CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-464

21-466

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA No.:	**21-464; 21,466 (N 000)**
Submission Date:	**May 13, 2003**
Drug Product:	**Voriconazole Tablet (50, 200 mg)++ and Voriconazole for I.V. Injection (200 mg per vial)**
Trade Name:	**VFEND®**
Sponsor:	**Pfizer, Inc. 235 East 42nd Street New York, NY 10017**
Submission Type	**Resubmission -Complete Response to Action Letter (Electronic)**
Review Category:	**Class II (6 months)**
OCPB Reviewer:	**Gerlie C. de los Reyes, Ph.D.**

I. Background:

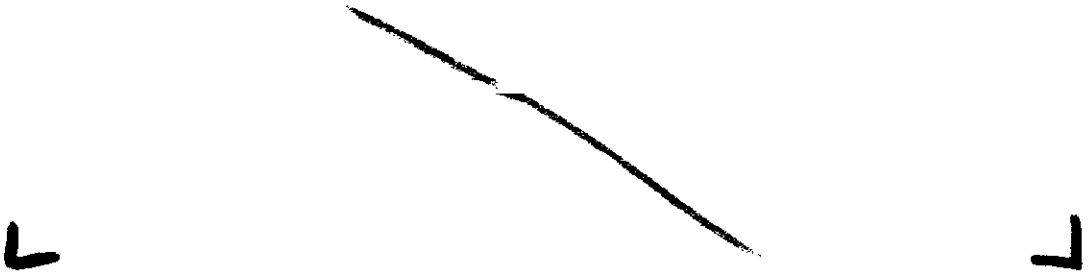
In an action letter dated 14 December 2001, the Agency informed the sponsor of the "approvability" of the application for the esophageal candidiasis indication of voriconazole provided certain requirements regarding manufacturing deficiencies and QT prolongation potential were satisfied. The Agency requested the sponsor to provide data that would allow adequate labeling regarding the risk of QT prolongation from the use of Voriconazole (VFEND®) Tablets and I.V. Injection. In response, the sponsor submitted the final clinical study report for A1501041 and a draft labeling with QT effect information and other proposed additions. The Clinical Pharmacology/ Biopharmaceutics-related changes in the package insert are as follows:

- **CLINICAL PHARMACOLOGY/Pharmacokinetic-pharmacodynamic Relationships**
  -Added this paragraph: "A placebo-controlled, randomized, crossover study to evaluate the effect on the QT interval of healthy male and female volunteers was conducted with three single oral doses of voriconazole and ketoconazole. Serial ECGs and plasma samples were obtained at specified intervals over a 24-hour post dose observation period. The placebo-adjusted mean maximum increases in QTc from baseline after 800, 1200 and 1600 mg of voriconazole [redacted]
  No subject in any group had an increase in QTc of ≥ 60 msec from baseline. No subject experienced an interval exceeding the potentially clinically relevant threshold of 500 msec. (SEE PRECAUTIONS)"

- **CLINICAL PHARMACOLOGY/Drug Interactions**
  -Added to Cyclosporine and Tacrolimus entries: "When voriconazole is discontinued, cyclosporine/tacrolimus levels should be frequently monitored and the dose increased as necessary."

- **DOSAGE AND ADMINISTRATION/Use in Adults**

[redacted]



II. STUDY REPORT SYNOPSIS

PROTOCOL A1501041: A multi-centre, randomised, single-blind, single dose, placebo-controlled, five-way crossover study to investigate the effect of three oral doses of voriconazole (800mg, 1200mg and 1600mg) and active comparator (oral ketoconazole 800mg) on QTc interval in healthy subjects aged 18 to 65 years.

Study Objectives: The objectives were to investigate the effect of voriconazole and its primary metabolite (UK-121,265) on QTc interval in healthy subjects, and to evaluate the safety and toleration of 800, 1200 and 1600mg oral doses of voriconazole.

Study Design: Three single oral doses of voriconazole (800, 1200 and 1600mg), a single oral dose of ketoconazole (800mg) as an active comparator, and a single oral dose of placebo were given in a single-blind (open for ketoconazole), five-period crossover study. The study was powered to rule out a 7msec increase in QTc in the active groups compared to placebo. There was a minimum of a seven day washout period between each dosing day.

Evaluation Groups:

	Voriconazole 800mg (n=77)	Voriconazole 1200mg (n=78)	Voriconazole 1600mg (n=76)	Ketoconazole 800mg (n=76)	Placebo (n=77)
Entered Study	80				
Completed Study	75	77	74	75	76
Discontinued from Study	2	1	2	1	1
Evaluated for Pharmacokinetics	77	78	76	76	0
Evaluated for Pharmacodynamics	77	78	76	76	77
Assessed for Safety:					
Adverse Events	77	78	76	76	77
Laboratory Tests	77	78	76	76	77

n = the number of subjects entering each study period

Diagnoses and Criteria for Inclusion of Subjects: Healthy male and female subjects, aged 18 to 65 years (actual subject disposition: 40 males and 40 females).

Drug Administration:

Dosage Form: 200mg voriconazole tablets [formulation identification number (FID) S00350AF Lot number 6926-087] and matching placebo tablets (FID S00558AB Lot 7697-013) 200mg ketoconazole tablets Lot 8978-041.

Dosing: Subjects took 8 tablets on each study period for the voriconazole/placebo dose (1600mg of voriconazole was 8 x 200mg voriconazole tablets; 1200mg of voriconazole was 6 x 200mg voriconazole and 2 x placebo tablets; 800mg of voriconazole was 4 x 200mg voriconazole and 4 x placebo tablets; and placebo was 8 x placebo tablets.
The open ketoconazole dose subjects were given 4 ketoconazole tablets.

Duration: Subjects took the medication as a single dose followed by a minimum of seven day washout period before the next dose.

Pharmacokinetic, Pharmacodynamic and Safety Evaluations: ECG measurements and blood samples were taken 0 to 24 hours post dose on Day 1 of each study period. On Day 0 (baseline run-in day), of each period, 12-lead electrocardiogram (ECG) were collected 0 to 16 hours post dose corresponding to those planned on Day 1.

Safety evaluations comprising of adverse event recording, physical examinations, laboratory tests, vital signs and an ECG performed at intervals during the study.

Analytical Methods:

For RR, PR, QRS duration and QT interval, the values given were based on the average of the obtained measurements. The QT interval measurements corrected for heart rate using Bazett's and Fridericia's correction formulae were also provided.

Statistical Methods:
Pharmacodynamic Data

Primary Analyses: Treatment Comparisons
Change from baseline analyses were performed for each of the following primary endpoints: (1) maximum increase from baseline in QTc over the ECG assessments collected till 24 hours post-dose; (2) average QTc change from baseline over the ECG assessments collected till 24 hours post-dose, calculated as $AUEC_{0-24}/24$; (3) QTc change from baseline at median Tmax for

voriconazole for each dose; (4) QTc change from baseline at median Tmax for UK-121,265 for each dose.
Two baselines were to be used. Firstly, time specific baselines were to be calculated for endpoints 1, 2, 3 and 4 in each study period. Secondly, for endpoints 1, 3 and 4 the mean of all QTc values obtained on Day 0 in each period were to be used as baseline for that period (Mean Day 0). Comparisons of the active doses against placebo were carried out for all four primary endpoints. A separate analysis of variance (ANOVA) was used for each treatment pairwise comparison of interest. The comparisons of interest were voriconazole 1600mg vs placebo, voriconazole 1200mg vs placebo, voriconazole 800mg vs placebo and ketoconazole 800mg vs placebo. The ANOVA allowed for variation due to subject (random effect), period and treatment (fixed effects). The mean changes from baseline for each treatment and the differences between the active treatments and placebo were estimated along with 90% confidence intervals.

Secondary Analyses: Relationship of QTc with exposure to voriconazole, UK-121,265 and ketoconazole
The following relationships were to be investigated; (1) the maximum increase from baseline in QTc versus voriconazole, UK-121,265 and ketoconazole AUC_{24}, and the maximum increase from baseline in QTc versus voriconazole, UK-121,265 and ketoconazole concentration at maximum increase in QTc; (2) the QTc change from baseline versus voriconazole concentration at the individual's Tmax for voriconazole; (3) the QTc change from baseline versus metabolite concentration at the individuals Tmax for UK-121,265; (4) the QTc changes from baseline versus voriconazole/UK-121,265 concentration and time; (5) the QTc change from baseline versus ketoconazole concentration at the individuals Tmax for ketoconazole. For endpoint 1 the slope between maximum increase in QTc and voriconazole/UK-121,265 AUC_{24} was to be derived for each subject and the mean slope (across subjects) was to be calculated along with its 95% confidence interval.
The analysis of this voriconazole/UK-121,265 pharmacokinetic/pharmacodynamic relationship was to be summarised using the mean, standard deviation and 95% confidence intervals for the slopes.
Scatter plots of maximum increase in QTc against AUC24 were to be presented for voriconazole, UK-121,265 and ketoconazole on separate graphs.
The same analyses were to be done for endpoint 1 using concentration at the time of maximum increase in QTc as the measure of exposure instead of AUC24 in the above.
The relationship between QTc measurements and drug concentrations at each individual's Tmax for voriconazole and UK-121,265 (endpoints 2 and 3) was also to be investigated using the same approach. Namely, the mean slope of change from baseline QTc at Tmax versus maximum drug concentration was to be calculated with 95% confidence intervals. Scatter plots and profile plots were also to be done as in the analysis of endpoint 1.
For the analysis of endpoint 5 scatter plots of change from baseline QTc at ketoconazole Tmax, against ketoconazole concentration were to be produced.
The relationship between QTc changes from baseline versus voriconazole concentration were to be investigated for endpoint 4 by considering a time course profile of the overall mean change from baseline against mean concentration. A similar plot would be produced for UK-121,265 concentrations.

Pharmacokinetic Data
No formal statistical analyses were conducted on the pharmacokinetic data. The pharmacokinetic parameters maximum observed plasma concentration (Cmax), time to first occurrence of Cmax (Tmax), area under the plasma concentration-time curve (AUC), area under the plasma concentration-time curve from zero to the last measurable concentration (AUClast), area under the plasma concentration-time curve from zero until 24 hours post-dose (AUC_{0-24}), terminal phase rate constant (kel), terminal half-life of plasma-concentration time curve (t1/2) for each dose of voriconazole, UK-121,265 and ketoconazole were to be summarised using descriptive statistics. Individual plasma concentrations of voriconazole and UK-121,265 were to be listed and summarised for each of the three dose levels of voriconazole, as were plasma concentrations of ketoconazole. Mean profiles on Day 1 up to 72 hours post-dose were to be plotted for each

treatment of voriconazole, UK-121,265 and ketoconazole. Box and Whisker plots were also to be presented for each dose on the same plot to illustrate the variability of values at each time point.

III. Summary Findings of Study A1501041

A. Primary Analysis: Treatment Comparisons

Following an investigation of the Day 0 QTc data, Fridericia's was found to be a more appropriate correction factor than Bazett's , therefore the main analyses were presented for Friderica's correction factor only.

TABLE 1

Endpoint	Comparison*	N	Mean Difference	90% Confidence Interval	
				Lower	Upper
ΔQTcF(1) Maximum increase in QTcF (msec)	Voriconazole 800mg vs Placebo	76	5.05	2.75	7.35
	Voriconazole 1200mg vs Placebo	76	4.81	2.63	6.99
	Voriconazole 1600mg vs Placebo	75	8.23	6.01	10.45
	Ketoconazole 800mg vs Placebo	74	7.04	4.65	9.43
ΔQTCF(2) Average increase in QTcF (msec)	Voriconazole 800mg vs Placebo	76	4.33	2.85	5.82
	Voriconazole 1200mg vs Placebo	76	5.19	3.82	6.57
	Voriconazole 1600mg vs Placebo	75	7.18	5.63	8.72
	Ketoconazole 800mg vs Placebo	74	4.02	2.60	5.44
ΔQTcF(3) Change in QTcF at median Tmax[a] For Voriconazole (msec)	Voriconazole 800mg vs Placebo	74	4.64	1.21	8.07
	Voriconazole 1200mg vs Placebo	74	9.24	5.76	12.71
	Voriconazole 1600mg vs Placebo	74	9.09	5.75	12.42
ΔQTcF(4) Change in QTcF at median Tmax[b] For UK-121,265 (msec)	Voriconazole 800mg vs Placebo	74	4.16	1.08	7.25
	Voriconazole 1200mg vs Placebo	75	5.12	1.78	8.46
	Voriconazole 1600mg vs Placebo	74	8.25	4.84	11.66
Change in QTcF at median Tmax[c] for Ketoconazole (msec)	Ketoconazole 800mg vs Placebo	72	8.63	5.39	11.88

*Treatment comparison using the Time Specific Day 0 baseline.

[a] Median Tmax for voriconazole 800mg was 2hrs; Median Tmax for voriconazole 1200mg was 3hrs; Median Tmax for voriconazole 1600mg was 3hrs.

[b] Median Tmax for voriconazole 800mg was 8hrs; Median Tmax for voriconazole 1200mg was 10hrs; Median Tmax for voriconazole 1600mg was 12hrs.

[c] Median Tmax for ketoconazole 800mg was 2hrs

The mean maximum increase in QTcF-Time Specific baseline, (also referred to as QTcF(1)), for voriconazole 800, 1200 and 1600mg was 5.05, 4.81 and 8.23msec respectively. The mean increase in QTcF for voriconazole compared to placebo was <10msec for all endpoints. The study was designed with the intention of being able to exclude a 7msec increase in QTc following dosing with voriconazole 1600mg. For each of the four primary endpoints this could not be concluded as the upper limit of the 90% confidence interval exceeded 7msec.

There was no clear relationship between the maximum increase in QTcF and either the maximum voriconazole plasma concentration or the voriconazole plasma concentration at the time of the maximum increase in QTcF. These results were consistent across baselines. The analyses for UK-121,265 also showed no clear relationship.

No subject in any treatment group had a maximum increase in QTcB or QTcF of ≥60msec from baseline. Fourteen subjects had a maximum increase in QTcF from the Time Specific Day 0 baseline of 30 to 59msec after voriconazole 1600mg dosing. There were six subjects with similar

increases following both voriconazole 800mg and voriconazole 1200mg dosing, respectively. In comparison,12 subjects following ketoconazole 800mg and one subject following placebo had increases of 30 to 59msec.

A.1. Influence of Gender

The robustness of the primary analyses with respect to gender was explored graphically, as in Figure 1. Females appeared to consistently have a greater increase in QTcF than males. For instance, the mean maximum increase in QTcF, from the Time Specific baseline, for the comparison of voriconazole 1600mg vs placebo for females was 9.50msec (90% CI = 6.82, 12.17) and 7.02msec (90% CI = 3.26, 10.79) for males. Similarly, the change from baseline in mean QTcF at median Tmax for voriconazole 1600mg was 11.46msec (90% CI = 6.85, 16.08) for females and 6.73msec (90% CI = 2.00, 11.47) for males (Figure not shown).

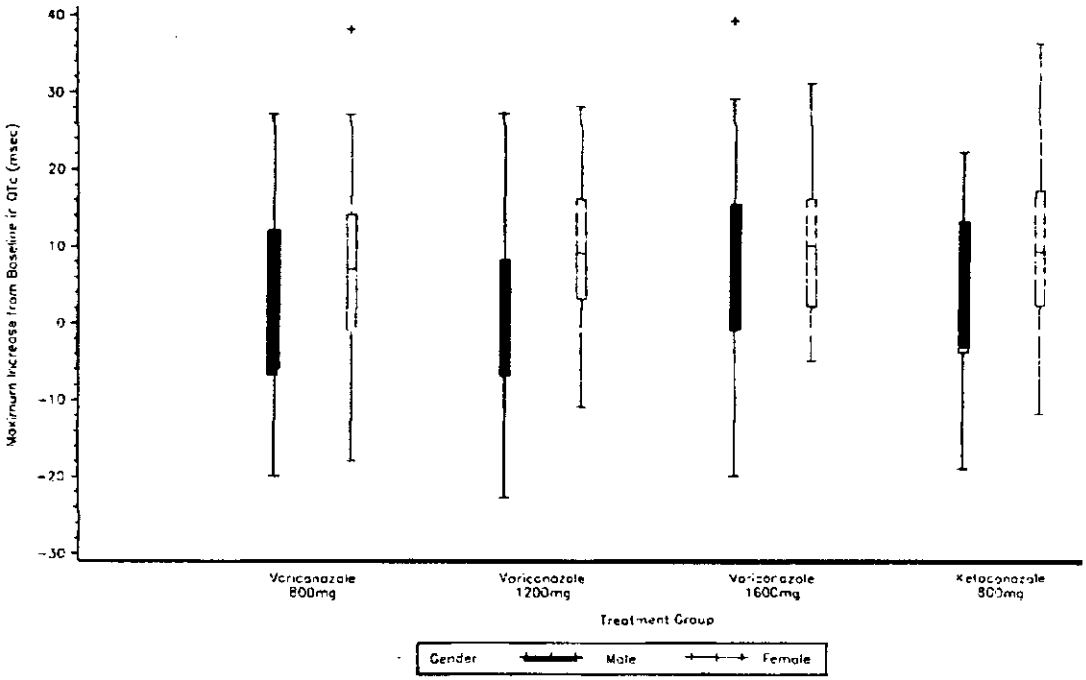


Figure 1. Box and Whisker Plot: Maximum increase from baseline in QTcF from 0-24 hours post dose (Time specific Day 0), — QTcF(1) by Gender compared with placebo.

A.2. Influence of Age

The robustness of the primary analyses with respect to age was explored graphically, as in Figure 2. Age was not found to have an effect on the magnitude of the increase in QTcF.

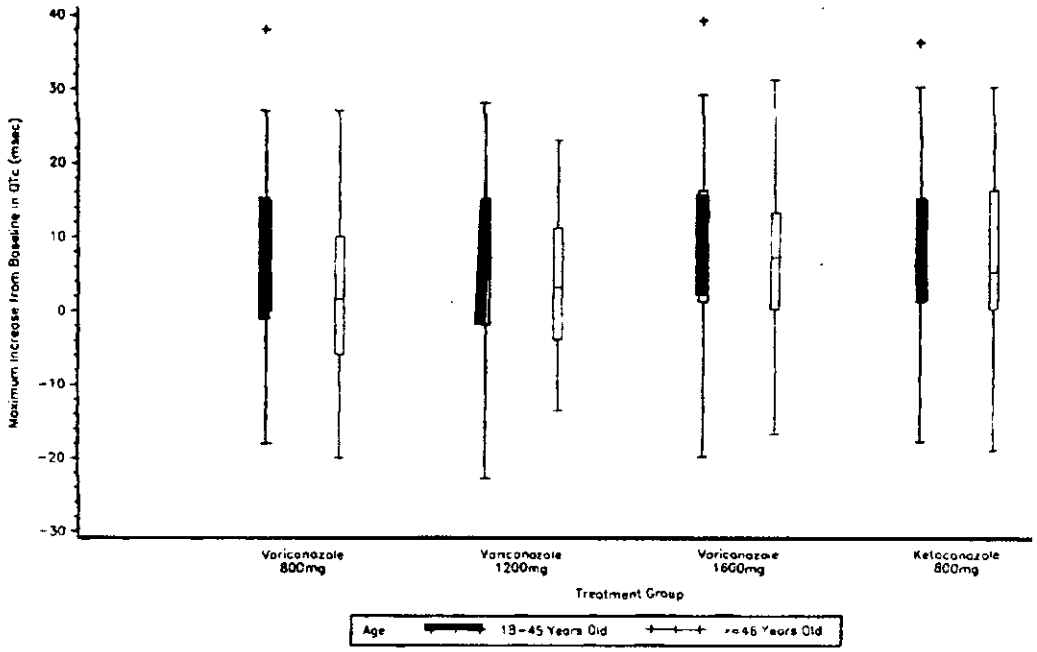


Figure 2. Box and Whisker Plot: Maximum increase from baseline in QTcF from 0-24 hours post dose (Time specific Day 0)— ΔQTcF(1) by Age compared with placebo.

COMMENTS:

The mean change from baseline in QTcF effect of voriconazole was plotted as a function of voriconazole dose (Figure 3). There was a trend towards increasing QTcF effect with increasing dose of voriconazole, regardless of the manner by which ΔQTcF was quantified. However among the different measures of QTcF, that which demonstrated the strongest association with voriconazole dose was QTcF(2) (calculated as the $AUEC_{0-24}/24$), followed by QTcF(4) (ΔQTc at median T_{max} of UK-121,265-change from baseline).

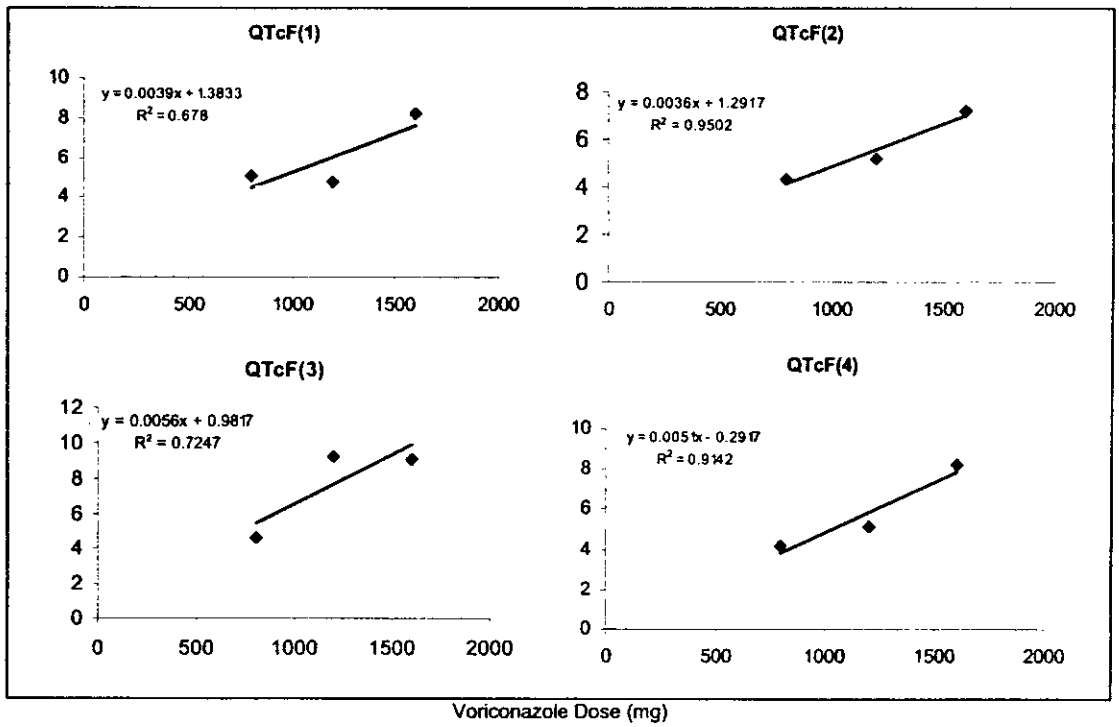


Figure 3. ΔQTcF as a function of voriconazole dose.
ΔQTcF(1) - max increase from baseline in QTc from 0 to 24 hours post dose
ΔQTcF(2)- average increase from baseline in QTc from 0 to 24 hours post-dose, calculated as AUEC0-24/24
ΔQTcF(3)- QTc at median Tmax for voriconazole-change from baseline
ΔQTcF(4)- At median Tmax for UK-121,265-change from baseline

The QTcF(x) effect of voriconazole relative to the comparator drug was also dependent on the manner of QTc measurement. The ΔQTcF effect of ketoconazole was comparable to voriconazole 1600 mg when x = 1or 4. Ketoconazole was comparable to voriconazole 800 mg when x = 2; voriconazole 1200 mg and 1600 mg when x = 3. Though there was an obvious trend towards increasing QT prolongation effect with increasing doses of voriconazole, the placebo-adjusted mean increase from baseline values following the administration of 4 to 8 times the recommended maintenance dose of voriconazole were all less than 10 msec.

B. Pharmacokinetic Results

The pharmacokinetic parameters were calculated from voriconazole plasma concentrations collected from 0 to 72 hours post dose on Day 1 of each study period. The ranges of maximum plasma concentrations observed following single doses of 800, 1200 or 1600mg of voriconazole [redacted] . respectively. Table 2 summarises the pharmacokinetic parameters for Cmax, Tmax, AUC_{24}.

TABLE 2
Exposure Parameters of voriconazole (800 mg, 1200 mg, 1600 mg) and Ketoconazole 800 mg

Treatment	Geometric Mean		Arithmetic mean
	C_{max} (ng/ml)	AUC_{24} (ng.h/ml)	T_{max}(h)
Voriconazole 800mg	5302	46204	2.1
Voriconazole 1200mg	7298	82357	2.7
Voriconazole 1600mg	10028	131240	3.0
Ketoconazole 800mg	13719	102151	2.5

Voriconazole plasma concentrations in females were similar to those seen in males. Figure 4 is the time course of voriconazole plasma concentrations in male and female subjects.

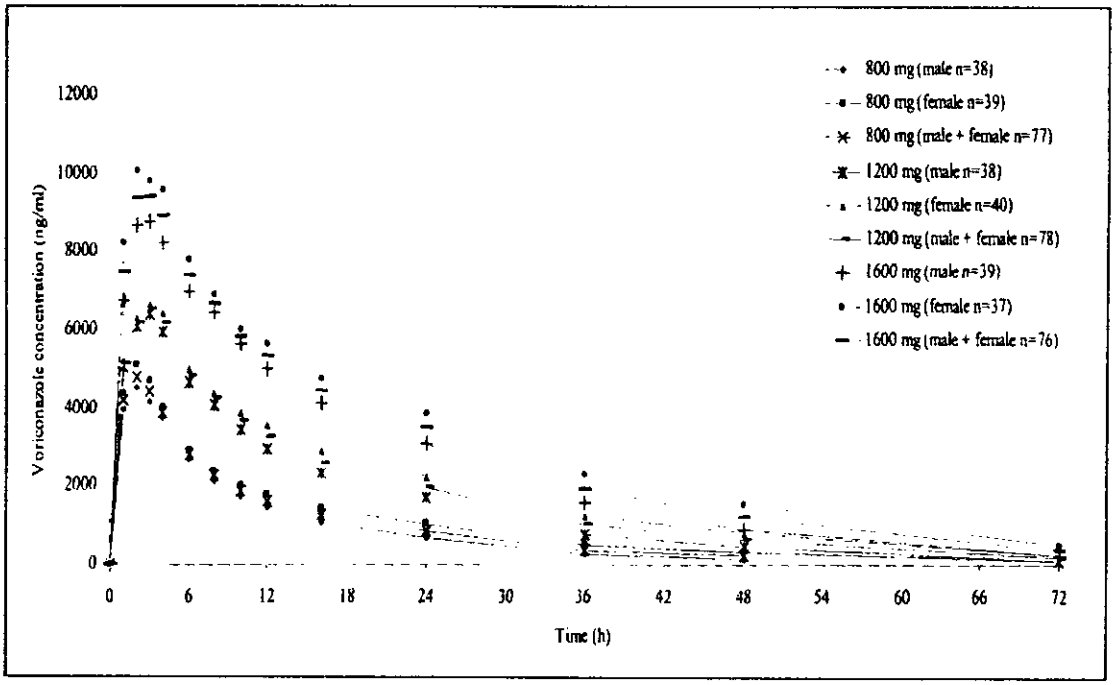


Figure 4. Mean plasma voriconazole concentration for healthy male and female subjects receiving single oral doses of voriconazole (800, 1200 and 1600 mg) on separate occasions.

COMMENTS:

Table 3 summarizes the equations describing the linear relationship between the voriconazole dose and voriconazole/UK-121,265 pharmacokinetic parameters. Cmax and AUC_{24} were shown to increase proportionally with voriconazole dose. As the voriconazole dose increased, there was a trend towards increasing half-life of voriconazole, half-life of UK-121,265 and (mean or median) voriconazole T_{max}. These trends confirm the non-linearity of voriconazole pharmacokinetics.

TABLE 3
INFLUENCE OF DOSE ON VORICONAZOLE PHARMACOKINETICS

PK PARAMETER	LINEAR EQUATION (Dose is the x variable.)	CORRELATION COEFFICIENT (r^2)
Voriconazole		
C_{max}	3.6075x + 2235.3	
AUC_{24}	69.363x + 13228	
C_{max}/dose	-0.0018x + 7.79	
AUC/dose	-0.0111x + 94.67	
Half-life	0.0034x + 6.33	
T_{max} (mean)	0.0029x + 2.67	
T_{max} (median)	0.0038x + 5.83	
UK-121,265		
C_{max}	5.1838x + 669.83	
AUC_{24}	34.604x + 69428	
C_{max}/dose	-0009x + 6.9301	
AUC/dose	-0.0538x + 161.84	
Half-life	0.0064x + 5.09	

Increasing the dose 2-fold (from 800 mg to 1600 mg) produced a 10% decrease in the dose-normalized AUC_{24}, a 22% decrease in the dose-normalized C_{max} of voriconazole, and a 30% decrease in the dose-normalized AUC_{24} of UK-121,265. The 2-fold increase in voriconazole dose also resulted to a 1.3-fold increase in voriconazole half-life, a 1.5-fold increase in UK-121,265 half-life, and a 1.5-fold increase in voriconazole T_{max}.

The dose-dependent increases in voriconazole exposure (as C_{max} and AUC) and metabolite exposure (as AUC) are consistent with the dose-related increase in the QTcF(x) effect of voriconazole. Likewise, the dose-dependent increases in the half-lives of the parent drug and the metabolite are in line with the observed dose-dependence of voriconazole QTcF(x) effect.

Influence of Gender

The AUC_{0-24} values were consistently, albeit slightly higher in females than in males. This gender-dependent difference in AUC appeared to be more prominent for voriconazole than for UK-121,265 (Figure 5).

Similarly, the half-lives of voriconazole (parent compound or metabolite) and ketoconazole were consistently slightly higher in females than in males (Figure 6).

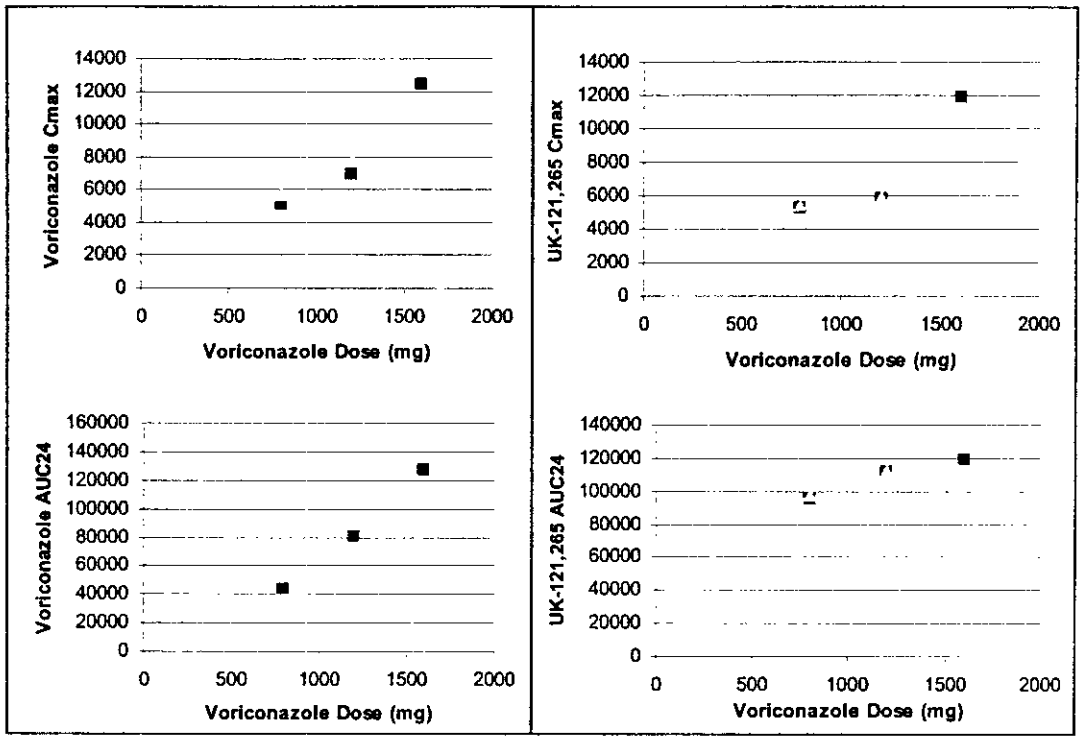


Figure 5. Plot of Cmax and AUC_{24} of voriconazole or UK-121,265 as a function of voriconazole dose.
Legend: ΔFemale, □Male.

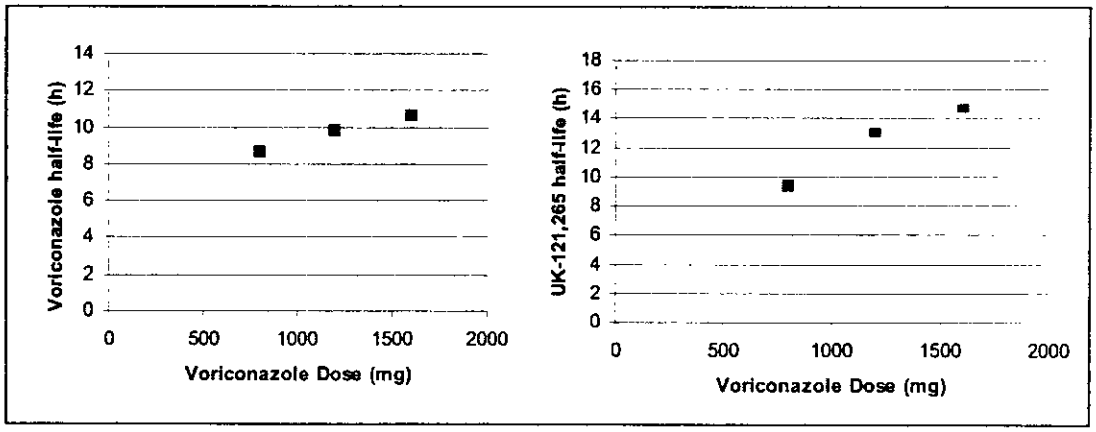


Figure 6. Plot of half-life of voriconazole or UK-121,265 as a function of voriconazole dose.
Legend: ΔFemale, □Male.

Influence of Age

Across the voriconazole dose range studied, there was a slight yet consistently higher exposure to voriconazole, as well as a slight yet consistently lower exposure to UK-121,265 in the 46 & older group than in the 18-45 year old subjects (Figure 7). The higher exposure to the parent compound, coupled with the lower exposure to the metabolite in the elderly, is most likely due to the less efficient renal clearance and hepatic (metabolic) processes in this age group. The lower efficiency of elimination pathways in the elderly subjects was evident from the slightly longer half-lives of both the parent compound and the metabolite in subjects 46 years and older compared to those aged 18 to 45 years (Figure 8).

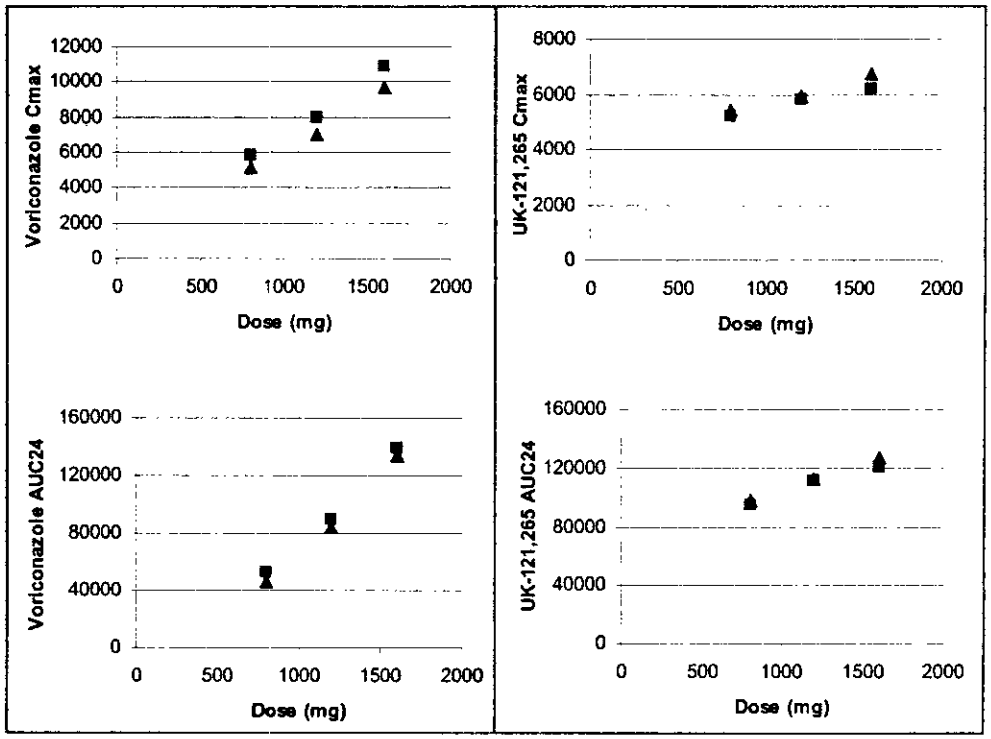


Figure 7. Plot of voriconazole Cmax or AUC_{24} versus dose, as a function of age.
Legend: Δ18-45 years old, □ 45 years and older.

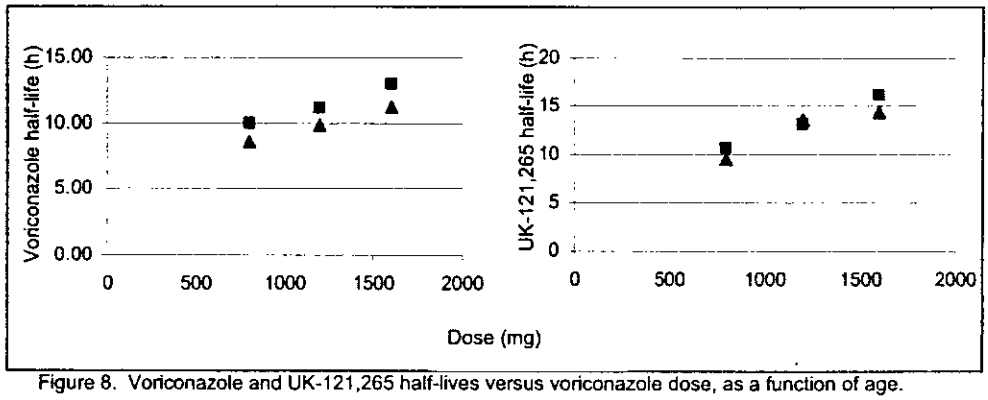


Figure 8. Voriconazole and UK-121,265 half-lives versus voriconazole dose, as a function of age.
Legend: Δ18-45 years old, □ 45 years and older.

These small age-dependent differences in exposure to voriconazole and its metabolite may not be clinically significant because there was no strong association found between either voriconazole and UK-121,265 Cmax/AUC and any measure of QTc.

C. Secondary Analyses

Relationship of QTc with voriconazole, UK-121,265 and ketoconazole exposure

The maximum increase in QTcF (QTcF(1)) is plotted against the voriconazole/UK-121,265/ketoconazole plasma concentration against Cmax in Figure 9. The relationship between QTcF and voriconazole/UK-121,265/ketoconazole AUC_{24} is explored in Figure 10. Based on Figure 9, there was no clear relationship between QTcF(1) and the maximum voriconazole plasma concentration. This result was consistent across baselines. The analyses for UK-121,265 also showed no clear relationship. Based on Figure 10, there was no clear relationship between the QTcF(1) and either voriconazole or UK-121,265 AUC_{24} and hence a linear model is inappropriate.

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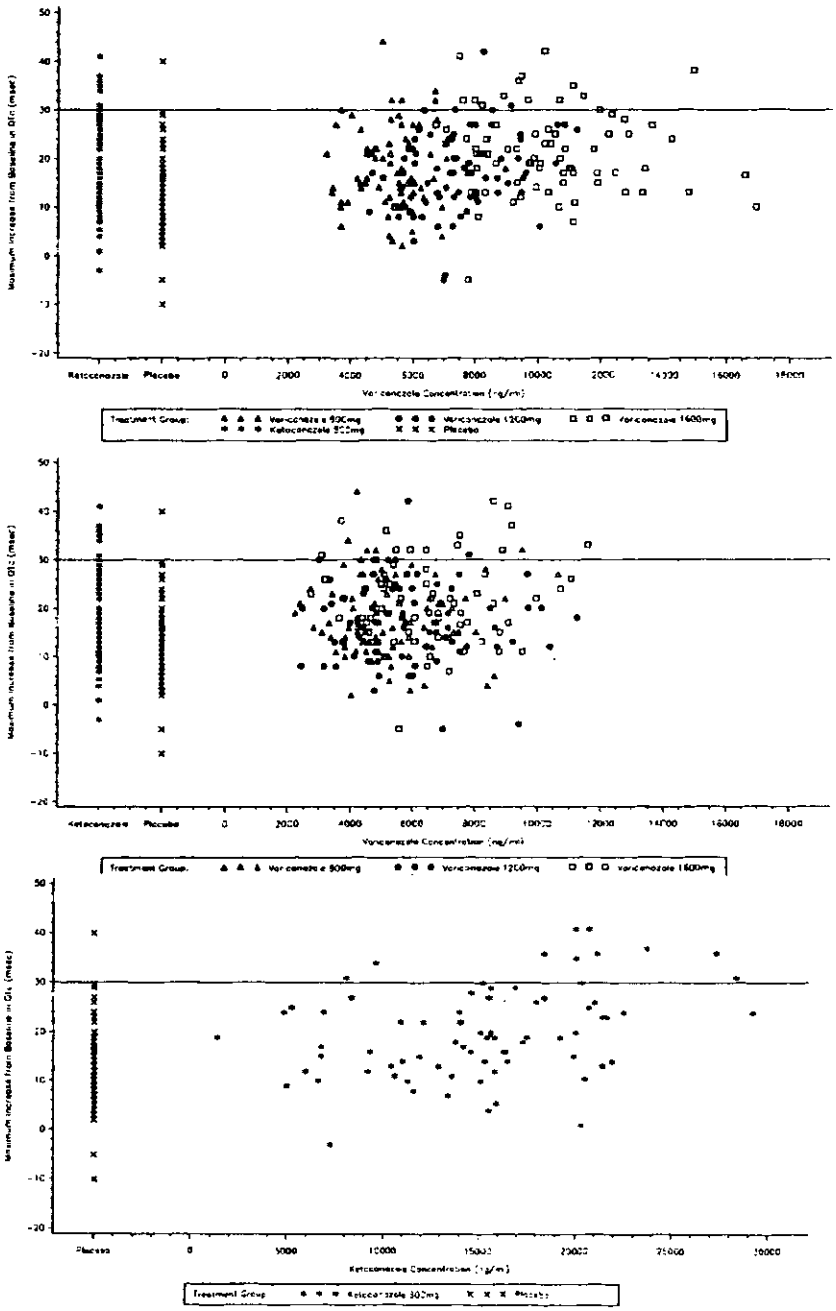


Figure 9. Scatterplots of maximum increase from baseline (Time Specific Day 0) in ΔQTcF(1) vs Cmax of Voriconazole (Uppermost panel), UK-121,265 (Middle panel), and ketoconazole (Lowermost panel).

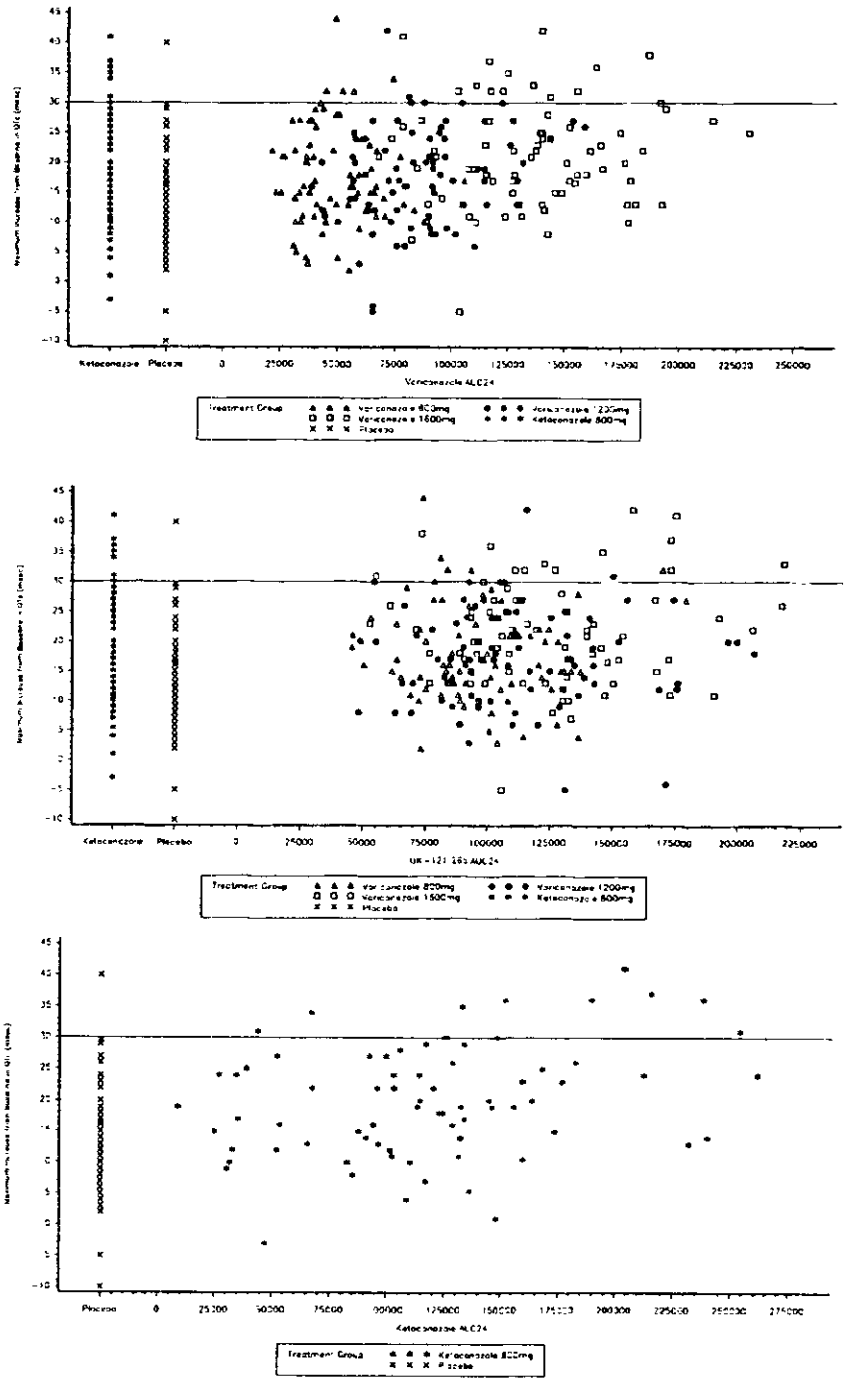


Figure 10. Scatterplots of maximum increase from baseline (Time Specific Day 0) in ΔQTcF(1) vs $\underline{AUC_{24}}$ of Voriconazole (Uppermost panel), UK-121,265 (Middle panel), and ketoconazole (Lowermost panel).

COMMENTS:

The ΔQTcF(x) effect of voriconazole (800 mg, 1200 mg, and 1600 mg) was plotted as a function of mean C_{max} and AUC_{24} of voriconazole or its metabolite, UK-121,265. Each graph was constructed to plot mean data points based on gender (Figure 11). The best fit for both male and female data sets was obtained between exposure (C_{max}, AUC) and ΔQTcF(2). The linear plot for females was always above of the plot for males suggesting that the female population of this study was more susceptible to the QT prolonging effect of voriconazole. This gender-dependent trend could be attributed to the higher AUCs of voriconazole and its major metabolite achieved in females than in males following any of the voriconazole doses studied.

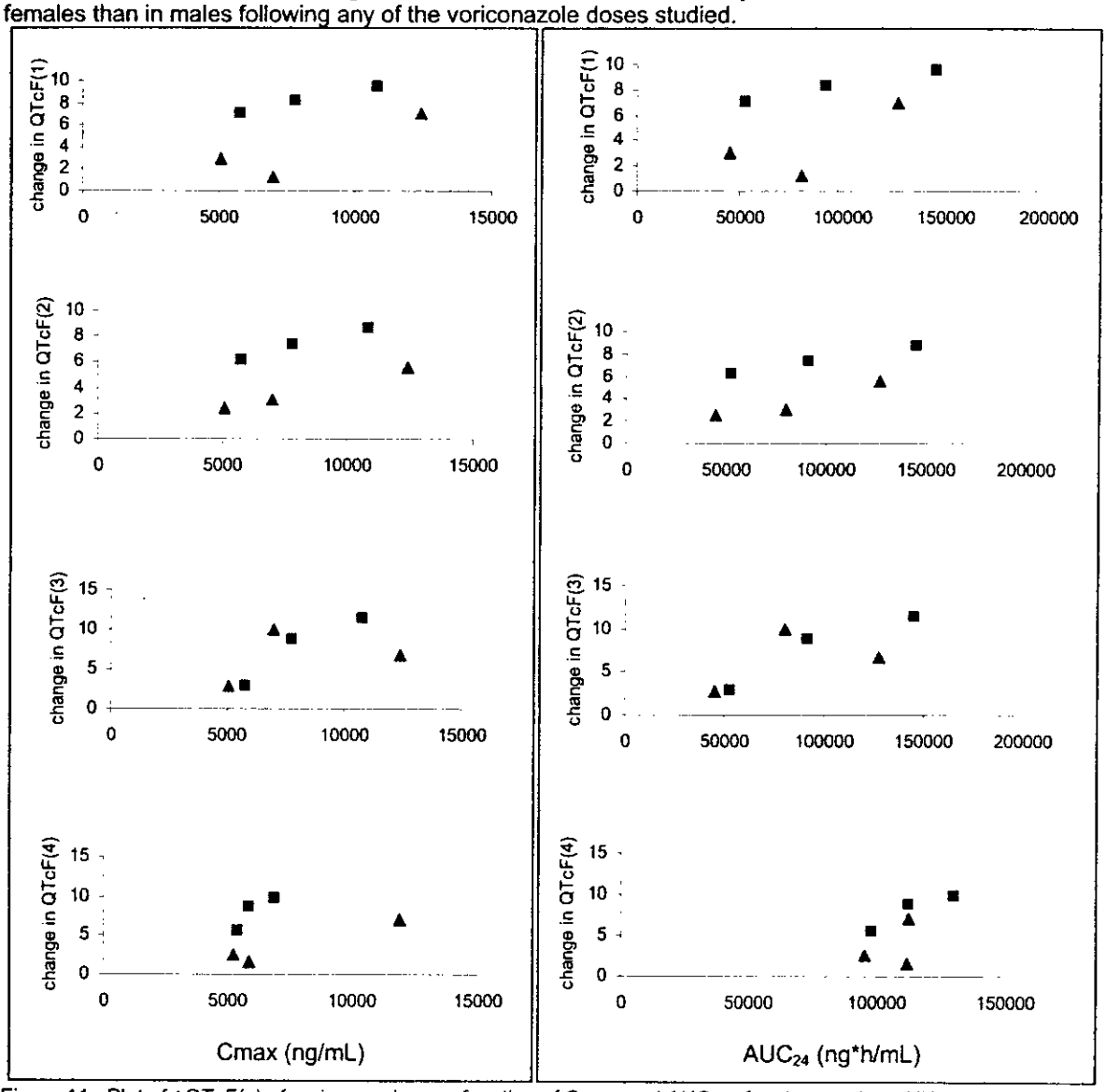


Figure 11. Plot of ΔQTcF(x) of voriconazole as a function of Cmax and AUC_{24} of voriconazole or UK-121,265.

Legend: ΔMale, □Female.

ΔQTcF(1) - max increase from baseline in QTc from 0 to 24 hours post dose

ΔQTcF(2)- average increase from baseline in QTc from 0 to 24 hours post-dose, calculated as $AUEC_{0-24}/24$

ΔQTcF(3)- QTc at median Tmax for voriconazole-change from baseline

ΔQTcF(4)- at median Tmax for UK-121,265-change from baseline

The ΔQTcF(x) of voriconazole (800 mg, 1200 mg, and 1600 mg) was plotted as a function of mean half-life of voriconazole or its metabolite, UK-121,265. The graph was constructed to plot data points based on gender (Figure 12). Regardless of voriconazole dose, longer half-lives of voriconazole were achieved in females than in males. At least for the females, the half-life of voriconazole or its metabolite was directly proportional to the ΔQTcF(x) of voriconazole. Thus, the higher QT prolonging effect of voriconazole observed in females compared to males could be partly attributed to the longer half-life of the drug in the former.

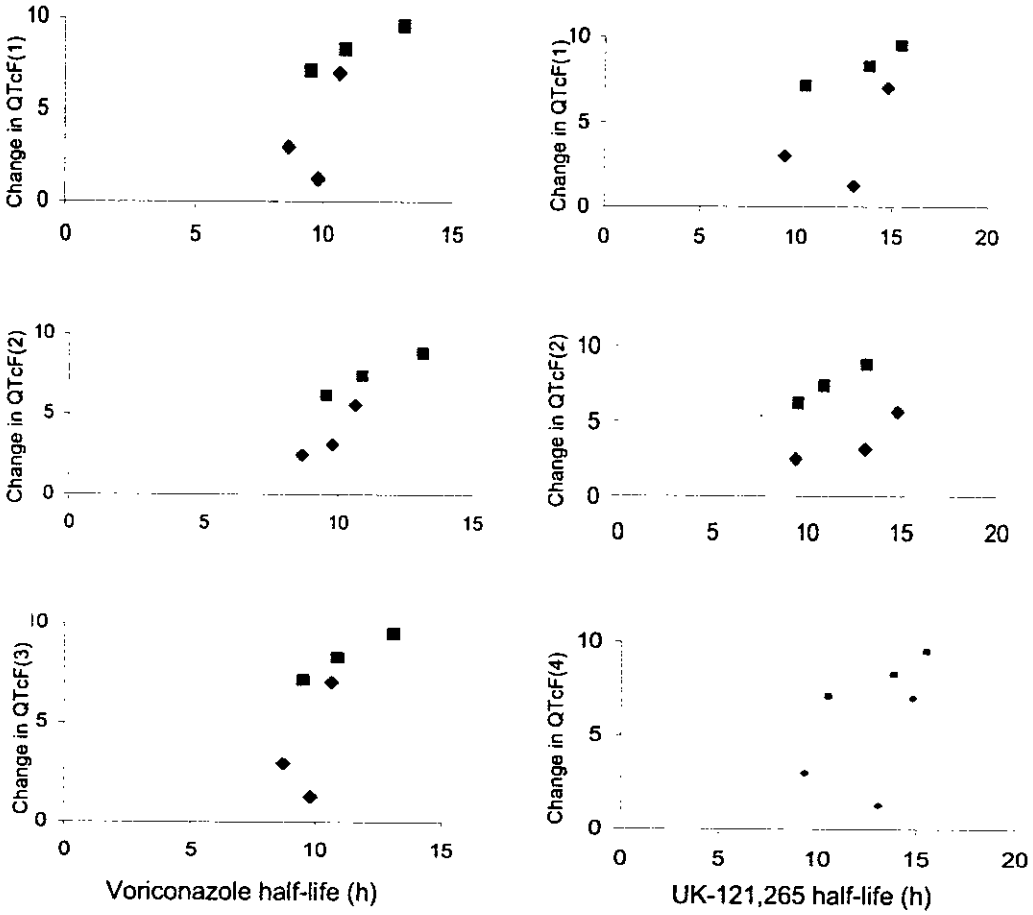


Figure 12. Plot of half-life ΔQTcF(x) versus half-life of voriconazole or UK-121,265.
Legend: ◊Male, □Female.
ΔQTcF(1) - max increase from baseline in QTc from 0 to 24 hours post dose
ΔQTcF(2)- average increase from baseline in QTc from 0 to 24 hours post-dose, calculated as AUEC0-24/24
ΔQTcF(3)- QTc at median Tmax for voriconazole-change from baseline
ΔQTcF(4)- QTc at median Tmax for UK-121,265-change from baseline

Safety Results:

Number of Subjects with:	Voriconazole 800mg (n=77)	Voriconazole 1200mg (n=78)	Voriconazole 1600mg (n=76)	Ketoconazole 800mg (n=76)	Placebo (n=77)
Adverse Events (all causality)	64	73	74	50	30
Adverse Events (treatment related)	61	72	73	40	14
Serious Adverse Events (all causality)	0	0	0	0	0
Clinically significant laboratory abnormality	7	7	5	6	7

Seven subjects discontinued from the study, two of which were considered treatment related (one due to an adverse event of vomiting and the other due to a laboratory abnormality of elevated transamines). Fifty-four subjects reported severe adverse events during the study, 48 of which were considered treatment related. These consisted of eight subjects during the voriconazole 800mg study period, 18 subjects during the 1200mg study period, 21 subjects during the 1600mg study period, one subject whilst receiving ketoconazole 800mg, and no subjects who received placebo. Voriconazole 1600mg dose resulted in a higher frequency of severe visual adverse events. Visual adverse events were the most commonly reported adverse event, the median onset time of the visual adverse events was 40, 50 and 50 minutes in the 800, 1200 and 1600mg voriconazole groups respectively. The duration of these visual adverse events was longest in the 1600mg group where the median duration was 226 minutes, and ranged from one to 2855 minutes. There were no serious adverse events reported.

CONCLUSIONS

The mean maximum increase in QTcF from (Time Specific QTcF(1)) baseline for voriconazole 800, 1200 and 1600mg was 5.05, 4.81 and 8.23msec respectively. The mean increase in QTcF for voriconazole compared to placebo was <10msec for all endpoints. The study was designed with the intention of being able to exclude a 7msec increase in QTc following dosing with voriconazole 1600mg. For each of the four primary endpoints this could not be concluded as the upper limit of the 90% confidence interval exceeded 7msec. The results seen with the positive control (ketoconazole) support the validity of the study.

The ranges of maximum plasma concentrations observed following single doses of 800, 1200 or 1600mg of voriconazole were [redacted] respectively.

Seven subjects discontinued from the study, two of which were considered treatment related. There were 54 subjects with a severe adverse events, 48 of which were considered treatment related. Visual adverse events were the most commonly reported adverse event, and the duration of visual disturbance increased with voriconazole dose. There were no serious adverse events reported.

IV. GENERAL COMMENTS:

The average increase in QTcF from baseline, QTcF(2), appears to provides the best fit in terms of:

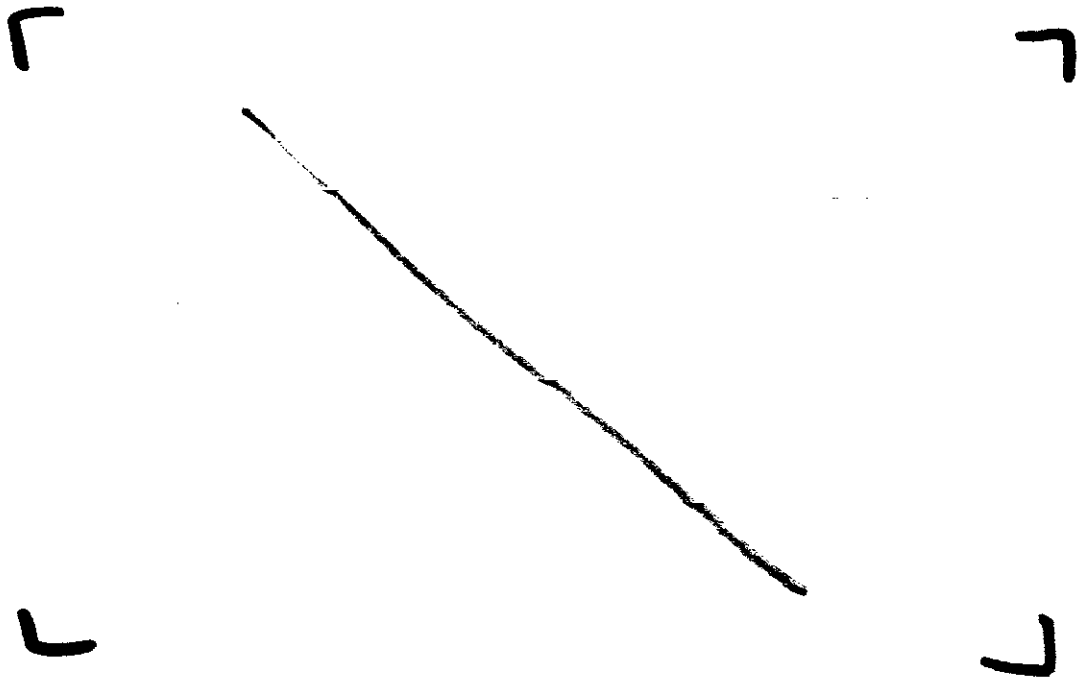
A. the linear associations between:
   -ΔQTcF and voriconazole dose
   -ΔQTcF and voriconazole exposure
   -ΔQTcF and voriconazole/UK-121,265 half-life.

B. the influence of gender on the ΔQTcF of voriconazole.

IV. LABELING COMMENTS:

The proposed labeling for voriconazole (Vfend®) I.V. and tablets was reviewed by the Office of Clinical Pharmacology and Biopharmaceutics and the reviewer finds the proposed labeling acceptable provided the labeling changes recommended by the reviewer are made. Deleted text is shown with a strikethrough; added text appears with a double underscore.

- **CLINICAL PHARMACOLOGY/Pharmacokinetic-Pharmacodynamic Relationships**



Gerlie C. de los Reyes, Ph.D.
Office Clinical Pharmacology/Biopharmaceutics,
Division of Pharmaceutical Evaluation 3

RD/FT signed by Philip M. Colangelo, Pharm.D., Ph.D. (TL) _____

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Gerlie De Los Reyes
10/15/03 04:13:27 PM
BIOPHARMACEUTICS

Phil, you signed off on the hard copy on 10/15/03.

Phil Colangelo
11/7/03 04:38:29 PM
BIOPHARMACEUTICS