancies as only those patients with hematologic malignancies were specified in the amended inclusion criteria. The applicant responded that indeed certain patients (ITR 5 and AMP B 1) did not meet the inclusion criteria, however these patients were treated on a hematology unit, had had a BMT and were similar in nature to patients with AML. The MO determined that there was little value in excluding these subjects from the ITT analyses.

The applicant was also queried as to the number of patients evaluated for neutropenia. As noted in the demographics table 180 ITR patients and 187 AMP B patients were evaluated for this parameter at study entry. The sponsor stated that the investigators were initially confused regarding testing.

The status of the underlying hematological disease was first treatment in 54% of the subjects in each of the two groups (ITR 104, 103 Ampho B), peripheral blood stem cell transplant in 27% (52) of the subjects in the itraconazole group and 26% (49) of the subjects in the amphotericin B group, and first relapse in 23% (44) and 19% (37) of the subjects, respectively.

The main predisposing factors were central catheter (94% itraconazole subjects and 93% amphotericin B subjects), mucositis (54% and 48%, respectively), corticosteroids (34% and 31%), and construction work in the hospital (32% of the subjects in each group).

**Table 8**  
**Predisposing Factors**

Predisposing Factors	Itraconazole		Amphotericin B	
	N	%	N	%
Corticosteroids	66	34	60	31
Diabetes	7	4	9	5
Foley catheter	7	4	10	5
Central catheter	181	94	178	93
Peripheral catheter	7	4	13	7
Concomitant cases of aspergillosis	8	4	12	6
Construction	90	47	89	46
TPN	40	21	40	21
Fungal GI colonization	26	14	20	10
Mucositis	104	54	93	48
Other	1	0.5	1	0.5

**Medical Officer's Comment:** Both the itraconazole and the concurrent control groups appeared to be sufficiently similar and therefore the introduction of bias should have been adequately minimized.

The applicant was predominantly able to include high-risk patients in the study. This determination was made by evaluating a number of factors including underlying disease, degrees and duration of neutropenia, the presence or absence of mucositis, the presence or absence of central catheters, as well as other factors. The inclusion of a high-risk population ensured that the comparison between itraconazole and the "gold standard" amphotericin B was performed in a population where alternative antifungal agents are necessary.

Of note, approximately 75% of the patients on both study arms had no signs or symptoms and therefore could be categorized as true FUOs.

Abnormalities observed during physical examination, were mainly noted for ears, nose and throat (96/192 (51%) of the itraconazole subjects and 83/192 (44%) of the amphotericin B subjects), skin (83/192 (45%) and 94/192 (49%) of the subjects,

respectively), chest and lungs (60/192 (32%) and 67/192 (35%), and abdomen (49/192 (26%) and 53/192 (26%).

All subjects had received previous therapy. The primary previous treatments were cytarabine (115/192 (59.9%) itraconazole and 120/192 (62.5%) amphotericin B), vancomycin (112/192 (58.3% itraconazole and 113/192 (58.9%) amphotericin B), acyclovir (88/192 (45.8%) itraconazole and 74/192 (38.4%) amphotericin B), ceftazidime (82/192 itraconazole and 81/192 amphotericin B or 42% of the subjects), etoposide (69/192 (35.9%) itraconazole and 66/192 (34.4%) amphotericin B), nystatin (66/192 (34.4%) itraconazole and 68/192 (35.4%) amphotericin B), gentamicin (67/192 (34.9%) itraconazole and 64/192 (34%) amphotericin B), amphotericin B (52/192 (27.1%) itraconazole and 60/192 (31.3%) amphotericin B), **fluconazole (52/192 (27.1%) itraconazole and 59/192 (30.7%) amphotericin B)**, and ciprofloxacin (51/192 (26.6% itraconazole and 57/192 (29.7%) amphotericin B). **Itraconazole had been received by 16/192 (8.3%) of the itraconazole subjects and 17/192 (8.9%) of the amphotericin B subjects.** Prophylactic amphotericin B was administered orally in 24% of the subjects, intravenously in 5% of the subjects, bronchially in 4% of the subjects and topically in 1% of the subjects.

***Medical Officer's Comment:*** *The number of patients receiving effective antifungal prophylaxis was near 40% of the patient population.*

#### **Concomitant Diseases and Treatments:**

Apart from hematological abnormalities (i.e., the underlying disease), concomitant diseases were mainly noted for the following body systems: GI 72% of the subjects, ears, nose, and throat (39%), respiratory (26%), and cardiovascular (25%).

All subjects received concomitant treatment. The most frequently administered classes of concomitant medications (noted in at least 25% of the subjects in any group) are summarized in the following table:

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**Table 9**  
**Most frequently administered classes of concomitant treatments**

Class of medication (medication noted in at least 25% of the subjects in any group)	No. (%) of subjects	
	Itraconazole	Amphotericin B
Analgesics	170 (91%)	164 (88%)
Antacids, drugs for treatment of peptic ulcer and flatulence	111 (59%)	109 (58%)
Antibacterials for systemic use	186 (100%)	178 (95%)
Antidiarrheals, intestinal anti-inflammatory/antiinfective agents	77 (41%)	62 (33%)
Antifungals for dermatological use	50 (27%)	58 (31%)
Antihistamines for systemic use	111 (59%)	135 (72%)
<b>Antimycotics for systemic use</b>	<b>50 (27%)</b>	<b>55 (29%)</b>
Antivirals for systemic use	102 (55%)	87 (47%)
Corticosteroids for systemic use	52 (28%)	98 (52%)
Diuretics	95 (51%)	91 (49%)
Immunomodulating agents	92 (49%)	81 (43%)
Mineral supplements	128 (68%)	138 (74%)
Plasma substitutes and perfusion solutions	95 (51%)	94 (50%)
Psycholeptics	133 (71%)	140 (75%)
Stomatological preparations	38 (20%)	49 (26%)

The majority of concomitant medications of a particular class were given to a comparable number of subjects in the two groups. Antihistamines and corticosteroids, both for systemic use, were administered more frequently in the amphotericin B group.

***Medical Officer's Comment:*** *Of the 53 itraconazole and 60 amphotericin B subjects that received antimycotics for systemic use, the majority (42/192 both arms or 22%) received intravenous amphotericin B. Liposomal preparations were received by an additional 1 patient on the itraconazole arm and 2 patients on the amphotericin B arm. This is unusual given the availability of liposomal products today, however at the time this study was underway, liposomal products were not yet approved. Fluconazole was received by 15/192 (8%) of the itraconazole recipients and 22/192 (12%) of the amphotericin B recipients. 4/192 (2%) itraconazole recipients and 5/192 (3%) amphotericin B recipients received itraconazole. 1 itraconazole patient received ketoconazole. These patients were appropriately categorized as failures.*

Concomitant therapy to support the trial medication was given to 9 (5%) subjects in the itraconazole group and to 112 (60%) subjects in the amphotericin B group. There were marked differences in the incidence of administration of analgesics (4% itraconazole

subjects versus 42% amphotericin B subjects), antihistamines for systemic use (3% versus 35%, respectively), and corticosteroids for systemic use (< 1% versus 27%).

***Medical Officer's Comments:*** *As expected a larger number of amphotericin B recipients received a variety of concomitant medications in order to minimize or treat AEs related to the administration of this product.*

#### **Pharmacokinetic Indices:**

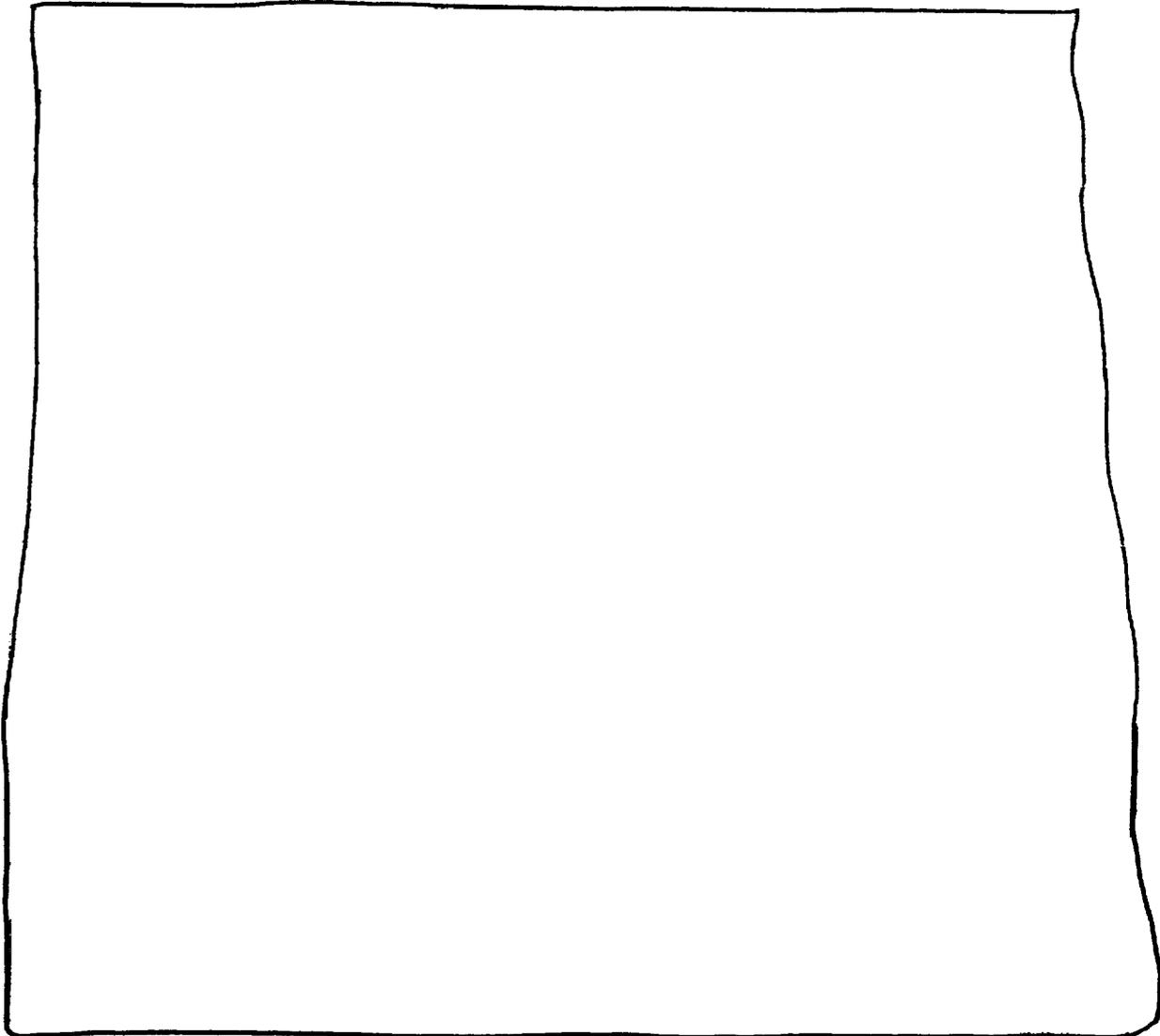
##### **Predose plasma concentrations of itraconazole** [REDACTED]

Mean itraconazole levels during the intravenous treatment were 768, 854 and 1337 ng/ml on day 3, 8 and 15, respectively. These levels remained approximately stable after switching to follow-up treatment with the oral solution: mean concentrations were 1133 and 975 ng/ml on day 15 and 22 of the oral treatment, respectively.

The average ratio of [REDACTED] itraconazole was  $1.54 \pm 0.73$  during the intravenous phase and  $1.61 \pm 0.58$  during the oral follow-up phase.

On day 3 of the intravenous itraconazole treatment, 96% of the subjects had pre-dose plasma concentrations that were higher than 250 ng/ml, which is considered as the minimum level required for efficacy. After one week of treatment, these levels were maintained or slightly increased. Effective levels were also maintained during the oral follow-up phase.

If the treatment was stopped before day 28, a last sample was also taken, either 24 hours after the last intravenous administration or 12 hours after the last oral administration. For subjects who stopped during the intravenous phase, the concentration averaged  $976 \pm 565$  ng/ml. For 95% of the subjects, these values were > 250 ng/ml. For the oral follow-up phase, the mean end of treatment concentration was  $1608 \pm 867$  ng/ml. For 95% of the subjects these values were > 250 ng/ml. Therefore the reason for stopping the treatment in each of the phases was not associated with inferior itraconazole concentrations.

**Drug dose and drug concentration conclusion:**

On day three of intravenous itraconazole treatment, adequate plasma concentrations were attained in 96% of the subjects. After one week of treatment, these levels were maintained or slightly increased. Levels were maintained during the oral follow-up phase with 200 mg itraconazole b.i.d. Steady-state plasma levels largely exceeded the minimal effective concentration of 250 ng/ml. [redacted] [redacted] levels were only detected in significant amounts in subjects when itraconazole solutions were given intravenously.

**Efficacy:**

(NOTE: After review of a random sample (generated by the FDA statistician) of CRFs, the MO elected to accept the applicant's patient population).

**Duration of Treatment:**

**Table 10**  
**Duration of Treatment**  
**(Original Dataset)**

Duration of treatment (days)	Itraconazole (IV + PO)	Amphotericin B
	<b>N = 192 (100%)</b>	<b>N = 192 (100%)</b>
1 – 7	88 (46%)	106 (55%)
8 – 14	56 (29%)	57 (30%)
15 – 21	26 (14%)	21 (11%)
22 – 28	19 (10%)	9 (4%)
29 -35	3 (2%)	0
Mean	10.6	8.4
Median	8.5	7

***Medical Officer's Comment:*** The median duration of treatment days in the itraconazole group was 1.5 days longer as compared to the amphotericin B group. As expected and due to bone marrow recovery, fewer patients received longer courses of either study drug. However, more itraconazole patients received > 14 days of therapy. The reasons for this could be attributed not only to longer duration of fever but possibly to prolonged duration of neutropenia. This observation is of concern and its significance is unknown. Itraconazole has not been associated with neutropenia in other patient populations and an explanation was not found.

For itraconazole IV versus PO treatment, the median duration of treatment was 7 (2; 28) days and 7 (1; 24) days, respectively. For those subjects who received PO treatment, N = 65, the median (min; max) duration of intravenous treatment was 9 (7; 15) days and the median (min; max) duration of oral treatment was 7 (1; 24) days.

**Duration of Neutropenia:**

Similar numbers of patients in each study group had at least one neutrophil count <  $0.1 \times 10^9/L$  (128/187 (74%) in the itraconazole group and 130/187 (76%) in the amphotericin B group). The mean neutrophil count was  $0.05 \times 10^9/L$  at baseline in both groups. The median (min; max) duration of neutropenia was 10 (0; 35) days in the itraconazole group and 8 (0; 29) days in the amphotericin B group. A larger number of itraconazole patients had more prolonged neutropenia as compared to the amphotericin B group. Specifically in ITT subjects with available data, 48/168 (28.6%) of itraconazole-treated patients as compared to 28/166 (16.8%) of the amphotericin B patients had neutropenia for > 14 days.

**Primary efficacy parameter (ITT):**

The primary parameter of efficacy was response at the EOT based on the global evaluation. The response rate was defined as response/(response + failure + unevaluable). As noted previously, those patients who were not unevaluable or who did not fail were determined to be cures.

The response rates per stratum and the overall response rate are given in the following table:

**Table 11**  
**Response rates (ITT)**  
**As per the applicant**

Stratum Signs/ Transplant	Response rate n/n assessed (%)		Equivalence testing Itraconazole minus Amphotericin B			
	Itraconazole (n = 179)	Amphotericin B (n = 181)	two-sided		one-sided	
			95% CI ( $\Delta = \pm 15\%$ )	p-value	95% CI ( $\Delta = \pm 15\%$ )	p-value
No/No	51/103 (49%)	34/105 (32%)	(3%, 31%)		(5%, 100%)	
No/Yes	24/52 (46%)	22/48 (46%)	(-21%, 22%)		(-18%, 100%)	
Yes/No	4/14 (29%)	6/18 (33%)	(-43%, 34%)		(-38%, 100%)	
Yes/Yes	5/10 (50%)	6/10 (50%)	(-63%, 43%)		(-56%, 100%)	
<b>Total</b>	<b>84/179 (47%)</b>	<b>68/181 (38%)</b>	<b>(-1%, 19%)</b>	<b>0.156 (1)</b> <b>0.119 (2)</b>	<b>(1%, 100%)</b>	<b>&lt; 0.001 (1)</b> <b>&lt; 0.001 (2)</b>

(1)  method for difference in proportions controlling for stratum

(2)  method for difference in proportions controlling for stratum

As per the applicant:

At the end of treatment, the overall response rates in the intent-to-treat population were 47% in the itraconazole group and 38% in the amphotericin B group. For the two-sided equivalence testing, the 95% confidence interval was (-1%; 19%); since the upper bound of this interval was >15%, the two treatments were not statistically significantly equivalent ( $p = 0.156$ ,  method). However, for the one-sided equivalence testing, the lower bound of the 95% confidence interval was >-15% (1%; 100%), that means that itraconazole was at least as effective as amphotericin B ( $p < 0.001$ ,  method).

The results of the  method were confirmed by the  method, both for the two-sided and for the one-sided equivalence testing.