

As an exploratory analysis, statistical testing for superiority (Cochran-Mantel-Haenszel test) indicated that itraconazole was marginally significantly superior to amphotericin B ($p = 0.083$);).

Medical Officer's Comment: The MO-generated 95 % CI with CCF for the total ITT population was - 1.4%, 20% ($\Delta = \pm 15\%$). Based on this calculation, the MO determined that ITR was non inferior to AMP B for the primary parameter of efficacy. The MO defers to the statistical reviewer for further comment on the analyses. ITR was numerically superior to AMP B in the subgroup of subjects without transplant and without signs (FUO); 95% CI with CCF 3%, 31%. ITR was NOT equivalent to AMP B in that subgroup of transplant recipients who had no localizing signs of disease (95% CI with CCF -21%, 22%). The MO also points out that the above response rates were obtained from the total population independent of the receipt or not of previous antifungal prophylaxis.

After consultation with the statistical reviewer, the MO performed an analysis of response versus transplant status. In this analysis the response 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.

Table 12
Response rates (ITT) by Transplant Status

Transplant	Itraconazole	Amphotericin B	95 % CI with CCF per MO
YES	29/62 (47%)	28/58 (48%)	-21%, 18%, $\Delta = \pm 15$
NO	55/117 (47%)	40/123 (32%)	1.4%, 27.6%, $\Delta = \pm 15$

A further breakdown of patients by the applicant into the reasons for failure revealed the following:

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Table 13
Response Rate
ITT Population

Response	Itraconazole		Amphotericin B	
	N = 179	100%	N = 181	100%
Success Total	84	47%	68	37%
Not unevaluable or failure	52	29%	44	25%
10 days medication and afebrile	32	18%	24	13%
Unevaluable (R/x < 3 days)	24	13%	44	24%
Failure Total	71	40%	69	39%
Documented clinical or microbiological infection	7	4%	8	5%
Insufficient response	6	3%	5	3%
Persistent fever at end of neutropenia	20	11%	7	4%
Change in R/x due to fever	13	7%	1	1%
Documented deep fungal infection	10	6%	9	5%
Intolerance	12	7%	37	20%
Deterioration of signs and symptoms	2	1%	0	-
Death after > 3 days	1	0.5%	2	1%

Medical Officer's Comment: Of note was the larger number of AMP B patients who were unevaluable as compared to the ITR arm. This difference may have been due to toxicity in the AMP B recipients however, the applicant was requested to clarify this issue as the later analyses could have been altered by such a difference. This was later confirmed.

A larger proportion of amphotericin B patients were classified as failures due to toxicity as opposed to the itraconazole arm. The primary reasons for failure in the itraconazole treated patients were fever requiring a change in the antifungal regimen or persistent fever at the end of neutropenia. However, the survival rate and the rate of EFIs were similar. The above may indicate a bias on the part of the investigators due to the open nature of the study. In persistently febrile itraconazole patients it could have been easier to change to amphotericin B whereas there was no easy alternative regimen for similar patients on the amphotericin arm. The MO modified the applicant's table to that below. This modified table provides a more accurate picture of the relative efficacy and limitations of each study drug because the exclusion of subjects receiving < 3 days of treatment or who had a baseline infection is not consistent with what occurs in clinical practice and is inaccurate.

Modified Table 13

Response	ITR N = 179	AMP B N = 181
Success	84 (47%)	68 (38%)
Failure because unevaluable	24 (13%)	44 (24%)
Failure due to intolerance	12 (7%)	37 (20%)
Failure due to lack of efficacy	59 (33%)	32 (18%)

Time to response:

In the time to response analysis, the response rates were 84/182 (46%) in the itraconazole group and 68/182 (37%) in the amphotericin B group. As per the applicant:

In the first quartile of subjects, the estimated time to response was 8 days in the itraconazole group and 9 days in the amphotericin B group; in the third quartile of subjects, the estimated time to response was 24 and 25 days respectively ($p = 0.589$).

Medical Officer's Comment: *The mean time to response was 16.5 days in the itraconazole group and 16.1 days in the amphotericin B group. The median time to response was 16 days in the itraconazole group and 15 days in the amphotericin B group. Thus it appeared as if the amphotericin B-treated patients had a slightly shorter time to response as compared to the itraconazole-treated patients.*

The applicant provided additional sensitivity analyses for the primary parameter of efficacy (response):

As per the applicant:

An additional sensitivity analysis (as specified in the protocol) was performed for subjects who had no data after baseline, viz. these subjects were treated as failure. The results confirmed the results of the primary analysis: the response rates at the end of treatment were 84/182 (46%) in the itraconazole group and 68/181 (38%) in the amphotericin B group for the two-sided equivalence testing, the 95% confidence interval was (-2%; 18%), i.e., the two treatments were not statistically significantly equivalent ($p = 0.096$, Fleiss method).

Medical Officer's Comment: *The MO-generated 95% CI with CCF for the sensitivity analysis was -2.1%, 19.2% ($\Delta = \pm 15$), confirming the non-inferiority of ITR.*

Subgroup Analyses (ITT population):

As per the applicant:

Overall, the response rates in the subgroups were higher in the itraconazole group than in the amphotericin B group; statistically

significant equivalence was, however, not reached, due to a lack of power, except in the subgroup with a duration of non-response to antibiotic therapy of four days at most.

Analysis by Duration of Neutropenia:

As per the applicant:

A subgroup analysis was performed for subjects with a duration of neutropenia of less than seven days versus subjects with a duration of neutropenia of at least seven days.

In the subgroup of subjects with a duration of neutropenia ($<0.5 \times 10^9/l$) of less than seven days, the response rates at the end of treatment were 27/60 (45%) in the itraconazole group and 23/58 (40%) in the amphotericin B group. The two-sided 95% confidence limits were (-7%; 26%) ($p = 0.251$, [] method).

In the subgroup of subjects with a duration of neutropenia ($<0.5 \times 10^9/l$) of at least seven days, the response rates were 56/107 (52%) in the itraconazole group and 44/108 (41%) in the amphotericin B group [95% confidence limits: (-2%; 24%); $p = 0.26$].

Medial Officer's Comment: The MO noted that ITR was numerically superior in both analyses i.e. the relatively low risk group of patients with a shorter duration of neutropenia and the higher risk group with neutropenia > 7 days.

Analysis by Depth of Neutropenia:

As per the applicant:

In the subgroup of subjects with at least one neutrophil count $< 0.1 \times 10^9/l$, the response rates were 58/123 (47%) in the itraconazole group and 48/127 (38%) in the amphotericin B group. The two-sided 95% confidence limits were (-3%; 21%) ($p = 0.169$, [] method).

Of all responders in the intent-to-treat population, 58/84 (70%) had at least one neutrophil count $< 0.1 \times 10^9/l$ in the itraconazole group, and in the amphotericin B group, this was 48/68 (72%).

Medical Officer's Comment: *The MO agreed that itraconazole was numerically superior to amphotericin B in this analysis of high-risk patients and defers to the statistical reviewer for further comment.*

Analysis by Duration of Non-response to Antibiotic Therapy:

As per the applicant:

Subjects were grouped according to the number of days they had been on antibiotic therapy without response before the start of administration of the trial medication. The following subgroups were defined: duration of non-response to antibiotic therapy four days at most; and duration of non-response to antibiotic therapy at least five days.

In the subgroup with a duration of non-response to antibiotic therapy of four days at most, the overall response rates at the end of treatment were 46% in the itraconazole group and 49% in the amphotericin B group; the two treatments were statistically significantly equivalent ($p = 0.082$, [] method).

Table 18
Response rates by duration of non-response to antibiotic

Subgroup	Response rate n/n assessed (%)		Equivalence testing Itraconazole minus Amphotericin B	
	Itraconazole N = 179	Amphotericin B N = 180	two-sided	
Duration of non-response to antibiotic therapy:			95% CI ($\Delta = \pm 15\%$)	p-value
≤ 4 days	32/70 (46%)	34/70 (49%)	- 20%, 13%	0.082 (1) 0.076 (2)
≥ 5 days	52/109 (48%)	34/110 (31%)	4%, 29%	0.586 (1) 0.587 (2)

(1) [] method for difference in proportions controlling for stratum

(2) [] method for difference in proportions controlling for stratum

Medical Officer's Comment: *Equivalence was not shown in the subgroup of patients who received antibiotic treatment of ≤ 4 days (MO 95% CI: - 21%, 15% ($\Delta = \pm 15$)). Alternatively ITR was numerically superior in those patients with a more prolonged duration of neutropenia (MO 95% CI with CCF: 3.1%, 31% ($\Delta = \pm 15$)). The MO deferred to the statistical reviewer for further comment regarding confidence intervals but was unable to provide a clinical explanation for this finding.*

Analysis by Use and Type of Growth Factors:

As per the applicant:

Another subgroup analysis was performed for the use and type of growth factors, i.e., whether subjects were being treated with G-CSF, GM-CSF, or both, or not.

Table 19
Response rates by use and type of growth factors
As per the applicant
Revised Analysis

Type and use of growth factors	Response rate n/n assessed (%)		Equivalence testing Itraconazole minus Amphotericin B	
	Itraconazole N = 179	Amphotericin B N = 181	two-sided	
G-CSF/ GM-CSF			95% CI ($\Delta = \pm 15\%$)	p-value
No/No	44/97 (45%)	37/103 (36%)	-4%, 23%	0.211 (1) 0.219 (2)
No/Yes	5/11 (46%)	6/12 (50%)	- 63%, 19%	0.631 (1) 0.467 (2)
Yes/No	35/70 (50%)	25/66 (38%)	- 4%, 29%	0.375 (1) 0.379 (2)
Yes/Yes	0/1 (0)	-	-	-

(1)  method for difference in proportions controlling for stratum

(2)  method for difference in proportions controlling for stratum

Medical Officer's Comment: For the subgroups of patients who received no GFs or who received only G-CSF, itraconazole was numerically superior and equivalent to amphotericin B. For the small number of patients who received GM-CSF, no statistically valid conclusions could be drawn. Overall, no valid conclusions could be drawn from this analysis.

Analysis by use of Antifungal Prophylaxis:

Table 20
Response Rates by Use of Antifungal Prophylaxis

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

Medical Officer's Comment: Response rates for itraconazole-treated patients who had not received antifungal prophylaxis were numerically inferior to those obtained for

similar amphotericin B-treated patients and utilizing a delta of 15, equivalence was not shown between the treatment arms (MO-generated 95% CI with CCF: -26%, 20% ($\Delta = 15$). Equivalence was shown for patients who received antifungal prophylaxis and who constituted the bulk of the patient population (MO-generated 95% CI with CCF: 1%, 25.5% ($\Delta = \pm 15$).

Secondary Parameters of Efficacy:

EFIs:

As per the applicant, 5 subjects from each study arm developed EFIs. Of the five cases in the itraconazole group, two were identified in the blood and 3 from the lung; of the five cases in the amphotericin B group, two were identified in the blood, one from the lung, 1 was identified in bronchoscopic BAL fluid and one in the sputum. The MO reviewed the CRFs on all patients.

Itraconazole subjects (N = 5):

A03143: 55 YO male died day 8 as a consequence of an AE. Causes of death were dyspnea and fungal infection both classified as not drug related. Patient had a history of AML and had received 1 dose of PO amphotericin B prior to the start of the study. Other medications included acyclovir, amikacin, ceftazidime, ciprofloxacin, netilmicin, as well as chemotherapeutic agents. The patient received 8 days of IV itraconazole. At the time of randomization the patient had an abnormal chest exam with crepitation on the right. On day 4 dyspnea, not drug-related developed. A CT revealed pleuropneumopathy of the right upper and middle lobes. Patient continued IV ITR through day 8 when he died. Patient had *Aspergillus fumigatus* isolated from a pulmonary specimen (BAL). This patient was considered an evaluable failure due to an insufficient response.

A03198: 45 YO male died 2 days after the EOT. Patient had received 5 days of ITR IV and cause of death was undetermined. Underlying disease was AML with FUO. At the time of entry into the trial the patient had clinical evidence of a pneumonic process including a cough and left basilar rales. Prior to randomization the patient had received 3 days of IV fluconazole followed by 3 days of oral itraconazole solution as prophylaxis. On trial concomitant medications included acyclovir, amphotericin B (2 days after EOT), vancomycin, ceftazidime, chemotherapeutic agents, and oral ITR solution 50 mg PO qd. Bronchial washings (BAL) obtained on study day 5 were positive for *Geotrichium capitatum* and *Aspergillus* spp. Subsequent to the BAL and because the patient was persistently febrile, therapy was changed to AMP B. This patient was considered an evaluable failure due to an insufficient response.

A03331: 54 YO female with AML and FUO. At the time of entry into the study the patient had evidence of inflammation at the insertion site of the central catheter. Prior to randomization, the patient had received 14 days of oral fluconazole (100 PO QD) as well as 12 days of oral AMP B (10 mg QID). Concomitant medications included gentamicin, ticarcillin-clavulanate, acyclovir, and chemotherapeutic agents. Discontinued therapy

prematurely after 3 days because of a skin reaction (histologic evaluation consistent with non-specific inflammatory changes) and blood cultures (from study days 1 and 2) positive for *Candida krusei*. No further details provided. This patient was considered an evaluable failure due to an insufficient response.

AO3533: 36 YO female with AML. Prior to randomization the patient had received PO fluconazole 200 mg QD for an unspecified duration. Concomitant medications included gentamicin, vancomycin, ticarcillin-clavulanate, acyclovir, and chemotherapeutic agents. Blood cultures obtained on study day 7 because of a temperature spike were positive for *Candida guilliermondii* on study day 9. The patient's antifungal medication was changed to AMP B on study day 9. This patient was considered an evaluable failure due to an insufficient response.

A03552: 57 YO female with AML s/p transplant and FUE and a history of a recently treated pneumonia died on study day 15, 1 day after discontinuing ITR R/x (14 days). Prior to randomization the patient had received fluconazole prophylaxis for 6 days (200 mg PO QD). Concomitant study medications included imipenem and erythromycin. On study day 4, patient developed pneumonia classified as severe and not drug-related. Diagnosis was made by CxR and BAL. The patient continued on unaltered therapy despite the persistent fever and the development of hemoptysis. 1 day prior to death the patient developed a left sided hemiparesis and *Aspergillus sydowii* was isolated from a lung specimen (BAL) obtained on study day 4. Cause of death was *Aspergillus* pneumonia with brain dissemination. This patient was considered an evaluable failure due to an insufficient response.

Medical Officer's Comment: 3 ITR-treated patients had evidence of deep-seated fungal infections with either *Aspergillus* or *Geotrichium*. An additional 2 patients had evidence of systemic infections with *Candida* spp. The MO agreed that the patients were appropriately classified as failures.

Amphotericin B (N = 5)

AO3021: 60 YO male with AML and a history of COPD, perianal abscess, and oral candidiasis. Prior to randomization the patient had received oral fluconazole (400 mg QD) for 3 weeks and nystatin suspension. Concomitant medications included amoxicillin-clavulanate, amikacin, cefixime, acyclovir, and chemotherapeutic agents. On study day 5 the patient had an abnormal CxR and *Aspergillus fumigatus* was isolated from sputum obtained 3 days prior to randomization. This patient was considered an evaluable failure due to an insufficient response.

AO3217: 58 YO female with AML and FUE died on study day 9 as a consequence of an AE (aggravated condition, unrelated). At the time of entry into the study the patient had evidence of dyspnea and ronchi on exam. Prior to randomization the patient had received fluconazole (50 mg PO QD) for 30 days and oral amphotericin B. Concomitant medications included ciprofloxacin, vancomycin, ceftazidime, and chemotherapeutic agents. Patient had an abnormal CxR with respiratory insufficiency and *Aspergillus fumigatus* was isolated from a pulmonary specimen obtained from BAL performed on

study day 4. . Patient had received 5 days of amphotericin B and then prematurely discontinued the study due to deterioration and was classified as a failure. The patient died of the infection that was classified as an AE.

A03461: 49 YO female with AML and FUO developed an abnormal CxR and had *Aspergillus fumigatus* and *Candida glabrata* isolated from BAL specimens. At the time of entry into the study the patient had bilateral rales on exam. Prior antifungal prophylaxis included PO fluconazole (200 mg QD) for 20 days and PO AMP B. Concomitant medications included ciprofloxacin, tobramycin, vancomycin, imipenem, teicoplanin, and chemotherapeutic agents. On study day 4 the patient remained febrile and had a CT read as suggestive of an *Aspergillus* infection. The patient had received 16 days of amphotericin B when she discontinued due to abnormal renal function. At that time the patient was afebrile. Positive cultures were obtained after the institution of a liposomal product. The patient was classified as a failure due to an EFI

A03565: 52 YO male with lymphoma and FUO died on study day 12, 4 days after the EOT. Concomitant therapy included vancomycin, amikacin, and chemotherapeutic agents. The patient discontinued treatment prematurely on study day 8 because of severe moniliasis. *Candida albicans* from blood cultures was obtained on the first day of therapy. The investigator classified this patient as an evaluable failure despite the presence of a documented fungal infection at study start. Patient blood cultures had cleared after 48 hours of therapy. Cause of death was reported as candidemia despite the absence of positive BCs.

A03615: 21 YO male with ALL s/p transplant and FUO died on study day 26. Mucositis was present pre-study and the patient was treated with mycelelex for 13 days. Concomitant medications included imipenem and norfloxacin. On study day 23 the patient developed increased fever and bilateral rhonchi associated with tachypnea. Blood cultures obtained via a central line were positive for *Candida albicans*. Cause of death was fungal infection. The patient had bilateral upper lobe infiltrates consistent with *Aspergillus* pneumonia but no confirmatory evidence was obtained. The patient was classified as a failure with an insufficient response.

Medical Officer's Comment: *As on the ITR arm, 3 AMP B cases had evidence of deep-seated fungal infections due to aspergillosis and 2 patients had candidemia.*

Medical Officer's Comment: *The MO also found 1 itraconazole subject (#3033) with a pulmonary culture of *Aspergillus fumigatus* (unevaluable) and 1 AMP B patient (#3623) with *Candida guilliermondii* isolated from the blood (unevaluable). The FDA microbiology reviewer also found an additional 5 itraconazole subjects with positive cultures for yeast (#3087; abnormal CxR with bilateral infiltrates at EOS, #3173; abnormal CxR during trial with bilateral rales, #3180; crackles R base with normal CxR, #3423; new R-sided infiltrate and death 8 days post treatment due to pneumonia); all failures due to a change in therapy, and #3444 a failure due to death after 3 days of treatment). On the AMP B arm, an additional 4 subjects were found with positive cultures (#3097 with bacteria and yeast from a central catheter, classified as a failure due to a change in therapy, #3112 with an IV site swab with bacteria and yeast, classified*

as a failure due to persistent fever at the end of neutropenia, #3439 with Staphylococcus epidermidis and Candida krusei from a BAL culture determined to be contaminant; CxR abnormal, and #3462, yeast unknown source, classified as a failure due to renal toxicity with abnormal CxR at EOT). Further details were requested from the applicant.

As per the MO the total # of ITR patients with EFIs (microbiologically documented) was 10 (6%) vs. 9 (5%) on the AMP B arm.

Bacterial Infections:

Documented systemic bacterial infections were noted in 8 failures and 6 unevaluable subjects in the itraconazole group and in 6 and 10 subjects, respectively, in the amphotericin B group.

Viral Infections:

Documented systemic viral infections were noted in 1 failure and 1 unevaluable subject in the itraconazole group and in 3 failures and 1 unevaluable subject in the amphotericin B group.

All infections:

(Some patients had evidence of more than 1 type of infection)

Overall, any documented systemic infection was noted in 12 failures and 8 unevaluable subjects in the itraconazole group and in 12 failures and 14 unevaluable subjects in the amphotericin B group.

Survival:

In the survival analysis (ITT population), the total number of subjects who died was 18/179 (10%) in the itraconazole group and 25/181 (14%) in the amphotericin B group. The estimated median time to death was 47 days in the itraconazole group and 34 days in the amphotericin B.

Medical Officer's Comment: *Itraconazole demonstrated equivalence versus amphotericin B for this parameter using a conservative Δ of $\pm 5\%$ (MO-generated 95% CI with CCF: -3.8%, 11%).*

Fever assessment and body temperature:

As per the applicant:

Overall, 131 (73%) itraconazole subjects and 127 (70%) amphotericin B subjects defervesced; the median time to defervescence was 7 days and 6 days, respectively.

For the two-sided equivalence testing, the 95% confidence interval was (-17%; 11%); the two treatments were statistically significantly equivalent ($p = 0.044$, [redacted] method).

The median (min; max) number of febrile days during the trial was 10 (2; 32) days in the itraconazole group and 8 (1; 26) days in the amphotericin B group (The median (min; max) number of febrile days during treatment was 5 (0; 25) days in the itraconazole group and 4 (0; 21) days in the amphotericin B group).

The mean daily body temperature was 37.9°C at day -6 and 39.2°C at baseline in the itraconazole group, and 37.8°C at day -6 and 39.3°C at baseline in the amphotericin B group. During the trial, a gradual decrease in mean daily body temperature was noted in the two groups, with some fluctuations during the last 10-day period, when data were available in few subjects and the variability among the subjects was large.

Table 21
Fever assessment at day 8
Revised Analysis/ITT/As per the applicant

Stratum	Afebrile at day 8 n/n assessed (%)		Equivalence testing Itraconazole minus Amphotericin B	
	Itraconazole N = 106	Amphotericin B N = 93	two-sided	
Signs/Transplant			95% CI ($\Delta = \pm 15\%$)	p-value
No/No	34/74 (46%)	27/58 (47%)	(- 18%, 19%)	
No/Yes	14/23 (61%)	8/17 (47%)	(- 50%, 22%)	
Yes/No	4/6 (67%)	8/14 (57%)	(- 67%, 48%)	
Yes/Yes	2/3 (67%)	3/4 (75%)	(- 89%, 1%)	
Total	54/106 (51%)	46/93 (50%)	(- 17% ,11%)	0.044 (1) 0.042 (2)

(1) [redacted] method for difference in proportions controlling for stratum

(2) [redacted] method for difference in proportions controlling for stratum

Medical Officer's Comment: the MO generated 95% CI with CCF was -13.4%, 16.4% ($\Delta = 15$). Thus equivalence was shown between treatment arms for this parameter.

Duration of hospitalization:

As per the applicant:

The median (min; max) duration of hospitalization was 31 (5; 75) days in the itraconazole group and 32 (5; 111) days in the amphotericin B group.

Environmental conditions:

As per the applicant:

The majority of subjects stayed in a conventional area in the hospital (35% of the subjects in the itraconazole group and 43% of the subjects in the amphotericin B group;). In addition, 21% of the subjects in the itraconazole group and 21% of the subjects in the amphotericin B group were in a positive pressure room, 20% and 18% stayed under laminar air flow conditions, and 3% and <1% were in an intensive care unit.

72% of the subjects in the itraconazole group and 73% of the subjects in the amphotericin B group) did not undergo any environmental changes.

The maximum number of environmental changes was six in the itraconazole group and three in the amphotericin B group.

Clinical signs and symptoms:

As per the applicant:

During the trial, clinical signs and symptoms potentially attributable to systemic fungal infection were noted in 54/182 (29.7%) itraconazole subjects and 61/182 (33.5%) amphotericin B subjects.

Factor analysis:**Single-factor model:**

As per the applicant:

The only significant factor is 'days of chemotherapy before start of the treatment'. The interpretation is as follows:

The probability of response increases if the number of days between chemotherapy and the start of treatment increases.

The other factors had no statistically significantly predictive value for the probability of response.

Multifactor model:

As per the applicant:

The only factor, besides the stratification factors, that remained in the multifactor model (stepwise backward technique) was the 'days of chemotherapy before start of the treatment', which is then the same as the single factor model as described above.

Medical Officer's Comment: *The MO defers to the statistical reviewer for comment.*

Efficacy conclusions:

Trial ITR-62 was a multinational, randomized, comparative, non-blinded trial of ITR IV/PO versus AMP B in the empiric therapy of febrile neutropenic subjects. The applicant received concurrence from the FDA that in view of the previously demonstrated antifungal activity of ITR, 1 trial was adequate in order to attain this indication. The applicant provided multiple analyses on the ITT and the per protocol populations. However, the MO determined that the reporting of the analyses from both was not indicated given the small differences in patient #s between them. Additionally, it was determined that the ITT population was a more accurate one to assess given that it is more consistent with clinical practice. The primary parameter of efficacy was "response at the EOT" defined as the absence of failure or unevaluability by the applicant who provided a composite endpoint of survival, defervescence, and presence or absence of EFIs. The MO determined that response was assessable in the ITT population (received 1 dose with follow-up) and defined it as resolution of fever and neutropenia, survival, and absence of EFIs.

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.

Overall response rates in the ITT were 84/179 (47%) ITR versus 68/181 (38%) AMP B (MO 95% CI – 1.4%, 20%, $\Delta = \pm 15$) demonstrating equivalence between the treatment arms. This rate included patients that had received previous antifungal prophylaxis. The majority of patients in whom a "response" was seen had an FUO and were non-transplant recipients. In those subjects who had FUO and transplant the response rates were

numerically similar (46%) each arm. A review of the “responders” revealed that 32/179 (18%) of ITR patients as compared to 24/181 (13%) of AMP B patients received 10 days of therapy and became afebrile. 52/179 (29%) ITR versus 44/181 (25%) of AMP B patients were classified as responders because they were not failures or unevaluable.

71/179 ITR patients (40%) were failures as compared to 69/181 (39%) of AMP B patients.

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 37/181 (20%) amphotericin B).

The response rate obtained when subjects that discontinued treatment due to an adverse event were excluded was 83/144 (58%) on the itraconazole arm versus 67/111 (60%) on the amphotericin B arm (95% CI – 14.8%, 9.4%, $\Delta = \pm 15$).

When patients were assessed by transplant status the response 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.

Equivalent results were obtained when the data were analyzed for response rate by duration of neutropenia (duration < 7 days: 27/60 (45%) ITR versus 23/58 (40%) AMP B, duration > 7 days: 56/107 (52%) ITR vs. 44/108 (41%) AMP B) and by depth of neutropenia (ANC < 100: 58/123 (47%) ITR vs. 48/127 (38%) AMP B).

When response rate was assessed by the duration of previous antimicrobial therapy, those patients who had received ≤ 4 days had response rates of 32/70 (46%) ITR vs. 34/70 (49%) AMP B (95% CI – 21%, 13%, $\Delta = \pm 15$) demonstrating a lack of equivalence between treatment arms. When the duration was ≥ 5 days, equivalence was shown (52/109 (48%) ITR vs. 34/110 (31%) AMP B, (95% CI 3.1%, 31%, $\Delta = \pm 15$).

The MO assessed response rates in the ITT population by the use of previous antifungal prophylaxis and found that equivalence was NOT demonstrated in those patients who had not received prophylaxis (ITR 21/47 (45%) vs. AMP B 20/42 (48%): (95 CI –25.9%, 20%, $\Delta = \pm 15$), as compared to those that received it (ITR 63/132 (48%) vs. AMP B 48/139 (35%); (95% CI 0.8%, 25.5%, $\Delta = \pm 15$). The significance of this finding was unclear however, concerns were raised as to the true effectiveness of ITR as compared to AMP B in an azole or antifungal naive population requiring ET for FN.

As per the sponsor 5 subjects on each arm developed EFIs. 3 ITR subjects had evidence of *Aspergillus* infection and 2 had evidence of *Candida* spp. On the AMP B arm, 3 subjects had evidence of *Aspergillus* and 2 had evidence of *Candida* spp. A review by the FDA revealed an additional 5 ITR and 4 AMP B subjects with positive fungal cultures that were classified as failures due to insufficient response. Thus the total # of EFIs was 10 (6%) on the ITR arm and 9 (5%) on the AMP B arm.

18/179 ITR subjects (10%) died as compared to 25/181 (14%) AMP B (95% CI – 3.8%, 11%, $\Delta = \pm 5$). Similar percentages of patients defervesced (131/179 (73%) ITR vs. 127/181 (70%) AMP B) and median time to defervescence was 7 and 6 days respectively. 50% of subjects on each arm were afebrile by day 8.

In conclusion, ITR appeared non-inferior to AMP B in the empiric therapy of febrile neutropenic subjects in the ITT population. If only patients who were treatment naïve (no previous antifungal prophylaxis) were assessed, equivalence was not shown.

A larger number of ITR patients discontinued therapy because of an insufficient response as compared to the AMP B arm where patients discontinued because of intolerance. Due to the open, non-blinded nature of this trial, an element of investigator bias could have been introduced regarding the early termination of ITR and a switch to AMP B. ITR appeared most effective in those patients with FUO and non-transplant recipients.

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Safety:

As stated in the introduction, the safety of study ITR-INT-62 was reviewed as part of the original NDA 20,966. Specifically, an initial review was performed on the first 191 patients (ITR 95, AMP B 96) enrolled (Addendum I to MOR NDA 20,966, pages 70 – 87). Subsequent to the above review, the applicant submitted a 4 month (9/10/98) and a 6 month (11/10/98) safety update. The 4 month update contained information on deaths and SAEs. The MO concluded that the additional safety information provided no significant changes to the original conclusion. The 6 month safety update contained data tabulations on an additional 193 patients from the completed trial 62. The MO concluded “the addition of 97 itraconazole patients and 96 amphotericin B patients had minimal impact on the overall incidence of AEs as well as the type of AEs seen” (Addendum II to MOR 20,966 pages 1 – 27). The MO made a final determination of concurrence with the applicant’s analyses.

A brief review of all AEs can be found below. For all death summaries, Please see the original MOR of NDA 20-966.

Safety Population Analyzed:

The all subjects population, that is all randomized patients who received at least one dose of study drug were included in the analyses (192 per arm).

The median duration of exposure was 8.5 (2; 35) days for the ITR-treated patients and 7 (1; 28) days for the AMP-B-treated patients. For those subjects who received oral treatment, i.e., 65 subjects in the itraconazole group, the median duration of intravenous treatment was 9 (7; 15) days and the median duration of oral treatment was 7 (1; 24) days.

The most frequently reported AEs were from the GI tract and the body as a whole - general disorders and were noted in 172/192 (89.6%) itraconazole subjects and 181/192 (94.3%) amphotericin B subjects. Adverse events reported in at least 2% of the subjects in any group are summarized in the following table.

Table 22
Kind and incidence of adverse events by body system by at least 2% of subjects

ADVERSE EVENT	Itraconazole N = 192 (100%)	Amphotericin B N = 192 (100%)
GASTRO-INTESTINAL SYSTEM	114 (59%)	114 (59%)
Diarrhea	39 (20%)	53 (28%)
Nausea	46 (24%)	45 (23%)
Vomiting	37 (19%)	40 (21%)
Abdominal Pain	15 (8%)	19 (10%)
Stomatitis	13 (7%)	7 (4%)
Constipation	10 (5%)	8 (4%)

Mucositis NOS	7 (4%)	11 (6%)
Dry Mouth	5 (3%)	4 (2%)
Ulcerative Stomatitis	4 (2%)	5 (3%)
Hemorrhoids	4 (2%)	4 (2%)
GI disorder NOS	4 (2%)	4 (2%)
Oral Hemorrhage	2 (1%)	4 (2%)
BODY AS A WHOLE	82 (43%)**	115 (60%)
Rigors	19 (10%)***	77 (40%)
Fever	12 (6%)	20 (10%)
Chest Pain	15 (8%)	8 (4%)
Edema	13 (7%)	9 (5%)
Edema Peripheral	8 (4%)	14 (7%)
Back Pain	9 (5%)	9 (5%)
Injury	7 (4%)	6 (3%)
Allergic Reaction	6 (3%)	5 (3%)
Pain	6 (3%)	7 (4%)
Condition Aggravated	3 (2%)	7 (4%)
Abdomen Enlarged	5 (3%)	4 (2%)
Fatigue	3 (2%)	5 (3%)
Malaise	2 (1%)	5 (3%)
METABOLIC AND NUTRITIONAL DISORDERS	69 (36%)***	118 (61%)
Hypokalemia	34 (18%)**	59 (31%)
Creatinine Increased	8 (4%)***	50 (26%)
Hypomagnesemia	14 (7%)	17 (9%)
Edema generalized	16 (8%)	13 (7%)
Fluid Overload	10 (5%)	15 (8%)
BUN Increased	4 (2%)**	15 (8%)
Hyperglycemia	6 (3%)	9 (5%)
Hypocalcemia	7 (4%)	8 (4%)
Alkaline Phosphatase Increased	9 (5%)	5 (3%)
Hypophosphatemia	6 (3%)	6 (3%)
LDH Increased	5 (3%)	-
RESPIRATORY SYSTEM DISORDERS	77 (40%)	71 (37%)
Dyspnea	17 (9%)	21 (11%)
Coughing	25 (13%)**	10 (5%)
Pulmonary Edema	10 (5%)	12 (6%)
Pneumonia	10 (5%)	11 (6%)
Pulmonary Infiltration	13 (7%)*	4 (2%)
Respiratory Disorder	7 (4%)	10 (5%)
Pleural Effusion	6 (3%)	5 (3%)
Pneumonitis	5 (3%)	6 (3%)
Hemoptysis	4 (2%)	6 (3%)

Bronchospasm	3 (2%)	6 (3%)
CxR Abnormal	4 (2%)	5 (3%)
Respiratory Insufficiency	4 (2%)	5 (3%)
Hypoxia	5 (3%)	2 (1%)
Pharyngitis	5 (3%)	3 (2%)
SKIN AND APPENDAGES DISORDERS	56 (29%)	48 (25%)
Rash	25 (13%)*	14 (7%)
Rash Erythematous	13 (7%)	10 (5%)
Sweating Increased	11 (6%)	4 (2%)
Bullous Eruption	4 (2%)	2 (1%)
Pruritus	7 (4%)	5 (3%)
Skin Disorder	4 (2%)	3 (2%)
Skin Discoloration	1 (0.5%)	4 (2%)
URINARY SYSTEM DISORDERS	35 (18%)	49 (26%)
Renal Function Abnormal	8 (4%)**	24 (13%)
Hematuria	8 (4%)	4 (2%)
Urine Abnormal	8 (4%)	2 (1%)
Incontinence	5 (3%)	4 (2%)
Albuminuria	4 (2%)	1 (0.5%)
PSYCHIATRIC DISORDERS	43 (22%)	35 (18%)
Confusion	10 (5%)	7 (4%)
Anxiety	8 (4%)	8 (4%)
Somnolence	5 (3%)	8 (4%)
Insomnia	5 (3%)	7 (4%)
Hallucination	6 (3%)	5 (3%)
Agitation	8 (4%)	1 (0.5%)
Sleep disorder	4 (2%)	3 (2%)
Anorexia	3 (2%)	3 (2%)
Depression	3 (2%)	-
LIVER AND BILIARY SYSTEM DISORDERS	35 (18%)	30 (16%)
Bilirubinemia	19 (10%)*	9 (5%)
Hepatic Function Abnormal	6 (3%)	9 (5%)
Jaundice	5 (3%)	6 (3%)
SGPT Increased	5 (3%)	3 (2%)
gGT Increased	4 (2%)	3 (2%)
CENTR & PERIPH NERVOUS SYSTEM DISORDERS	36 (19%)	27 (14%)
Headache	13 (7%)	15 (8%)
Dizziness	8 (4%)	7 (4%)
Tremor	8 (4%)	3 (2%)
CARDIOVASCULAR DISORDERS, GENERAL	27 (14%)	36 (19%)

Hypotension	13 (7%)	21 (11%)
Hypertension	4 (2%)	7 (4%)
Cardiac Failure	7 (4%)	2 (1%)
PLATELET, BLEEDING & CLOTTING DISORDERS	21 (11%)	24 (13%)
Epistaxis	9 (5%)	15 (8%)
Purpura	6 (3%)	6 (3%)
RESISTANCE MECHANISM DISORDERS	20 (10%)	23 (12%)
Bacterial Infection	7 (4%)	3 (2%)
Sepsis	2 (1%)	8 (4%)
Herpes Simplex	5 (3%)	3 (2%)
Fungal Infection	1 (0.5%)	6 (3%)
HEART RATE AND RHYTHM DISORDERS	12 (6%)	19 (10%)
Tachycardia	6 (3%)	12 (6%)
Atrial fibrillation	5 (3%)	3 (2%)
VISION DISORDERS	13 (7%)	15 (8%)
Conjunctivitis	4 (2%)	6 (3%)
Abnormal Vision	3 (2%)	3 (2%)
APPLICATION SITE DISORDERS	11 (6%)	11(6%)
Application Site reaction	7 (4%)	6 (3%)
Injection Site Inflammation	3 (2%)	1 (0.5%)
VASCULAR	6 (3%)	7 (4%)
Flushing	4 (2%)	3 (2%)
WHITE CELL DISORDERS	4 (2%)	1 (0.5%)
Granulocytopenia	3 (2%)	1 (0.5%)
No. (%) with any AE	172 (90%)	181 (94%)

Asterisks refer to differences with amphotericin B. Levels of statistical significance: * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$

Medical Officer's Comment: Differences between the two treatment groups were noted for rigors (10% itraconazole subjects versus 40% amphotericin B subjects; $p = 0.001$), and for metabolic and nutritional disorders in general (36% versus 61% of the subjects, respectively, $p = 0.001$; CREATININE increased: 4% ITR versus 26% AMP B, $p = 0.001$). A statistically significant difference ($p \leq 0.05$) was noted in the incidence of bilirubinemia and rash in favor of the AMP-B arm. These differences were consistent with the well-delineated AE profiles of both ITR and AMP-B.

Because of the results of a recent report to the agency from Janssen regarding a negative inotropic effect of the IV formulation of itraconazole leading to decreased left ventricular function in humans, the MO assessed the incidence of cardiac failure on both study arms and found a 4% incidence of cardiac failure on the itraconazole arm as compared to 1% on the AMP B arm. A review of the CRFs did not reveal any clear connection between

this AE and itraconazole treatment because of the subjects' overall debilitated states and concurrent therapies to which these events could be attributed.

AEs by Treatment Formulation:

For itraconazole, adverse events were also analyzed by treatment formulation, i.e., with onset either during the intravenous or the oral treatment period. The total number of subjects with an AE was 169/192 (88%) IV versus 39/65 (60%) PO. In general, most adverse events had already started during the intravenous treatment period. The most striking differences were noted for hypokalemia (percentage of subjects with onset during intravenous/oral treatment: 33/192 (17%)/ 3/65 (5%); hypocalcemia: 6/192 (3%)/0%; bilirubinemia: 18/192 (9%)/ 2/65 (3%); rigors (19/192 (10%)/0%); vomiting (34/192 (18%)/ 6/65 (9%); dyspnea (17/192 (9%)/0%); generalized edema (16/192 (8%)/0%); coughing (23/192 (12%)/ 3/65 (5%); headache (13/192 (7%)/0%); rash (22/192 (11%)/ 3/65 (5%), and erythematous rash (13/192 (7%)/ 1/65 (2%).

AEs by Age Group:

Adverse events were also analyzed per age group, i.e., ≤65 years or >65 years. For the adverse events with the most remarkable differences in incidence between the two groups, i.e., rigors and creatinine in blood increased, the incidence was higher in the amphotericin B group, and this effect was more pronounced in the older subjects.

Severity:

Severe adverse events were noted in 37/192 (19%) itraconazole subjects and in 65/192 (34%) amphotericin B subjects ($p = 0.001$). The most frequently reported severe adverse events were dyspnea (5 itraconazole subjects and 7 amphotericin B subjects), rigors (0 and 11 subjects, respectively), hypotension (3 and 6 subjects), creatinine increased (0 and 7 subjects), hypokalemia (0 and 6 subjects), fever (1 and 5 subjects), renal function abnormal (0 and 5 subjects), and bilirubinemia (4 and 2 subjects).

Relatedness to Study Drug:

The investigators considered one or more AEs to be definitely drug-related in 9/192 (5%) itraconazole subjects and in 103/192 (54%) amphotericin B subjects ($p < 0.001$). Possibly drug-related AEs were noted in 83/192 (43%) itraconazole subjects and 105/192 (55%) amphotericin B subjects ($p = 0.025$). All definitely and possibly drug-related adverse events are summarized below.

Table 23
Definitely and Possibly Drug-related Adverse Events

Adverse event (WHO preferred term)	No. of subjects	
	Itraconazole N = 192	Amphotericin B N = 192
Definitely Drug-related AE		
TOTAL	9 (4.7%)	103 (54%)
General/Whole Body		
Rigors	-	50 (26%)
Fever	-	11 (5.7%)
Allergic Reaction	-	1 (0.5%)
Increased Drug Level	1 (0.5%)	-
Hyperpyrexia	-	1 (0.5%)
Temperature Sensation	-	1 (0.5%)
Flushing	-	2 (1%)
Medication Error	1 (0.5%)	-
GI System		
Nausea	3 (1.5%)	1 (0.5%)
Vomiting	1 (0.5%)	1 (0.5%)
Renal And Electrolyte		
Creatinine Increased	-	29 (15%)
Hypokalemia	1 (0.5%)	24 (12.5%)
Hypomagnesemia	-	1 (0.5%)
Increased BUN	-	4 (2%)
Hypocalcemia	-	1 (0.5%)
Abnormal Renal function	-	12
Decreased Cr. Clearance	-	1 (0.5%)
Toxic Nephropathy	-	3 (1.5%)
Interstitial Nephritis	-	1 (0.5%)
Glomerulonephritis	-	1 (0.5%)
Cardiovascular		
Tachycardia	-	1 (0.5%)
Hypotension	-	1 (0.5%)
Hypertension	-	1 (0.5%)
CNS		
Headache	1 (0.5%)	-
Dizziness	1 (0.5%)	-
Nervousness	-	1 (0.5%)
Confusion	-	1 (0.5%)
Abnormal Hepatic Function		
Bilirubinemia	-	1 (0.5%)
Abnormal Hepatic Function	-	1 (0.5%)
SGOT Increased	-	1(0.5%)

Respiratory		
Cyanosis	-	1 (0.5%)
Dyspnea	-	2 (1%)
Bronchospasm	-	2 (1%)
Possibly drug-related AE		
Total No. (%)	83 (43%)	105 (55%)
Body as a Whole/General		
Rigors	1 (0.5%)	14 (7.3%)
Periorbital Edema	1 (0.5%)	-
Oral Edema	1 (0.5%)	-
Decreased Tolerance	-	1 (0.5%)
Decreased Therapeutic Response	-	1 (0.5%)
Edema	29 (1%)	1 (0.5%)
Peripheral Edema	1 (0.5%)	2 (1%)
Back Pain	-	1 (0.5%)
Injury	1 (0.5%)	-
Pain	1 (0.5%)	1 (0.5%)
Fatigue	1 (0.5%)	1 (0.5%)
Malaise	-	2 (1%)
Taste Perversion	1 (0.5%)	1 (0.5%)
Taste Loss	-	1 (0.5%)
Flushing	1 (0.5%)	1 (0.5%)
Myalgia	1 (0.5%)	-
Eye Burning	-	1 (0.5%)
GI System		
Nausea	18 (9.4%)	25 (13%)
Diarrhea	19 (9.9%)	15 (7.8%)
Vomiting	12 (6.2%)	17 (8.8%)
Abdominal Pain	5 (2.6%)	6 (3%)
Mucositis	3 (1.5%)	1 (0.5%)
Dyspepsia	-	1 (0.5%)
Melena	-	1 (0.5%)
Renal and Electrolyte		
Hypokalemia	17 (8.8%)	29 (15.1%)
Creatinine Increased	5 (2.6%)	19 (9.9%)
Abnormal Renal Function	1 (0.5%)	10 (5.2%)
Hypomagnesemia	3 (1.5%)	7 (3.6%)
Hyponatremia	-	1 (0.5%)
Hyperuricemia	1 (0.5%)	-
Hyperchloremia	1 (0.5%)	-
Electrolyte Abnormality	-	2 (1%)
Hypoproteinemia	-	1 (0.5%)
Dehydration	-	1 (0.5%)

Acidosis	1 (0.5%)	2 (1%)
Hypophosphatemia	2 (1%)	3 (1.5%)
Hypocalcemia	2 (1%)	3 (1.5%)
Hyperglycemia	1 (0.5%)	1 (0.5%)
Fluid Overload	2 (1%)	5 (2.6%)
Generalized Edema	1 (0.5%)	2 (1%)
BUN Increased	2 (1%)	8 (4.1%)
Abnormal Renal Function	1 (0.5%)	10 (5.2%)
Hematuria	1 (0.5%)	-
Abnormal Urine	1 (0.5%)	-
Urinary Incontinence	1 (0.5%)	-
Acute Renal Failure	-	2 (1%)
Albuminuria	1 (0.5%)	-
Decreased Cr. Clearance	1 (0.5%)	1 (0.5%)
Micturition Disorder	-	1 (0.5%)
Fluid Overload	2 (1%)	5 (2.6%)
Abnormal Hepatic Function		
Bilirubinemia	11 (5.7%)	5 (2.6%)
Jaundice	4 (2%)	-
Enzyme Abnormality	-	2 (1%)
Increased LDH	4 (2%)	-
Increased Alk. Phos.	4 (2%)	4 (2%)
Abnormal Hepatic Function	5 (2.6%)	3 (1.5%)
SGPT Increased	5 (2.6%)	2 (1%)
SGOT Increased	4 (2%)	-
gGT Increased	2 (1%)	1 (0.5%)
Cholestatic Hepatitis	2 (1%)	1 (0.5%)
Hepatomegaly	2 (1%)	1 (0.5%)
Hepatitis	1 (0.5%)	1 (0.5%)
Hepatocellular Damage	1 (0.5%)	-
Skin		
Rash	9 (4.6%)	5 (2.6%)
Erythematous Rash	3 (1.5%)	1 (0.5%)
Increased Sweating	4 (2%)	1 (0.5%)
Pruritus	2 (1%)	1 (0.5%)
Maculopapular Rash	1 (0.5%)	-
Localized Skin Reaction	1 (0.5%)	-
Acne	-	1 (0.5%)
Dry Skin	-	1 (0.5%)
Urticaria	-	1 (0.5%)
Injection Site Inflammation	1 (0.5%)	1 (0.5%)
Cardiovascular		
Hypotension	2 (1%)	5 (2.6%)
Syncope	1 (0.5%)	-

Tachycardia	2 (1%)	4 (2%)
Atrial Fibrillation	-	1 (0.5%)
Arrhythmia	-	1 (0.5%)
Cardiac Arrest	-	1 (0.5%)
Aggravated Hypertension	-	1 (0.5%)
Hypertension	-	3 (1.5%)
Cardiac Failure	-	1 (0.5%)
Dependent Edema	-	1 (0.5%)
Postural Hypotension	-	1 (0.5%)
Eye		
Abnormal Vision	1 (0.5%)	1 (0.5%)
Mydriasis	1 (0.5%)	-
Conjunctivitis	-	1 (0.5%)
Infection		
Sepsis	-	1 (0.5%)
Fungal Infection	-	1 (0.5%)
CNS and Peripheral Nervous System		
Headache	3 (1.5%)	4 (2%)
Dizziness	1 (0.5%)	2 (1%)
Tremor	2 (1%)	1 (0.5%)
Abnormal Gait	1 (0.5%)	-
Fecal Incontinence	-	1 (0.5%)
Dystonia	-	1 (0.5%)
Hypoesthesia	1 (0.5%)	-
Involuntary Muscle Contr.	1 (0.5%)	-
Aggressive Reaction	1 (0.5%)	-
Apathy	-	1 (0.5%)
Confusion	1 (0.5%)	2 (1%)
Anxiety	-	1 (0.5%)
Somnolence	1 (0.5%)	2 (1%)
Hallucination	1 (0.5%)	1 (0.5%)
Anorexia	-	2 (1%)
Respiratory		
Dyspnea	2 (1%)	3 (1.5%)
Coughing	1 (0.5%)	-
Pulmonary Edema	1 (0.5%)	3 (1.5%)
Pulmonary Infiltration	2 (1%)	-
Respiratory Disorder	-	2 (1%)
Pleural Effusion	1 (0.5%)	1 (0.5%)
Bronchospasm	1 (0.5%)	1 (0.5%)
Abnormal CxR	-	1 (0.5%)
Hypoxia	1 (0.5%)	-
Sinusitis	-	1 (0.5%)

Medical Officer's Comment: *Of note were the 11 cases of bilirubinemia possibly attributed to ITR as compared to the 5 cases on the AMP-B arm. Additionally there were 4 ITR cases with therapy-associated jaundice and 5, and 4 cases with SGOT and SGPT increases. These events were previously reviewed in the MOR of NDA 20-966.*

Due to the recently reported negative inotropic effect of itraconazole on cardiac function, the MO assessed the incidence of cardiac failure attributable to treatment and found only 1 case on the amphotericin B arm where the investigator determined a possible relationship to study drug as compared to no cases on the itraconazole arm,

Deaths:

The total number of deaths during this trial was 19/192 (10%) in the itraconazole group and 27/192 (14 %) in the amphotericin B group. 16 of the ITR deaths and 23 of the AMP B deaths occurred during the treatment period. Of these, all but two amphotericin B subjects were included in the survival analysis. All death summaries can be found in the Appendix to the MOR of NDA 20,966 (pp. 72 – 74). The MO concluded that none of the deaths on either study arm were related to study drug.

Serious AEs other than Death:

Other serious AEs were reported in 22 (11%) itraconazole subjects and 28 (15%) amphotericin B subjects. Other serious adverse events noted in more than one subject on either arm are summarized below:

Table 24
Serious AEs

Adverse event (WHO preferred term)	ITR (N = 192)	AMPHO B (N = 192)
Renal Function Abnormal	1 (1%)	7 (4%)
Bilirubinemia	3 (2%)	2 (1%)
Dyspnea	2 (1%)	3 (2%)
Sepsis	-	4 (2%)
Fever	3 (2%)	1 (1%)
Hypotension	1 (1%)	4 (2%)
Hypoxia	4 (2%)	-
Creatinine increased	-	3 (2%)
Pulmonary infiltration	3 (2%)	-
Cerebrovascular disorder	1 (1%)	1 (1%)
Confusion	2 (1%)	-
Fibrillation atrial	2 (1%)	-
Hepatic function abnormal	2 (1%)	-
Hypernatremia	2 (1%)	-
Nausea	2 (1%)	-
Renal failure acute	1 (1%)	1 (1%)
No. (%) with any other SAE	22 (11%)	28 (15%)

Medical Officer's Comment: Remarkable differences between the two groups were noted for abnormal renal function: (1 ITR subject versus 7 AMP B subjects) and for hypotension (1 ITR and 4 AMP B subjects). Both of these events are strongly associated with AMP B administration and not unexpected. Additionally, hepatic dysfunction expressed as "Hepatic Function Abnormal" was seen in 2 ITR patients and 0 AMP B patients. Serious bilirubinemia was seen in 2 patients on both arms. All of these events have been reviewed and can be found in the MOR of NDA 20-966.

1 ITR subject had other serious AEs during the post-treatment period (including the period up to 30 days after the last intake of trial medication; #3328: *Pneumocystis carinii* infection and respiratory insufficiency). Therefore, the total number of subjects with other serious adverse events was 23 in the itraconazole group and 28 in the amphotericin B group.

Discontinuations due to an AE:

36 (19%) ITR subjects and 73 (38%) AMP-B subjects discontinued treatment because of AEs ($p < 0.001$). Adverse events leading to withdrawal noted in more than one subject in any group are summarized in the below:

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Table 25
AEs leading to discontinuation in > 0.5% of patients

Adverse event (WHO preferred term)	No. of subjects	
	ITR (n = 192)	AMP-B (n = 192)
Creatinine increased	1 (0.5%)	24 (12.5%)
Abnormal renal function	-	16 (8.3%)
Rigors	-	8 (4.2%)
Dyspnea	6 (3.1%)	5 (2.6%)
Nausea	6 (3.1%)	1 (0.5%)
BUN increased	1 (0.5%)	5 (2.6%)
Rash	5 (2.6%)	-
Hypoxia	3 (1.5%)	2 (1%)
Fever	2 (1%)	3 (1.5%)
Hypotension	-	5 (2.6%)
Bilirubinemia	3 (1.5%)	1 (0.5%)
Sepsis	1 (0.5%)	3 (1.5%)
Pulmonary infiltration	3 (1.5%)	-
Vomiting	3 (1.5%)	-
Hepatic function abnormal	2 (1%)	1 (0.5%)
Pneumonia	2 (1%)	1 (0.5%)
Respiratory insufficiency	2 (1%)	1 (0.5%)
Bronchospasm	1 (0.5%)	2 (1%)
Confusion	1 (0.5%)	2 (1%)
Tachycardia	1 (0.5%)	2 (1%)
Hypokalemia	-	3 (1.5%)
Toxic nephropathy	-	3 (1.5%)
Cardiac failure	2 (1%)	-
Jaundice	2 (1%)	-
SGPT increased	2 (1%)	-
SGOT increased	2 (1%)	-
Total No. (%)	36 (19%)	73 (38%)

Medical Officer's Comment: Major differences between the two groups were noted for creatinine increased (1 ITR versus 24 AMP B subjects) and abnormal renal function (0 ITR versus 16 AMP B subjects). 2 ITR subjects discontinued therapy due to hepatic function abnormalities as compared to none of the AMP B subjects and 3 ITR subjects discontinued due to bilirubinemia as compared to 1 AMP B subject.

6/65 (9%) subjects who continued itraconazole oral solution therapy, stopped the oral treatment due to nausea or vomiting.

Of note, 2 itraconazole subjects discontinued treatment because of cardiac failure. A review of the CRFs did not reveal a clear relationship to study drug.

Laboratory:

Clinical laboratory data were available for all subjects; 187/192 (97%) itraconazole subjects and 173/192 (90%) amphotericin B subjects had data both at baseline and at least once during or at the end of treatment.

As per the applicant:

Overall, from baseline to end point, there was a tendency towards an increase in electrolytes (chloride, phosphorus and sodium), liver function tests (alkaline phosphatase, lactate dehydrogenase, AST and ALT) and neutrophils and monocytes, there was a tendency towards a decrease in glucose, and towards a change (decrease as well as increase) in potassium, urea, and blood urea nitrogen in the itraconazole group. In the amphotericin B group, there was a tendency towards an increase in electrolytes (chloride, phosphorus, and sodium but not potassium, which tended to decrease), an increase in liver function tests (alkaline phosphatase, gGT, lactate dehydrogenase, AST and ALT), a tendency towards an increase in renal function tests (blood urea nitrogen, urea, uric acid and creatinine) and triglycerides, neutrophils and monocytes, and a tendency towards a decrease in lymphocytes.

A separate analysis for creatinine levels and creatinine clearance indicated that the median creatinine level decreased from 70.0 micromol/l at baseline to 67.1 micromol/l at end point in the itraconazole group and increased from 70.7 micromol/l to 102.3 micromol/l at end point in the amphotericin B group. The median creatinine clearance increased from 111.3 ml/min at selection to 117.5 ml/min at end point in the itraconazole group and decreased from 106.5 ml/min to 73.0 ml/min in the amphotericin B group. For creatinine levels and for creatinine clearance, the intergroup differences were statistically significant at all time points after baseline, except for day 28. Renal toxicity was defined as a creatinine level of more than twice the baseline value or a difference with the baseline value of more than 88.4 micromol/l, or a percentage change in

creatinine clearance of less than -50%. Renal toxicity was noted in 10 (5%) itraconazole subjects and 46 (24%) amphotericin B subjects ($p < 0.001$; During the trial, there were no consistent changes in any of the urine parameters).

Individual clinically significant abnormalities:

Code 4 or 5 (Lippert and Lehmann) that developed during the trial from a normal baseline.

- Bilirubinemia: 21/187 (12.3%) ITR subjects and 15/173 (8.6%) AMP B subjects had a code 4 or 5 abnormality.
- Hyperchloremia: 9/187 (4.8%) ITR subjects and 35/173 (20.2%) AMP B subjects had a code 4 or 5 abnormality
- Hypochloremia: 4/187 (2.1%) ITR subjects and 2/173 (1.1%) AMP B subjects had a code 4 or 5 abnormality
- Hypoalbuminemia: 31/187 (16.5%) ITR subjects and 33/173 (19%) AMP B subjects had a code 4 or 5 abnormality
- Hypouricemia: 22/187 (11.7%) ITR subjects and 2/173 (1.1%) AMP B subjects had a code 4 or 5 abnormality
- BUN: 15/187 (8%) ITR subjects and 66/173 (38.1%) AMP B subjects had a code 4 or 5 abnormality

Overall the clinically significant laboratory abnormalities seen between the 2 treatment groups were similar and could be accounted for by the underlying disease process. Differences between the two groups were noted for chloride (9 subjects in the itraconazole group and 35 subjects in the amphotericin B group), urea (15 and 66 subjects, respectively), and uric acid (22 and 2 subjects). For chloride, the increases in the amphotericin B group may have been related to the infusion of sodium chloride.

When laboratory values were assessed by NIH toxicity grades, 72/187 (39%) ITR patients and 101/173 (58%) AMP B patients had a 'code-4' or a 'code-5' important abnormality during the trial (NIH toxicity grade 2 or 3).

Code 4 or 5 abnormalities (NIH) were as follows:

- Hypocalcemia: 39/187(20.8%) ITR subjects and 34/173 (19.6%) AMP B subjects had a code 4 or 5 abnormality.
- Hyperkalemia: 1/187 (0.5%) ITR subjects and 6/173 (3.5%) AMP B subjects had a code 4 or 5 abnormality.
- Creatinine increased: 8/187 (4.3%) ITR subjects and 24/173 (13.9%) AMP B subjects had a code 4 or 5 abnormality.
- Hyperglycemia: 14/187 (7.5%) ITR subjects and 26/173 (15%) AMP B subjects had a code 4 or 5 abnormality.

- Alkaline Phosphatase: 7/187 (3.7%) ITR subjects and 10/173 (5.7%) AMP B subjects had a code 4 or 5 abnormality.
- gGT Increased: 19/187 (10.2%) ITR subjects and 34/173 (19.6%) AMP B subjects had a code 4 or 5 abnormality
- AST Increased: 8/187 (4.3%) ITR subjects and 8/173 (4.6%) AMP B subjects had a code 4 or 5 abnormality
- ALT Increased: 14/187 (7.5%) ITR subjects and 18/173 (10.4%) AMP B subjects had a code 4 or 5 abnormality

As per the applicant:

As compared with the itraconazole group, more abnormalities were noted in the amphotericin B group for potassium, creatinine, glucose, gGT and ALT, and more NIH grade 3 abnormalities were noted for calcium, potassium, glucose and alkaline phosphatase.

For potassium, the lower limit of the NIH toxicity grades was 0 mmol/l. Therefore, hypokalemia, reported as an adverse event in 34 itraconazole subjects and 59 amphotericin B subjects, could not be detected in this analysis. When the lower limit for potassium was set at 3.5 mmol/l (which is accepted practice), the number of subjects with a 'code-4' decrease in potassium was 32 in the itraconazole group and 53 in the amphotericin B group, which is in line with the incidence reported for the adverse event.

For ALT, generally more NIH grade 2 and grade 3 abnormalities were noted in the amphotericin B group, but more NIH grade 3 abnormalities were noted in the itraconazole group (6 abnormalities) than in the amphotericin B group (3 abnormalities).

Medical Officer's Review of Patients with LFT abnormalities:

Based on a review of individual patient line listings and laboratory values, no deaths were associated with LFT abnormalities.

Bilirubin: The MO found that 21 ITR patients with normal bilirubin values at baseline had increased levels by study day 3 in 10, study day 8 in 8, and study day 15 in 3 patients. In 17 of these patients the last value obtained was above normal. In 4 cases resolution of the abnormality occurred by study day 28.

Additionally the following ITR patients were found that were not listed in the above line listings but were found in the premature discontinuation summaries:

- A03002: severe, possibly drug-related jaundice and bilirubinemia after 2 days of IV ITR. Therapy was discontinued on day 4. No follow-up.
- A03033: Bilirubinemia developed after 3 days of ITR treatment and was determined to be severe and possibly drug-related. Therapy was terminated on day 6 for other causes.
- A03274: Bilirubinemia developed after 3 days of ITR treatment and was determined to be severe and possibly drug-related. Transaminase elevations were also found and rated similarly. Therapy was terminated on day 4 and outcome was not provided. (Bilirubin 11 $\mu\text{mol/L}$ at entry to 39 at day 3, AST 15 U/L at entry to 220 U/L, and ALT 29 U/L at entry to 292 U/L at day 3).
- A03528: Discontinued therapy on day 3 because of bilirubinemia determined to be of moderate severity and not drug-related.
- A03137: Jaundice developed on day 3 and treatment was discontinued on day 5. The event was rated as moderate and possibly drug-related. No lab or outcome was provided.

Therefore 26/187 (13.9%) ITR patients had significant elevations of serum bilirubin, most frequently occurring during the IV treatment phase. No additional AMP B-treated patients were found.

SGOT/SGPT:

A total of 7 ITR patients (4 in the study report and an additional 3 found by the MO) had normal ALT and/or AST at baseline that tripled by day 3 of IV R/x.

- A3102: Discontinued ITR therapy after 2 days because of an increase in LFTs that was determined to be severe and possibly drug-related (ALT at entry 15U/L, increased to 332 U/L (nl = 0 – 200 U/L) and AST at entry 83 U/L to 186 U/L (nl = 0 – 100 U/L)
- A03642: Elevated LFTs and hepatocellular damage. No data were provided on severity, date of onset, or attribution.
- A03191: Elevated AST (92 U/L at entry to 551 U/L day 3), ALT (166 U/L at entry to 1254 U/L on day 3), and gGT (73 U/L at entry to 232 U/L day 3) all severe and possible drug-related. Developed after 1 day of treatment. ITR was discontinued on day 3 and outcome was not provided.
- A03434: Discontinued therapy on day 15 after an increase in AST (117 U/L at entry to 474 U/L at day 15), ALT (63 U/L at entry to 171 U/L day 15), and gGT (56 U/L at entry to 95 U/L at day 15). . Both AEs were determined to be of moderate severity and possibly drug-related.

Safety Conclusions:

AEs were reported from 172/192 (90%) ITR patients and 181/192 (94%) AMP 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 19/192 (10%) itraconazole subjects versus 77/192 (40%) amphotericin B subjects, and for metabolic and nutritional disorders in 69/192 (36%) ITR versus 118/192 (61%) AMP B. Additionally, creatinine was increased in 8/192 (4%) ITR versus 50/192 (26%) AMP B subjects.

The investigators considered one or more adverse events to be definitely drug-related in 9/192 (5%) itraconazole subjects and 103/192 (54%) amphotericin B subjects. The most frequently reported drug-related adverse events were rigors (0 versus 50 subjects), creatinine increased (0 versus 29 subjects), hypokalemia (1 versus 24 subjects), abnormal renal function (0 versus 12 subjects), and fever (0 versus 11 subjects). Nausea was the AE most frequently related to therapy in the ITR-treated patients (3 or 1.5%) vs. 1 (0.5%) AMP B).

Possibly drug-related adverse events were noted in 83 (43%) itraconazole subjects and 105 (55%) amphotericin B subjects. GI events including nausea, vomiting, and diarrhea and were the most frequent events possibly related to therapy on both study arms. Additionally, hypokalemia was found in 17 (8.8%) of ITR subjects versus 29 (15.1%) of AMP B subjects. Other events possibly associated with treatment on the AMP B arm included rigors, increased creatinine, and abnormal renal function. On the ITR arm, bilirubinemia was seen in 11 (5.7%) of patients as compared to 5 (2.6%) on the AMP B arm. Additionally, there were more reports of transaminase elevations, hepatitis, hepatomegaly, and cholestatic hepatitis on the ITR arm.

The total number of deaths during this trial was 19/192 (10%) in the itraconazole group and 27/192 (14%) in the amphotericin B group. 16 ITR deaths (8%) and 23/192 (12%) of the AMP B deaths occurred during the treatment phase or the immediate 14 days following treatment. The main causes of death were condition aggravated (two itraconazole subjects and nine amphotericin B subjects), pneumonia (five and four subjects, respectively), dyspnea (four subjects in each group), and respiratory insufficiency (three subjects in each group).

Apart from adverse events leading to death, other serious adverse events were reported in a total of 23/192 (12%) ITR subjects and 28/192 (14.6%) AMP B subjects. The most remarkable difference between the two groups was noted for abnormal renal function (1 ITR (0.5%) subject vs. 7/192 (3.6%) AMP B subjects).

36 (19%) itraconazole subjects and 73 (38%) amphotericin B subjects discontinued treatment permanently because of adverse events. The most remarkable differences between the two groups were noted for creatinine increased (1 (0.5%) ITR subject and 24 (12.5%) AMP B subjects) and abnormal renal function (0 ITR and 16 (8.3%) subjects).

Gastrointestinal adverse events noted by toxicity grades were noted in 114 subjects (59%) in each group. The majority of these cases were rated as either grade 1 or grade 2 toxicity.

For clinical laboratory data, from baseline to end point, there was a tendency toward hyperchloremia, hyperphosphatemia, hypernatremia, hypoglycemia, hypokalemia, hypouricemia, and decreased BUN as well as increased liver function tests (alkaline phosphatase, lactate dehydrogenase, AST and ALT) in the ITR group. In the amphotericin B group, there was a tendency towards hyperchloremia, hyperphosphatemia, hypernatremia, and hypokalemia. Additionally patients had increases in liver function tests (alkaline phosphatase, gGT, lactate dehydrogenase, AST and ALT) and a tendency towards an increase in renal function tests (blood urea nitrogen, urea, uric acid and creatinine). Renal toxicity was noted in 10 (5%) itraconazole subjects and 46 (24%) amphotericin B subjects.

In conclusion, the toxicities sustained by the patients in both study groups were expected given the well-known safety profiles of each agent. Overall, subjects on ITR had fewer dose or treatment limiting toxicities. AMP B-treated subjects experienced more severe adverse events, drug-related adverse events, and premature discontinuation of treatment due to adverse events. Adverse events that were reported more in the amphotericin B group were rigors, hypokalemia, increased BUN and abnormal renal function as evidenced by intergroup difference in renal toxicity. On the ITR arm, more patients developed bilirubinemia and LFT abnormalities.

MO Overall Conclusions regarding study ITR-62:

Itraconazole, an azole derivative, with known antifungal activity versus *Candida albicans*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Aspergillus* spp. was able to demonstrate non-inferiority versus amphotericin B in the empiric therapy of febrile neutropenic patients. The population studied was primarily comprised of adults diagnosed with hematologic malignancies with or without bone marrow transplantation. The efficacy assessment of response was based on a composite endpoint and required survival of the patient with resolution of fever and neutropenia within 28 days of treatment, the absence of EFIs, and no discontinuation due to toxicity or failure. Efficacy was assessed in the ITT population (subjects receiving 1 dose that met the inclusion/exclusion criteria who had follow-up information). As can be seen in the table below, itraconazole was non-inferior to amphotericin B in the ITT population.

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Overview of Efficacy

Efficacy Parameters	ITR	AMP B	95% CI (FDA)
Response Rate ITT	84/179 (47%)	68/181 (38%)	- 1.4%, 20%, $\Delta = \pm 15$
Fever Resolution	131/179 (73%)	127/181 (70%)	- 6.8%, 12.9%, $\Delta = \pm 15$
Without EFI	169/179 (94%)	172/181 (95%)	- 5.8%, 4.5%, $\Delta = \pm 15$
Survival	168/192 (90%)	162/187 (86%)	- 3.9%, 10.3%, $\Delta = \pm 5$
No premature discontinuation due to toxicity	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 (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 37/181 (20%) amphotericin B).

Outcome

	ITR N = 179	AMP B N = 181
Cure	84 (47%)	68 (38%)
Failure because unevaluable	24 (13%)	44 (24%)
Failure due to intolerance	12 (7%)	37 (20%)
Failure due to lack of efficacy	59 (33%)	32 (18%)

When patients were assessed by transplant status the response 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.

Efficacy in the ITT Transplant and Non-Transplant Populations

Transplant Status	Itraconazole	Amphotericin B	95% CI ($\Delta = \pm 15\%$)
Response Rate with transplant	29/62 (47%)	28/58 (48%)	- 21%, 18%
Response Rate without transplant	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.

**Response Rate by Antifungal Prophylaxis
ITT Population**

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

The total number of deaths during trial 62 was 18/179 (10%) on the itraconazole arm and 25/181 (14%) on the amphotericin B arm. 16 of the itraconazole deaths and 23 of the amphotericin B deaths occurred during the treatment period. 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 49 (26%) of the ITR subjects had neutropenia for > 14 days as compared to 30 (16%) of the AMP B subjects despite baseline comparability between the treatment groups for this factor. The significance of this finding is unknown.

Subgroup analyses of subjects at higher risk versus lower risk (due to ANC of < 100, duration of neutropenia > 7 days, duration of previous antibiotic therapy) revealed non-inferiority between the treatment arms with numerical superiority of itraconazole in many groups. However, the numbers of subjects analyzed was small due to the larger number of amphotericin B subjects who dropped out due to toxicity.

10 (6%) subjects on the ITR arm and 9 (5%) on the AMP B arm developed EFIs, primarily due to *Candida* or *Aspergillus* spp.

Regarding safety, subjects on both study arms exhibited known toxicities of the treatment agents including renal dysfunction on the amphotericin arm and hepatic abnormalities on the itraconazole arm. Overall none of the reported events were unusual or unexpected.

In conclusion, itraconazole appeared effective in the antifungal treatment of febrile neutropenic patients with hematologic malignancies both overall and in a non-transplant population. Additionally, the role of previous antifungal prophylaxis remains to be further assessed. In view of the large numerical differences in toxicity, the MO recommends approval for itraconazole in the empiric therapy of febrile neutropenic subjects as the benefit of decreased toxicity appears to be balanced by the risk of potentially less efficacy in certain subgroups such as subjects not receiving previous prophylaxis.

PK STUDIES:
(Excerpts from MOR of NDA 20-966)

MO Overall Conclusions from the PK Studies (see Table):

4 studies were included in the safety dataset of the original NDA 20-966 as well as in the currently under review SNDAs. Reviews of each study can be found in the original MOR. The MOs conclusions have been reproduced below:

Clinical and laboratory AEs seen with increased frequency in the PK trials:

Application Site Reactions or Vein Disorders: The incidence of application site disorders was higher in 1 of the US PK studies, #113 as compared to the 3 other PK trials reviewed (127, 58, and 59). Overall the incidence of application site disorders in the PK studies was 16/95 (16.8%/12 patients: study 113, 3 patients: study 127, 1 patient: Study 59). In addition, 1 patient in study 113 had an application site disorder coded as "implantation complication". Thus the total was 17/95 (17.9%). As noted above, the majority of these events occurred in study 113. 2 sites participated in this trial. 10 patients were enrolled at site 1 where 3 patients reported application site disorders (2 moderate, 1 mild), and 20 patients were enrolled at site 2 where 14 patients reported an application site disorder (14 mild, 3 moderate). All 17 reports were assessed as definitely or possibly related to the study drug and all resolved. The verbatim adverse event reports included the following: IV site irritation, pain, edema, inflammation of skin, and vein hardness. In addition to the above, 11 events were coded as "vein disorder". All reports were from study 113 site 2. Verbatim terms included vein hardness and vein redness. The total # of patients from the PK trials with application site or vein disorders secondary to itraconazole infusion was 28/95 (29.5%). However, the data suggested that this event was site specific.

Granulocytopenia: 9/95 (9.5%) of patients from the PK studies developed granulocytopenia. All reports were from the US PK studies 113 and 127. Both of these trials were performed in HIV patients, which suggests that the AE was patient population specific.

Overall Conclusions:

GI events were the most common on both the IV and PO arms of the PK studies. Diarrhea was the most frequent complaint overall 20/95 (21.1%) and appeared to be more frequent in the patients receiving oral itraconazole 19/95 (20%) as compared to those receiving IV 4/95 (4.2%). Interestingly, constipation also appeared with greater frequency on the IV arm 7/95 (7.4%) as compared to the PO arms 4/95 (4.2%) with an overall complaint rate of 8/95 (8.4%). Nausea, vomiting, abdominal pain, dyspepsia, and the non-specified GI disorder were seen with increased frequency on the PO arms of the studies.

Fever was a frequent event on both the IV 7/95 (7.4%) and PO arms 13/95 (13.7%) with a total of 16/95 (16.8%) but the significance of this is unclear as most of the patients with fever had underlying active malignant diseases.

As noted above, the most frequent complaint on the IV arm was application site or vein disorder.

From the laboratory standpoint, granulocytopenia was seen in 4/95 (4.2%) of the IV patients and 7/95 (7.4%) of the PO patients with a total of 9/95 (9.5%) frequency. However, the population in which this was seen most frequently was that of patients with hematologic malignancies and the significance is unknown.

Mild disturbances in hepatic function were noted in < 3% of the patients on both arms and no cases of significant renal dysfunction developed.

Overall it appeared as if patients on oral itraconazole developed more complaints from the GI tract as compared to the IV patients who developed more complaints associated with infusion.

Table 29
Overall Percent of Patients Enrolled in the PK trials Reporting Possibly or Definitely-Related AEs as per the Investigators

Adverse Event	IV Phase N = 95		PO Phase N = 95		Total N = 95	
	n	%	n	%	n	%
Gastrointestinal System Disorders						
Constipation	7	7.4	4	4.2	8	8.4
Nausea	5	5.3	8	8.4	11	11.6
Diarrhea	4	4.2	19	20	20	21.1
Abdominal Pain	3	3.2	7	7.4	8	8.4
Vomiting	2	2.1	4	4.2	4	4.2
Taste Perversion	2	2.1	3	3.2	3	3.2
GI Disorders	1	1			1	1
Dyspepsia	-	-	3	3.2	3	3.2
Body as a Whole-General Disorders						
Fever	7	7.4	13	13.7	16	16.8
Pain	3	3.2	2	2.1	3	3.2
Allergic Reaction	1	1	2	2.1	3	3.2
Pruritus	1	1	1	1	1	1
Central and Peripheral Nervous System Disorders						
Headache	5	5.3	4	4.2	8	8.4
Increased Sweating	2	2.1	-	-	2	2.1
Liver and Biliary Disorders						
Bilirubinemia	2	2.1	3	3.2	3	3.2
gGT	1	1	2	2.1	2	2.1
SGPT Increased	-	-	1	1	1	1

Jaundice	-	-	1	1	1	1
Cardiovascular Disorders						
Hypotension	3	3.2	2	2.1	3	3.2
Skin and Appendages Disorders						
Rash	2	2.1	6	6.3	2	2.1
Urticaria	-	-	1	1	1	1
WBC Disorders						
Granulocytopenia	4	4.2	7	7.4	9	9.5
Leucopenia	1	1	1	1	1	1
Marrow depression	1	1	1	1	1	1
RBC Disorders						
Anemia	1	1	3	3.2	3	3.2
Urinary System Disorders						
Albuminuria	4	4.2	2	2.1	4	4.2
Glycosuria	2	2.1	1	1	3	3.2
Hematuria	1	1	1	1	1	1
Metabolic and Nutritional System Disorders						
Hyperglycemia	4	4.2	3	3.2	5	5.3
Diabetes Insipidus	1	1	-	-	1	1
Vascular Disorders						
Application Site Reaction/Vein Disorder	25	26.3	13	13.7	25	26.3
Psychiatric Disorders						
Anxiety	2	2.1	3	3.2	3	3.2

*Total is not additive but per patient.

ITR-INT-60:

(This study was previously reviewed as part of the MOR of NDA 20-966 and is included here as the subjects received the itraconazole IV/PO regimen and were utilized as part of the safety database for the indication of ETFN).

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

Study Dates: April 11, 1996 – October 7, 1997

Investigator: D. Calliot, M.D., Dijon, France with investigators in Australia, Canada, France, England, and Greece (13 sites total)

Study Synopsis: This was an open-label, phase III clinical trial with the primary objective of establishing the efficacy and safety of itraconazole IV (10 mg/mL) for 14 days followed by oral capsules (2 x 100 mg capsules PO BID). On days 1 and 2, subjects received 200 mg ITR IV BID and on days 3 – 14 200 mg IV QD. Subjects then received 200 mg PO BID for the duration of the trial (14 weeks). Additional objectives included

pharmacokinetic measurements. Safety was assessed through the reporting of adverse events and laboratory abnormalities throughout the trial. The trial plan included an inclusion visit, assessments on days 3, 8, and 15 of the IV phase and at weeks 8 and 14 of the PO phase.

The inclusion criteria specified male or female patients ≥ 18 years of age with proven or possible aspergillosis.

Excluded were patients with cerebral aspergillosis or those who were expected to undergo surgical treatment within 7 days.

31 patients enrolled and were evaluated for efficacy and safety. 20/31 subjects (65%) were male. Median age was 48 (25 – 78). 19 or 61% of the subjects were neutropenic. 21 of these had an unspecified hematologic malignancy, 6 had received a transplant for a hematologic malignancy, 2 had chronic granulomatous disease, and 1 had AIDS. 17 patients discontinued study medication before completion. 11 of the 17 discontinued due to an AE (7 IV, 4 PO).

Medical Officer's Comment: *The route of administration, dose, and duration of treatment were similar to those in trial 62. Additionally, the population under study was similar to the population studied in trial 62. It should be noted however that the subjects in this trial received itraconazole capsules and not the oral solution.*

During the IV phase, AEs occurred in 28/31 (90%) of subjects and in 19/31 (73%) during the PO phase. During the IV phase, AEs were primarily fever (7/31, 23%), dyspnea (6/31, 19%), diarrhea, pulmonary edema, and rash in 5/31 (16%). AEs that began during the IV phase usually continued into the oral phase.

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Table 30
All Adverse Events ITT Population

ADVERSE EVENT	Itraconazole IV N = 31 (100%)	Itraconazole PO N = 26 (100%)
GASTRO-INTESTINAL SYSTEM		
Diarrhea	5 (16.1%)	2 (7.7%)
Dyspepsia	2 (6.5%)	-
Nausea	4 (12.9%)	4 (15.4%)
Vomiting	4 (12.9%)	2 (7.7%)
Abdominal Pain	2 (6.5%)	2 (7.7%)
Stomatitis	1 (3.2%)	1 (3.8%)
Constipation	3 (9.7%)	1 (3.8%)
Mucositis Nos	1 (3.2%)	-
GI Hemorrhage	1 (3.2%)	-
Rectal Hemorrhage	1 (3.2%)	-
BODY AS A WHOLE - GENERAL DISORDERS		
Rigors	3 (9.7%)	1 (3.8%)
Fever	7 (22.6%)	3 (11.5%)
Fatigue	4 (12.9%)	1 (3.8%)
Injury	2 (6.5%)	3 (11.5%)
Chest Pain	2 (6.5%)	-
Temperature Sensation	1 (3.2%)	-
Edema Generalized	2 (6.5%)	-
Peripheral Edema	-	-
Syncope	2 (6.5%)	-
Allergic Reaction	1 (3.2%)	-
Condition Aggravated	2 (6.5%)	2 (7.7%)
Leg Pain	-	1 (3.8%)
Hot Flushes	1 (3.2%)	-
Abdomen Enlarged	-	1 (3.8%)
Abnormal Lab	1 (3.2%)	1 (3.8%)
METABOLIC AND NUTRITIONAL DISORDERS		
Hypokalemia	1 (3.2%)	-
Fluid Overload	2 (6.5%)	-
Hypomagnesemia	1 (3.2%)	-
Creatinine Increased	2 (6.5%)	-
LDH Increased	-	1 (3.8%)
Xerophthalmia	-	1 (3.8%)
Leg edema	2 (6.5%)	-
Hyperglycemia	-	1 (3.8%)
Hypocalcemia	1 (3.2%)	-
Hyponatremia	1 (3.2%)	-
Acidosis	1 (3.2%)	1 (3.8%)

RESPIRATORY SYSTEM DISORDERS		
Dyspnea	6 (19.4%)	1 (3.8%)
Coughing	4 (12.9%)	-
Pneumonia	-	3 (11.5%)
Pulmonary Edema	5 (16.1%)	-
Respiratory Disorder	3 (9.7%)	-
Respiratory Insufficiency	-	-
Hemoptysis	2 (6.5%)	2 (7.7%)
Bronchospasm	3 (9.7%)	1 (3.8%)
Hypoxia	2 (6.5%)	-
Sinusitis	-	2 (7.7%)
Stridor	2 (6.5%)	-
CxR Abnormal	1 (3.2%)	-
Pleural Effusion	-	1 (3.8%)
Pleural Pain	-	1 (3.8%)
Pleurisy	1 (3.2%)	-
Pneumonitis	-	1 (3.8%)
Rhinitis	-	1 (3.8%)
URI	-	1 (3.8%)
SKIN AND APPENDAGES DISORDERS		
Rash	4 (12.9%)	2 (7.7%)
Rash Erythematous	1 (3.2%)	-
Maculopapular Rash	-	1 (3.8%)
Ulceration	1 (3.2%)	-
Increased sweating	1 (3.2%)	-
URINARY SYSTEM DISORDERS		
Renal Function Abnormal	1 (3.2%)	-
Decreased CrCl	1 (3.2%)	-
UTI	-	1 (3.8%)
Cystitis	-	1 (3.8%)
Facial Edema	2 (6.5%)	-
Hematuria	1 (3.2%)	1 (3.8%)
PSYCHIATRIC DISORDERS		
Confusion	2 (6.5%)	-
Anxiety	1 (3.2%)	-
Insomnia	2 (6.5%)	-
LIVER AND BILIARY SYSTEM DISORDERS		
Bilirubinemia	-	1 (3.8%)
Hepatic Failure	-	1 (3.8%)
Hepatic Function Abnormal	-	1 (3.8%)
Hepatocellular Damage	1 (3.2%)	-
CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS		
Headache	3 (9.7%)	1 (3.8%)
Coma	-	1 (3.8%)

Convulsions	1 (3.2%)	1 (3.8%)
Dizziness	1 (3.2%)	-
Dysphonia	1 (3.2%)	-
Abnormal Gait	-	1 (3.8%)
Hypertonia	1 (3.2%)	-
Stupor	1 (3.2%)	-
Tremor	1 (3.2%)	-
PLATELET, BLEEDING & CLOTTING DISORDERS		
Epistaxis	2 (6.5%)	-
RESISTANCE MECHANISM DISORDERS		
Abscess	1 (3.2%)	-
Infection	-	1 (3.8%)
Bacterial Infection	1 (3.2%)	2 (7.7%)
Sepsis	1 (3.2%)	-
Herpes Simplex	1 (3.2%)	2 (7.7%)
Herpes Zoster	-	1 (3.8%)
Fungal Infection	-	4 (15.4%)
CARDIOVASCULAR		
Circulatory Failure	-	1 (3.8%)
Hypertension	-	1 (3.8%)
Hypotension	1 (3.2%)	-
HEART RATE AND RHYTHM DISORDERS		
Arrhythmia	1 (3.2%)	-
VISION DISORDERS		
Eye Abnormality	1 (3.2%)	-
NEOPLASMS		
Hyperimmunoglobulinemia	-	1 (3.8%)
APPLICATION SITE DISORDERS		
Application Site reaction	1 (3.2%)	-
Cellulitis	1 (3.2%)	-
MUSCULOSKELETAL DISORDERS		
Myalgia	1 (3.2%)	-
VASCULAR		
Thrombophlebitis Arm	1 (3.2%)	-
Thrombophlebitis Leg	-	1 (3.8%)
Thrombophlebitis Superficial	-	1 (3.8%)
WHITE CELL DISORDERS		
Lymphadenopathy	1 (3.2%)	-
Granulocytopenia	-	1 (3.8%)
VALVULAR DISORDERS		
MI	1 (3.2%)	-
REPRODUCTIVE DISORDERS		
Vaginal Hemorrhage	1 (3.2%)	-

Medical Officer's Comment: As expected events from the GI tract including diarrhea, nausea, and vomiting were amongst the most frequently reported during both the IV and PO phases. Of note, respiratory tract events occurred with increased frequency in this trial including 3 reports of pulmonary edema. It is the MOs determination that these events were primarily due to the underlying disease (pulmonary aspergillosis) as opposed to the administration of ITR.. Hepatic events occurred infrequently and primarily during the PO phase.

Of the 31 ITR patients, 3/31 (10%) had AEs reported as definitely related to therapy. These events included 2 episodes of rash during the IV phase that persisted into the PO phase and 1 episode of rigors during the IV phase. 16/31 (51.6%) had events reported as possibly related. In 13 of these subjects the events started during the IV phase and continued into the PO phase. The most frequently reported possibly drug-related adverse events were diarrhea (3 IV and 1 PO itraconazole subject), fever (3 IV subjects), increased creatinine (2 IV subjects), nausea (1 IV and 3 PO subjects), and fungal infection (3 PO subjects).

Table 31
AEs Definitely-Related to Therapy

ADVERSE EVENT	Itraconazole IV N = 31 (100 %)	Itraconazole PO N = 26 (100 %)
BODY AS A WHOLE - GENERAL DISORDERS		
Rigors	1 (3.2%)	-
SKIN and APPENDAGES DISORDERS		
Rash	1 (3.2%)	1 (3.8%)

Table 32
AEs Possibly Related to Treatment

ADVERSE EVENT	Itraconazole IV N = 31 (100 %)	Itraconazole PO N = 26 (100 %)
GASTRO-INTESTINAL SYSTEM		
Diarrhea	3 (9.7%)	1 (3.8%)
Nausea	1 (3.2%)	3 (11.5%)
Vomiting	-	1 (3.8%)
Abdominal Pain	-	1 (3.8%)
Constipation	-	1 (3.8%)
BODY AS A WHOLE - GENERAL DISORDERS		
Fever	3 (9.7%)	-
Chest Pain	1 (3.2%)	-
Edema	1 (3.2%)	-
Syncope	1 (3.2%)	-
Abdomen enlarged	-	1 (3.8%)
Lab Values Abnormal	1 (3.2%)	-
Temperature changed Sensation	1 (3.2%)	-
METABOLIC AND NUTRITIONAL DISORDERS		

Hypocalcemia	1 (3.2%)	-
Hypochloremia	1 (3.2%)	-
Hyponatremia	1 (3.2%)	-
Hypomagnesemia	1 (3.2%)	-
LDH Increased	-	1 (3.8%)
Increased Creatinine	2 (6.4%)	-
Acidosis	1 (3.2%)	1 (3.8%)
RESPIRATORY SYSTEM DISORDERS		
Dyspnea	1 (3.2%)	-
Hemoptysis	-	1 (3.8%)
Respiratory Disorder	1 (3.2%)	-
SKIN AND APPENDAGES DISORDERS		
Rash	1 (3.2%)	1 (3.8%)
LIVER AND BILIARY SYSTEM DISORDERS		
Hepatic Function Abnormal	-	1 (3.8%)
Hepatocellular Damage	1 (3.2%)	-
CENTR & PERIPH NERVOUS SYSTEM DISORDERS		
Dizziness	1 (3.2%)	-
Hypertonia	1 (3.2%)	-
Gait Abnormal	-	1 (3.8%)
NEOPLASMS		
Hyperhemoglobinemia	-	1 (3.8%)
URINARY SYSTEM DISORDERS		
Creatinine Clearance Decreased	1 (3.2%)	-
Cystitis	-	1 (3.8%)
Renal Function Abnormal	1 (3.2%)	-
MUSCULOSKELETAL SYSTEM DISORDERS		
Myalgia	1 (3.2%)	-
RESISTANCE MECHANISM DISORDERS		
Fungal Infection	-	3 (11.5%)
Infection	-	1 (3.8%)

Severe AEs:

Severe adverse events were reported in 18/31 (58%) of subjects. In 12/31 (39%) the events started during the IV phase and in 9/26 (35%) the event occurred during the PO phase or worsened. The most frequently reported severe adverse events were rash in 2 (6.4%) IV subjects and 1 (3.8%) PO subject, dyspnea in 2 (6.4%) IV ITR subjects and 0 PO ITR subjects, condition aggravated in 1 IV ITR and 2 (7.6%) PO ITR subjects, hemoptysis in 2 (7.6%) PO ITR and 0 IV ITR subjects, and pneumonia in 2 (7.6%) PO ITR and 0 IV ITR subjects.

3 hepatic events on the PO arm were considered severe and included 1 event each of bilirubinemia, hepatic failure, and hepatic function abnormal. Additionally, 1 event of increased creatinine on the IV arm was considered severe.

Serious AEs including Deaths:

There were 6/31 (19.4%) deaths during the trial. 2 of these occurred during the IV phase. AEs leading to death were arrhythmia, dyspnea, bacterial infection, and MI in 1 subject, and GI hemorrhage in 1 subject. 4 occurred during the PO phase. AEs leading to death were condition aggravated, convulsions, and coma in 1 subject, condition aggravated in 1 subject, hepatic failure in 1 subject, and circulatory failure, respiratory insufficiency, condition aggravated, and pneumonia in 1 subject.

Synopses of the deaths can be found in appendix A to the MOR:

Medical Officer's Comment: *None of the deaths were attributable to the study medication and all were due to complications of the underlying diseases.*

Other serious AEs occurred in 10/31 subjects (34%). 4 of these had serious AEs during the IV phase and all 10 had serious AEs during the PO phase. Most events occurred in 1 subject with the exception of fever, hemoptysis, and fungal infection each reported in 2 subjects during the PO phase.

Discontinuations due to AEs:

11 subjects discontinued therapy during the trial. 5 during the IV phase and the remaining during the PO phase.

All discontinuations were reviewed in the MOR of NDA 20-966.

Laboratory:

Individual labs were reviewed as part of NDA 20-966. Interestingly hypokalemia was not reported in this study. Hepatic enzyme abnormalities that occurred were due to underlying disease processes.

MO Conclusions for ITR-INT-60:

AEs occurred in 28/31 (90%) of IV ITR subjects and in 19/26 (73%) of PO ITR subjects. Main AEs included GI events, fever, rigors, pulmonary edema, and other respiratory complaints. Drug related events occurred in 2 IV subjects and included rash and rigors as well as in 1 PO subject (rash). Possibly related events occurred with greater frequency (13/31 (42%) IV subjects and 9/26 (35%) PO subjects). Fever, GI events, and fungal infection were the most frequent.

6 subjects died, all deaths were not attributable to treatment. Hepatotoxicity was also observed, primarily in 1 subject with Hodgkin's disease and all abnormalities could be attributed to that process.