CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: **20-966**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

NDA: 20,966 **Submission Date:** 4/27/98

Generic Name, Dose and Formulation: Itraconazole 10 mg/mL Injection for IV Infusion

Brand Name: Sporanox(R) **Final Review Date:** 3/12/99

Applicant: Janssen Pharmaceutica **Reviewer:** Kofi A. Kumi, Ph.D.

Type of Submission: Original NDA (New Formulation)

Submission Code: 3S

Synopsis

The studies submitted to NDA 20,966 primarily described the pharmacokinetics of itraconazole, hydroxyitraconazole (the active metabolite) and hyroxypropyl-β-cyclodextrin (HPBCD) the solubilizing agent, after intravenous administration to healthy subjects, bone marrow transplant subjects, subjects with hematological malignancy, subjects in intensive care and those with HIV or renal impairment. An intravenous formulation of itraconazole was developed because the applicant states that oral drug administration is not possible in some patient populations. The applicant is seeking approval for itraconazole intravenous (IV) injection for the treatment of histoplasmosis, blastomycosis and aspergillosis in patients refractory to amphotericin B. Itraconazole oral capsule has been approved for these indications.

The pharmacokinetics of itraconazole in healthy volunteers after single intravenous dosing were non-linear in the range of 50 to 200 mg. An increase in dose from 50 to 200 mg resulted in an increase in mean AUC(0-∞) from 1695 ± 440 to 11958 ± 4187 ng*h/mL and the clearance of itraconazole decreased from 523 ± 139 to 312 ± 112 mL/min. The AUC(0-∞) of the active metabolite, hydroxyitraconazole increased from 1481 ± 704 to 15784 ± 6625 ng*h/mL. More than dose-proportional increase in concentration of itraconazole was observed when the dose was increased from 50 to 200 mg. The pharmacokinetics of HPBCD were linear in the range of 2-to 8 gm after administration of 50 to 200 mg itraconazole in HPBCD intravenous solution.

Thirty healthy male HIV seropositive volunteers with CD4 < 300 cells/cu mm were administered 200 mg of IV itraconazole solution twice daily (BID) for two days and then 200 mg every day (QD) for five days. After the IV infusion, the patients received itraconazole oral capsules either 200 mg BID or 200 mg QD for 28 days. Following the IV infusion, Cmax and AUC(0-24h) were 2856 ± 866 ng/mL and 30605 ± 8961 ng*h/mL, respectively. The Cmax and AUC(0-24h) following the end of the QD oral dosing regimen were 889 ± 596 ng/mL and 13613 ± 8887 ng*h/mL; respectively. Following the BID oral dosing regimen, the Cmax and AUC(0-24h) were 2010 ± 1420 ng/mL and 33562 ± 25348 ng*h/mL, respectively. After the IV infusion period, trough concentrations ranged from 915 to 1039 ng/mL for itraconazole and from 1760 to 1837 ng/mL for hydroxyitraconazole. Steady state concentrations of itraconazole and hydroxyitraconazole achieved during the IV phase were maintained or increased after the BID oral dosing; however, they were not maintained for either itraconazole or hydroxyitraconazole after the QD oral capsule dosing.

Plasma concentrations were more variable after the oral than IV administration of itraconazole. Most of HPBCD were eliminated within the first 12 hours after infusing itraconazole in HPBCD solution.

Twelve patients with hematological malignancy were administered repeated doses of itraconazole IV 200 mg BID on days 1-2 followed by QD on days 3-7. The IV treatment was followed with an oral dosing scheme in which patients received itraconazole 200 mg either BID or QD. During the 2-day loading dose scheme, the mean trough concentration of itraconazole increased gradually from 192 ng/mL at 8 hours to 270 ng/mL at 24 hours, 553 ng/mL at 32 hours and 503 hours at 48 hours. The oral follow up with itraconazole 200 mg BID maintained itraconazole and hydroxy-itraconazole plasma concentrations obtained at the end of the IV treatment, whereas the QD could not in all patients. Itraconazole and hydroxitraconazole trough plasma concentrations were more variable after the oral solution than after IV administration.

Itraconazole 200 mg as an IV infusion was administered over 1 hour to thirty-six renally impaired subjects. The urine creatinine clearance were: Group I had CrCl≥ 80 mL/min/1.73m^2, Group II CrCl = 50 - 79 mL/min/1.73m^2, Group III CrCl = 20-49 mL/min/1.73m^2 and Group IV CrCl ≤ 19 mL/min/1.73m^2 Severe renal impairment affected the elimination of itraconazole; the clearance was approximately twice that observed in patients with normal renal function. However, less than 1% of itraconazole administered dose was excreted in the urine. The amount of hdyroxyitraconazole excreted in the urine of subjects with severe renal impairment was reduced by half when compared with patients with normal renal function. The half-life and AUC of hydroxyitraconazole decreased 2 and 3- fold, respectively, in the group with severe renal impairment as compared with the normal subjects. Clearance of HPBCD was reduced 6-fold and elimination half-life was prolonged 6-fold in patients with severe renal dysfunction compared to normal renal function patients.

Intensive care patients were administered four 1-hour infusions of itraconazole 200 mg plus 8 gm hydroxypropyl-β-cyclodextrin (HPBCD) twice daily over two days. Five additional infusions were administered daily for 5 days. A 14 day follow up dosing regimen of oral itraconazole was administered daily to the first six patients and twice daily to the six remaining patients. The trough concentrations for itraconazole and hydroxyitraconazole at the end of the IV dosing regimen were 344 ± 140 and 605 ± 205 ng/mL, respectively. For the group that received oral itraconazole at a dose of 200 mg daily, the mean trough concentrations decreased from, 344 ± 140 ng/mL at the end of the 1-week IV treatment to 245 ± 165 ng/mL at the end of the two week oral treatment. The mean trough concentration observed after administration of oral itraconazole twice daily increased from 369 ± 162 ng/mL at the end of 1 week intravenous treatment to 805 ± 708 ng/mL at the end of 2-week oral treatment. The variability (81%) in itraconazole trough concentrations at the end of oral administration was higher than that observed (41%) after IV administration. Similar observations were made for hydroxyitraconazole.

Bone marrow transplant patients were administered itraconazole IV and oral in two treatments. Treatment A consisted of a single dose of 100 mg itraconazole intravenously (IV) infused over 60 mins and treatment B was a single oral dose of 100 mg itraconazole orally. Treatments A and B were administered to the patients on 1 to 2 and 7 to 10 days after the bone marrow transplantation, according to a randomized cross over design. Treatment B was repeated 14 to 23 days after the bone marrow transplantation. No statistically significant differences were observed in the pharmacokinetic parameters but there was a trend of higher Cmax after IV than oral administration. Mean Cmax value was 1441 ± 1140 ng/mL after IV administration and 185 ± 154 ng/mL after oral administration. Mean AUC(0-∞) values were 8928 ± 5701 ng*h/mL after IV administration and 1806 ± 1293 ng*h/mL after oral administration

Comments (To be forwarded to sponsor)

1) It is strongly recommended that the applicant re-evaluate the pharmacokinetics of itraconazole, hydroxyitraconazole and hydroxypropyl-beta-cyclodextrin after administration of itraconazole IV in patients with severe renal impairment (including dialysis patients) using the reduced model approach (please refer to the guidance on the conduct of pharmacokinetic studies in patients with impaired renal function). The applicant is encouraged to discuss the protocol for this study with the agency prior to commencing the study.

Label: A copy of the label will be on file in the Division of Pharmaceutical Evaluation III

Recommendation: The pharmacokinetic studies submitted under the Human Pharmacokinetics and Bioavailability section of NDA 20,657 to fulfill section 320 and 201.5 of 21 CFR provided an understanding of the pharmacokinetics of itraconazole, hydroxitraconazole and hdyroxypropyl-β-cyclodextrin and support a recommendation for approval of this NDA. However, the applicant should be asked to make a phase IV commitment to address the recommendation for a reevaluation of the pharmacokinetics of itraconazole, hydroxitraconazole and hydroxypropyl-β-cyclodextrin in patients with severe renal dysfunction.

/S/ 3/15/99

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Concurrence: /S/ 3/15/99

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HFD-880	/TLDPEIII/Ajayi
	/DPEIII/KKumi
	/DPE Drug Files
CDR	/BMurphy

Table of Content

APPEARS THIS WAY
ON ORIGINAL

Review:

Background

The review contains a summary of the studies submitted to section 6 (Human Pharmacokinetics and Bioavailability) in support of NDA 20,966. Itraconazole capsules (NDA 20,083) oral solution (NDA 20,657) were approved in 1992 and 1996, respectively. The applicant cross referenced the studies submitted in NDA 20,083 and 20,657 in this submission. Studies already reviewed under NDA 20,083 and 20,657 were not evaluated again. The studies submitted under this NDA (20,966) primarily described the pharmacokinetics of itraconazole after intravenous administration to healthy subjects, bone marrow transplant subjects, subjects with hematological malignancy, subjects in intensive care and those with HIV or renal impairment.

The applicant is seeking approval for itraconazole intravenous (IV) injection for the treatment of histoplasmosis, blastomycosis and aspergillosis in patients refractory to amphotericin B. An intravenous formulation of itraconazole was developed because the applicant states in some patient populations oral drug administration is not possible. Moreover, in compromised patients, especially immunocompromised and/or neutropenic patient, periods of reduced drug absorption may occur. Therefore, the development strategy for the IV formulation was to find a dosing regimen that will achieve therapeutic concentrations rapidly and maintain such concentrations prior to switching to an oral formulation.

Itraconazole is an antifungal agent which acts by inhibiting cytochrome P450 dependent synthesis of ergosterol, which is a vital component of fungal cell membranes. The solubility of itraconazole is very limited in water and dilute acidic solutions. Aqueous solutions of itraconazole at 10 mg/mL were, therefore, prepared by the addition of hydroxypropyl-β-cyclodextrin (HPBCD), a chemically modified starch which is highly soluble in water.

Physicochemical Properties:

Itraconazole:

Structure: Provided on the following page

Chemical Formula: (±)-1-[(RS)-sec-butyl]-4-[p-[[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]-1-piperazinyl][phenyl]-Δ^2-1,2,4-triazolin-5-one.

Molecular Formula: $C_{47}H_{38}Cl_2N_8O_4$; Molecular Weight: 705.6

Solubility: Insoluble in water, very slightly soluble in alcohols and freely soluble in dichloromethane

Pka: 3.7

Log (octanol/water) partition coefficient of 5.66 at pH 8.1

Hydroxypropyl-β-cyclodextrin :

Structure: Provided on the following page

Solubility: Excellent aqueous solubility (> 50% at 25°C)

Formulations:

Commercial Formulation Composition

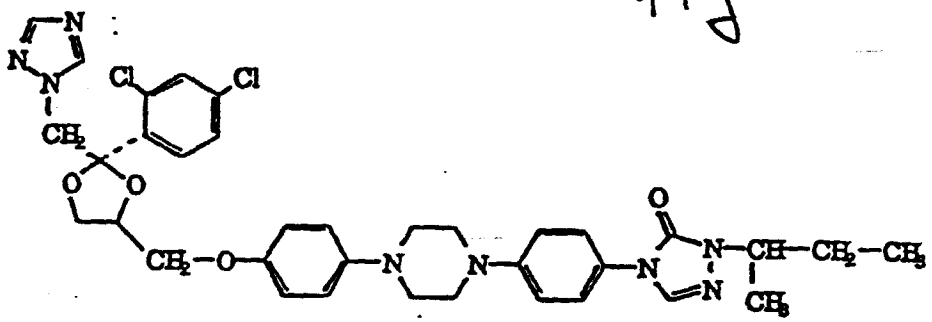
Ingredient	Amount

*Used to flush the solution and the headspace of the immediate container

Indication (per draft label): Sporanox (R) injection is indicated for the treatment of the following fungal infections in immunocompromised and non-immunocompromised patients: Blastomycosis, pulmonary and extrapulmonary; Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis; and Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy.

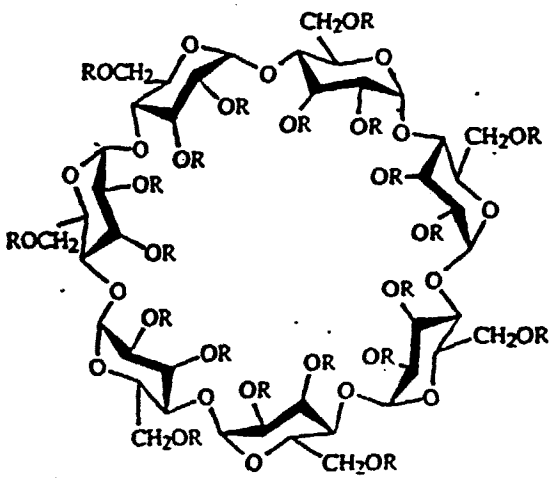
Dosage and Administration (per draft label): Treatment of blastomycosis, histoplasmosis and aspergillosis: The recommended intravenous dose is 200 mg b.i.d (2-one hour infusions) for 2 days, followed by 200 mg q.d. (one-hour infusion). For the treatment of histoplasmosis: Sporanox can be given as oral capsules or intravenously. There are limited data on the use of Sporanox injection for periods longer than fourteen days.

Fig 1



Structural formula of itraconazole (R051211). The position of the ^{3}H-label (T) in the studies on the metabolism (13, 14) and plasma protein binding (15) of itraconazole in man is also indicated.

Fig 2



R = [(* CH_2 $CH(*CH_3)O$)]$_n$H
n = 0. 1. 2. 3 . . .

Schematic representation of hydroxypropyl-β-cyclodextrin.
The position of the ^{14}C-labels in the metabolism study (2) are indicated by asterisks (*).

Summary of Pharmacokinetic Studies

Pharmacokinetics in Healthy Volunteers

Study N129325 (ITR-BEL-77): Dose proportionality of itraconazole and hydroxypropyl-β-cyclodextrin pharmacokinetics after intravenous administration of single doses of 50, 100 and 200 mg itraconazole in healthy subjects (Volume 22 page 119)

Objective: To assess the dose-proportionality of the pharmacokinetics of itraconazole and hydroxypropyl-β-cyclodextrin (HPBCD) after single intravenous doses between 50 and 200 mg

Design: This was an open label, single dose, randomized, 3-way cross-over study. Three single dose treatments were administered according to a randomized scheme. Twelve healthy subjects participated in the study. The subjects were administered 50, 100, 200 mg of itraconazole in HPBCD solution (containing 2, 4 and 8 gm HPBCD, respectively). The doses were infused over 1 hour in the morning after an overnight fast for at least 10 hours. The doses were separated by a 2 week washout period. Acetaminophen, not more than 1500 mg per day and no more than 3 gm per study, was allowed. Blood samples were taken immediately before and at 30, 60 (end of infusion), 65, 75, 90, 105, 120 and 150 min, and 3,4,5,7,9,24,32,48,72,96 and 168 hours after the start of the infusion.

Analytical Method:

Results: The mean pharmacokinetic parameters for itraconazole are provided in the following table.

Parameter	50 mg	100 mg	200 mg
Cend (ng/mL)	400 ± 74	856 ± 209	1839 ± 340
AUC∞ (ng*h/mL)	1695 ± 440	4539 ± 1439	11958 ± 4187
t ½ (h)	23.4 ± 6.7	28.0 ± 6.4	32.9 ± 10.0
Cl (mL/min)	523 ± 139	399 ± 114	312 ± 112
Vdarea (L)	1034 ± 313	962 ± 322	858 ± 278

Cend= concentration at the end of 1 hour infusion.

The results indicate that AUC∞ increased with increasing dose such that there is more than proportional increase in concentration after increasing the dose from 50 to 200 mg. An evaluation of the dose normalized AUC indicated that there was a statistically significant difference in concentration as the dose is increased from 50 to 200 mg. The terminal elimination half-life after administration of the 100 and 200 mg dose was significantly different from the one computed for 50 mg dose. The clearance of itraconazole decreased after increasing the dose from 50 to 200 mg. The pharmacokinetics of itraconazole after single intravenous administration is nonlinear.

Dose normalised C_{end} and AUC_{48h} of itraconazole as a function of the itraconazole dose

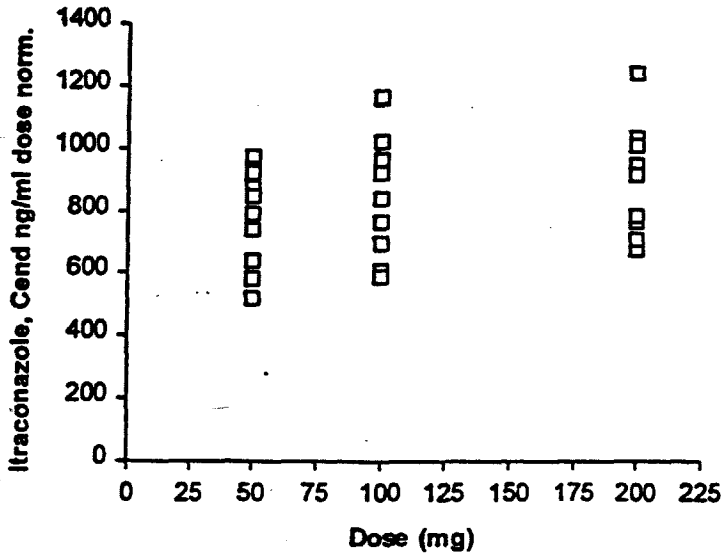
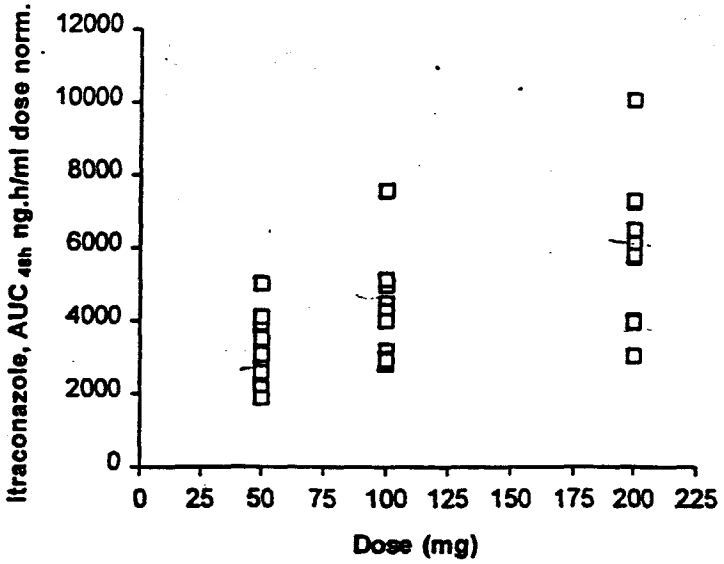


Fig 3



The mean pharmacokinetic parameters for hydroxyitraconazole are provided in the following table

Parameter	50 mg itraconazole	100 mg itraconazole	200 mg itraconazole
Cmax (ng/mL)	105 ± 31	229 ± 62	519 ± 116
AUC∞ (ng*h/mL)	1481 ± 704	4911 ± 2639	15784 ± 6625
Metabolic Ratio	0.84 ± 0.25	1.03 ± 0.30	1.29 ± 0.17
t ½ (h)	17.8 ± 20.7	16.1 ± 14.8	17.2 ± 5.6

Cmax and AUC of hydroxyitraconazole increased as the dose was increased from 50 to 200 mg. A statistical evaluation of the dose normalized AUC and Cmax indicated there was significant difference in Cmax and AUC after administration of the 200 mg dose relative to the 50 mg. The half-life did not change with an increase in dose.

The mean pharmacokinetic parameters for HPBCD is provided in the following table

Parameter	2 gm HPBCD	4 gm HPBCD	8 gm HPBCD
Cend	155 ± 21	296 ± 48	583 ± 67
AUC∞	330 ± 49	698 ± 98	1385 ± 174
t ½	1.5 ± 0.3	1.7 ± 0.2	1.8 ± 0.2
Cl	103 ± 17	97.4 ± 13.9	97.7 ± 12.3
Clrenal	87.7 ± 22.3	86.5 ± 29.3	95.9 ± 14.4
Vdarea	13.7 ± 3.1	14.0 ± 1.7	14.9 ± 1.4

The concentration increased proportionally with dose when the amount of HPBCD administered was increased from 2 to 8 gm. There was no significant difference in the dose normalized AUC and Cend. T ½ obtained after administration of 8 gm HPBCD was significantly different from that obtained after administration of 2gm; however, no statistically significant difference in clearance was calculated. No statistical difference in renal clearance was noticed.

Conclusion: The pharmacokinetics of itraconazole after single intravenous dosing were non-linear in the range of 50 to 200 mg. An increase in dose from 50 to 200 mg resulted in a more than proportional increase in concentration. The plasma concentration of the active metabolite, hydroxyitraconazole also increased more than proportional to dose when itraconazole concentrations were increased from 50 to 200 mg. The pharmacokinetics of hydroxy-propyl-β-cyclodextran were linear in the range of 2 to 8 gm after administration of 50 to 200 mg itraconazole in HPBCD intravenous solution.

Study N104593 (ITR-BEL-57): Tolerability, safety and pharmacokinetics of repeated 1-hour intravenous infusions of 200 mg itraconazole in healthy volunteers: Pharmacokinetics of itraconazole (volume 23 page 1)

Objective: To assess the tolerability and the safety and to describe the itraconazole, hydroxyitraconazole and hydroxypropyl-β-cyclodextrin (HPBCD) kinetics after four 1-hour IV infusions of 200 mg itraconazole and 8 gm hydroxypropyl-β-cyclodextrin given over two days in a group of four healthy volunteers.

Study Design: This was an open label study in 4 healthy volunteers. The mean age and weight were 37 ± 5 years and 77 ± 8, kg respectively. Four 1-hour infusions of 200 mg itraconazole and 8 gm HPBCD were administered over two days at time 0,8, 24 and 32 hours to four healthy volunteers. The batch number of the formulation used was 94D14/F33. Blood samples for determination of plasma concentration were taken before and at 1, 1.25, 1.5, 2, 4, 6, 8, 9, 9.25, 10, 12, 24, 25, 25.25, 26, 28, 30, 32, 33, 33.25, 33.5, 34, 36, 48, 52, 56,72, 80, 86, 104, 168, 192, 216, 240, 264, 336 hours after the start of the first infusion. Urine concentrations of itraconazole and hydroxyitraconazole during the intervals 0-8h, 8-24h, 24-32h, 32-48h, 48-56h and 56-72h after the first administration.

Analytical Method:

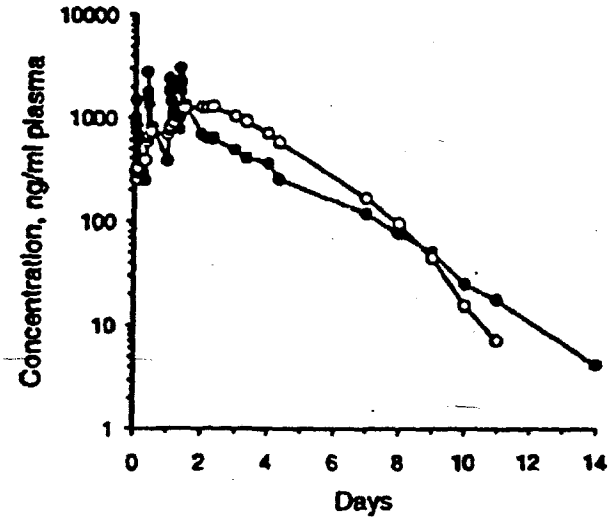
Data Analysis: The following pharmacokinetic parameters were computed: peak concentrations (Cpeak), trough plasma (Ctrough), elimination rate constant (β), terminal half-life (t ½), area under the plasma concentration-time curve (AUC∞) and AUCratio = (AUC∞ hydroxy-itraconazole/AUC∞ itraconazole) X (MW itraconazole/MW hydroxyitraconazole).

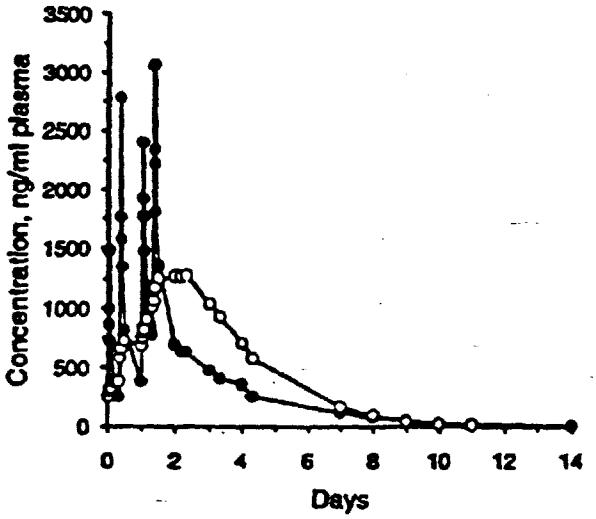
Results: The mean plasma concentration time profiles are presented in the figure on the following page. The mean pharmacokinetic parameters are presented in the following table.

Mean plasma concentration-time profile of itraconazole (●) and hydroxy-itraconazole (○) after four 1-hour i.v. infusions of 200 mg itraconazole and 8 g hydroxypropyl-ß-cyclodextrin given over 2 days in four healthy male volunteers.

Upper graph : log-linear plot.
Lower graph : linear-linear plot.

Fig 4





Parameters	Itraconazole	Hydroxyitraconazole
	Mean ± SD	
Cmax (4th) (ng/mL)	3055 ± 942	1058 ± 116
Ctrough (4th) (ng/mL)	687 ± 146	1263 ± 109
AUC(0-∞) (ng*h/mL)	89111 ± 30023	123053 ± 34862
AUC ratio*	1	1.37 ± 0.16
t ½ (h)	32.5 ± 3.5	15.6 ± 4.3
U(0-72)	0.27 ± 0.02	0.68 ± 0.11
fu(0h) (%)	0.17 ± 0.05	-
fu (1h) (%)	0.30 ± 0.04	-
fu (48hr) (%)	0.18 ± 0.03	-

*AUCratio = AUC∞ hydroxy-itraconazole/AUC∞ itraconazole X MW itraconazole/MW hydroxyitraconazole

The elimination of itraconazole and hydroxyitraconazole after IV administration is biphasic with rapid distribution phase and an slow elimination period. The elimination half-life was calculated as 32.5 ± 3.5 hours. The mean ± SD percentages of the dose excreted in the urine as itraconazole and hydroxy-itraconazole after the entire itraconazole iv dosing scheme were 0.27 ± 0.02% and 0.68 ± 0.11%, respectively. In vitro studies determined that free fraction of itraconazole in plasma transiently increased from 0.17% at baseline to 0.30% at peak times. However, values returned to baseline at 48 hours after the last infusion. It is not known whether this transient increase is of any clinical significance.

Conclusion: The dosing scheme of four infusions of 200 mg itraconazole over 2 days produced trough concentrations that were above the target concentration of 500 ng/mL on day 2. After the 4th infusion, the peak and trough concentrations observed were above 3055 ± 942 ng/mL and 687 ± 146 ng/mL, respectively. The hydroxyitraconazole concentrations observed at the same times were 1058 ± 116 and 1263 ± 109 ng/mL, respectively. Less than 1% of the itraconazole doses were excreted in the urine as itraconazole or hydroxyitraconazole. This dosing regimen was incorporated in other studies as a loading dose to enable rapid achievement of target concentrations.

Study N104594 (ITR-BEL-57): Tolerability, safety and pharmacokinetics of repeated 1-hour intravenous infusions of 200 mg itraconazole in healthy volunteers. Part II: Pharmacokinetics of hydroxypropyl-β-cyclodextrin (Volume 31 page 56)

Objectives: The aim of the present study was to assess the tolerability and the safety and to describe the itraconazole, hydroxypropyl-β-cyclodextrin (HPBCD) kinetics after four 1-hour IV infusions of 200 mg itraconazole and 8 g hydroxypropyl-β-cyclodextrin given over two days in a group of four healthy volunteers

Design: This was an open label study. Four subjects were enrolled. Four 1-hour infusions of 200 mg itraconazole and 8 g hydroxypropyl-β-cyclodextrin were administered over two days at time 0, 8, 24 and 32 hours to four healthy volunteers. Blood samples (10 mL) for drug analysis were taken immediately before and at 1, 1.25, 1.5, 2, 4, 6, 8, 9, 9.25, 9.5, 10, 12, 24, 25 25.25, 25.5, 26, 28, 30, 32, 33, 33.25, 33.5, 34, 36, 48, 52, 56, 72, 80, 96, 104, 168, 192, 216, 240, 264, 336 hours after the start of the first infusion. The complete urinary output was collected during the intervals 0-8h, 8-24h, 24-32h, 32-48h, 48-56h, and 56 - 72h after the first administration. HPBCD was determined by size exclusion chromatography with post column complexation in plasma samples from time 0 h up to time 56 hour and in all urine samples. The quantitation limit was 2 μg/mL in plasma and 40 μg/mL in urine.

Data Analysis: Individual plasma concentration time curves of HPBCD were fitted using the non-linear regression software PCNONLIN according to an open two-compartment model for intravenous (IV) infusion. The following pharmacokinetic parameters were computed: Plasma clearance (Cl), volumes of distribution (Vc, Vdss, Vdarea), total area under the curve (AUC_∞) and half-lives. Peak concentration (Cpeak) was observed just at the end of the nth-1 hour infusion and trough plasma concentration was observed after the nth 1-hour infusion. The amount excreted in the urine during a collection interval (Ut1-t2) and renal clearance (Clrenal) were also calculated.

Results: The mean pharmacokinetic parameters of HPBCD is provided on the following page. The mean trough plasma concentrations were 26.4 ± 5.8 μg/mL and 21.8 ± 6.0 μg/mL just before the 2nd and 4th infusions, respectively. The mean ± SD percentage of the dose excreted in the urine 0 to 72 hours as unchanged HPBCD was 98.5 ± 2.7%. About 98.2% of the HPBCD doses was already excreted 16 hours after the last administration. The renal clearance of HPBCD was 97.6 ± 5.5 mL/min.

Conclusion: The majority of HPBCD was eliminated via the kidneys within 16 hours after administration of the last dose.

Pharmacokinetics in Patients

Study N19720 (ITR-USA-113): A pharmacokinetic study of intravenous itraconazole followed by oral dosing of itraconazole capsules at 200 mg twice daily or 200 mg once daily in patients with advanced HIV infection (volume 25 page 1)

Introduction: It has been reported that the bioavailability of orally administered itraconazole tends to be lower in HIV-positive patients. The applicant reported that the pharmacokinetics of a 200 mg oral dose in AIDS patients was similar to the pharmacokinetics of a 100 mg dose in healthy volunteers. This study was to evaluate the pharmacokinetics of the intravenous (IV) formulation of itraconazole; the parameters obtained will be compared with those observed after continuous dosing for 28 days of itraconazole capsules, 200 mg twice daily (BID) and 200 mg once daily (QD).

Objective: To determine the dosing regimen for intravenous itraconazole solution that produces a plasma concentration range comparable to that obtained after currently-indicated oral doses of itraconazole capsules; to obtain safety data in patients with advanced HIV disease

Design: The study was a multi center, randomized, open-label, comparative study. Thirty healthy male HIV seropositive volunteers with CD4 < 300 cells/cu mm participated in the study. All patients received 200 mg of IV itraconazole solution BID for two days and then 200 mg QD for five days. Patients, who were randomized at study entry, then received itraconazole capsules either 200 mg BID or 200 mg QD for 28 days. Twenty-five mL ampules containing itraconazole 10 mg/mL in 40% hydroxypropyl-β-

Individual and mean pharmacokinetic parameters of hydroxypropyl-ß-cyclodextrin after four 1-hour i.v. infusions of 200 mg itraconazole and 8 g hydroxypropyl-ß-cyclodextrin given over 2 days in four healthy male volunteers.

Hydroxypropyl-ß-cyclodextrin					
Parameters	1	2	3	4	Mean ± S.D.
C_1, µg/ml	625	621	499	475	555 ± 79
C_{T1}, µg/ml	22.9	20.9	27.9	33.9	26.4 ± 5.8
C_{T2}, µg/ml	628	693	462	545	582 ± 100
C_{T2}, µg/ml	ND[1]	ND	4.1	4.6	2.7 ± 1.9
C_{T3}, µg/ml	577	624	426	650	569 ± 100
C_{T3}, µg/ml	16.0	17.3	25.6	28.2	21.8 ± 6.0
C_{24}, µg/ml	506	551	527	410	499 ± 62
C_{T4}, µg/ml	ND	4.6	2.6	ND	2.3 ± 1.7
α, h^{-1}	0.971	0.781	0.782	0.999	0.883 ± 0.118
β, h^{-1}	0.377	0.198	0.278	0.302	0.289 ± 0.074
$t_{1/2\alpha}$, h	0.714	0.887	0.887	0.694	0.796 ± 0.106
$t_{1/2\beta}$, h	1.84	3.51	2.49	2.29	2.53 ± 0.71
k_{10}, h^{-1}	0.618	0.604	0.481	0.480	0.546 ± 0.076
k_{12}, h^{-1}	0.138	0.119	0.127	0.192	0.144 ± 0.033
k_{21}, h^{-1}	0.592	0.256	0.451	0.628	0.482 ± 0.169
V_c, l	9.79	10.0	12.9	11.4	11.0 ± 1.4
Vd_{area}, l	16.1	30.6	22.4	18.1	21.8 ± 6.4
Vd_{ss}, l	12.1	14.7	16.6	14.9	14.6 ± 1.9
$AUC_{0-\infty}$, µg.h/ml	5289	5282	5142	5860	5393 ± 318
Cl_{tot}, ml/min	101	101	104	91.0	99.3 ± 5.7
U_{0-72h}, % of dose	96.3	102	96.4	99.1	98.5 ± 2.7
Cl_{ren}, ml/min	97.1	103	100	90.2	97.6 ± 5.5

[1]ND: not detectable by the HPLC-method (hydroxypropyl-ß-cyclodextrin ≤ 2.0 µg/ml plasma). ND=1

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cyclodextrin in water was supplied to the study centers by the sponsor. Itraconazole capsules (100 mg/mL) was also supplied by the sponsor. The batch numbers for the IV solution and capsules were 94K14/F33 and 94K303A, respectively. Blood samples were collected at specified time periods after both the IV and oral administration of itraconazole. Urine samples for the determination of HPBCD was collected during 12-hour intervals periods before dosing and on days 1 and 7 after the IV administration.

Analytical Methods

Data Analysis: Concentrations and pharmacokinetic parameters of itraconazole, hydroxy-itraconazole and HPBCD were determined in plasma using validated high performance liquid chromatography (HPLC) methods. The lower limit of quantitation of both itraconazole and hydroxy-itraconazole in plasma was 5 ng/mL; the detection limit of HPBCD in plasma was 1.0 μg/mL; the detection limit of HPBCD in plasma was 1.0 μg/mL.

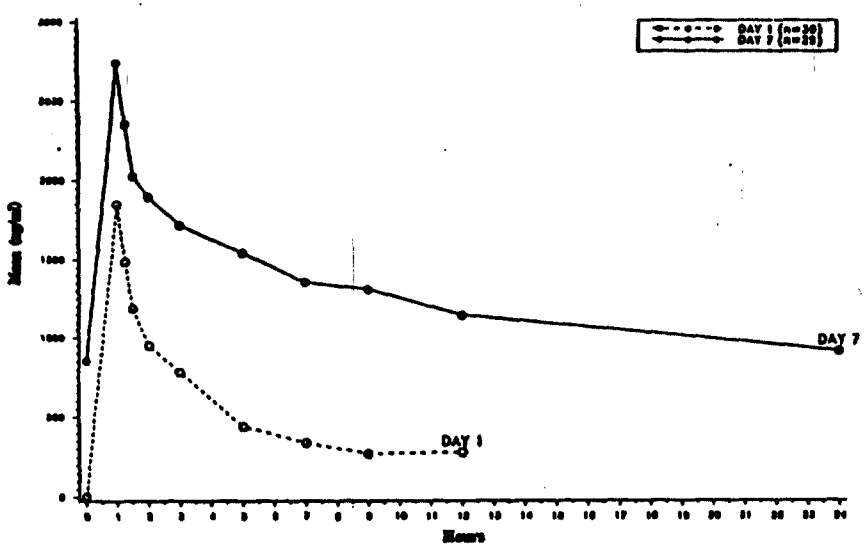
Results: The mean plasma concentration time profiles are provided in the following figures on the next page. Evaluation of itraconazole trough concentrations after IV infusion indicated that steady state was achieved after day 3 of twice a day infusion for 2 days and then daily for 5 days. The steady state trough concentration was maintained through the infusion period. After the oral administration, steady state concentrations were reached on day 15 for both the BID and QD dosing. The trough concentrations obtained after IV administration were maintained or increased while on oral capsule dosage form. The mean itraconazole trough concentration varied between 778 ng/mL and 915 ng/mL.

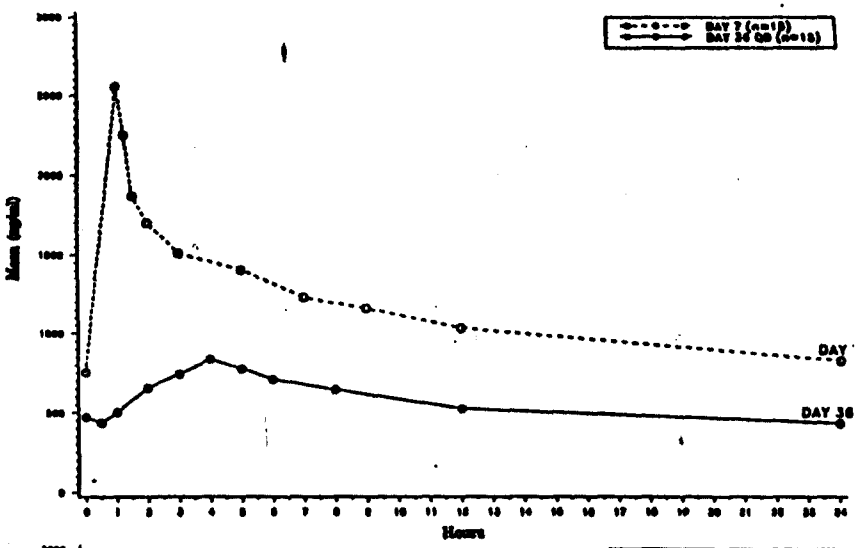
The pharmacokinetic parameters of itraconazole are presented in the following table
Mean (SD) Pharmacokinetic Parameters of Itraconazole

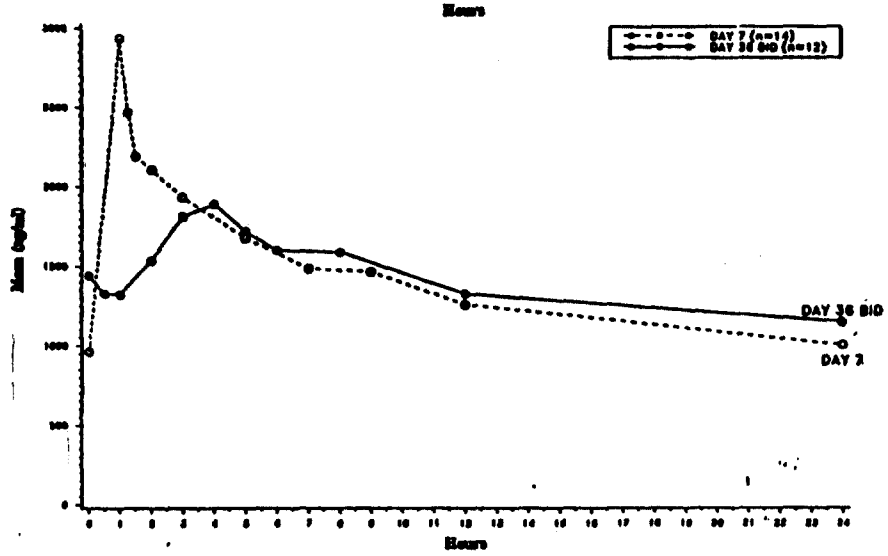
Parameter	IV Phase		Oral (Capsule) Phase	
	Day 1 (n=30)	Day 7 (n=29)	Day 36 QD (n=15)	Day 36 BID n=12
Cmax (ng/mL)	1941 ± 546	2856 ± 866	889 ± 596	2010 ± 1420
Tmax (hr)	1.82 ± 2.79	1.08 ± 0.14	4.20 ± 1.57	3.92 ± 1.83
Cav (ng/mL)	-	1275 ± 373	567 ± 370	1564 ± 1161
AUC(0-12h) (ng*hr/mL)	6511 ± 1864	18255 ± 5330	7819 ± 5182	18768 ± 13933
AUC(0-24h) (ng*hr/mL)	-	30605 ± 8961	13613 ± 8887	33562 ± 25348
t ½ (hr)	-	35.4 ± 29.4	45.7 ± 44.9	38.0 ± 23.8

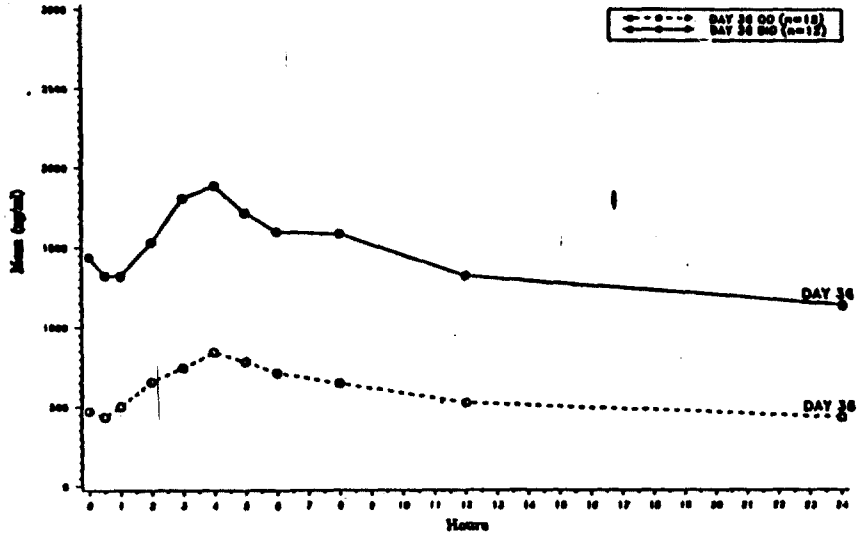
Fig 5

-Mean Plasma Concentrations on Days 1, 7, 36 Versus Scheduled Time – Itraconazole









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A comparison of the pharmacokinetic parameters for itraconazole indicated that at day 7, after multiple IV infusions, the Cmax and AUC12 increased by 47% and 177%, respectively when compared with results obtained after a single IV dosing on day 1. The values for Cmax and AUC24 on day 36 for the capsule QD group decreased significantly from the end of the IV phase; however, t ½ was not significantly different. Cmax of itraconazole on day 36 after BID dosing of the capsule was significantly different from that after the IV administration; however, the average concentration, t ½ and AUC were not significantly different between groups. Cmax and Cav of itraconazole after the BID dosing was significantly different from the QD dosing of the oral capsule, but the tmax and t ½ were not significantly different.

The concentration of hydroxy-itraconazole reached steady state by day 6 after IV infusions of itraconazole 200 mg BID for 2 days and QD for 3 days. In the oral capsule phase, steady state plasma concentrations of hydroxy-itraconazole were attained by day 15 in the BID capsule group and by day 22 in the QD group.

The mean (±SD) pharmacokinetic parameters for hydroxy-itraconazole is provided in the following table.

Parameter	IV Phase		Capsule Phase	
	Day 1(n=30)	Day 7(n=29)	Day 36 QD(n=15)	Day36 BID(n=12)
Cmax (ng/mL)	464 ± 150	1906 ± 612	1114 ± 661	2614 ± 1703
Tmax (hr)	3.63 ± 2.84	8.53 ± 6.36	5.67 ± 5.62	5.92 ± 6.14
Cav (ng/mL)	-	1769 ± 553	953 ± 566	2376 ± 1596
AUC(0-12) (ng*hr/mL)	4578 ± 1588	21241 ± 6901	11890 ± 7156	28516 ± 19149
AUC(0-24) (ng*hr/mL)	-	42445 ± 13282	22864 ± 13574	55583 ± 37963
R	0.72 ± 0.18	1.39 ± 0.16	1.7 ± 0.19	1.65 ± 0.32

R= metabolic ratio= ratio of AUC(0-t) OH-itraconazole to AUC(0-t) of itraconazole. t= 12 hours for BID dosing regimen and 24 hours for a QD dosing regimen.

The mean metabolic ratio was doubled from day 1 to day 7 after IV administration. Cmax and AUC(0-12) were significantly increased when day 7 values are compared with day 1. Cmax and AUC(0-12) were significantly lower at the end of the QD capsule phase than at the end of the IV phase. The metabolic ratio was significantly increased. After the BID oral phase, there was no significant difference in Cmax and Cav values from the oral phase and the day 7 values of the IV phase. The metabolic ratio was significantly different.

The Cmax and Cav of OH-itraconazole were significantly higher in the oral capsule BID group than the capsule QD group. The metabolic ratios and Tmax were not significantly different.

The pharmacokinetic parameters for HPBCD are provided in the following table.

Parameter	Day 1		Day 7	
	n	Mean ±SD	n	Mean ± SD
Cmax (μg/mL)	30	562 ± 99	29	528 ± 98
AUC(0-∞) (μg*hr/mL)	30	1323 ± 233	29	1223 ± 228
t ½ (hr)	30	1.9 ± 0.4	29	2.2 ± 1.3
U(0-12) gm	26	8.09 ± 1.48	27	7.42 ± 2.53
Cl (mL/min)	30	104 ± 19	29	113 ± 22
Clrenal (mL/min)	26	108 ± 28	27	104 ± 38
% Renal Cl	26	101 ± 19	27	93 ± 32

After IV infusion, the pharmacokinetic parameters on day 1 were similar to those of day 7; however, Cmax, AUC(0-∞) and Cl were significantly different. The clinical significance of this is not known. The majority (greater than 90%) of HPBCD were excreted unchanged in the urine within the first 12 hours of dosing

Safety: The applicant reported that the most common adverse events were infusion related (irritation at infusion site) and nausea. The applicant reported only one patient withdrew due to an adverse event (depression) and this was deemed not related to study drug. Thrombocytopenia was reported in 20% of the patients. The applicant concluded that because of the underlying disease of the patients, the clinical significance of this event is not known. Refer to the medical officer's review for evaluation of adverse events. The applicant reported no biological or clinically significant changes in RNA copy numbers were observed in the HIV seropositive patients that participated in this study.

Conclusion: Steady state concentrations achieved during the IV phase were not maintained for either itraconazole or hydroxy-itraconazole for the QD oral capsule dosing. The itraconazole and hydroxyitraconazole trough concentrations after the BID oral dosing were maintained or increased when compared to the values observed after the IV phase. Most of HPBCD were eliminated within the first 12 hours after infusing the itraconazole in HPBCD solution. The total plasma clearance, renal clearance and terminal half-life of HPBCD observed in this were similar to that reported for healthy volunteers. The steady state concentrations achieved were above the minimum target concentration of 250 ng/mL and the exposures (AUC) were higher than that observed after administration of itraconazole 200 mg every day for 15 days (see comments section).

Study N130309 (ITR-USA-127): Pharmacokinetics study of IV itraconazole followed by oral dosing at 200 mg twice daily or 200 mg once daily in patients with advanced HIV infection (volume 27 page 1)

Objective: The primary objective was to demonstrate a dosage regimen for intravenous (IV) itraconazole that produced a plasma concentration range comparable to that obtained after currently used oral dosages of itraconazole oral solution in subjects with advanced HIV disease (CD4 lymphocyte count less than 300 cells/mm^3).

Design: Thirty two subjects with HIV infection (CD4< 300 cells/mm^3) participated in the study. The study was not blinded. The subjects received 200 mg of IV itraconazole solution twice daily (BID) for 2 days and then once daily (QD) for 5 more days. Subjects were then sequentially assigned to receive either itraconazole oral solution 200 mg BID or 200 mg QD for an additional 28 days. Blood samples were obtained before and immediately at the end of the first IV dose at 15 and 30 minutes and 1,2, 4, 6, 8, 11 hours post dose. Blood samples on day 7 after the last IV dose was similar to the first dose except an additional sample was taken at 23 hours post dose. Twelve hour urine collections for creatinine clearance and hydroxypropyl-β-cyclodextrin (HPBCD) excretion were performed during and after the day 1 and 7 infusions. Blood samples were obtained before and following a single oral dose on day 36, at the completion of 28 days of oral dosing at 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 12 and 24 hours post dose. Additional blood samples were taken before administration of each IV dose and weekly, before the morning dose during the oral dosing phase of the study. Urine for cyclodextrin was collected starting at the time of infusion and continuing for 12 hours on day 1 and 7 of IV infusion. The formulation number of itraconazole IV and oral solution used were 95F09/F33 and 95B03/F88, respectively.

Analytical Method

[redacted]

Data Analysis: Non compartmental methods were used to compute the pharmacokinetic parameters.

Results: The mean plasma concentration time profiles and the trough concentrations are provided on the following pages. Based on evaluation of the trough concentrations, steady state conditions were obtained after administration of the itraconazole IV on day 3. Steady state for both the QD and BID oral solution group was established on day 29 of dosing. The trough concentrations are provided in the following table:

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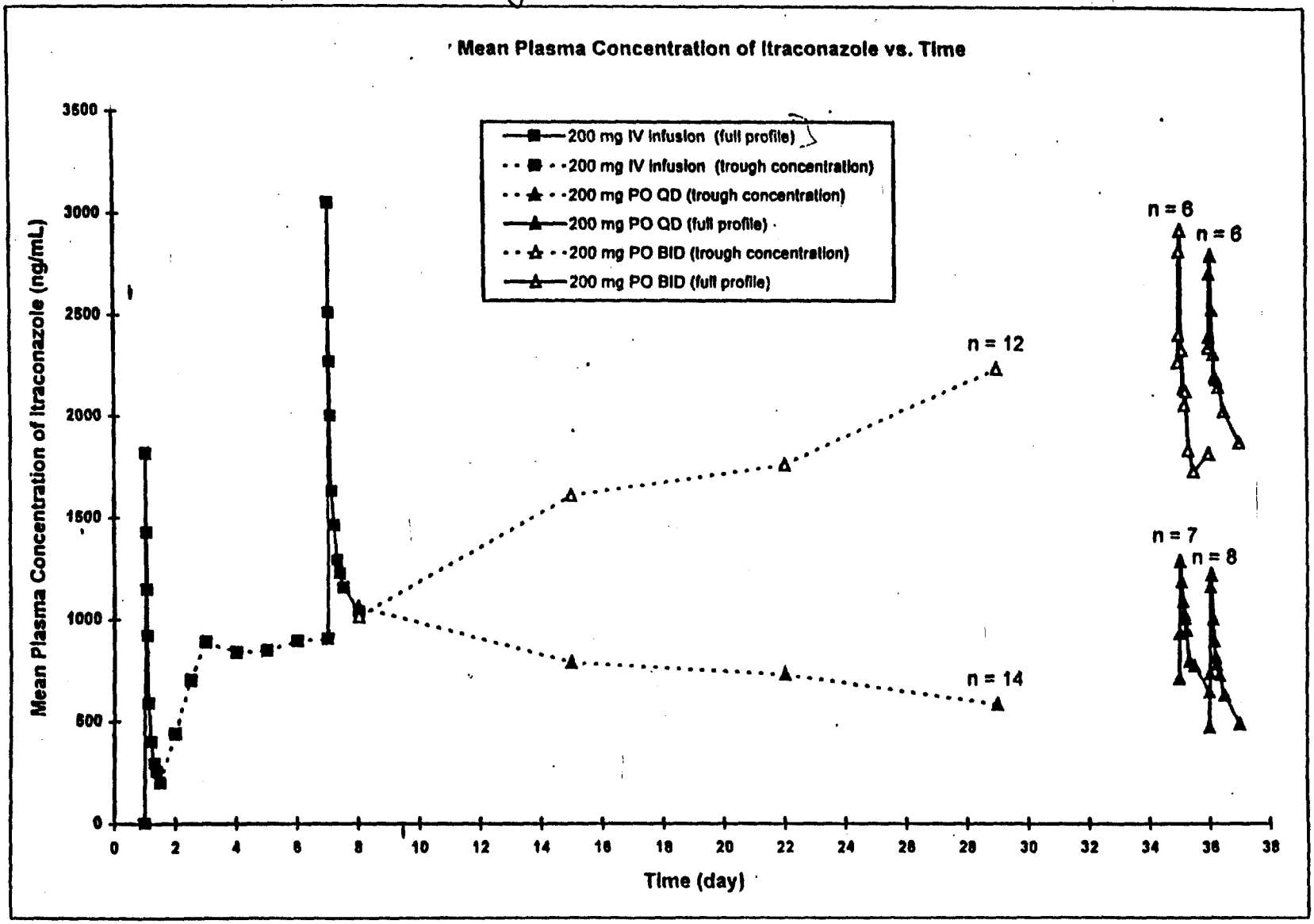
Fig 6


Mean Plasma Concentration of Itraconazole vs. Time
200 mg IV infusion (full profile)
200 mg IV infusion (trough concentration)
200 mg PO QD (trough concentration)
200 mg PO QD (full profile)
200 mg PO BID (trough concentration)
200 mg PO BID (full profile)
Mean Plasma Concentration of Itraconazole (ng/mL)
Time (day)
n = 12
n = 14
n = 6
n = 6
n = 7
n = 8

22

Fig 7

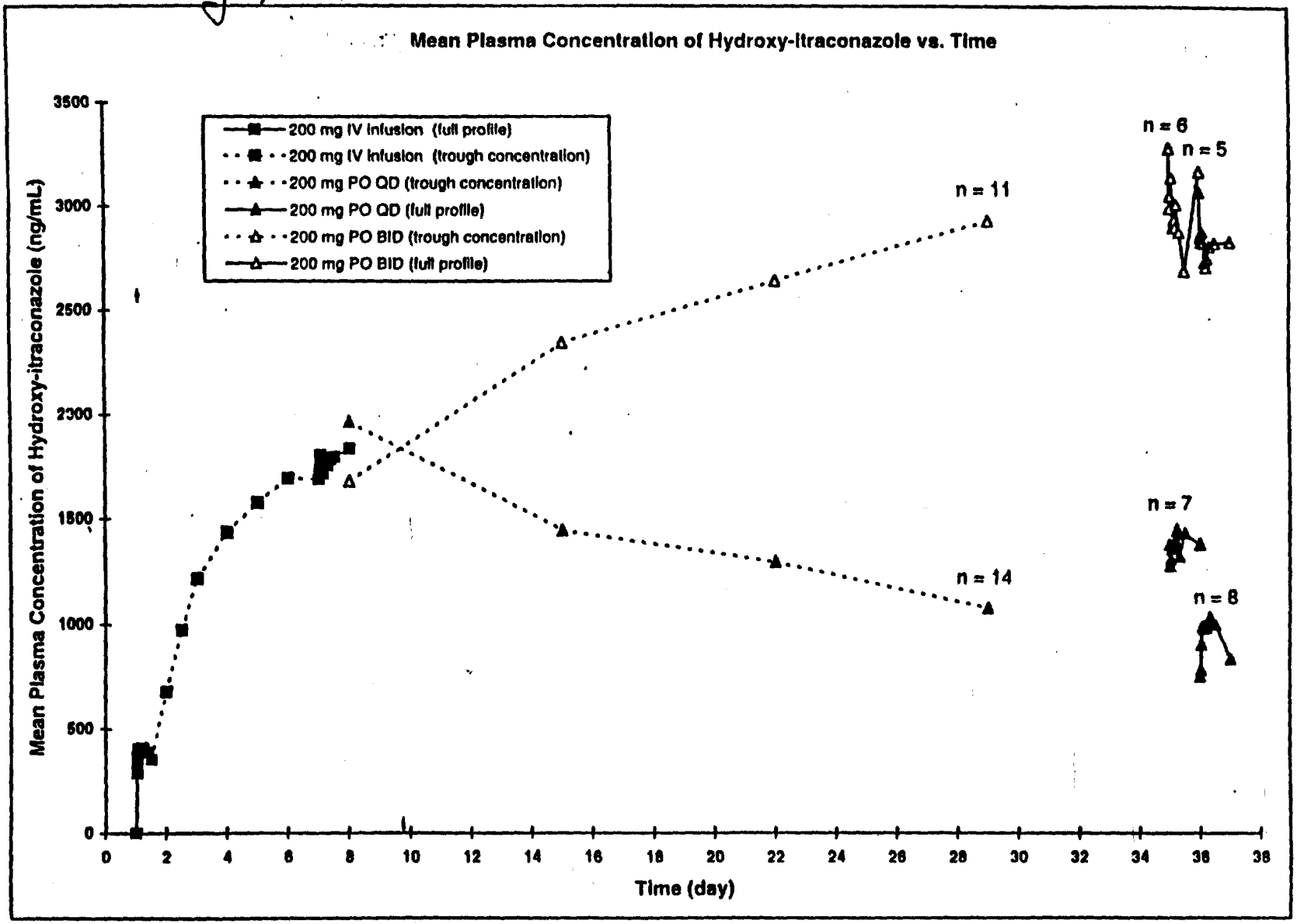

Mean Plasma Concentration of Hydroxy-itraconazole vs. Time
200 mg IV infusion (full profile)
200 mg IV infusion (trough concentration)
200 mg PO QD (trough concentration)
200 mg PO QD (full profile)
200 mg PO BID (trough concentration)
200 mg PO BID (full profile)
n = 11
n = 14
n = 6
n = 5
n = 7
n = 8
Mean Plasma Concentration of Hydroxy-itraconazole (ng/mL)
Time (day)
0
500
1000
1500
2000
2500
3000
3500
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
38

Fig 8

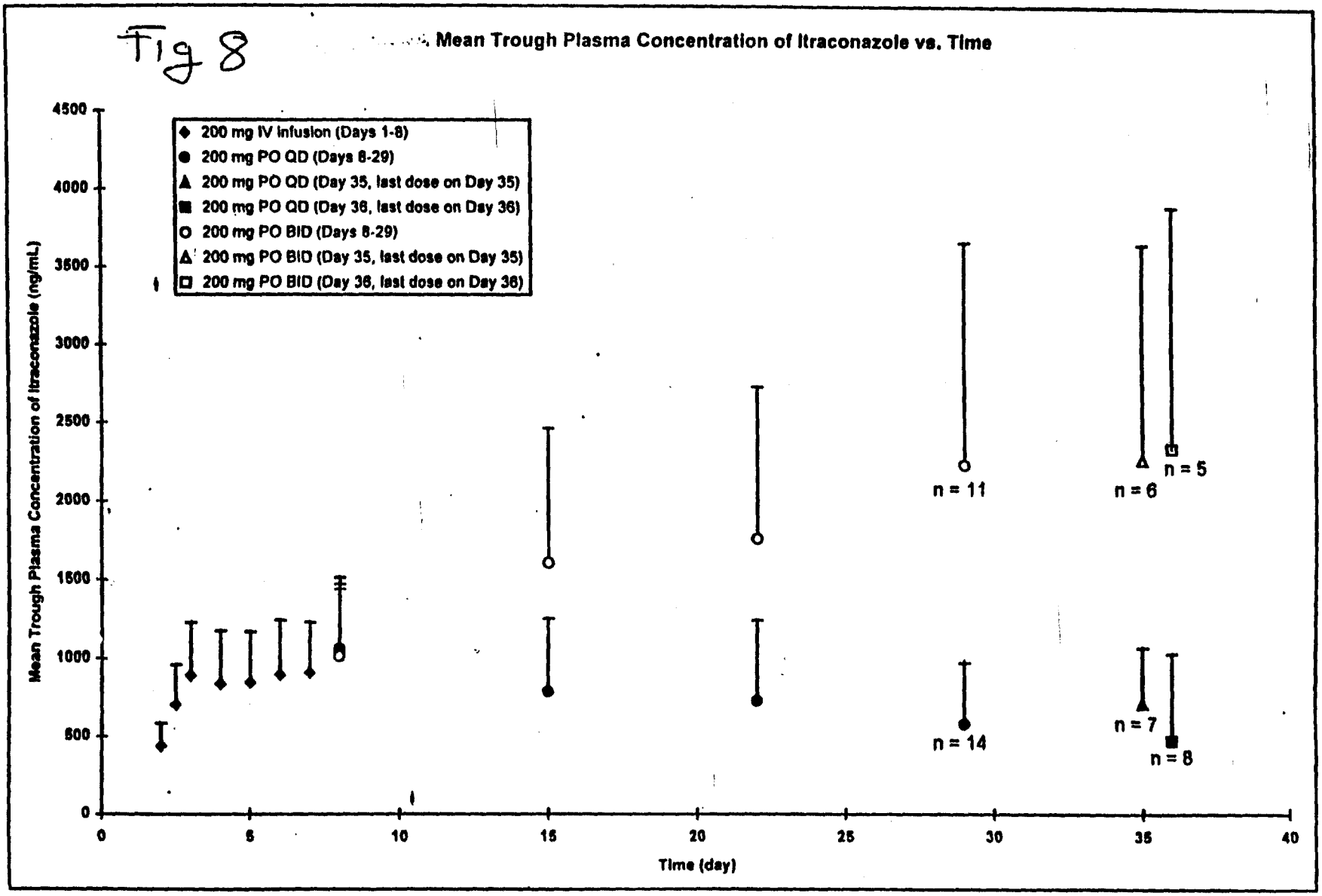

Mean Trough Plasma Concentration of Itraconazole vs. Time
200 mg IV Infusion (Days 1-8)
200 mg PO QD (Days 8-29)
200 mg PO QD (Day 35, last dose on Day 35)
200 mg PO QD (Day 36, last dose on Day 36)
200 mg PO BID (Days 8-29)
200 mg PO BID (Day 35, last dose on Day 35)
200 mg PO BID (Day 36, last dose on Day 36)
Mean Trough Plasma Concentration of Itraconazole (ng/mL)
4500
4000
3500
3000
2500
2000
1500
1000
500
0
0
5
10
15
20
25
30
35
40
Time (day)
n = 11
n = 6
n = 5
n = 14
n = 7
n = 8

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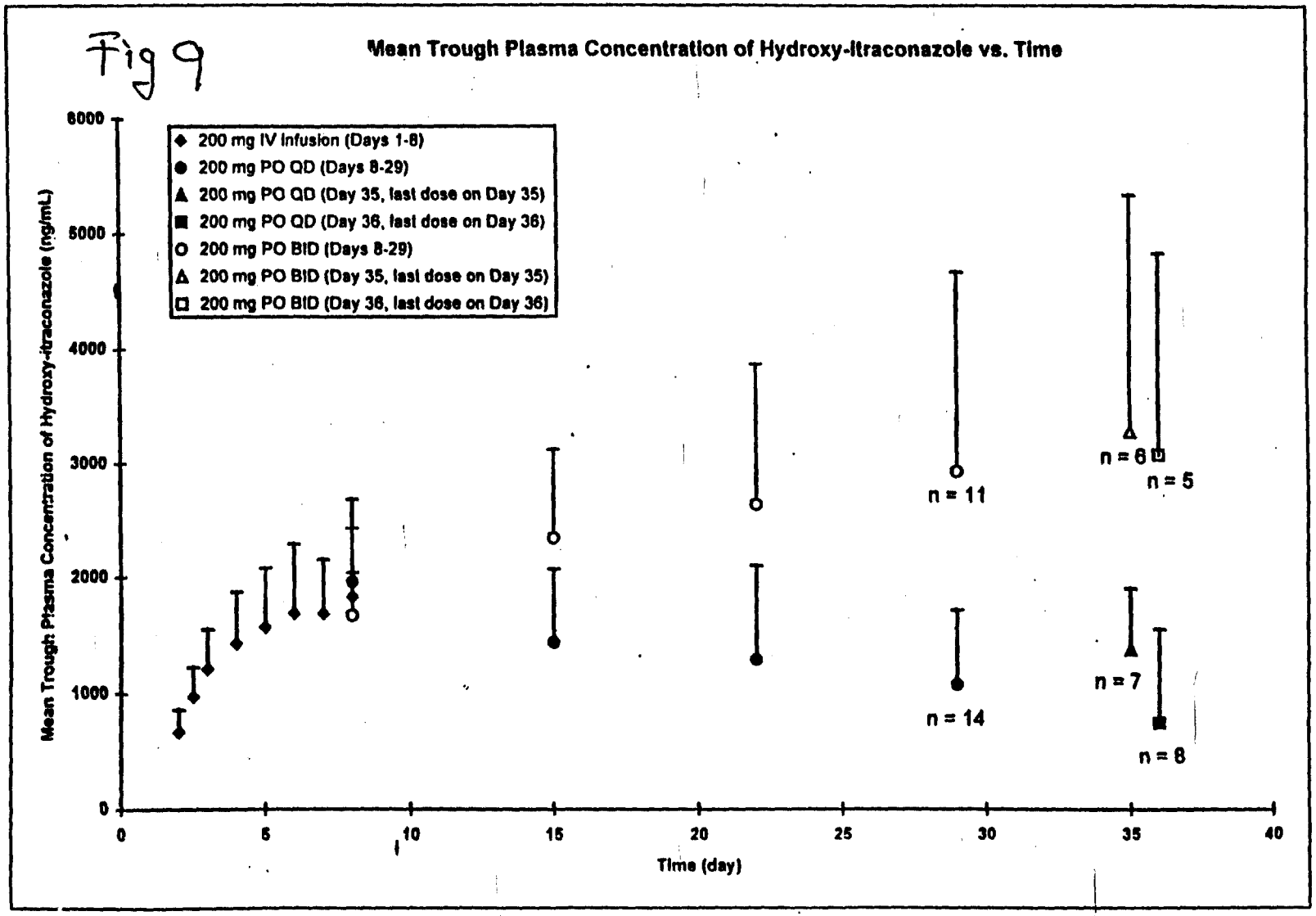
Fig 9


Mean Trough Plasma Concentration of Hydroxy-Itraconazole vs. Time
200 mg IV Infusion (Days 1-8)
200 mg PO QD (Days 8-29)
200 mg PO QD (Day 35, last dose on Day 35)
200 mg PO QD (Day 36, last dose on Day 36)
200 mg PO BID (Days 8-29)
200 mg PO BID (Day 35, last dose on Day 35)
200 mg PO BID (Day 36, last dose on Day 36)
Mean Trough Plasma Concentration of Hydroxy-itraconazole (ng/mL)
6000
5000
4000
3000
2000
1000
0
0
5
10
15
20
25
30
35
40
Time (day)
n = 11
n = 14
n = 6
n = 5
n = 7
n = 8

Mean Trough plasma concentrations (ng/mL) of itraconazole

Day (hour)	Mean ± SD (n)		
	IV Infusion (200 mg)	Oral Solution QD Group (200 mg)	Oral Solution BID Group (200 mg)
2 (24)	439 ± 144 (32)	459 ± 155 (16)	419 ± 134 (16)
2 (36)	703 ± 253 (32)	744 ± 292 (16)	662 ± 208 (16)
3 (48)	890 ± 334 (32)	931 ± 405 (15)	785 ± 248 (15)
4 (72)	837 ± 334 (30)	889 ± 405 (15)	785 ± 248 (15)
5 (96)	846 ± 319 (28)	912 ± 346 (14)	780 ± 247 (14)
6 (120)	894 ± 346 (28)	967 ± 395 (15)	809 ± 270 (13)
7 (144)	906 ± 346 (27)	914 ± 366 (14)	896 ± 273 (13)
8 (168)	1039 ± 433 (28)	1061 ± 453 (15)	1013 ± 427 (13)
15 (336)	-	789 ± 465 (15)	1609 ± 855 (13)
22 (504)	-	732 ± 514 (15)	1761 ± 970 (12)
29 (672)	-	583 ± 391 (14)	2236 ± 1423 (12)
36 (840)	-	474 ± 560 (8)	2342 ± 1546 (6)

The mean pharmacokinetic parameters of itraconazole are presented in the following table

Parameter	IV Phase		Oral Solution Phase	
	Day 1 (BID)	Day 7 (QD)	Last Day (QD)	Last Day (BID)
Cmax (ng/mL)	1899 ± 541	3124 ± 953	1336 ± 757	3027 ± 1387
Tmax (hr)	1.0 ± 0.1	1.0 ± 0.1	2.3 ± 2.9	1.8 ± 0.6
Cav (ng/mL)	-	1339 ± 366	756 ± 499	2206 ± 1186
AUC(0-12h) (ng*hr/mL)	5825 ± 1525	-	-	26476 ± 14236
AUC(0-24h) ng*hr/mL)	-	32126 ± 8790	18153 ± 11969	-

After multiple IV infusions on day 7, the mean Cmax of itraconazole was significantly increased by 63% compared to the day 1 value. Compared to the values at the end of the IV phase (day 7), the Cmax and AUC(0-24h) on last day of the oral solution QD phase were significantly decreased by 65% and 57%, respectively. The Cmax, Cav and AUC of itraconazole on the last day of oral solution phase was not significantly different ($P< 0.05$) from day 7 (last day) after the IV phase. The average concentration (Cav) , Cmax were significantly different when the QD and BID oral solutions were compared with the values for the BID higher than that for the oral dose. The AUC values when the QD and BID oral solution phase were not significantly different, but there was a trend of higher concentrations after the BID dosing.

Hydroxyitraconazole is the major active metabolite of itraconazole. The mean trough concentrations for hydroxyitraconazole is provided in the following table. Steady state concentrations were achieved after day 6 of IV administration. During the oral solution phase, the steady state conditions were achieved after day 29 of BID dosing.

Trough Plasma concentrations (ng/mL) of Hydroxyitraconazole

Day (hour)	Mean ± SD (n)		
	IV infusion (200 mg)	Oral Solution QD Group (200mg)	Oral Solution BID Group (200mg)
2 (24)	677 ± 184 (31)	713 ± 201 (16)	639 ± 163 (15)
2 (36)	974 ± 253 (31)	1035 ± 265 (16)	908 ± 229 (15)
3 (48)	1214 ± 339 (31)	1288 ± 368 (16)	1136 ± 296 (15)
4 (72)	1433 ± 439 (29)	1525 ± 544 (15)	1335 ± 276 (14)
5 (96)	1575 ± 502 (27)	1741 ± 597 (14)	1396 ± 306 (13)
6 (120)	1693 ± 599 (27)	1818 ± 733 (15)	1537 ± 341 (12)
7 (144)	1690 ± 463 (26)	1735 ± 557 (14)	1637 ± 340 (12)
8 (168)	1837 ± 598 (27)	1965 ± 721 (15)	1678 ± 363 (12)
15 (336)	-	1444 ± 625 (15)	2344 ± 777 (12)
22 (504)	-	1296 ± 804 (15)	2640 ± 1229 (11)
29 (672)	-	1079 ± 642 (14)	2929 ± 1744 (11)
36 (840)	-	751 ± 807 (8)	3073 ± 1759 (5)

The pharmacokinetic parameters for hydroxyitraconazole are presented in the following tables.

Parameter	Mean ± SD			
	IV Phase		Oral Solution Phase	
	Day 1 (n=31)	Day 7 (n=27)	Last Day QD (n=15)	Last Day BID (n=11)
Cmax (ng/mL)	462 ± 134	2008 ± 542	1303 ± 683	3282 ± 1752
Tmax (hr)	4.6 ± 3.6	8.4 ± 9.2	7.0 ± 6.0	3.1 ± 3.7
Cav (ng/mL)	-	1790 ± 514	1158 ± 656	2867 ± 1559
AUC(0-12h) (ng*hr/mL)	4399 ± 1343	-	-	34400 ± 18712
AUC(0-24) (ng*hr/mL)	-	42960 ± 12334	27781 ± 15753	-
R#	0.8 ± 0.3	1.4 ± 0.2	1.7 ± 0.4	1.4 ± 0.2

Ratio of AUC(0-t) of hydroxyitraconazole to AUC(0-t) of itraconazole; t = 12 hours for the BID dosing regimen and 24 hours for the QD dosing regimen.

The mean Cmax of hydroxyitraconazole was 4.4 times higher than the first IV dose on day 1. The difference was significant. The metabolic AUC ratio was also increased by 75%. In the oral solution QD group, the mean Cmax of hydroxyitraconazole was significantly decreased by 48% on last day of the oral solution phase when compared with that on day 7 of the IV phase. The mean value of AUC(0-24h) for the metabolite was also significantly reduced by approximately 49% from day 7 to last day. For the oral solution BID group, the Cmax and Cav of hydroxyitraconazole were significantly increased ($p<0.05$) from day 7 to last day. The Cmax and Cav of hydroxyitraconazole was significantly higher in the BID than QD oral solution group. The metabolic ratio was significantly ($p<0.05$) higher on the last day in the QD than in the BID oral solution group. The mean metabolic ratio (R) of hydroxyitraconazole was increased from 0.8 on day 1 to 1.4 on day 7 during the IV phase. On the last day of the oral phase, R averaged 1.7 in the oral solution QD group and 1.4 in the BID group.

The mean pharmacokinetic parameters of hydroxy-propyl-beta cyclodextrin (HPBCD) is contained in the following table

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Mean ± SD Pharmacokinetic Parameters of Hydroxypropyl-beta cyclodextrin

Parameters	Day 1		Day 7	
	N	Mean ± SD	N	Mean ± SD
tmax (hr)	31	1.02 ± 0.07	28	1.03 ± 0.09
Cmax (μg/mL)	31	577 ± 86.3	28	770 ± 729
AUCt (μg*hr/mL)	14	1188 ± 169	28	1435 ± 457
AUC∞ (μg*hr/mL)	32	1294 ± 251	28	1424 ± 457
Cl (mL/min)	31	107 ± 22	28	99.3 ± 22.6
Cav	31	-	28	59.8 ± 19.0
T ½ (hr)	32	1.65 ± 0.25	28	1.83 ± 0.44

Except for Cl and T ½ ,no significant differences ($p<0.05$) was observed in the pharmacokinetic parameters after IV administration when day 1 and day 7 were compared.

Safety: The applicant stated that the most common adverse events reported were diarrhea and granulocytopenia. The applicant reported that adverse event occurring in ≥ 5% of subjects included application site reactions, fever, headache, abdominal pain, diarrhea, nausea, bilirubinaemia. No serious adverse events were reported by the applicant. The events that the applicant reported related to the drug included application site reaction, headache, bilirubinaemia, jaundice and taste perversion.

Conclusion: A goal of this study was to identify an oral dosing regimen of itraconazole solution that produces similar concentration observed after IV administration of itraconazole. The mean itraconazole concentrations at steady state were decreased in the QD oral regimen and increased in the BID oral regimen when they are compared to the mean concentrations after IV administration. The 200 mg BID oral solution is the regimen that produces concentration that would produce at least similar concentrations to that observed after IV administration. The mean average and trough concentrations values of itraconazole observed at steady state exceeded the target concentration of 250 ng/mL for both the intravenous and oral solution phases (see comments section for discussion of significance of 250 ng/mL target concentration).

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Study N112680 (ITR-INT-59): Pharmacokinetics and safety of 7 days IV itraconazole followed by two weeks of oral itraconazole solution in patients with hematological malignancy. Part I: Pharmacokinetics of itraconazole and safety (Volume 24 page 1)

Objective: To assess the tolerability and safety and to describe the itraconazole, hydroxyitraconazole and hydroxypropyl-β-cyclodextrin plasma levels after four 1-hour intravenous (IV) infusions of itraconazole 200 mg given over 2 days and once daily infusion of 200 mg during the next 5 days, followed by a 14-day oral dosing at 200 mg o.d or 200 mg bid of itraconazole oral solution in 12 patients with hematological malignancy.

Design: This was an open label study in which four 1 hour infusions of itraconazole 200 mg were administered over two days at time 0, 8, 24 and 32 hours. Five additional infusions were administered at 48, 72, 96, 120 and 144 hours after the first infusion. After the IV infusions, oral itraconazole regimens were started; six patients received itraconazole solution 200 mg every day (QD) and another 6 patients received itraconazole solution 200 mg twice a day (BID). Itraconazole IV solution was composed of 20 mL of a 10 mg/mL solution ; batch # 94K10/F33. Itraconazole oral solution consisted of 100 mg of itraconazole per 10 mL of a 40% hydroxypropyl-β-cyclodextrin solution. Blood samples (6mL) for drug analysis (itraconazole, hydroxyitraconazole and hydroxypropyl-β-cyclodextrin) were taken immediately before treatment and at 1, 2, 8, 24, 48, 96, 144, 145, 146, 156 and 168 hours after the first infusion. Blood samples were also taken at 5 and 24 hour after the first oral administration and just before and 5 hour after the morning dose on days 13, 17 and 21. Urine samples were collected before drug administration on day 7. The complete urinary output was collected during the interval 144 to 168 hour of the last infusion.

Analytical Method:

Data Analysis: Descriptive statistics was calculated for plasma concentrations. Metabolic ratio was defined as the ratio between the trough concentration of hydroxyitraxonazole to itraconazole. It was calculated at days 3 (after 2-day IV loading dose), 8(end of IV treatment) and 21 (end of oral follow-up treatment)

Results: The mean ± SD plasma concentrations for itraconazole and hydroxyitraconazole are provided in following tables.

Itraconazole Concentration

Day	Time(hr)	Mean ± SD (ng/mL)	
1	1	1844 ± 534	
	2	783 ± 395	
	8	192 ± 78	
2	24	270 ± 89	
	32	553 ± 202	
	33	2205 ± 860	
	34	1498 ± 570	
3	48	503 ± 204	
5	96	505 ± 159	
7	144	532 ± 223	
	145	2250 ± 740	
	146	1496 ± 444	
	156	702 ± 251	
8	168	535 ± 203	

During the 2-day loading dose scheme, the mean trough concentration of itraconazole increased gradually from 192 ng/mL at 8 hours to 270 ng/mL at 24 hours, 553 ng/mL at 32 hours and 503 hours at 48 hours. The steady state plasma concentration of itraconazole was achieved after 48 hours of intravenous infusion of itraconazole. At the end of IV treatment, 14 out of 15 patients had reached trough plasma concentrations of itraconazole higher than 250 ng/mL. Seven out of these 14 patients had trough plasma concentrations higher than 500 ng/mL.

Hydroxy-itraconazole, plasma concentration

Day	Time(hr)	Mean ± SD (ng/mL)	
1	1	316 ± 177	
	2	362 ± 133	
	8	288 ± 104	
2	24	481 ± 158	
	32	692 ± 230	
	33	786 ± 235	
	34	796 ± 244	
3	48	776 ± 214	
5	96	988 ± 251	
7	144	1074 ± 338	
	145	1251 ± 392	
	146	1247 ± 357	
	156	1292 ± 424	
8	168	1123 ± 346	

The mean trough plasma concentrations of hydroxyitraconazole increased from 288 ng/mL at 8 hours to 481 ng/mL at 24 hours, 692 at 32 hours, 776 ng/mL at 48 hours and 988 ng/mL at 96 hours. Based on trough concentrations, steady state plasma concentrations for hydroxyitraconazole reached after 96 hours after IV infusion. The mean metabolic ratio was 2.2 with a minimum of 1.4 and maximum of 3.2.

Following oral administration of 200 mg QD, the trough concentration of itraconazole decreased in 3 patients and remained steady in the other 2 patients when compared to the trough concentrations after the IV administration. However, in the group that received BID dosing regimen, the trough concentration remained steady in 2 and increased in 3 patients. The results indicate that itraconazole 200 mg BID regimen is the best to maintain the concentrations obtained after the IV administration.

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The following tables contain the mean plasma concentrations of itraconazole after the BID and QD dosing regimen.

Mean plasma Itraconazole, ng/mL		
Oral administration 200 mg QD		
Day	Time (hrs after start of infusion)	Mean ± SD (n=5)
8	168	634 ± 239
	173	982 ± 531
9	192	562 ± 308
13	288	356 ± 322 (n=4)
	293	571 ± 361
17	384	361 ± 280
	389	535 ± 321

Mean Plasma Itraconazole, ng/mL		
Oral administration 200 mg BID		
Day	Time (hrs after start of infusion)	Mean ± SD (n=5)
8	168	426 ± 88
	173	768 ± 95
9	192	574 ± 163
13	288	852 ± 446
	293	1361 ± 875
17	384	825 ± 429
	389	1107 ± 352 (n=3)
21	480	1123 ± 733 (n=4)
	485	1405 ± 558 (n=4)

At steady state, 0.18 ± 0.14% of the itraconazole dose was excreted as itraconazole in the urine and 0.82 ± 0.35% as hydroxy-itraconazole after intravenous administration.

For hydroxyitraconazole, the group that received itraconazole solution 200 mg QD, hydroxyitraconazole concentrations decreased in 2 patients and remained about the same in 3 patients. For the group that received 200 mg BID oral follow up, the concentrations remained steady in 2 patients and increased in 3 patients. Again, the 200 mg BID regimen was the best to maintain the concentrations of hydroxyitraconazole obtained after the IV administration. After the oral follow-up with 200 mg QD or BID, the itraconazole and hydroxyitraconazole concentrations were more variable than at the end of the intravenous treatment.

Mean plasma hyroxy-itraconazole, ng/mL		
Oral administration of 200 mg itraconazole QD		
Day	Time (hrs after start of infusion)	Mean ± SD (n=5)
8	168	1243 ± 472
	173	1381 ± 390
9	192	1052 ± 405
13	288	712 ± 669 (n=4)
	293	980 ± 606
17	384	836 ± 664
	389	988 ± 632

Mean plasma hyroxy-itraconazole concentration, ng/mL		
Oral administration 200 mg itraconazole BID		
Day	Time (hrs after start of infusion)	Mean ± SD (n=5)
8	168	946 ± 239
	173	1212 ± 264
9	192	1103 ± 236
13	288	1531 ± 792
	293	1827 ± 646
17	384	1617 ± 912
	389	2224 ± 917 (n=3)
21	480	2060 ± 700 (n=4)
	485	2483 ± 1036 (n=4)

Summary of Pharmacokinetic Parameters

Parameters	Itraconazole (mean ± SD)	Hydroxy-itraconazole (Mean ±SD)
Intravenous Treatment		
Ctrough 48h, ng/mL	503 ± 204	776 ± 214
Cpeak end of last IV, ng/mL	2250 ± 740	1251 ± 392
Ctrough end IV, ng/mL	535 ± 203	1123 ± 346
Metabolic Ratio (MR) end IV	-	2.2 ± 0.5
200 mg QD Oral		
Ctrough 48h, ng/mL	361 ± 280*	836 ± 664*
Metabolic Ratio, end po	-	2.2 ± 0.5*
200 mg BID Oral		
Ctrough end po, ng/mL	1123 ± 733	2060 ± 700
Metabolic Ratio, ng/mL	-	2.2 ± 0.9

Safety: After IV administration, constipation and fever were the most frequent reported adverse events. After the oral administration, diarrhea and fever were the most frequently reported adverse events. Two and five patients in the IV and Oral groups had their treatment terminated due to adverse events. Generally, taking into consideration the patient population with the underlying disease, the sponsor reported the treatment was well tolerated and safe. Refer to medical review for a discussion of adverse events.

Conclusion: After 1-hour infusions of itraconazole 200 mg BID for 2 days and QD for 5 additional days, steady state was achieved 48 hours after the first dose; hydroxyitraconazole infusion was achieved 96 hours after the first dose. The oral follow up with 200 mg QD could not maintain the itraconazole and hydroxy-itraconazole plasma concentrations obtained at the end of the IV treatment in some patients , whereas the BID maintained or increased these concentrations in all patients. The oral follow up regimen of itraconazole solution 200 mg BID appears to be the best regimen to maintain similar concentrations observed after IV administration. Itraconazole and hydroxitraconazole trough plasma concentrations were more variable after the oral solution than after IV administration.

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Study N130310(ITR-USA-116) Single dose pharmacokinetic study of intravenous itraconazole in subjects with mild, moderate and severe renal impairment (volume 29 page 1)

Objective: To determine the pharmacokinetic profiles of itraconazole, hydroxyitraconazole-β-cyclodextrin in healthy and renally impaired subjects after I.V. administration of a formulation containing 200 mg of itraconazole and 8 grams of hydroxy propyl-β-cyclodextrin

Design: This was an open label study at a single center. Thirty-six subjects completed this study and were stratified into four groups based on their urine creatinine clearance. Group I had CrCl≥ 80 mL/min/1.73m^2, Group II CrCl = 50 - 79 mL/min/1.73m^2, Group III CrCl = 20-49 mL/min/1.73m^2 and Group IV CrCl ≤ 19 mL/min/1.73m^2. Itraconazole 200 mg as an IV infusion was administered over 1 hour after an approximately 12 hour overnight fast. The subjects were not allowed to eat until at least 2 hours after the dose has been administered. A 5 mL blood sample was obtained before the start of the infusion to determine itraconazole plasma protein binding. Plasma samples for the determination of itraconazole, hydroxyitraconazole and hydroxy propyl-β-cyclodextrin (HPBCD) concentrations were obtained before beginning the infusion on day 1; at 0, 15, 30, 45 mins after the infusion started; immediately before the end of the infusion; at 10, 20, 30 and 45 mins after the infusion started; at 1, 1.5, 2, 4, 6, 8, 12, 18, 24, 36, 48, 72, 96, and 120 hours post infusion. Urine samples for the determination of itraconazole, hydroxyitraconazole and HPBCD were obtained before infusion started (-8 to 0 hour); at 0 to 4 hours after completion of the infusion; at 4 to 8, 8 to 12 and 12 to 24 hours post dose; and every 12-hour period until checkout (120 hours post-infusion).

Topical antifungal agents for treating or preventing oropharyngeal or vaginal candidiasis were permitted but ketoconazole and fluconazole were prohibited. If a subject had to take a drug metabolized by the cytochrome P4503A system, he was monitored for adverse events associated with an interaction with itraconazole.

Analytical Method:

Data Analysis: Primary pharmacokinetic parameters were determined by non-compartmental methods.

Results: The mean plasma concentration time profiles for itraconazole, hydroxyitraconazole and HPBCD and graphical representation of exposures are presented on the following pages. Renal function appears to have a greater impact on hydroxyitraconazole and HPBCD elimination than itraconazole. The elimination of hydroxyitraconazole appears to be slower in subjects with normal and mildly impaired renal function than moderate to severely impaired renal function patients. The elimination of HPBCD appeared to be prolonged by renal impairment with the slowest rate in patients with severe impairment. The mean pharmacokinetic parameters for itraconazole are presented in the following table

Fig 9

Itraconazole Mean Plasma Concentration vs. Scheduled Time (on semi-logarithmic scale)

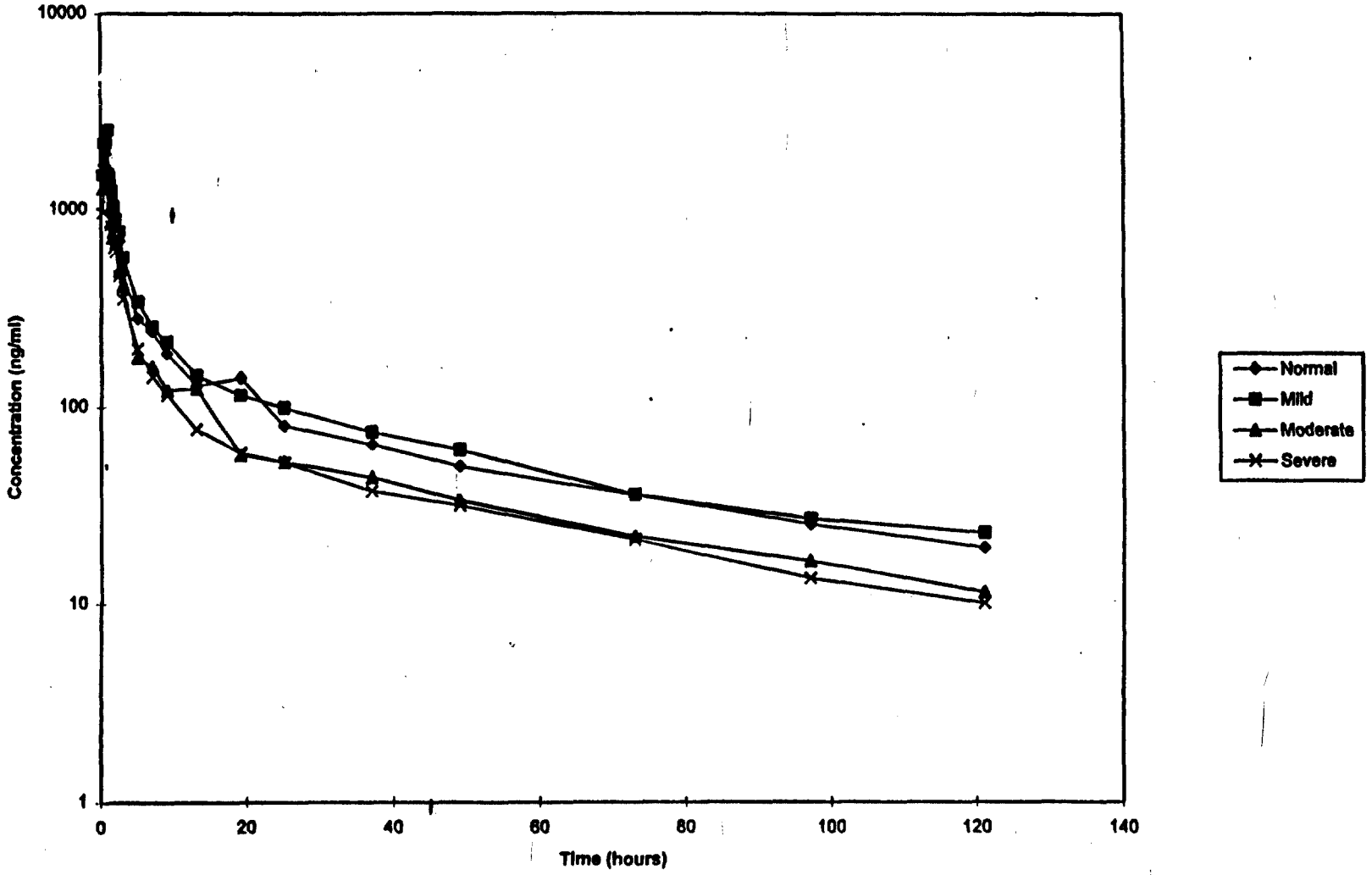


Fig 10

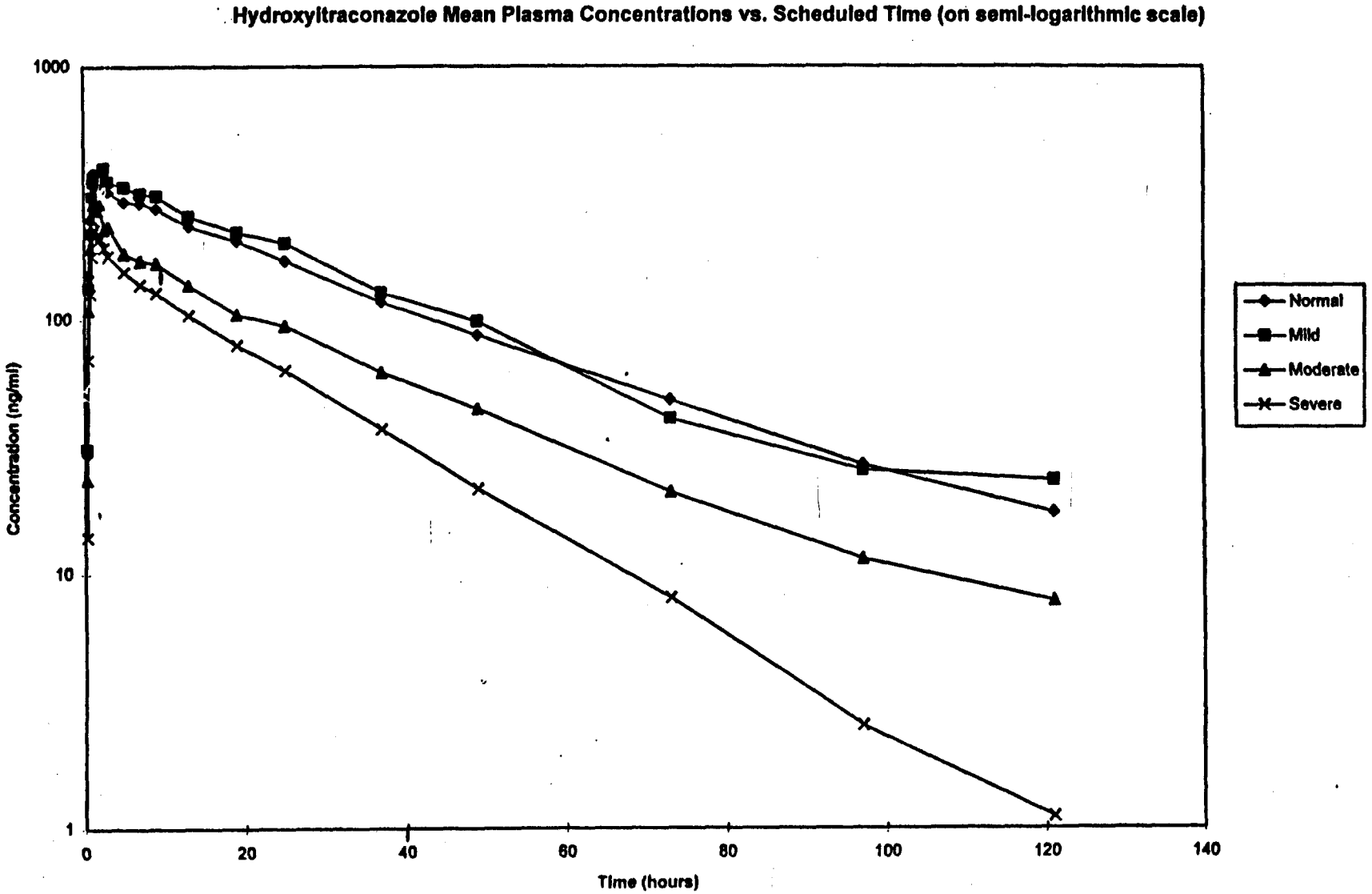
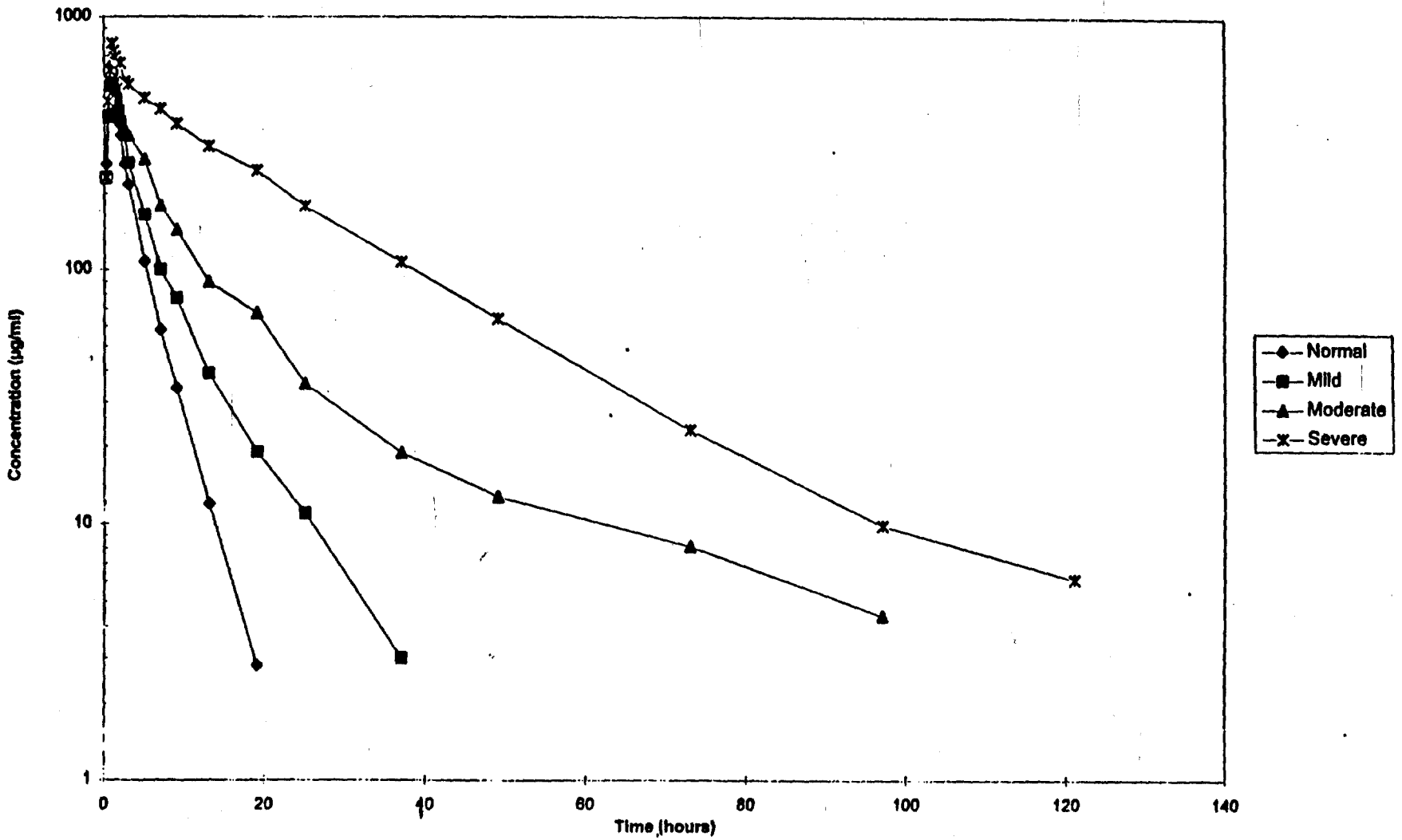

Hydroxyitraconazole Mean Plasma Concentrations vs. Scheduled Time (on semi-logarithmic scale)
Concentration (ng/ml)
1000
100
10
1
0
20
40
60
80
100
120
140
Time (hours)
Normal
Mild
Moderate
Severe

Fig 11

Hydroxypropyl-ß-cyclodextrin Mean Plasma Concentrations vs. Scheduled Time (on semi-logarithmic scale)



39

Fig 12

Fig 12

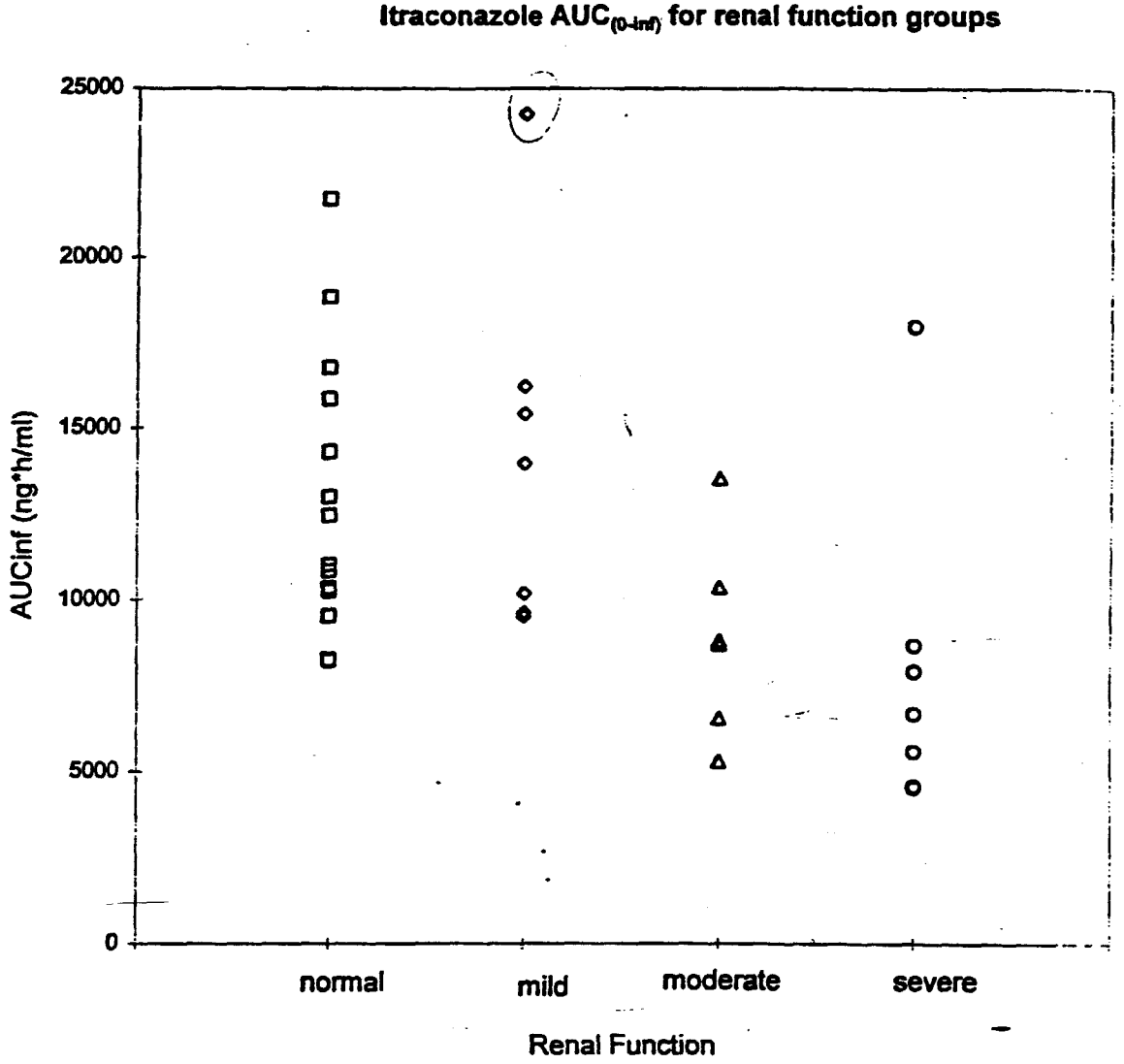
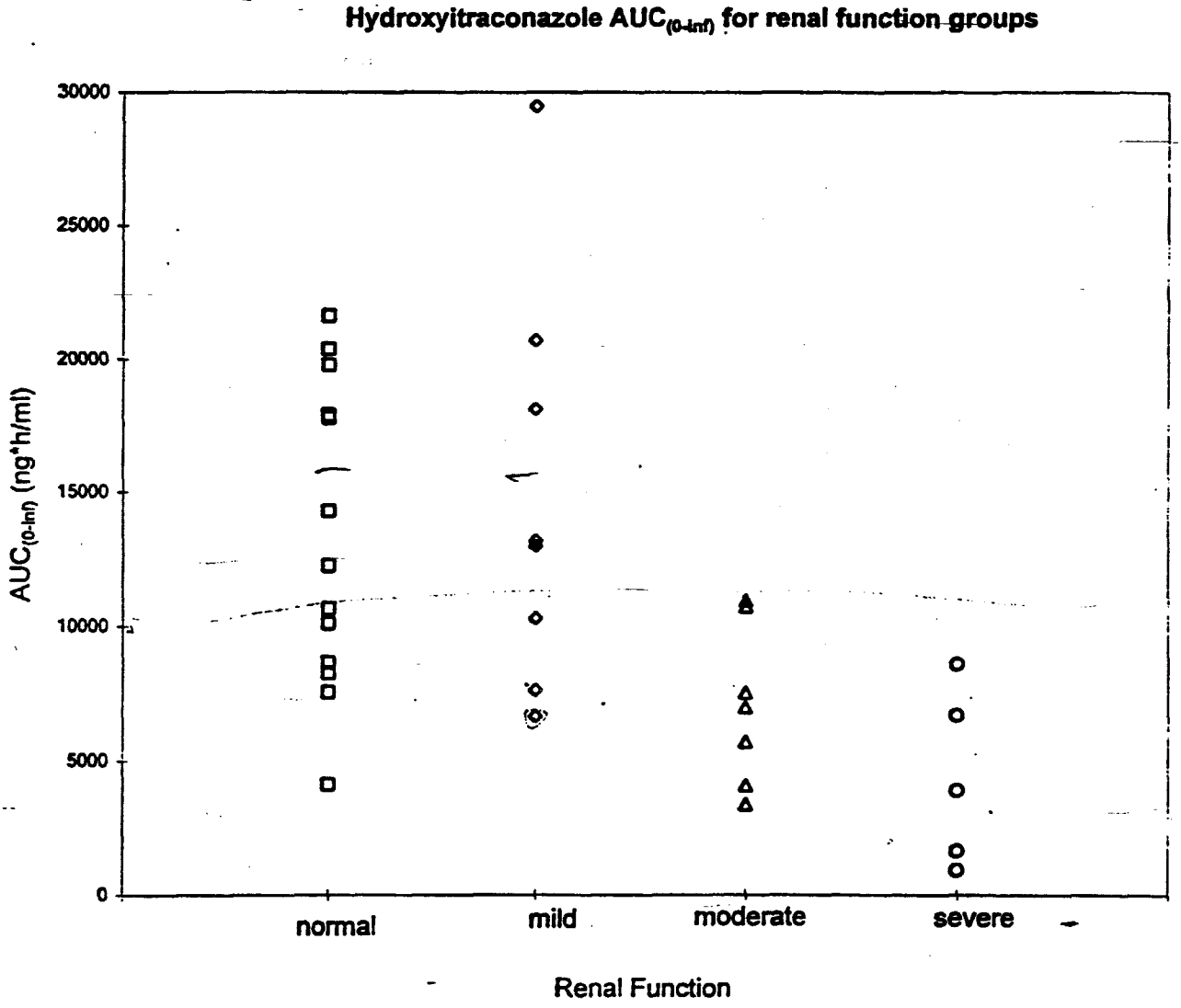
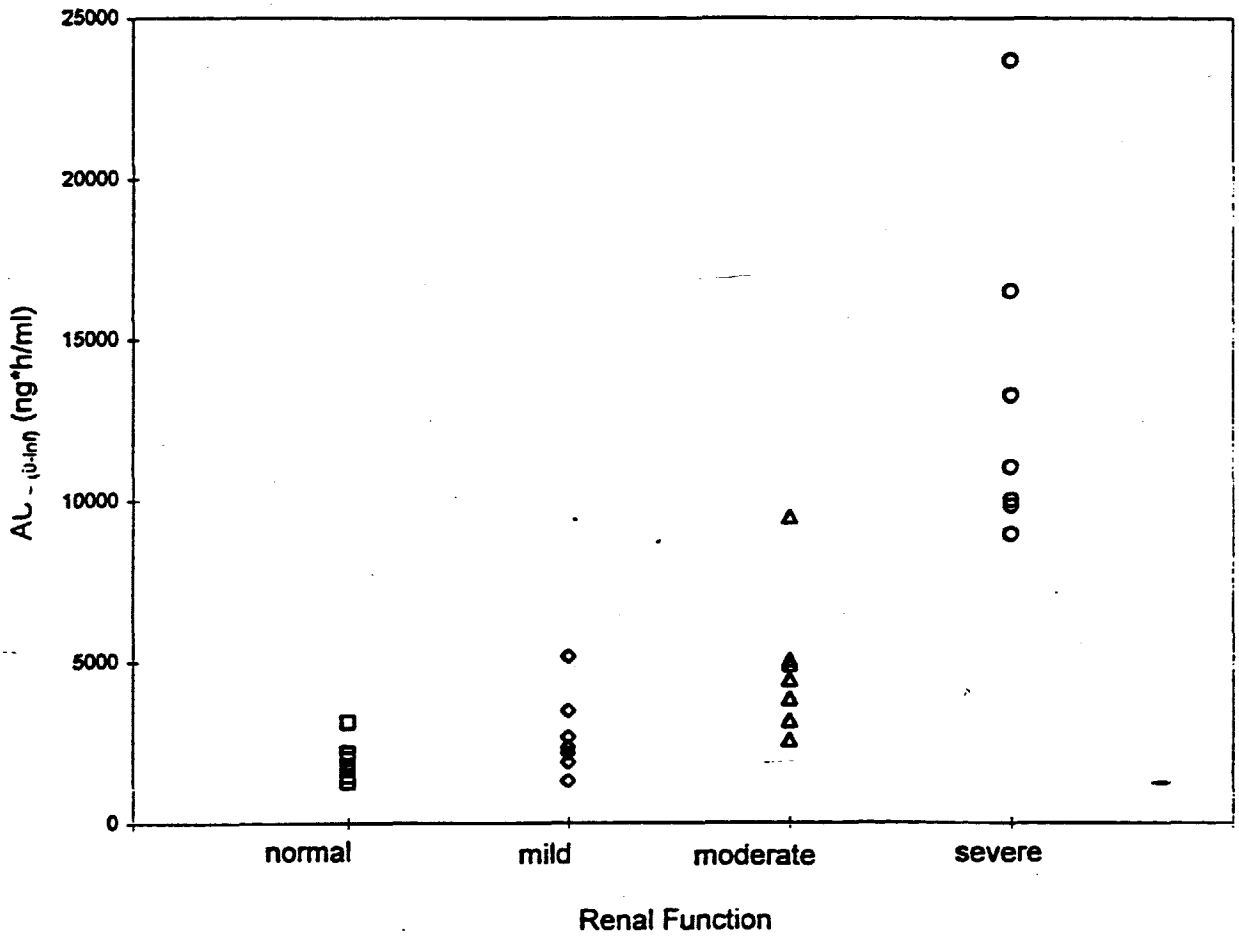

Itraconazole AUC(0-inf) for renal function groups
25000
20000
15000
10000
5000
0
AUCinf (ng*h/ml)
normal
mild
moderate
severe
Renal Function

Fig 13


Hydroxyitraconazole AUC(0-inf) for renal function groups
AUC(0-inf) (ng*h/ml)
30000
25000
20000
15000
10000
5000
0
normal
mild
moderate
severe
Renal Function

Hydroxypropyl-β-cyclodextrin
$AUC_{(0\text{-}inf)}$ for renal function groups

Fig 14



Mean Pharmacokinetic Parameters of Itraconazole

Parameter	Renal Impairment Group				
	I (Normal) n=14	II (Mild) n = 8	III (Moderate) n = 7	IV (Severe) n = 7	Comparison P value**
Tmax (hr)	1.00	0.75	0.75	1	NS
Cmax (ng/mL)	2870 ± 452	2675 ± 941	2079 ± 287	1600 ± 478	I, III (0.006) I, IV (<0.001) II,IV (0.001)
k (1/hr)	0.017±0.006	0.019±0.012	0.017±0.005	0.020±0.008	NS
t ½ (hr)	47.7 ± 20.7	49.4 ± 26.6	46.4 ± 16.7	41.8 ± 20.5	NS
AUClast (ng.hr/mL)	11288±2801	13101±4916	7949±2330	6926±3071	I,III(0.039) I,IV(0.008) II,III(0.006) II,IV(0.001)
AUC∞ (ng*hr/mL)	12980±4068	15434±6022	8876±2655	8020±4686	I,IV(0.023) II,III(0.008) II,IV(0.003)
Cl (L/hr)	16.7 ± 4.75	14.7 ± 5.25	24.4 ± 7.51	30.3 ± 11.8	I,III(0.029) I,IV(0.001) II,III(0.014) II,IV(<0.001)
Vss (L)	664± 270	734 ± 512	900 ± 444	862 ± 167	NS
Vk (L)	1081 ± 367	1023 ± 640	1573 ± 587	1605 ± 512	I,III(0.049) I,IV(0.037) II,III(0.049) II,IV(0.038)
% unbound itraconazole	0.25 ± 0.03	0.27 ± 0.04	0.27 ± 0.04	0.31 ± 0.06	I,IV (0.004)

* Mean reported for all parameters except Tmax for which median is reported
NS: Not statistically significant; ** Based on untransformed data, Vk = Varea

Significant differences were found between groups with normal renal function and severe renal impairment in Cmax, AUC, Clearance, Vk and %unbound itraconazole. AUClast, Vk, Cmax and clearance were significantly different between the groups with normal function and moderate renal impairment. AUCs and clearance differed between the groups with mild and moderate impairment. Cmax, Vk, AUCs and clearance of itraconazole differed between the groups with mild and severe impairment. Subjects with normal renal function had the lowest percentage of unbound itraconazole. There was large within group variability in the pharmacokinetic parameters observed. These results were not similar to that reported after oral administration of the capsule formulation in NDA 20,083. In the

renal impairment studies in NDA 20,083, it was reported that there was no difference in the pharmacokinetics of itraconazole when patients with renal impairment were compared to those with normal renal function. The reasons for the discrepancy in results between the studies is not clear. It must be noted that itraconazole capsule does not contain the hydroxy-propyl-beta-cyclodextrin.

The mean pharmacokinetic parameters for hydroxyitaconazole is contained in the following table.

Pharmacokinetic Parameters* of hydroxyitraconazole

Parameter	Renal Impairment Group				
	I (Normal) n = 13	II (Mild) n = 8	III (Moderate) n = 7	IV (Severe) n=5	p-value**
Tmax (hr)	1.50	1.54	1.33	1.50	NS
Cmax (ng/mL)	410 ± 148	411 ± 159	326 ± 131	234 ± 64.4	I, IV (0.022)
k (1/hr)	0.033 ± 0.016	0.033 ± 0.017	0.038 ± 0.020	0.065 ± 0.029	I,IV (0.004) II,IV (0.008) III,IV (0.023)
t ½ (hr)	28.5 ± 19.5	27.7 ± 18.7	24.4 ± 14.9	12.7 ± 6.06	NS
AUClast (ng*hr/mL)	12027 ± 4485	12941±4882	6585 ± 2847	4212 ± 3208	I, III (0.009) I,IV (0.001) II,III(0.006) II,IV(<0.001)
AUC∞ (ng*hr/mL)	13361 ± 5675	14894 ±7600	7083 ± 2976	4365 ± 3276	I,III (0.022) I,IV (0.004) II,III (0.011) II,IV (0.002)

* Mean reported for all parameters except Tmax, for which median reported
NS: Not statistically significant; ** Based on untransformed data

There were no significant differences observed in pharmacokinetic parameters for hydroxyitraconazole between the groups with normal renal function and those with mild renal impairment. However, significant differences were noted between the groups with normal renal function and severe renal impairment in Cmax,, k and AUC determinations.

The mean pharmacokinetic parameters for HPBCD is presented in the following table. The renal impairment group was significantly different from the normal, mild and moderate groups for Cmax. The severe and moderate groups were significantly different from the normal and mild groups with respect to k, t ½ , AUClast, AUC∞, and Cl.

Pharmacokinetic Parameters* of Hydoxy-β-Cyclodextrin

Parameter	Renal Impairment Group				
	I (Normal) n=14	II (Mild) n=8	III (Moderate) n=7	IV(Severe) n=7	Comparison P value**
Tmax (hr)	1.00	1.00	1.00	1.00	NS
Cmax(μg/mL) median	656 ± 100	617 ± 129	594 ± 147	785 ± 96	I,IV (0.022) II,IV (0.009) III,IV (0.004)
k (1/hr)	0.304± 0.077	0.207 ± 077	0.107 ± 0.046	0.050 ± 0.018	I,II (0.002) I,III (<0.001) I,IV (<0.001) II,III(0.005) II,IV(0.016)
t ½ (hr)	2.5 ± 0.84	4.1 ± 2.3	9.2 ± 8.4	15.6 ± 6.0	I,III(0.004) I,IV(<0.001) II,III(0.039) II,IV(<0.001) III,IV(0.016)
AUClast (ng*hr/mL)	1842 ± 456	2570 ± 1131	4697 ± 2141	13074 ± 4928	I,III(0.015) I,IV(<0.001) II,IV(<0.001) III,IV(<0.001)
AUC∞ (ng*hr/mL)	1870 ± 450	2662 ± 1188	4781 ± 2260	13323 ± 5250	I,III(0.019) I,IV(<0.001) II,IV(<0.001) III,IV(<0.001)
Cl (L/hr)	4.47 ± 0.90	3.48 ± 1.37	1.94 ± 0.73	0.67 ± 0.20	I,II(0.022) I,III(<0.001) I,IV(<0.001) II,III(<0.003) II,IV(<0.001) III,IV(0.015)
Vss (L)	12.1 ± 2.41	14.6 ± 3.26	17.9 ± 6.57	12.9 ± 2.35	I,III (0.002) III,IV(0.017)
Vk (L)	15.2 ± 3.04	17.5 ± 4.15	20.1 ± 6.69	13.6 ± 2.52	I,III (0.016) III,IV(0.006)

* Mean reported for all parameters except Tmax for which median reported
NS Not statistically significant; ** Based on untransformed data

Mean ± SD Urinary Parameters

Parameter	Renal Impairment Group				
	I (Normal) n=14	II (Mild) n=9	III (Moderate) n=7	IV (Severe) n=7	Comparison P value**
Itraconazole					
U(0-t)(μg)	384.921± 264.163	363.101± 247.605	117.627± 947.88	28.623± 20.819	I,III (0.009) I,IV (<0.001) II,III(0.030) II,IV (0.004)
Clr (L/hr)	0.0330 ± 0.0231	0.0253 ± 0.0157	0.0136 ± 0.0106	0.0037 ± 0.0019	I,III (0.020) I,IV(<0.001) II,IV(0.020)
%Dose excreted (0-120)	0.19 ± 0.13	0.18 ± 0.12	0.06 ± 0.05	0.01 ± 0.01	NA
Hydroxyitraconazole					
U(0-t)(μg)	572.410 ± 388.931	708.861 ± 228.617	471.234 ± 173.937	241.435 ± 194.045	I,IV (0.015) II,IV (0.002)
Clr (L/hr)	0.0568 ± 0.0453	0.0606 ± 0.0285	0.0799 ± 0.0424	0.0634 ± 0.0228	NS
% Dose excreted (0-120)	0.28 ± 0.19	0.35 ± 0.11	0.23 ± 0.09	0.12 ± 0.09	NA
Hydroxy propyl-β-cyclodextrin					
U(0-t)(μg)	7134753 ± 2936506	8597939 ± 534437	7899341 ± 680092	8173906 ± 793959	NS
% Dose excreted (0-120)	89.2 ± 36.7	107 ± 6.68	98.7 ± 8.50	102 ± 9.92	NS

Renal excretion of itraconazole and hydroxyitraconazole were below detection limit by 120 hours administration of the dose; however, HPBCD levels were detectable. There were no significant differences in the renal parameters for itraconazole, hydroxyitraconazole and hydroxy propyl-β-cyclodextrin between the groups with normal renal function and mild renal impairment.

Differences were observed between normal renal function and moderate and severe renal impairment for itraconazole, and between normal renal function and severe renal impairment for hydroxyitraconazole. Less than 1% of either itraconazole or hydroxyitraconazole was excreted in the urine over 120 hour collection period. The majority of HPBCD was eliminated in the urine during the 120 hour collection period.

Adverse Events: The most common adverse event reported were rhinitis and headache. One subject in the mild renal impairment group was reported to have had prolonged QT interval that the investigator described a definitely related to study drug. The infusion was discontinued as a result of the adverse event reported. Refer to medical officers review for evaluation of adverse events.

Conclusion: Severe renal impairment affected the elimination of itraconazole; the clearance was approximately twice that observed in patients with normal renal function. Less than 1% of itraconazole administered dose was excreted in the urine. The half-life and AUC of hydroxyitraconazole decreased 2 and 3- fold, respectively, in the group with severe renal impairment as compared with the normal subjects. The amount of hdyroxyitraconazole excreted in the urine of subjects with severe renal impairment was reduced by half when compared with patients with normal renal function. Clearance of HPBCD was reduced 6-fold and elimination half-life was prolonged 6-fold in patients with severe renal function compared to normal renal function patients.

Generally, the clearance of itraconazole was doubled and the half-life of its metabolite, hydroxyitraconazole was reduced by half in subjects with severe renal impairment compared with subjects having normal renal function. A dosage modification in patients with severe renal impairment may be needed (see comments section).

Study N112679 (ITR-INT-58): Pharmacokinetics and safety of 7 days IV itraconazole followed by two weeks of oral itraconazole solution in intensive care patients. Part I: Pharmacokinetics of itraconazole and safety (volume 23 page 121)

Objective: To assess the tolerability and safety and to describe the itraconazole, hydroxy-itraconazole and hydroxypropyl-β-cyclodextrin plasma levels after four 1-hour infusions of itraconazole 200 mg given over two days, and once daily infusion of 200 mg during the next 5 days followed by a 14-day oral dosing at 200 mg o.d. or 200 mg bid of itraconazole oral solution in 12 patients treated in intensive care units

Study Design: This was an open label study in 16 patients treated in intensive care unit. The median (range) and weight (range) were 42.5 (18-53) years and 70 (50 - 100) kg, respectively. Four 1-hour infusions of itraconazole 200 mg plus 8 gm hydroxypropyl-β-cyclodextrin (HPBCD) were administered over two days at time 0, 8, 24 and 32 hours. The next five infusions were administered at time 48, 72, 96, 120 and 144 hours. The oral 14 day follow up was administered daily to the first six patients and twice daily to the six remaining patients. The oral dosing started after the last intravenous (IV) infusion. Blood samples for determination of itraconazole and hydroxy-itraconazole were taken before treatment and at 1, 2, 8, 24, 32, 33, 48, 96, 144, 145, 146, 156, 168 hour after the start of the first infusion. For the oral administration, blood samples were taken before and 5 and 24 hour after the first oral administration and at 5 hour after the morning administration on days 13, 17, and 21. Complete urine samples were collected during the interval 144 to 168 hour of the last infusion. The IV formulation used contained 200 mg itraconazole and 8 gm HPBCD and the oral solution contained 10 mg/mL itraconazole + 400 mg/mL HPBCD. The pharmacokinetic measures determined were Cpeak, Cmin and metabolite ratio (Ratio(met))

Results: The mean pharmacokinetic measures determined after the intravenous and oral administration to patients in the intensive care units are provided in the following table.

Pharmacokinetic Parameter	Itraconazole (mean ± SD)	Hydroxy-itraconazole (mean ± SD)
Intravenous treatment (n=14)		
Ctrough 48th (ng/mL)	316 ± 200	287 ± 140
Cmax last iv (ng/mL)	1576 ± 734	737 ± 289
Ctrough, end, iv (ng/mL)	344 ± 140 (n=11)	605 ± 205
Ratio met/parent, end iv	-	1.9 ± 0.5
200 mg every day oral (n=6)		
Ctrough, end,po (ng/mL)	245 ± 165	491 ± 419
Ratio met/parent, end, po	-	1.8 ± 0.6
200 mg twice a day (n=6)		
Ctrough, end,po (ng/mL)	805 ± 708	1234 ± 1021
Ratio met/parent, end, po	-	1.5 ± 0.4

Cmax = concentration at end of last infusion

Steady state itraconazole concentrations were achieved after 48 hours dosing twice a day. This indicates that there is rapid distribution of itraconazole after IV infusion. Steady state trough concentrations of hydroxyitraconazole was achieved after 96 hours of administration of itraconazole. At steady state, the mean metabolic ratio was 1.9. For the group that received itraconazole at a dose of 200 mg daily, the mean trough concentrations decreased from, 340 ± 148 ng/mL at the end of the 1-week IV treatment to 245 ± 165 ng/mL at the end of the two week oral treatment. The mean trough concentration observed after administration of oral itraconazole twice daily increased from 369 ± 162 at the end of 1 week intravenous treatment to 805 ± 708 ng/mL at the end of 2-week oral treatment. The variability (81%) in itraconazole trough concentrations at the end of oral administration was higher than that observed (41%) after IV administration. A follow up oral dose of 200 mg BID maintained or increase in some trough concentrations. Similar observations were made for hydroxyitraconazole.

Adverse Events: The applicant reported a dose related incidence of gastrointestinal adverse events, mainly diarrhea, during the oral treatment. Refer to the medical review for a discussion of the adverse event profile of itraconazole.

Conclusion: The trough concentrations for itraconazole and hydroxyitraconazole were more variable after oral than after the IV administration. The 200 mg twice a day follow up better maintained or even increased the concentrations of itraconazole obtained at the end of the IV treatment.

Study N118889 (ITR-INT-58): Pharmacokinetics and safety of 7 days IV itraconazole followed by two weeks of oral itraconazole solution in intensive care unit patients. Part II: Pharmacokinetics of hydroxypropyl-β-cyclodextrin (volume 31 page 93).

Objective: To assess the tolerability and safety and to describe the itraconazole, hydroxy-itraconazole and hydroxypropyl-β-cyclodextrin (HPBCD) plasma levels after four 1-hour IV infusions of 200 mg itraconazole and 8 g HPBCD given over two days, and once daily 1-hour infusions of 200 mg itraconazole and 8 gm HPBCD during the next 5 days, followed by a 14-day once daily or twice daily oral dosing of itraconazole 200 mg and HPBCD 8g as a solution in 12 patients treated in intensive care units.

Design: This was an open label study in which four 1-hour infusions of 200 mg itraconazole and 8 gm HPBCD were administered over two days at time 0, 8, 24 and 32 hours. The next five identical 1-hour infusions were administered at time 48, 72, 96, 120 and 144 hours. During the following oral treatment period, six patients received 200 mg itraconazole and 8 gm HPBCD in oral solution once daily and the other six received it twice daily. Plasma concentrations of HPBCD were attained before treatment and at 1, 2, 8, 24, 32, 33, 34, 48, 96, 144, 145, 146, 156, 168, 173 and 192 hour after the start of the first infusion. Twenty four hour urine samples were collected from 144 to 168 hour after the start of the first infusion. The pharmacokinetic parameters measured were Cpeak and Ctrough.

Results:

Time	HPBCD Plasma concentration (μg/mL)	
	Trough	Peak
	Mean ± SD (range)	
1st 1- hour infusion	ND (ND-ND)	411 ± 82 (264 - 529)
4th 1-hour infusion	45.7 ± 33.2 (8.2 - 117)	441 ± 93 (250 - 615)
5th 1-hour infusion	13.3 ± 14.9 (ND - 52.8)	-
7th 1-hour infusion	ND (ND - 15.6)	-
9th 1-hour infusion	ND (ND - 10.8)	392 ± 121 (234-615)
1st oral administration	ND (ND - 27.1)	ND (ND- 19.9)

ND: non quantifiable by HPLC-method (<2.0 μg/mL and < 20 ng/mL urine)

The peak plasma concentrations of HPBCD were comparable during the treatment period consisting of four 1-hour infusions of 8 g HPBCD given over two days and five 1-hour infusions given over 5 days. Trough plasma concentrations of HPBCD during the intravenous period and at 24 hours after the last intravenous administration ranged from not quantifiable to 27.1 μg/mL. The patients with quantifiable HPBCD trough plasma concentrations during the maintenance period had reduced creatinine clearance ranging from 80 to 43 mL/min. The applicant reported urine samples were not collected at the appropriate times per protocol hence amount of HPBCD excreted in the urine could not be computed.

Conclusion: HPBCD was essentially eliminated through the kidney in this group of patients with a clearance corresponding to the glomerular filtration rate.

Study N85583 (ITR-BEL-1): Intravenous pharmacokinetics and oral bioavailability of itraconazole in bone marrow transplant patients (volume 23 page 46)

Objective: To determine the intravenous pharmacokinetics of itraconazole in bone marrow transplant patients and to assess the oral absorption of itraconazole from a solution at different stages in the patients physical condition: in the first week and about three weeks after bone marrow transplantation.

Study Design: Two treatments (A and B) were administered to the patients on 1 to 2 (session I) and 7 to 10 days (session II) days after the bone marrow transplantation, according to a randomized cross over design. Treatment B was repeated 14 to 23 days after the bone marrow transplantation (session III). Treatment A consisted of a single oral dose of 100 mg itraconazole intravenously (IV) infused over 60 mins and treatment B was a single oral dose of 100 mg itraconazole orally as 10 mL of a 10 mg/mL solution administered immediately after breakfast with a glass of water. Blood samples were collected after the IV administration at predose, at the end of infusion and 0.5, 1, 3, 6, 9, 12, 24, 36, 48, 60 and 72 hours after the end of infusion. For oral administration, blood samples were collected immediately before itraconazole intake, 1, 2, 4, 6, 9, 12, 24, 36, 48, 60 and 72 hours after itraconazole dosing.

Analytical Method:

Data Analysis: Pharmacokinetic parameters were determined using 2 and 3 compartment models or by visual inspection of the individual plasma concentration-time profiles.

Results: The mean pharmacokinetic parameters for itraconazole and hydroxyitraconazole (OH-itra) IV and oral administration are provided in the following tables.

Mean Pharmacokinetic parameters of itraconazole after single IV and oral administration of 100 mg itraconazole to bone marrow (BMT) transplant patients.

Parameter	IV(I)*	Oral (II)*	Oral (III)*
	Mean ± SD (n=9)		
Tmax (h)	1 (n=8)	2.4 ± 1.2	3.0 ± 3.8
Cmax (ng/mL)	1441 ± 1140 (n=7)	180 ± 119	185 ± 154
T ½ (h)	34.9 ± 9.2	32.5 ± 14.2	34.6 ± 11.9
Vdss (L)	508 ± 272	-	-
Vdβ (L)	801 ± 606	-	-
Cl (mL/min)	259 ± 154	-	-
AUC(0-∞)(ng*h/mL)	8928 ± 5701	2673 ± 1869	1806 ± 1293
Fabs(AUC oral/IV)*100	-	41.8 ± 40.5	21 ± 11.8

I= 1-10 days after transplantation, II = 1-10 days after transplantation, III = 14-23 days after transplantation.

No statistically significant differences were observed in the pharmacokinetic parameters but there was a trend of higher Cmax after IV than oral administration. There was large inter patient variability observed in itraconazole pharmacokinetics in bone marrow patients. Cmax values ranged from 392 to 3733 ng/mL after IV administration and 11.4 to 453 ng/mL after oral administration. The reasons for these huge differences in Cmax is not apparent from the report submitted.

Mean Pharmacokinetic parameters of hydroxy-itraconazole after single IV and oral administration of 100 mg itraconazole to bone marrow (BMT) transplant patients

Parameter	IV(I)*	Oral (II)*	Oral (III)*
	Mean ± SD (n=9)		
Tmax (h)	5.7 ± 7.8	2.4 ± 1.2	3.0 ± 3.8
Cmax (ng/mL)	207 ± 49	180 ± 119	185 ± 154
T ½ (h)	21.4 ± 7.3	32.5 ± 14.2	34.6 ± 11.9
AUC(0-∞) (ng.h/mL)	7852 ± 4953	5584 ± 4297	3150 ± 2558
AUC(ratio)	1.0 ± 0.6	2.0 ± 0.5	1.6 ± 0.9

I= 1-10 days after transplantation, II = 1-10 days after transplantation, III = 14-23 days after transplantation. AUC ratio= AUC(OH-itra)/AUC(itra) X MW(itra)/MW(OH-itra)

As observed for itraconazole, interindividual variability on the pharmacokinetic parameters of hydroxyitraconazole after intravenous and oral itraconazole dosing was large in BMT patients.

The pharmacokinetic parameters for hydroxypropyl-β-cyclodextrin (HPBCD) is provided in the following table.

Mean pharmacokinetic parameters of HPBCD after combined administration of 100 mg itraconazole and 7.6 g HPBCD intravenously as a 1-hour infusion to 7 BMT patients, 1 to 10 days after bone marrow transplantation

Parameter	Mean ± SD
T ½ (h)	1.83 ± 0.34
AUC(0-∞) (ng.h/mL)	1058 ± 199
Vdarea (l)	19.5 ± 4.8
Clpl, mL/min	123 ± 25

There were no significant observations in the pharmacokinetic parameters for HPBCD and are similar to that for other populations.

Conclusion: The pharmacokinetics of itraconazole and hydroxyitraconazole after IV administration were not significantly different from that observed following oral administration in BMT patients. However, there was large interpatient variability in the pharmacokinetic data.