CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: **20-966**

STATISTICAL REVIEW(S)

HFD-590/MS. KIMZEY

Statistical Review and Evaluation

NDA:	20966
Drug Name:	Sporanox® (itraconazole) injection
Applicant:	Janssen Research Foundation
Indications:	Treatment of blastomycosis, histoplasmosis, and aspergillosis in immunocompromised and non-immunocompromised patients.
Documents Reviewed:	NDA volumes 1.1, 1.66-1.87 dated April 27, 1998, NDA volumes 3.1-3.6 dated November 25, 1998
Medical Officer:	Regina Alivisatos, M.D., HFD-590

1. Background

NDA 20-966, Sporanox® (itraconazole) injection, is submitted for approval of the following fungal infections in immunocompromised and non-immunocompromised patients as an intravenous solution, 10mg/mL:

1. Balstomycosis, 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.

Itraconazole as a capsule formulation (10 mg/mL) was approved by the FDA for the above indications. Itraconazole oral solution was also approved for the treatment of oropharyngeal and esophageal candidiasis. As agreed at the End-of-Phase II meeting with the FDA on November 3, 1995, the follow-up meeting held December 18, 1995, and the pre-NDA teleconference held October 21, 1997, a safety database of approximately 150-200 patients treated with this intravenous formulation would form the basis for this application. In May of 1998 at the 45-day reviewers' meeting, the applicant was requested to submit safety data for the ongoing trials between May 1997 and May 1998. The updated safety data were submitted to the FDA on November 25, 1998, and included ITR-INT-60 and ITR-INT-62, two studies that were completed by that time. As of November 25, 1998, six months after the 45-day review meeting, the safety data of this NDA have been updated. Currently, this NDA includes 360 patients treated with itraconazole injection for 7-14 days in nine clinical trials. Among them, 255 patients were in the original submission.

As of May 1998, The nine clinical and pharmacokinetic trials in the integrated database are:

- Two ongoing US open-label, active-controlled trials

[redacted]

[redacted]

- One completed international open-label active-controlled trial
  - ITR-INT-62: An open randomized trial comparing the efficacy and safety of intravenous followed by oral itraconazole with intravenous amphotericin B for empiric therapy in neutropenic patients with hematological malignancy.
- One ongoing international open-label, active-controlled trial

[redacted]

- 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 (AIDS), 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 (HIV) infection.
  - ITR-USA-127: A pharmacokinetic trial of itraconazole injection followed by itraconazole oral solution in patients with advanced HIV infection.
- Two completed international open-label pharmacokinetic trials
  - ITR-INT-58: A pharmacokinetic trial of itraconazole injection followed by itraconazole oral solution in intensive care unit patients.
  - ITR-INT-59: A pharmacokinetic trial of itraconazole injection followed by itraconazole oral solution in patients with hematological malignancy.

The number of patients in the integrated safety database is summarized in Table 1-1 by indication, trial and treatment group.

Table 1-1: Summary of treatment with itraconazole injection or comparator by indication and trial

Patient population	Trial	ITR*	FLU*	AMB*	Total # in ISS
BMT leukemia, lymphoma, multiple Myeloma	ITR-INT-62 ITR-INT-59	192 17		192	384 17
HIV+, CD4 count<300 cell/mm^3	ITR-USA-113 ITR-USA-127	30 32			30 32
ICU	ITR-INT-58	16			16
Disseminated aspergillosis	ITR-INT-60	31			31
Total number of patients		360	32	202	594

*ITR=itraconazole injection, FLU=fluconazole, AMB=amphotericin B

Detailed information of these nine trials is also displayed in Tables 1-2 and 1-3. The information in these two tables includes number of patients planned per protocol, number of patients included in the interim safety analysis, study population, trial design, treatment assignment, dosing, and treatment duration. Table 1-2 includes four open-label, active-control, comparative studies (ITR-INT-62,), and one non-comparative trial (ITR-INT-60). Table 1-3 is for four parallel design pharmacokinetic studies (ITR-INT-58, ITR-INT-59, ITR-USA-113, and ITR-USA-127).

All trials specified an initial 7- to 14-day treatment phase with itraconazole injection followed by an oral maintenance treatment phase. Four pharmacokinetic trials had shorter intravenous treatment duration, which was planned for a 7-day I.V. injection. The other four controlled trials and one uncontrolled trial had treatment duration of 2-day 200 mg BID itraconazole injection plus 5- to 12-day 200 mg OD itraconazole injection. The four controlled trials included an active comparator: fluconazole or amphotericin B. Because sample sizes in the fluconazole groups were small, only limited safety comparisons can be made between itraconazole and fluconazole.

The statistical review will focus on comparisons of adverse events between itraconazole and amphotericin B in the I.V. treatment phase. The incidence rates of adverse events in the fluconazole group will also be presented.

Table 1-2: Controlled and uncontrolled clinical trials conducted with itraconazole injection

Trial	Total # planned	Total # In ISS	Indication	Design	Treatment arm	Daily dose and duration			Follow-up
						IV phase	Oral phase	Duration	
Controlled									
ITR-INT-62	390	384	Febrile neutropenia	open, randomized	itraconazole, amphotericin B	200 mg BID x 2D + 200 mg OD x 5-12D, 0.7-1.0 mg/kg	200 mg oral solution BID none	continued until the end of neutropenia	
Uncontrolled									
ITR-INT-60	30	31	Aspergillosis	Open	itraconazole	200 mg BID x 2D + 200 mg OD x 5-12D	200 mg BID capsule	up to 14 weeks	

Table 1-3: Pharmacokinetic trials conducted with itraconazole injection

Trial	Total #	Population	Design	Randomization	Daily dose and duration	
					IV phase	Oral phase
ITR-INT-58	16	ICU patients	open, parallel	ITR IV + 200 mg oral solution BID or ITR IV + 200 mg oral solution OD	200 mg BID x 2D + 200 mg OD x 5D	200 mg BID oral solution x 14D or 200 mg OD oral solution x 14D
ITR-INT-59	17	Hematological malignancy	open, parallel	ITR IV + 200 mg oral solution BID or ITR IV + 200 mg oral solution OD	200 mg BID x 2D + 200 mg OD x 5D	200 mg BID oral solution x 14D or 200 mg OD oral solution x 14D
ITR-USA-113	30	HIV+	open, parallel	ITR IV + 200 mg capsule BID or ITR IV + 200 mg capsule OD	200 mg BID x 2D + 200 mg OD x 5D	200 mg BID oral capsule x 28D or 200 mg OD oral capsule x 28D
ITR-USA-127	32	HIV+	open, parallel	ITR IV + 200 mg oral solution BID or ITR IV + 200 mg oral solution OD	200 mg BID x 2D + 200 mg OD x 5D	200 mg BID oral solution x 28D or 200 mg OD oral solution x 28D

2. Safety Review

2.1 Patient Demographics

Overall, there are no meaningful differences in age, gender, or race among treatment groups in the worldwide or US databases in the randomized controlled trials. The average age of the patients is around 40 to 50 years. Patients in the fluconazole group are older than the other groups with an average age of 56.3 years old. Male patients account for 55% to 70% of total patients across studies. Worldwide, about 80% of patients are whites, 15% are blacks, and the remaining are Hispanic or other races. In the U.S., whites account for about 60% of enrolled patients, blacks represent about 30% of patients, and Hispanic and others represent the remaining 10%.

2.2 Extent and duration of exposure to itraconazole injection

All trials specified the same dosing regimen: 200 mg itraconazole injection twice daily for 2 days followed by 200 mg itraconazole injection once daily. Only the total duration of I.V. therapy varied across trials. (See Tables 1-2, 1-3.) Details of actual duration and dosage of itraconazole injection are summarized in Table 2-1. All controlled and uncontrolled clinical trials specified a 7-day treatment duration with itraconazole injection that could be extended to 14 days or longer if the condition of the patient warranted additional intravenous therapy. In worldwide controlled trials, 56.8% of patients received itraconazole injection for up to one week and 37.6% received itraconazole injection between 8 and 14 days. Treatment durations beyond 2 weeks in worldwide controlled trials were low, 5.6% of patients. The maximum duration of intravenous treatment with itraconazole injection in pharmacokinetic studies was one week. The mean dose of itraconazole in the controlled studies at the intravenous injection phase is 228.74 mg and the standard deviation is 3.081 mg.

Table 2-1: Summary of itraconazole injection duration by study type

Total number of patients	N	Treatment Duration			
		≤7 days n (%)	>7-14 days n (%)	>14 days n (%)	Median days (min, max)
Worldwide					
Controlled	234	133(56.8)	88 (37.6)	13 (5.6)	7 (2,28)
Uncontrolled	31	2 (6.5)	25(80.6)	4 (12.9)	14 (4,28)
Pharmacokinetic	95	95 (100.0)	0 (0.0)	0 (0.0)	7 (1,7)

2.3 Extent and duration of exposure to amphotericin B injection

Because only very limited data are available for safety assessment of fluconazole in this submission, the review will be concentrated on comparison of adverse events between itraconazole and amphotericin B. Patients treated with amphotericin B were primarily in study ITA-INT-62. According to the design of the trial, patients in the amphotericin B group would receive no oral formulation after intravenous injection. Therefore, only safety profiles of patients in intravenous injection phase in the itraconazole group and the amphotericin B group are considered comparable. The duration of exposure to amphotericin B is presented in Table 2-2. Treatment duration is similar to that for itraconazole injection, with slightly more amphotericin B injection patients receiving more than 14 days of therapy. The mean dose of amphotericin B at the intravenous injection phase is 40.3 mg and the standard deviation is 1.201 mg.

Table 2-2: Summary of amphotericin B injection duration by study type

Total number of patients	N	Treatment Duration			
		≤7 days n (%)	>7-14 days n (%)	>14 days n (%)	Median days (min, max)
Worldwide					
Controlled	202	113(55.9)	60 (29.7)	29 (14.4)	7 (1,28)

2.4 Adverse Events: Comparison of Itraconazole and Amphotericin B

A meaningful statistical comparison of adverse events could only be conducted between the itraconazole group and the amphotericin B group in the controlled studies during the intravenous injection phase. Due to the small number of patients treated with fluconazole, conclusive comparison of adverse events between fluconazole and itraconazole is not attempted. However, adverse events of all three drugs will be included in the tables later. Summarized in Table 2-3 is the overall adverse event rate in the intravenous treatment phase.

Table 2-3: Adverse event incidence with onset in the intravenous treatment phase, n(%)

	Total	Controlled			PK	Uncontrolled
	ITR	ITR	FLU	AMB	ITR	ITR
Worldwide						
Number of patients	360	234	32	202	95	31
Incidence of patients with AE	301 (83.6)	209(89.3)	31 (96.9)	191(94.6)	64 (67.4)	28 (90.3)

Worldwide, an 83.6% incidence of adverse events with onset in the intravenous phase of treatment was noted for total itraconazole patients; 89.3% from controlled clinical trials, 67.4% from pharmacokinetics trials, and 90.3% from the one uncontrolled trial. The incidence of adverse events with onset in the intravenous phase was similarly high for fluconazole (96.9%) and for amphotericin B (94.6%). Table 2-4 displays more detailed information about adverse events by body system at the intravenous treatment phase.

Table 2-4: Adverse event incidence ≥5% with onset in the intravenous treatment phase in worldwide trials, by body system, n(%)

Body system	Total	Controlled			PK	Uncontrolled
	ITR n=360	ITR n=234	FLU n=32	AMB N=202	ITR N=95	ITR N=31
Gastrointestinal system	164 (45.6)	134 (57.3)	16 (50.0)	121 (59.9)	19 (20.0)	11 (35.5)
Body as a whole	138(38.3)	105 (44.9)	16 (50.0)	122 (60.4)	14 (14.7)	19 (61.3)
Respiratory system disorders	113 (31.4)	94 (40.2)	13 (40.6)	73 (36.1)	6 (6.3)	13 (41.9)
Metabolic and nutritional	96 (26.7)	85 (36.3)	18 (56.3)	127 (62.9)	5 (5.3)	6 (19.4)
Skin and appendages disorders	75 (20.8)	62 (26.5)	9 (28.1)	49 (24.3)	6 (6.3)	7 (22.6)
Psychiatric disorders	65 (18.1)	56 (23.9)	5 (15.6)	37 (18.3)	4 (4.2)	5 (16.1)
Central & peripheral nervous system disorder	59 (16.4)	46 (19.7)	3 (9.4)	29 (14.4)	6 (6.3)	7 (22.6)
Liver and biliary system	46 (12.8)	42 (17.9)	10 (31.3)	31 (15.3)	3 (3.2)	1 (3.2)
Cardiovascular disorders	47 (13.1)	41 (17.5)	7 (21.9)	39 (19.3)	5 (5.3)	1 (3.2)
Urinary system disorders	52 (14.4)	41 (17.5)	8 (25.0)	52 (25.7)	6 (6.3)	5 (16.1)
Platelet, bleeding & clotting	30 (8.3)	28 (12.0)	5 (15.6)	25 (12.4)	0 (0.0)	2 (6.5)
Resistance mechanism	38 (10.6)	27 (11.5)	7 (21.9)	24 (11.9)	6 (6.3)	5 (16.1)
Red blood cell disorders	14 (3.9)	12 (5.1)	1 (3.1)	2 (1.0)	2 (2.1)	0 (0.0)
Heart rate and rhythm	10 (3.9)	19 (8.1)	4 (12.5)	20 (9.9)	0 (0.0)	1 (3.2)
Application site disorders	31 (8.6)	12 (5.1)	1 (3.1)	11 (5.4)	17 (17.9)	2 (6.5)
Vascular (extracardiac)	20 (5.6)	9 (3.8)	1 (3.1)	11 (5.4)	10 (10.5)	1 (3.2)

Adverse event incidence did not differ substantially among the three treatments at the intravenous treatment phase for many body systems as shown in Table 2-4. As we compared itraconazole with amphotericin B in the controlled trials, substantially more patients in the amphotericin B group experienced adverse events in systems such as "body as a whole", "metabolic and nutritional disorders" and "urinary system disorders". In contrast, adverse events of "respiratory system disorders", "psychiatric disorders", "central & peripheral nervous system disorders" and "red blood cell disorders" were somewhat more likely in the itraconazole group than in the amphotericin B group. It is also worth noticing that fluconazole had the highest adverse event rates in both "liver and biliary system" and "resistant mechanism". Only certain types of adverse events in each body system cause difference of incidence rates in safety profiles. These specific adverse events are displayed in Table 2-5.

Table 2-5. Type of adverse events contributing to the difference by body system

Body system/ Adverse event	Total ITR n=360	Controlled ITR n=234	Controlled FLU n=32	Controlled AMB n=202	PK ITR n=95	Uncontrolled ITR n=31
Body as a whole						
Rigors	23 (6.4)	20 (8.5)	4 (12.5)	82 (40.6)	0 (0.0)	3 (9.7)
Gastrointestinal system						
Nausea	55 (15.3)	46 (19.7)	8 (25.0)	48 (23.8)	5 (5.3)	4 (12.9)
Diarrhea	48 (13.3)	39 (16.7)	5 (15.6)	57 (28.2)	4 (4.2)	5 (16.1)
Vomiting	45 (12.5)	39 (16.7)	3 (9.4)	43 (21.3)	2 (2.1)	4 (12.9)
Metabolic and nutritional						
Hypokalaemia	39 (10.8)	38 (16.2)	4 (12.5)	65 (32.2)	0 (0.0)	1 (3.2)
NPN increased	13(3.6)	11(4.7)	2 (6.2)	55 (27.2)	0 (0.0)	2 (6.5)
Bun increased	7 (1.9)	7 (3.0)	0 (0.0)	18 (8.9)	0 (0.0)	0 (0.0)
Liver and biliary system						
Bilirubinemia	25 (6.9)	23 (9.8)	5 (15.6)	10 (5.0)	2 (2.1)	0 (0.0)
Resistant Mechanism disorders						
Infection bacterial	14 (3.9)	10 (4.3)	0 (0.0)	3 (1.5)	3 (3.2)	1 (3.2)
Sepsis	6 (1.7)	3 (1.3)	4 (12.5)	9 (4.5)	2 (2.1)	1 (3.2)
Infection fungal	2 (0.6)	1 (0.4)	1 (3.1)	6 (3.0)	0 (0.0)	1 (3.2)
Central and peripheral nervous system disorders						
Tremor	9 (2.5)	8 (3.4)	0 (0.0)	3 (1.5)	0 (0.0)	1 (3.2)
Headache	25 (6.9)	17 (7.3)	0 (0.0)	17 (8.4)	5 (5.3)	3 (9.7)
Urinary system disorders						
Renal function abnormal	11(3.1)	10 (4.3)	0 (0.0)	25 (12.4)	0 (0.0)	1 (3.2)
Respiratory system disorders						
Coughing	32 (8.9)	28 (12.0)	3 (9.4)	10 (5.0)	0 (0.0)	4 (12.9)
Psychiatric disorders						
Confusion	16 (4.4)	14 (6.0)	0 (0.0)	7 (3.5)	0 (0.0)	2 (6.5)

2.5 Adverse event by relationship to study medication

The relationship of adverse events to the study drugs was discussed in the NDA. Drug-related adverse events were assessed by the investigators. Adverse events which were considered possible or definitely related to test medication by the investigators are presented in Table 2-6. In comparison of Table 2-6 with Table 2-3 and Table 2-4, higher percentages of patients in the amphotericin B group than in the itraconazole group experienced adverse events assessed by the investigators as possible or definitely related to the treatment. Validation of these classifications is beyond the scope of this review and is more appropriately discussed in a Medical review. Based on the applicant's results, amphotericin B has more drug-related adverse events compared to itraconazole. Fluconazole has fewer drug-related adverse events than itraconazole.

Table 2-6 Adverse events assessed by the investigator as possible or definitely related to test drug in intravenous phase, n(%)

Body system	Total	Controlled			PK	Uncontrolled
	ITR n=360	ITR n=234	FLU n=32	AMB n=202	ITR n=95	ITR n=31
Total Number of patients with adverse events	151 (41.9)	99 (42.3)	7 (21.9)	166 (82.2)	39 (41.1)	13 (41.9)
Gastrointestinal system	54 (15.0)	39 (16.7)	2 (6.3)	49 (24.3)	11 (11.6)	4 (12.9)
Body as a whole	26 (7.2)	17 (7.3)	0 (0.0)	77 (38.1)	2 (2.1)	7 (22.6)
Respiratory system disorders	6 (1.7)	5 (2.1)	0 (0.0)	16 (7.9)	0 (0.0)	1 (3.2)
Metabolic and nutritional	39 (10.8)	34 (14.5)	2 (6.3)	96 (47.5)	2 (2.1)	3 (9.7)
Skin and appendages disorders	21 (5.8)	16 (6.8)	2 (6.3)	12 (5.9)	3 (3.2)	2 (6.5)
Psychiatric disorders	4 (1.1)	4 (1.7)	0 (0.0)	10 (5.0)	0 (0.0)	0 (0.0)
Central & peripheral nervous system disorder	19 (5.3)	14 (6.0)	0 (0.0)	10 (5.0)	3 (3.2)	2 (6.5)
Liver and biliary system	30 (8.3)	26 (11.1)	4 (12.5)	15 (7.4)	3 (3.2)	1 (3.2)
Cardiovascular disorders	4 (1.1)	4 (1.7)	0 (0.0)	15 (7.4)	0 (0.0)	0 (0.0)
Urinary system disorders	14 (3.9)	7 (3.0)	0 (0.0)	32 (15.8)	5 (5.3)	2 (6.5)
Platelet, bleeding & clotting	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Resistance mechanism	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)	0 (0.0)
Red blood cell disorders	2 (0.6)	0 (0.0)	0 (0.0)	2 (1.0)	2 (2.1)	0 (0.0)
Heart rate and rhythm	3 (0.8)	3 (1.3)	0 (0.0)	8 (4.0)	0 (0.0)	0 (0.0)
Application site disorders	17 (4.7)	2 (0.9)	0 (0.0)	1 (0.5)	15 (15.8)	0 (0.0)
Vascular (extracardiac)	12 (3.3)	2 (0.9)	0 (0.0)	6 (3.0)	10 (10.5)	0 (0.0)
Vision	2 (0.6)	2 (0.9)	0 (0.0)	2 (1.0)	0 (0.0)	0 (0.0)
Special senses other	3 (0.8)	1 (0.4)	0 (0.0)	2 (1.0)	2 (2.1)	0 (0.0)

2.6 Death

Among those patients who are included in this review, i.e., those who are either in the original submission or in the completed clinical trials as of May 1998, death rates of each treatment group are summarized in Table 2-7. All deaths occurring up to 30 days after treatment stopped are included. The death rate observed in the itraconzole group (11.5%) was lower than that seen in the fluconazole group (31.3%) and higher than that observed in the amphotericin B group (5.4%) in the controlled clinical trials. The death rate of itraconazole in the uncontrolled clinical trial (ITR-INT-60) was 12.9%.

Table 2-7: Incidence of deaths in itraconazole injection or comparators

	Total	Controlled			PK	Uncontrolled
	ITR	ITR	FLU	AMB	ITR	ITR
Worldwide						
Number of patients	360	234	32	202	95	31
Incidence of patients with AE	35 (9.7)	27 (11.5)	10 (31.3)	11(5.4)	4 (4.2)	4 (12.9)

As we check the death rate in each clinical trial, death rates in the itraconazole injection group are similar to the comparator groups as shown in Table 2-8.

death rates in both the itraconazole group and the fluconazole group are as high as 25%. Death rate of itraconazole injection in ITR-INT-62 is 17/192 (8.9%) compared to 20/192 (10.4%) in the amphotericin B group.

Table 2-8: Summary of deaths in itraconazole injection or comparator groups by indication and trial

Patient population	Trial	ITR*	FLU*	AMB*
BMT leukemia, lymphoma, multiple Myeloma	ITR-INT-62♥ ITR-INT-59♥	17/192(8.9%) 1/17 (5.9%)		20/192(10.4%)
HIV+, CD4 count<300 cell/mm^3	ITR-USA-113♥ ITR-USA-127♥	0/30 (0%) 0/32 (0%)		
ICU	ITR-INT-58♥	3/16 (18.8%)		
Disseminated aspergillosis	ITR-INT-60♥	4/31 (12.9%)		
Total number of patients		35/360(9.7%)	10/32(31.2%)	20/202(9.9%)

*ITR=itraconazole injection, FLU=fluconazole, AMB=amphotericin B

♥Clinical trials are completed and the cut-off date of death data is May 1, 1998.

In additional to the deaths among total patients in the above tables, the applicant reported 12 deaths in the itraconazole group and 15 deaths in the fluconazole group in the ongoing clinical trials from May 1, 1997 to September 1, 1998. Because the total number of patients who were monitored is unknown, no inference can be made to these death data.

3. Conclusion

The statistical review focuses on the comparison of adverse event rates between itraconazole and amphotericin B during the I.V. phase of the controlled clinical trials. Exposure to study drug was similar for the two arms during this phase, with slightly more amphotericin B patients receiveing more than 14 days of therapy. Itraconazole intravenous injection in the controlled clinical trials shows no higher adverse event rates than amphotericin B in many body systems. Patients treated with itraconazole had higher rates of bilirubinemia and cough than those treated with amphotericin B. However, substantially more patients treated with amphotericin B than with itraconazole experienced diarrhea, hypokalemia, NPN increased, Bun increased, rigors and renal function abnormal. Incidence of nausea and vomiting is also higher in the amphotericin B group than in the itraconazole group. Total incidences of adverse events of itraconazole intravenous injection are similar to fluconazole except for more liver toxicity incidences in the fluconazole group. However, results are not considered to be conclusive due to the small sample of the fluconazole group.

More drug-related adverse events assessed by the investigator are found in the amphotericin B group than in the other groups. The fluconazole group has the least drug-related adverse events based on the given

sample size of 32 patients. Clinical judgement of the reliability of drug-related adverse events is deferred to the Medical Officer.

Within each clinical trial, death rates of itraconazole and its comparators are similar.

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This review contains 12 pages.