

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-630

CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA NUMBER:	21,630 (N-000)
SUBMISSION DATE:	March 14, 2003
BRAND NAME:	VFEND®
GENERIC NAME:	Voriconazole
DOSAGE FORM AND STRENGTH(S):	Powder for Oral Suspension (40 mg/mL) (when reconstituted)
INDICATION(S):	Invasive aspergillosis and infections caused by <i>Scedosporium</i> spp. and <i>Fusarium</i> spp.
SPONSOR:	Pfizer Global Research and Development 50 Pequot Avenue, New London, CT 06320
TYPE OF SUBMISSION:	Original Application (Electronic)
OCPB DIVISION:	DPE3
REVIEWER:	Gerlie C. De Los Reyes, Ph.D.
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1. Executive Summary

1.1 Recommendations

The sponsor is seeking approval for voriconazole (Vfend®) Powder for Oral Suspension (POS) based on three studies conducted to test the steady-state bioequivalence of the commercial tablet and the 'proposed commercial' POS, along with two other predecessor POS formulations in the development program. Two batches of the 'proposed commercial' POS formulation manufactured on a commercially representative scale, were shown to be bioequivalent to the commercial tablet in Study A1501028. Bioequivalence was also previously demonstrated between the 'research' POS and commercial tablet in Study 150-248. However, for the 'improved' or the 'initial multi-dose' POS formulation, the upper bound of the 90% CI for the C_{max} ratio versus the commercial tablet was outside of the acceptance criteria in Study A1501019. Bioequivalence was demonstrated amongst female subjects for both AUC and C_{max} , and amongst male subjects for AUC but not C_{max} . This 'improved' or initial multi-dose' POS formulation was used in the food-effect study.

Several other findings of Study A1501019 confirm what is already known for voriconazole commercial tablets, i.e, markedly higher drug exposures in CYP2C19 poor metabolizers and the detrimental effect of food on the oral voriconazole bioavailability. The C_{max} and the AUC of the drug after 'improved' POS dosing with food were reduced by 58% and 37%, respectively compared with dosing in the fasted state. In conjunction with the recommendation for the oral tablet, voriconazole POS should also be administered at least 1 hour before or after a meal.

The findings of Study A1501019 also showed that, compared to males, the voriconazole C_{max} values in females from the POS formulation were similar but the AUC values were about 45% higher. Although most of the female subjects with severe adverse events in this study were taking oral contraceptives (OCs) concurrently, it is currently not known whether the use of OCs contribute to the higher levels of voriconazole exposure in females compared to males.

The sponsor's decision not to include dissolution testing on the finished product release specifications is considered acceptable because this test did not prove to be a suitable stability-indicating method and thus could not be used to discriminate for unsatisfactory batches. In lieu of a dissolution test, drug substance particle size and viscosity of the suspension will be controlled since these two physical properties were shown to affect the dissolution rate of the drug.

Overall, this submission for Voriconazole (Vfend®) Powder for Oral Suspension (POS) is acceptable from a Clinical Pharmacology and Biopharmaceutics standpoint provided the sponsor implements the labeling and Phase IV study recommendations.

1.2 Phase IV Commitment

Based on the findings of Study A1501019 which enrolled both male and female subjects, it is highly recommended that the sponsor conduct a two-way drug interaction study between voriconazole and oral contraceptives (OCs) containing ethinyl estradiol in younger women (18 to 45 years old). This study should be designed so as to control the influence of the menstrual cycle.

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3. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Overview of the CPB development program and orientation of the review:

In May 2002, FDA approved voriconazole (VFEND®) intravenous and oral tablet formulations for primary treatment of invasive aspergillosis as well as for salvage therapy for infections due to *Scedosporium* sp. (*Scedosporium apiospermum*) or *Fusarium* sp. in patients refractory to or intolerant of other antifungal therapy. Voriconazole POS was developed to cater to the therapeutic needs of patients who have difficulty swallowing the oral tablet. The formulation of voriconazole as a solution or pre-formed suspension was not feasible because of the low drug solubility and stability in aqueous solutions upon prolonged storage. Voriconazole is stable in the dry state and as a constituted suspension for a reasonable period of time. The 40 mg/mL suspension provides convenience for administration of a wide range of doses including the standard adult maintenance dose of 200 mg (5 mL).

The 'research' formulation, though shown to be bioequivalent to the commercial tablet, was not further developed because of the limited use of the sweetener system in some countries of the world and the slow hydration of the suspending agent used. The 'initial multi-dose' or 'improved' formulation was subsequently developed prior to commencing formal stability studies with the 'proposed commercial' formulation. The composition of the initial multi-dose formulation is identical to that of the 'proposed commercial' formulation but the former was prepared with a

Pharmacokinetic-Pharmacodynamic Relationships:

a) Steady state trough voriconazole concentrations (C_{min}) and Adverse events

The 'improved' voriconazole POS and the commercial tablet forms evaluated in Study A1501019 have comparable adverse event profiles (Figures 1a and 1b). The female subjects reported adverse events at a higher rate compared with male subjects following 'improved' POS dosing, as well as during commercial tablet dosing. A relationship to voriconazole C_{max} , however, is not readily discernable, as a slightly higher, albeit comparable mean C_{max} for the 'improved' POS was observed amongst the male subjects (Table 2). Figure 2 shows that compared to C_{max} on Day 7, voriconazole trough concentration (C_{min}) on Day 6 produces a higher correlation coefficient (r^2) when plotted with the cumulative adverse event score calculated for each patient.

FIGURE 1
Adverse Event Profiles of the 'Improved' Powder for Oral Suspension (POS) and the Commercial Tablet of Voriconazole Following Multiple Doses Under Fasted Conditions

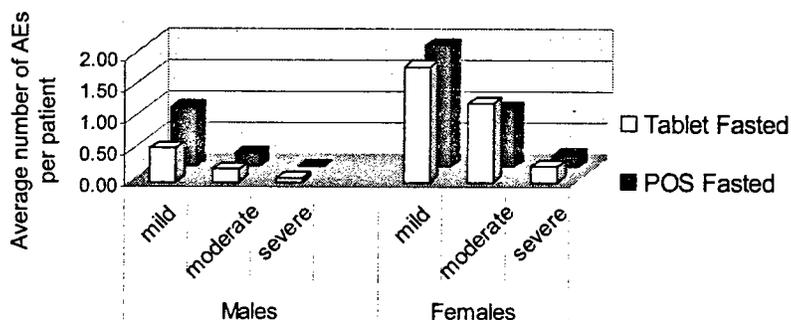


Figure 1a. Average number of adverse events per patient based on frequency and severity in males and females.

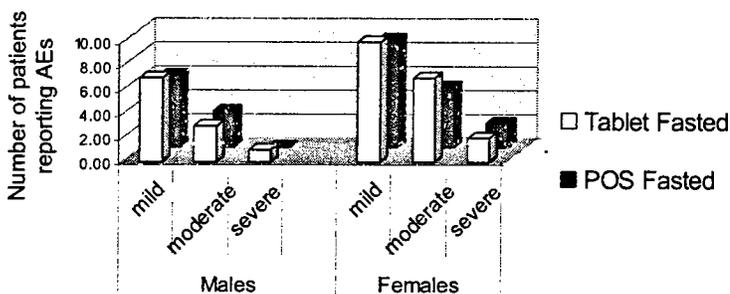


Figure 1b. Number of patients reporting at least 1 adverse event, based on frequency and severity in males and females.

TABLE 2
Pharmacokinetic Parameters for the Contrast of Suspension (Fasted) vs. Tablet (Fasted),
broken down by gender.

Contrast For Males	Parameter	Adjusted Means ^a		Ratio or Difference ^b	90% Confidence Interval
		Suspension Fasted	Tablet Fasted		
Suspension Fasted vs Tablet Fasted	AUC _{0-72h} (ng.h/ml)	14903	14545	103%	(97%, 109%)
	C _{max} (ng/ml)	3419	2664	128%	(116%, 143%)
	T _{max} (h)	0.54	1.00	-0.46h	(-1.03h, 0.11h)

Contrast for Females	Parameter	Adjusted Means ^a		Ratio or Difference ^b	90% Confidence Interval
		Suspension Fasted	Tablet Fasted		
Suspension Fasted vs Tablet Fasted	AUC _{0-72h} (ng.h/ml)	21672	22771	95%	(88%, 103%)
	C _{max} (ng/ml)	3345	3468	97%	(84%, 111%)
	T _{max} (h)	0.75	1.51	-0.76h	(-1.50h, -0.02h)

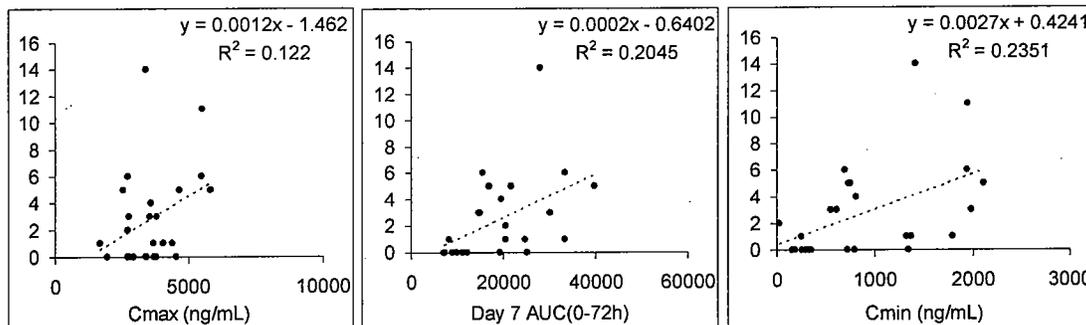
^a Means are geometric for AUC_{0-72h} and C_{max}, arithmetic for T_{max}

^b Ratios(%) for AUC_{0-72h} and C_{max}, difference for T_{max}

FIGURE 2

Scatterplots of Individual Patient Adverse Event Score versus C_{max} on Day 7 (leftmost panel), AUC on Day 7 (middle panel), or C_{min} on Day 6 (rightmost panel); exposure and adverse event data following dosing with the 'improved' or the 'initial multi-dose' POS formulation in male and female subjects.

Legend: ◆ Individual Cumulative Adverse Event Score, --- Best fit line



The cumulative treatment-related adverse event score was calculated using the formula:
[# of mild AEs * 1.0] + [# of moderate AEs * 2.0] + [# of severe AEs * 3.0].

b) Bioequivalence assessment based on C_{min}

Both batches of the 'proposed commercial' POS formulations were bioequivalent to the commercial tablet, based on AUC and C_{max} (Table 1). However, the 'initial multi-dose' or the 'improved' POS formulation (used in the study that determined the effect of food on voriconazole bioavailability in males and females) was bioequivalent to the commercial tablet by AUC in males and females but not by C_{max} in males. The observed correlations between voriconazole C_{min} and adverse event profile (Figure 2), as well as voriconazole AUC and adverse event scores were weak but better than that observed between voriconazole C_{max} and adverse event scores. In addition, because the bioavailability determinations were conducted under voriconazole steady state conditions, the reviewer's assessment of bioequivalence between the 'proposed commercial' POS and the commercial tablet was extended to include voriconazole C_{min}. For comparison, data for the 'initial multi-dose' or 'improved' POS was also included in summary tables. Tables 3 and 4 summarize the pre-dose trough concentration data obtained in

Studies A1501019 and A1501028. Based on this additional analyses by the reviewer, the relative bioavailability of the POS formulations were lower than that of the tablet but both the 'improved' and the two batches of the 'proposed commercial' POS formulations were bioequivalent to the commercial tablet, in terms of the steady state trough voriconazole levels. In agreement with the observed higher adverse event rate in females than in males, the $C_{min,ss}$ values obtained for females were about 2-fold higher than in males following the administration of either the POS or the oral tablet. A high fat meal reduced the steady state trough concentrations of voriconazole by about 25% (Table 4).

TABLE 3
Summary of Pre-dose Trough Concentration Data and Statistical Analyses for Initial Multi-Dose POS Formulation and Tablet in the Fasted State (calculated using the BE Test feature of WinNonLin)

Day 6 C_{min}	Commercial Tablet Fasted	Initial Multi-Dose Suspension Fasted	Ratio (%) Between Adjusted Geometric Means	90% CI
Study A1501019				
Males only ¹	719	694	92.3	87.5, 97.3
Females only ¹	1489	1323	90.5	83.2, 98.4
Males and Females ¹	1027	946	90.4	86.0, 95.1
Study A1501028				
		Proposed Commercial Suspension Fasted		
Males only ²	677	Batch 1: 656 Batch 2: 696	Batch 1: 91.02 Batch 2: 93.46	87.4, 94.8 88.9, 98.3

¹ Initial Multi-dose POS

² Proposed Commercial POS

TABLE 4
Summary of Pre-dose Trough Concentration Data and Statistical Analyses for Initial Multi-Dose POS Formulation in Fed and Fasted State (calculated using the BE Test feature of WinNonLin)

	Day 6 pre-dose trough (C_{min}) concentration (ng/mL)			
	Initial Multi-Dose Suspension Fed	Initial Multi-Dose Suspension Fasted	Ratio (%) Between Adjusted Geometric Means	90% CI
Males only	505	694	69.8	63.7, 76.4
Females only	1134	1323	83.5	69.8, 99.8
Males and Females	768	946	75.1	69.1, 81.5

Study A1501019

Conclusions: The 'proposed commercial' voriconazole POS was bioequivalent to the commercial tablet, in terms of AUC, C_{max} and C_{min} . The 'initial multi-dose' or 'improved' POS was found to be bioequivalent to the tablet in terms of AUC and C_{min} but not in terms of C_{max} . However, the adverse event scores appear to have a weak but better correlation with the AUC and C_{min} , as compared to C_{max} , with both AUC and C_{min} accounting for approximately 20 and 24% of the variability in cumulative AEs, respectively. Thus, steady state C_{min} was considered in an extended assessment of bioequivalence. Additionally, the adverse event profiles of the POS and tablet dosage forms were comparable to each other. These findings suggest that the basic clinical efficacy and safety database available for the oral tablet could be extrapolated to the POS formulation.

1. Following tablet and POS dosing, 2-fold higher steady state voriconazole C_{min} , 1.5-fold higher AUC_{ss}, and about 2-fold higher frequency of adverse events were observed in females compared to males. The average C_{max} values were comparable between genders after POS dosing, whereas the average C_{max} was 30% greater in females than males after tablet dosing.

2. Food effect: The labeling recommendation for the oral tablet may also apply to the POS, i.e., voriconazole POS should be taken at least 1 hour before or after a meal.
3. Store the dry powder at 2-8°C or under refrigerated conditions. Powders stored under higher temperature and relative humidity conditions dissolved faster and their reconstituted suspensions had reduced viscosities, factors that may affect the rate and extent of voriconazole absorption from the suspension.

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

4. Question-Based Review

4.1 Background information about the drug product

4.1.1 What are the highlights of the physico-chemical properties of the new dosage form?

Voriconazole (VFEND®) powder for oral suspension is a multi-dose formulation which, following constitution with water, gives a white to off-white orange flavoured suspension containing 40 mg/mL of voriconazole. The composition of voriconazole powder for oral suspension, 40 mg/mL is presented in Table 5.

TABLE 5
Composition of Voriconazole Powder for Oral Suspension, 40 mg/mL

<u>Component</u>	<u>Grade</u>	<u>Function</u>	<u>mg/bottle</u> ^{(a),(b)}
Voriconazole ^(e)	Pharm	Active	
Sucrose	NF		
Colloidal Silicon Dioxide	NF		
Titanium Dioxide	USP		
Xanthan Gum	NF		
Sodium Citrate ^(f)	USP		
Citric Acid ^(g)	USP		
Sodium Benzoate	NF		
Natural Orange Flavour ^(h)	Pharm		
Total Weight			

- (a)
- (b)
- (c)
- (d)
- (e)
- (f)
- (g)
- (h)

Source: Table 1, Section 3.2.P.1.1 (CMC)

The pH range 3.5 to 4.5 has been shown to maintain the preservative action of sodium benzoate. In addition voriconazole demonstrates satisfactory stability and limited solubility over this pH range.

The viscosity of the reconstituted suspension that has shown no significant change in product performance is . When samples of voriconazole powder for oral suspension were stored at elevated temperature and humidity the following changes were observed, accompanied by a reduction in viscosity:

-
-
-
-

The particle size of voriconazole powder for oral suspension will meet the specification requirement of particles .

4.1.2. What efficacy/safety information contributes to the assessment of CPB study data?

The relationship between the frequency/severity of adverse events from VFEND® POS and various pharmacokinetic parameters (steady state C_{max} , AUC and C_{min}) was assessed based on the influence of gender and CYP2C19 genotype.

4.1.2.1. Gender

Fifteen male and eleven female healthy volunteers were enrolled in Study A1501019. Visual inspection of the adverse event listings from this study suggests that female subjects reported events at a higher rate compared with male subjects during POS dosing (number of all treatment-related events per subject: approximately five for females and three for males). This trend was also observed with tablet dosing (approximately six for females and two for males). A relationship to C_{max} , however, is not recognizable, as a slightly higher mean C_{max} for POS was observed amongst the male subjects. This slight gender difference in voriconazole C_{max} could probably be attributed to the shorter gastric emptying time (GET) which leads to a shorter voriconazole T_{max} in males. Mean AUC was found to be about 1.5-fold higher in females than in males; mean steady-state C_{min} values were about 2-fold higher in females, in good agreement with the relative AE incidence rates observed based on gender. Five out of the six subjects who reported severe adverse events during this study were females. Table 6 summarizes the adverse event and pharmacokinetic profiles of these female subjects. One of these subjects was reported to experience extrasystoles that led to discontinuation. This subject was concurrently taking ethinyl estradiol/norgestimate at the onset of the serious adverse event. Laboratory test results were similar for males and females and no female subject was discontinued due to laboratory abnormalities.

TABLE 6
Profiles of Female Patients experiencing severe adverse events

FEMALE PATIENT ID NO.	ADVERSE EVENT (JUDGED AS RELATED TO STUDY DRUG)	CONCOMITANT MEDICATIONS	PHARMACOKINETIC PARAMETERS		
			AUC (ng·h/mL) (Mean for males and females combined 10825 (POS ^a); 17152 (tablet ^b))	C_{max} (ng/mL) Mean for males and females combined 3392 (POS ^a); 2951 (tablet ^b)	C_{min} (ng/mL) Mean for males and females combined 946 (POS ^a); 1027 (tablet ^b)
20540019	Extrasystoles (led to discontinuation)	Ethinyl estradiol/norgestimate	ND (discontinued)	ND (discontinued)	ND (discontinued)
20540021	Headache	Acetaminophen	16820 ^a 19683 ^b	3383 ^a 2558 ^b	734 ^a 957 ^b
20540022	Abnormal dreams	Ethinyl estradiol/Levonorgestrel	39724 ^a 43018 ^b	5293 ^a 5819 ^b	2109 ^a 2203 ^b
20540024	Abnormal dreams; Headache	Ethinyl estradiol/norgestimate	27847 ^a 23686 ^b	3684 ^a 3412 ^b	1408 ^a 1267 ^b
20540026	Abnormal vision	Ethinyl estradiol/Levonorgestrel	33331 ^a 32933 ^b	3912 ^a 5490 ^b	1936 ^a 1884 ^b

ND- Not determined

Seven of the 11 female subjects enrolled in this study were taking oral contraceptives (OCs) as concomitant medications. OCs have been reported to decrease the hepatic metabolism of various tricyclic antidepressants, beta blockers, caffeine, corticosteroids, theophyllines and other drugs, resulting in increased therapeutic effects or toxicity. In vitro studies with human microsomes that were reviewed with the original voriconazole NDA showed that ethinyl estradiol had the potential to inhibit voriconazole metabolism ($IC_{50} = 19 \mu M$). Relative to the rest of the females listed in Table 6, Patient 21 (who was not taking OCs concurrently with voriconazole) had lower

Compared to the commercial tablets, the T_{max} of the 'initial multi-dose' POS formulation was shorter for all subjects combined and when the male and female subject data were considered separately.

TABLE 8
Summary of Pre-dose Trough Concentration Data and Statistical Analyses for Initial Multi-Dose POS Formulation and Tablet in the Fasted State (calculated using the BE Test feature of WinNonlin)

Day 6 C_{min}	Commercial Tablet (Fasted)	Initial Multi-Dose Suspension (Fasted)	Ratio (%) Between Adjusted Geometric Means	90% CI
Males only	719	694	92.3	87.5, 97.3
Females only	1489	1323	90.5	83.2, 98.4
Males and Females	1027	946	90.4	86.0, 95.1

Study A1501019

The data in the foregoing table (Table 8) indicate that regardless of gender, based on pre-dose trough concentrations achieved on Day 6, the POS was bioequivalent to the oral tablet, since the 90% CI limits obtained from all the subjects were within the 80% to 125% bioequivalence acceptance region. The same conclusion is true for male and female subjects, when considered separately. The results also show that higher steady-state trough levels are likely to be achieved in female than in male subjects, even after a consideration of body surface area differences between genders. The higher mean steady state C_{min} values of voriconazole achieved in females from either the POS or the tablet forms were in agreement with the higher incidence of reported AE frequency/severity in this gender subgroup compared to males (Table 8 and Figure 1).

4.2.1.2. CYP2C19 Genotype

Genotyping of the CYP2C19 locus indicated that in Study A1501028, out of the 48 subjects, 37 were homozygous extensive metabolisers (EM), 8 were heterozygous extensive metabolizers (HEM) and one (Patient 24300018) was a homozygous poor metaboliser (PM) for CYP2C19. A visual inspection of the plots of trough concentrations (Figure 3) indicates that all subjects in this study achieved steady-state trough concentration levels by Day 5 except the PM subject who achieved steady state levels by Day 6 or Day 7. The PM patient exhibited Day 7 plasma voriconazole levels that were distinctly higher than that measured in any of the other subjects (Figure 4).

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FIGURE 3
VORICONAZOLE PROTOCOL 1028
INDIVIDUAL TROUGH PLASMA CONCENTRATIONS (ng/ml) FOR SUSPENSION 2

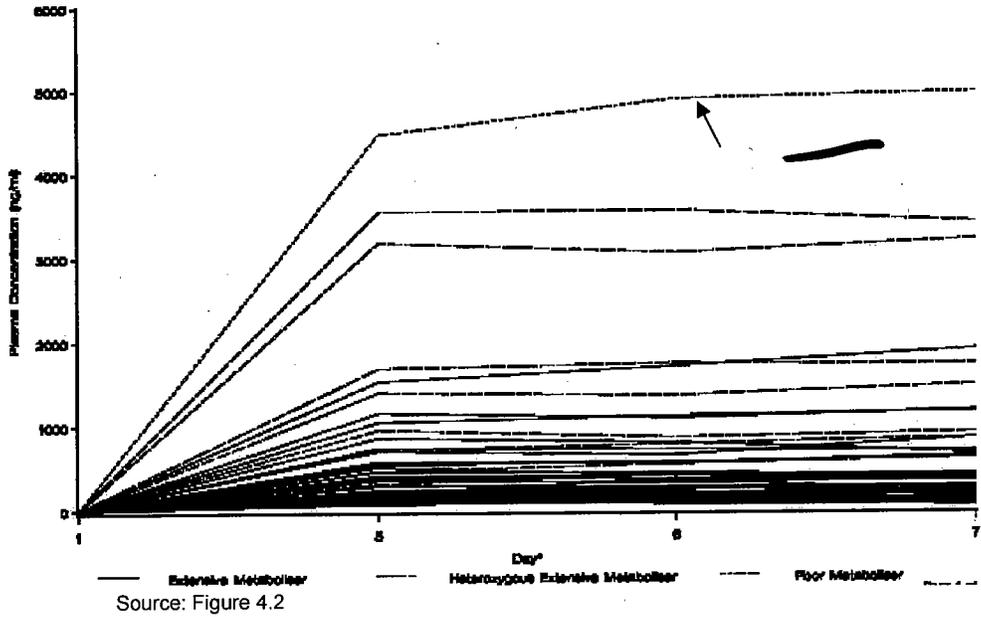
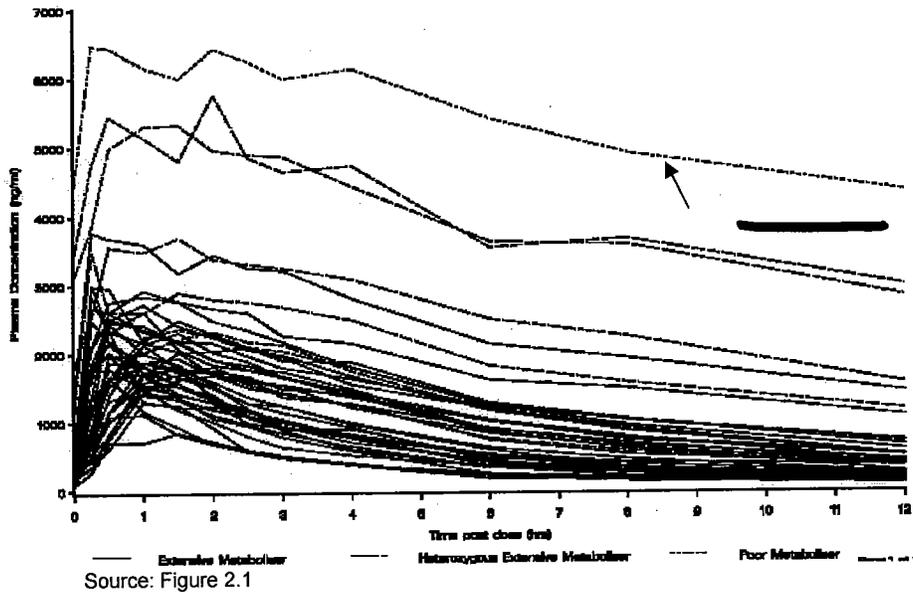


FIGURE 4
VORICONAZOLE PROTOCOL 1028
INDIVIDUAL PLASMA CONCENTRATIONS (ng/ml) FOR SUSPENSION 1 (DAY 7)



Thirteen subjects in Study 150-248 were homozygous extensive metabolizers (EM) and one subject (Subject 00110003) was a homozygous poor metabolizer (PM) for CYP2C19. Majority of subjects achieved steady state trough concentration levels by Day 2 for both formulations; the exception was the PM subject who reached a steady state level between Days 3 to 6.

On the other hand, none of the subjects in Study A1501019 was as a CYP2C19 PM; there were 22 of 27 EMs and 4 of 27 HEMs.

4.2.2 Based upon what is known about exposure-response relationships and their variability, and the groups studied (volunteers vs. patients); what dosage regimen adjustments, if any, are recommended for each of these subgroups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

The steady-state exposure (AUC_{ss}) to voriconazole following administration of the 'initial multi-dose' POS formulation was slightly (~45%) higher in females than in males; voriconazole $C_{max,ss}$ did not vary significantly between genders. On the other hand, steady state C_{min} values (for both the POS and the tablet) were about 2-fold higher in females than in males. However, owing to the higher variability in the female group, no statistically based conclusion could be drawn that would allow the recommendation of a reduced dosage in females at this time. However on account of the relatively higher voriconazole exposure and relatively greater frequency of adverse events in females (particularly those taking OCs) than males in Study A1501019, the sponsor should conduct a Phase IV drug interaction study between voriconazole and oral contraceptives in young females.

4.3. General Biopharmaceutics

4.3.1. Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Voriconazole can be considered a low solubility, high permeability (BCS Class II) compound.

The solubility of voriconazole in aqueous media over the pH range 1.0-7.5 has been determined at 37°C and these data are presented in Table 9. Based on a maximum dose of 300 mg, these data show the dose/solubility volume over the pH range 2.0-7.5 to be greater than — at this temperature.

TABLE 9
Solubility of Voriconazole in Aqueous buffers at 37 °C

Buffer	Solubility (mg/mL)	Dose/Solubility ¹ (mL)
pH 1.0 buffer		
pH 1.2 buffer		
pH 2.0 buffer		
pH 3.0 buffer		
pH 5.0 buffer		
pH 7.5 buffer		

¹Based on a dose of 300 mg

Voriconazole is rapidly absorbed following oral administration with oral bioavailability estimated to be — in man from population pharmacokinetics. As the extent of absorption is determined to be —, the drug is classified as high permeability.

4.3.2. What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%? Aside from C_{max} and AUC, were there any other PK or PD measures considered in assessing the bioequivalence of the test to the reference formulation?

Although bioequivalence with respect to AUC, C_{max} , C_{min} , and safety profile was demonstrated between the 'proposed commercial' POS formulation and the commercial tablet in Study A1501028, the study enrolled only male subjects. It is essential to establish the bioequivalence of the 'initial multi-dose' or 'improved' POS formulation to the commercial tablet because the effect of food on voriconazole bioavailability from the 'proposed commercial' POS will be extrapolated from the findings of the study that used the predecessor formulation (Study A1501019).

For Study A1501019, the upper bound of the 90% CI for the C_{max} ratio (initial multi-dose POS formulation/commercial tablet) was outside of the acceptance criteria for that study. Analysis of data indicated an effect of gender; bioequivalence was demonstrated amongst female subjects for both AUC_{τ} and C_{max} , and amongst male subjects for AUC_{τ} but not C_{max} . The ratio for geometric mean C_{max} for the male subjects was 128% (90% CI: 116%, 143%). This higher C_{max} in males did not seem to translate into an increased safety risk against the POS formulation. It was interesting to note that based on trough (C_{min}) concentrations, the 'initial multi-dose' POS formulation was bioequivalent to the commercial tablet because the ratios for the mean C_{min} on Day 6 were within a 90% confidence interval for male and female subjects, when considered either together or separately. Following both commercial tablet and the POS dosing, females had 1.5-fold higher mean voriconazole AUC, 2-fold higher C_{min} , and reported at least a 2-fold higher adverse event frequency, compared to males receiving the same dosage of the drug. These results show that there were intrinsic/extrinsic factors distinct to females enrolled in the study that increased their exposure to voriconazole and thus made them more susceptible to adverse effects associated with the drug.

4.3.3. What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Pharmacokinetic data and the results of the statistical analyses for the effect of food are presented in Table 10. The fasted state was used as the reference in these analyses. When combining the male and the female data the estimates were as follows:

TABLE 10

		Suspension Fed	Suspension Fasted		
Suspension Fed vs	AUC_{τ} (ng.h/ml)	10823	17152	63%	(60%, 67%)
	C_{max} (ng/ml)	1417	2951	42%	(39%, 46%)
Suspension Fasted	T_{max} (h)	2.08	0.62	1.46h	(1.02h, 1.91h)

* Means are geometric for AUC_{τ} , arithmetic for T_{max} .

¹ Ratios(%) for AUC_{τ} , difference for T_{max} .

Source: Study A1501019, Section 7.5

In Study A1501019, administration of the 'initial multi-dose' POS formulation with food reduced the C_{max} and AUC_{τ} by 58% and 37%, respectively compared with dosing in the fasted state. This reduction in C_{max} and AUC_{τ} after POS dosing is greater than the effect observed for the commercial tablet formulation in Study A1501005 (previously submitted). In that study, multiple dosing of the tablet with high fat meals reduced the C_{max} and AUC_{τ} by 34% and 24%, respectively, compared with dosing in the fasted state.

For the model including gender analysis, the effect of food on voriconazole C_{max} and AUC after POS dosing is discussed in Section 4.2.1.1.

Table 4 in Section 3 (Summary of CPB Findings) shows the effect of food on decreased voriconazole pre-dose trough concentrations on Day 6. The co-administration of a high fat meal decreased the steady-state plasma concentrations of this drug by about 25%, without regard to gender. It appears that males were more susceptible to this food effect on voriconazole bioavailability, an observation that is consistent with analysis in terms of steady state C_{max} and AUC. The greater decrease in voriconazole exposure from the POS observed in males than in females may be related to the shorter GET in the former.

The food-effect findings for the 'improved' or 'initial multi-dose' POS formulation may be extrapolated to the 'proposed commercial' POS formulation because both these formulations in the development program of voriconazole POS were found to be bioequivalent to the commercial tablet at least in terms of AUC and C_{min} , two exposure parameters that appear to be in good correlation to the adverse event scores of male and female subjects enrolled in the A1501019 study. As is the case with the commercial tablet, voriconazole POS should be administered at least 1 hour before or after a meal.

4.3.4. How do the dissolution conditions and specifications assure in vivo performance and quality of the product?

The dissolution test method was not included in the proposed final product release specifications because the sponsor proposed that product performance will be more appropriately assessed by controls on the _____

_____ The drug substance particle size distribution will meet the specification requirement of _____ In addition, the viscosity of the reconstituted suspension will be controlled so as to be within the _____

During the formal and supporting stability programs a dissolution specification of $Q =$ _____ minutes was met with either 6 or 12 samples after storage at 5°C or 25°C/60% RH.

TABLE 11
Summary of in vitro Dissolution Studies

Study Number	Formulation Batch Number	Dosage Form	Strength	Apparatus (USP)	Rotation speed (rpm)	Medium/ temp.	Number of Units ¹	Sampling Time (minutes)	Mean % Dissolved (range)	Study Report Location							
150-248	98DOS122	POS	200mg/ 5mL	Not tested ²	-	-	-	-	-	Module 5.3.1							
	98DOS124 ³	Tablet	200 mg		50	0.1M HCl / 37°C	6	15 30 45	84 (81-89) 100 (98-101) 100 (99-101)								
A1501019	5277-179 ⁴	POS	40 mg/mL		Not tested ²	50	0.1M HCl / 37°C	6	15 30 45	93 (90-96) 94 (92-96) 95 (94-97)	Module 5.3.1						
	5277-191 ⁵	Tablet	200 mg			50	0.1M HCl / 37°C	6	15 30 45	81 (70-88) 100 (98-100) 100 (99-101)							
A1501028	7877-055 ⁶	POS	40 mg/mL			Not tested ²	50	0.1M HCl / 37°C	6	15 30 45	60 (57-62) 87 (86-88) 89 (88-91)	Module 5.3.1					
	7877-056 ⁷	POS	40 mg/mL				50	0.1M HCl / 37°C	6	15 30 45	60 (55-63) 93 (92-94) 96 (95-96)						
							8978-009 ⁸			Tablet	200 mg		50	0.1M HCl / 37°C	6	15 30 45	81 (70-88) 100 (98-100) 100 (99-101)
													50			0.1M HCl / 37°C	6

Source: Table 2.7.1.1

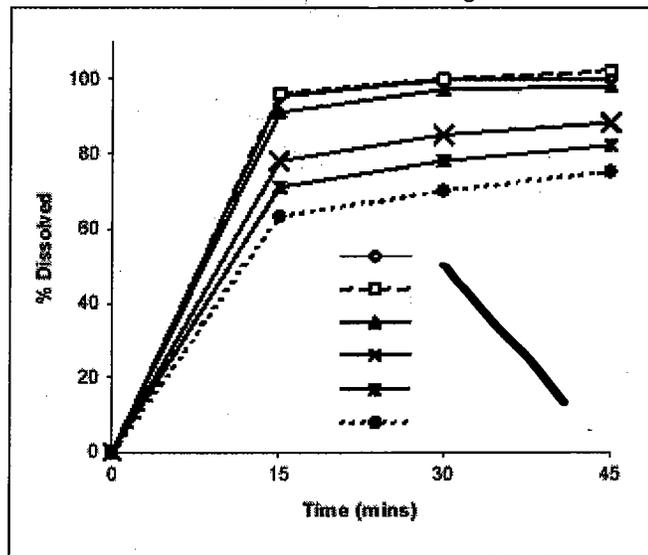
Though the dissolution method was able to discriminate between batches of suspension containing different drug substance particle size (Figure 5) and different viscosities (Figure 6), the

sponsor believes that dissolution is not an appropriate control test for voriconazole powder for oral suspension. [redacted] are controlled and therefore a test for dissolution was not included in the finished product specifications based on the following reasons:

a) [redacted]

b) [redacted]

FIGURE 5
Effect of [redacted] on the dissolution of voriconazole in the voriconazole powder for oral suspension formulation. All batches were manufactured with [redacted] xanthan gum.

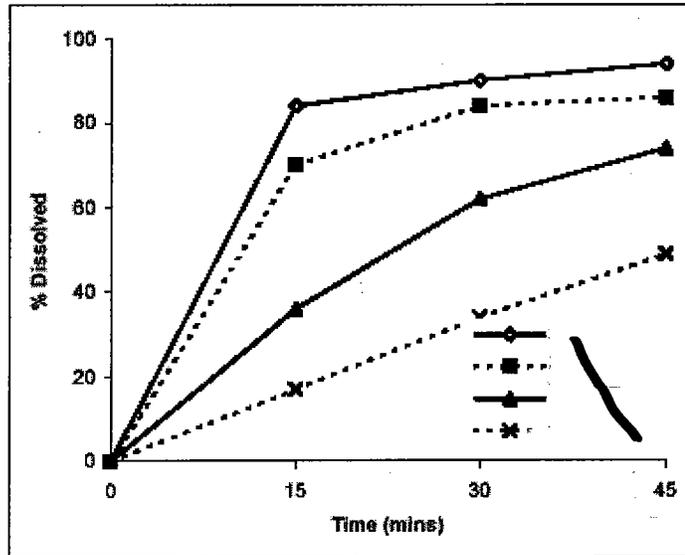


Source: Figure 1, Section 3.2.P.2.1.1.2, CMC

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FIGURE 6

Effect of _____ on the dissolution of voriconazole in the voriconazole powder for oral suspension formulation. All batches were manufactured with the same batch of drug substance _____ and different levels of xanthan gum _____



Source: Figure 2, Section 3.2.P.2.1.1.2, CMC

Findings of the bioequivalence studies suggest that POS batches manufactured with drug substance having a wide range of _____ were found to be clinically acceptable. The _____ of the different drug substance batches used to manufacture the formulations of voriconazole powder for oral suspension used in clinical studies is presented in Table 12. All batches of drug substance used met the proposed _____ acceptance criteria.

The findings of the dissolution studies and the bioequivalence studies are collated in the following table:

TABLE 12

Drug Substance Particle Size Distribution for the POS	Sampling time (minutes)	Mean % Dissolved (range)	POS/Tablet Ratio (%) Between Means (Males only)
Study A1501019	15	93	Cmax = 128
	30	94	AUC = 103
	45	95	Cmin = 90.4
	15	81	
	30	100	
	45	100	
Study A1501028	15	60	Cmax = 104
	30	87	AUC = 102
	45	89	Cmin = 91.0
	15	60	Cmax = 115
	30	93	AUC = 105
	45	96	Cmin = 93.5

██████████

Tablet	15	81
	30	100
	45	100

The data in the table above suggest that varying ██████████ of the ingoing drug substance did not result in a significant difference in the AUC and C_{min} of different voriconazole POS formulations. However, voriconazole C_{max} appears to be more sensitive to changes in ██████████ in the formulation. Of all the POS formulations in the sponsor's development program, POS Batch 1 with a drug substance ██████████ produced a C_{max} closest (104%) to the C_{max} achieved from tablet dosing. Based on this, the sponsor's decision to control the drug substance specification to an upper limit of ██████████ is considered acceptable.

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29 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft-Labeling

quantification were The subjects' cytochrome P450 2C19 (CYP2C19) genotype was also determined.

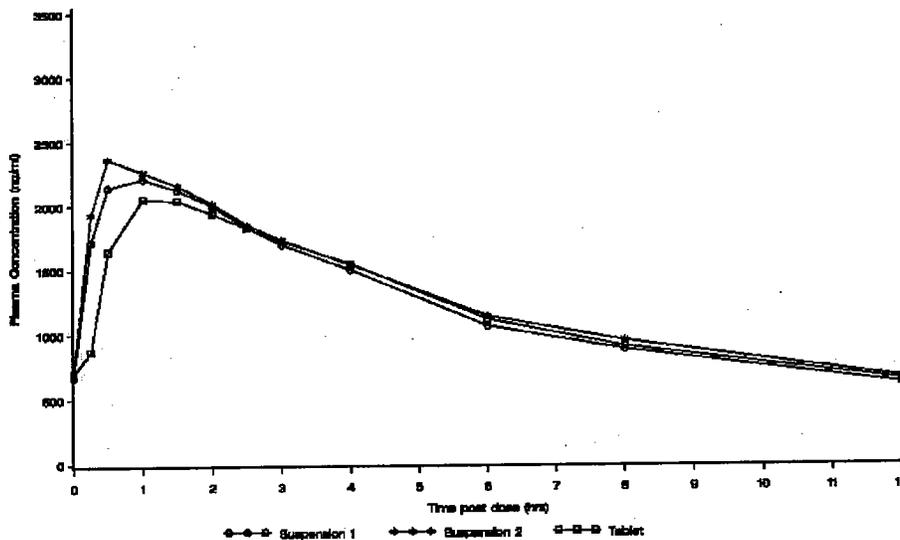
Statistical Methods: The sponsor used an analysis of variance (ANOVA), allowing for variation due to sequence, subject, period and treatment, to analyze log transformed AUC_τ and C_{max} and untransformed T_{max}. The sponsor assessed the sequence effect importance at the 10% significance level and, if important, investigated it further with exploratory analyses. The suspension formulation was considered bioequivalent to the tablet formulation if the AUC_τ and C_{max} 90% CIs were within 80 to 125% and 70 to 143% of each other, respectively.

Pharmacokinetic Results: Both POS Batches 1 and 2 were bioequivalent to the tablet formulation because the 90% CIs for the POS Batch 1/tablet and POS Batch 2/tablet ratios fell within the AUC_τ and C_{max} equivalence regions set by the sponsor. Furthermore the C_{max} 90% CIs fell within the tighter 80 to 125% equivalence region. The T_{max} was longer for the tablet formulation than both the POS formulations. Based on the plot of trough concentrations with time, steady state was reached after seven days of dosing for all three formulations. The table below summarizes the pharmacokinetic statistical analysis calculated from the voriconazole plasma concentration collected between baseline and 12 hours post-dose on Day 7.

Contrast	Parameter	Study Drug		Ratio or Difference	90% CIs (%)
		Suspension Batch 1	Tablet		
Suspension Batch 1 v Tablet	AUC _τ (ng.h/ml) ^a	11718	11478	Ratio=102%	(99,106)
	C _{max} (ng/ml) ^a	2253	2166	Ratio=104%	(98,111)
	T _{max} (h) ^b	0.95	1.39	Difference=-0.44	(-0.66, -0.23)
Suspension Batch 2 v Tablet	AUC _τ (ng.h/ml) ^a	12067	11478	Ratio=105%	(102,109)
	C _{max} (ng/ml) ^a	2488	2166	Ratio=115%	(108,122%)
	T _{max} (h) ^b	0.82	1.39	Difference=-0.57	(-0.78, -0.36)

^aAdjusted geometric means; ^bAdjusted arithmetic means; Ratio=suspension/tablet; Difference=suspension minus tablet.

FIGURE 1
VORICONAZOLE PROTOCOL 1028
MEAN PLASMA CONCENTRATIONS (ng/ml) FOR VORICONAZOLE (DAY 7)



One of the 48 subjects (Patient 24300018) was a homozygous poor metabolizer (PM) for CYP2C19. All the subjects in this study achieved steady-state trough concentration levels by Day 5 except the PM subject who achieved steady state levels by Day 6 or Day 7. This particular patient exhibited Day 7 plasma voriconazole levels that were markedly higher than that measured in any of the other subjects (Figure 4, page 11). This patient experienced headache, dry skin, pruritus, photophobia and abnormal vision and no laboratory abnormalities.

Reviewer's comment: Based on the sponsor's analysis, both batches of the proposed commercial POS formulation are bioequivalent to the commercial tablet form, in terms of AUC_τ and C_{max}. Additional BE analysis was done by the reviewer in order to evaluate the bioequivalence of the proposed commercial POS in terms of C_{min}. Table 3 (page 6) summarizes the pre-dose trough concentration data. The 90% confidence intervals of the suspension/tablet mean ratio for both batches of the proposed commercial POS were wholly contained in the (80-125%) acceptance criteria. The steady state C_{min} values obtained for females were about 2-fold higher than in males following the administration of either the POS or the oral tablet.

Safety Results:

	Suspension Batch 1 N=43	Suspension Batch 2 N=44	Tablet N=45
Adverse Events (All Causality)	31	30	31
Adverse Events (Treatment Related)	25	25	30
Serious Adverse Events	0	0	0
Clinically Significant Laboratory Abnormalities	3	5	4

The adverse event profile of all three formulations was similar to each other. The incidence and types of adverse events were consistent with the known safety profile of voriconazole. There were few laboratory abnormalities and there was no pattern to the distribution among the study drug groups.

Conclusions: The study showed that both batches of the proposed commercial formulation were bioequivalent to the intended commercial tablet in terms of AUC and C_{max}. That the time to peak concentration is shorter for the liquid dosage form (powder for oral suspension) compared to the tablet could explain why the C_{max} was slightly higher after POS dosing. Additionally, although the C_{min,ss} values of the POS formulations were significantly lower than that of the commercial tablet, bioequivalence between both batches of the proposed commercial POS and the commercial tablet was demonstrated in terms of C_{min}. This study did not raise any significant safety concerns. The incidence and types of adverse events was consistent with the known safety profile of voriconazole and the safety pattern was similar for the three formulations. Only male subjects were enrolled in this study.

PROTOCOL A1501019: An open, 3 period crossover, multiple dose study of voriconazole (400mg bid on day 1 followed by 200mg bid for 5.5 days) to investigate the bioequivalence of an improved suspension vs the tablet in the fasted state and to investigate the effect of food on the pharmacokinetics of voriconazole from the suspension

Study Objectives: (1) to investigate the bioequivalence of an improved (also referred to as a multi-dose) oral suspension vs the tablet in the fasted state, (2) to investigate the effect of food on the pharmacokinetics of voriconazole from the suspension, and (3) to assess the safety and toleration of voriconazole

Study Design: An open, multiple dose, crossover study that consisted of three periods. Subjects were randomized to receive the oral suspension formulation in a fed and fasted state and the tablet formulation in a fasted state. The study enrolled male and female subjects.

Evaluation Groups:

	Suspension fasted	Tablet fasted	Suspension fed
Entered Study	26		
Completed Study Period	25	25	25
Evaluated for Pharmacokinetics	24	24	24
Discontinued from study	0	0	1
Assessed for Safety:			
Adverse Events	25	25	26
Laboratory Tests	25	25	26

Diagnoses and Criteria for Inclusion of Subjects: Healthy subjects aged 18 to 45 years inclusive and weighing between 60 to 100kg for males and 50 to 80kg for females .

Drug Administration:

Dosage Form: Voriconazole tablets (200mg) and Voriconazole dry powder for oral suspension, (200mg/5ml when reconstituted).

Dosing/Duration: The study consisted of three periods, each including seven days of dosing separated by a washout period of at least seven days. Subjects were given voriconazole 400mg bid on Day 1 followed by voriconazole 200mg bid for 5.5 days.

Pharmacokinetic Evaluation: Blood samples were taken to determine pre-dose concentrations of voriconazole on the morning of Days 1, 5 and 6 of each study period. On Day 7 of each study period, blood samples were taken pre-dose and at specified times up to 12 hour post-dose.

Analytical Methods: Voriconazole concentrations were measured using a previously validated high performance liquid chromatography method that exhibited a lower LOQ for voriconazole of _____ and an upper limit of the calibration curve of _____. During the study the overall method imprecision was _____ whereas the inaccuracy (bias) of the assay at all concentrations ranged from _____.

Statistical Methods: ANOVA was used to analyze log transformed AUC_{τ} , log transformed C_{max} and untransformed T_{max} (measured on Day 7 of treatment and where τ was 12 hours), for subject, period and treatment effects. The two contrasts of interest were:

Suspension formulation (fasted) vs Tablet formulation (fasted)
 Suspension formulation (fed) vs Suspension formulation (fasted)

The two formulations were considered bioequivalent if the 90% confidence intervals for the ratio of the adjusted geometric means for both AUC_{τ} and C_{max} were contained within the 80 to 125% equivalence region. The above contrasts were shown separately for males and females due to the presence of statistically significant treatment by gender interactions.

Pharmacokinetic Results:

There was a statistically significant treatment by gender interaction for both AUC_{τ} and C_{max} but not for T_{max} . For the AUC_{τ} comparison of the suspension and the tablet formulations in the fasted state a similar effect was seen for males and females and the 90% confidence intervals were wholly contained within the acceptance range (ratio 99%; 90% CI: 94%, 105%) when combining the data from both sexes. The mean steady state AUC values were 1.5 and 1.6-fold higher in females than in males after POS and after tablet dosing, respectively.

For the C_{max} comparison, the 90% confidence interval for the suspension/tablet ratio (115%; 90% CI 104%-127%) was not contained within the (80-125%) acceptance region. The increase in mean C_{max} was greater with the males (ratio 128%; 90% CI 116%-143%) than the females (ratio 97%; 90% CI 84%-111%). T_{max} occurred earlier for the suspension formulation than for the tablet formulation by a mean of 0.57 hours (90% CI: 0.13 hours, 1.01 hours). The mean steady state C_{max} values were 30% higher in females than in males after tablet dosing; mean C_{max} was comparable (but higher than expected from tablet dosing data) in males compared to females after POS dosing. There was a demonstrated effect of food with AUC_τ being 57% and 75% of that in the fasted state for males and females respectively and C_{max} being 36% and 56% of that in the fasted state for males and females, respectively and T_{max} was later for the fed state (mean increase 1.5 hours).

Reviewer's comment:

Based on additional reviewer BE analysis of the test and reference formulations, although the relative C_{min} after POS dosing is significantly lower than that produced after tablet dosing, the POS formulation was bioequivalent to the commercial tablet in terms of this exposure parameter. The 90% confidence interval for the suspension/tablet C_{min} ratio (90%; 90% CI 86%-95%) was contained wholly within the 80-125% region when gender was not used to categorize data and also when data were broken down based on gender. The 100*C_{min} ratios (90%CI) for males and females were 92.8% (87.5, 97.3) and 90.5% (83.2, 98.4), respectively. The mean steady state C_{min} was about 2-fold higher in females than in males after either POS or tablet dosing. With a high fat meal, the mean trough (C_{min}) concentrations decreased by 30% and 17% in males and females, respectively, suggesting that the effect of food on trough voriconazole levels was greater in males than in females.

Safety Results:

Number of Subjects with:	Suspension fasted (n=25)	Tablet fasted (n=25)	Suspension fed (n=26)
Adverse events (all causality)	23	21	22
Adverse events (treatment related)	21	18	17
Serious adverse events	0	0	1
Clinically significant laboratory abnormality	8	3	4

The incidence of treatment emergent adverse events was generally similar across all three treatment arms. The most frequently reported treatment emergent adverse events for all three treatment arms were abnormal vision, headache and gastrointestinal disorder. The majority of adverse events were mild or moderate.

Conclusions: This study was unable to conclude bioequivalence between the POS and tablet formulations in the fasted state because the mean C_{max} was higher with the suspension formulation although the mean AUC_τ and the mean C_{min} were similar with that of the commercial tablet. Compared to females, the mean C_{max} in males was slightly higher but their mean AUC and mean C_{min} were lower after POS and tablet dosing. A food effect was also demonstrated with decreases in mean voriconazole C_{max}, AUC_τ, and C_{min} in the fed state. This effect of food on voriconazole exposure from the suspension appears to be greater in males than in females. The incidence of treatment emergent adverse events was similar across all three treatment arms. Majority of the subjects who were reported to experience severe adverse events were females. The adverse event was assessed as treatment related by the investigator and the subject was discontinued from the study. This subject was not on any other medication except oral contraceptives (ethinyl estradiol/ norgestimate). It is unknown whether the concurrent use of OCs contributed to higher voriconazole exposures and higher incidence of mild to moderate adverse events in the female subset of the population.

PROTOCOL 150-248: An Open, Randomised, 2-Way Crossover Study To Investigate The Bioequivalence And Bioavailability Of Multiple Doses Of Voriconazole (400mg Bid X 1 Day Followed By 200mg Bid X 5.5 Days) When Administered As The Proposed Commercial Formulation Compared To A Suspension Formulation

Study Objectives: (1) to compare the pharmacokinetics of voriconazole following multiple dosing of the intended commercial tablet formulation and a research suspension formulation to determine bioequivalence between the two formulations, (2) to assess the safety and toleration of voriconazole

Study Design: An open, randomized, two way crossover study, consisting of two periods of seven days separated by a minimum seven day washout. Subjects were randomized to receive both formulations of voriconazole.

Evaluation Groups:

	Suspension	Tablet
Entered Study	14	14
Completed Study	14	14
Evaluated for Pharmacokinetics	14	14
Assessed for Safety:		
Adverse Events	14	14
Laboratory Tests	14	14

Diagnoses and Criteria for Inclusion of Subjects: Healthy male subjects aged 18-45 years with a body weight of 60-100kg

Drug Administration:

Dosage Form: Voriconazole tablet (200mg) and Voriconazole Suspension formulation (200mg)

Dosing/Duration: Voriconazole 400mg bid Day 1, 200mg bid Days 2-6, 200mg od Day 7. Doses were administered at 12 hourly intervals.

Pharmacokinetic Evaluation: Blood samples were collected pre dose on Days 1-7 to assess trough concentrations of voriconazole (C_{min}) and also at regular intervals for up to 12 hours post dose on Day 7 to calculate pharmacokinetic parameters (AUC_τ, C_{max} and T_{max}). CYP2C19 genotyping and phenotyping were carried out at the follow up visit.

Analytical Methods: Blood samples were assayed for voriconazole concentrations using a previously validated high performance liquid chromatography (HPLC) method.

Statistical Methods: Analysis of Variance (ANOVA) was done on natural log transformed AUC_τ, natural log transformed C_{max} and untransformed T_{max} to test for variation due to sequences, subjects, periods and treatments. The commercial tablet was used as the reference treatment.

Pharmacokinetic Results:

Summary table of statistical analysis of Day 7 pharmacokinetic parameters:

	Suspension	Tablet	Ratio(%) or Difference Between Means	90% Confidence Intervals	
				lower	upper
C _{min} (ng/ml) ^a	1938	1899	102%	89%	118%
AUC _τ (ng.h/ml) ^a	10033	9633	104%	97%	112%
T _{max} (h) ^b	1.32	1.46	-0.143	-0.530	0.244

a = geometric mean. b = arithmetic mean.

The 90% confidence intervals for the ratio between the geometric means for both C_{max} and AUC_τ were contained wholly within the 80% to 125% bioequivalence range. There was no evidence of an effect of formulation upon either T_{max} or fluctuation index for voriconazole.

Genotyping of the CYP2C19 locus indicated that 13 subjects were homozygous extensive metabolisers (EM) and one subject (Subject 00110003) was a homozygous poor metabolizer (PM) for CYP2C19. Visual inspection of plots of trough plasma levels of voriconazole indicated that for the majority of the subjects, steady state levels were reached by Day 2 for both formulations, the exception was the PM subject who reached a steady state level between Days 3 to 6. C_{max} and AUC_τ ratios were similar for the PM subject to those for EM subjects.

Safety Results:

Number of subjects with event (withdrawn)	Suspension	Tablet
All Causality		
adverse events	11/14 (0)	13/14 (0)
serious adverse events	0/14 (0)	0/14 (0)
laboratory test abnormalities	1/14 (0)	2/14 (0)
Treatment Related		
adverse events	9/14 (0)	13/14 (0)

Adverse events were reported by a similar number of subjects receiving either the suspension or tablet formulation. Treatment related adverse events reported by more than one subject for either formulation were abnormal vision and photophobia.

Conclusions: The research suspension formulation and commercial tablet formulation were demonstrated to be bioequivalent in terms of both AUC_τ and C_{max}. There was no evidence of a difference in T_{max} between the two voriconazole formulations. A similar number of adverse events (including visual adverse events), which the investigator attributed to study treatment, were reported for both formulations. There were no serious adverse events or discontinuations due to safety. The subject who was a CYP2C19 poor metabolizer had achieved higher trough concentrations and took longer to reach steady state.

6.3. Consult Reviews (including Pharmacometric Reviews)

Jenny J. Zheng assisted in the statistical analysis of voriconazole C_{min} data and performed calculations to obtain the 90% confidence interval values about the geometric means (Tables 3, 4, and 8 of this review).

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6.4 Cover Sheet and OCPB Filing/Review Form (2-3 pages)

VI. Office of Clinical Pharmacology and Biopharmaceutics				
New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA Number	21-630	Brand Name	VFEND	
OCPB Division (I, II, III)	III	Generic Name	Voriconazole	
Medical Division	DSPIDP	Drug Class	Triazole Antifungal	
OCPB Reviewer	Gerlie C. De Los Reyes	Indication(s)	Invasive aspergillosis and infections caused by <i>Scedosporium</i> spp. and <i>Fusarium</i> spp.	
OCPB Team Leader	Philip Colangelo	Dosage Form	Powder for oral suspension	
		Dosing Regimen	400mg BID x 1 day followed by 200mg BID x 5.5 days	
Date of Submission	03/14/2003	Route of Administration	Oral	
Estimated Due Date of OCPB Review	08/13/2004	Sponsor	Pfizer	
PDUFA Due Date	01/13/2004	Priority Classification	10 months standard review	
Division Due Date	12/13/2003			
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:				
multiple dose:				
VII. Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	x	1 (included in BE study)		
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				

Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	x (multiple dose only)	3	3	Because of the nonlinear PK of the drug, the BA study was done under voriconazole steady state conditions.
replicate design; single / multi dose:				
Food-drug interaction studies:	x	1 (included in the BE study)	1	
Dissolution:	x	1	1	The USP Dissolution method was not useful in predicting the in vivo performance of the different batches of POS formulations, in terms of AUC and Cmin but will probably be useful in controlling the Cmax if it is desirable to achieve a peak concentration similar to that of the commercial tablet.
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				High permeability-Low solubility (Class II)
III. Other CPB Studies				
Genotype/phenotype studies:	x	2 (as part of the BE studies)		
Chronopharmacokinetics				
Pediatric development plan	IV to oral POS switch in immunocompromised pediatric patients (ongoing)			
Literature References				
Total Number of Studies		3	3	

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/s/

Gerlie De Los Reyes
12/4/03 12:27:09 PM
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Phil: sign-off date on hard copy is 12/4/03.

Phil Colangelo
12/4/03 03:17:10 PM
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