Effect of CYP3A4 Inhibitor Coadministration on the Pharmacokinetics of Avanafil, a New, Potent, Selective PDE-5 Inhibitor

TM Grant, PhD[1], M Obaidi, PhD[1], P Chai, PhD[1], KE Canonizado, MS[1], CM Brandquist, PharmD, MS[1],
E Offman, BSc Pharm[2], A Spivack, MD[3], S Yee, PhD[3]
[1]Celerion, Lincoln, NE, USA, [2]Celerion, Montreal, QC, Canada, [3]VIVUS, Inc., Mountain View, CA, USA

BAVCKGROUND:

- Erectile dysfunction (ED) is generally defined as a condition characterized by the inability to achieve or maintain firm erections sufficient for sexual intercourse. Although not life-threatening, ED causes considerable suffering to a large number of men and, therefore, represents a significant health concern. It is one of the inevitabilities of the aging process, and is also frequently found in men with certain conditions such as hypertension, smoking, diabetes, hyperlipidemia, cardiovascular disease, or from injuries such as spinal cord damage.
- Currently, first-line treatment for men with varied causes of ED consists of oral therapy with a class of compounds known as phosphodiesterase type 5 (PDE-5) inhibitors, which have been shown to help restore penile blood flow and erections in response to sexual stimulation.
- Avanafil is a potent and highly specific PDE-5 inhibitor that is rapidly absorbed from the gastrointestinal tract and that has a relatively short half-life (0.55 - 1.2 hours). The formation of the main metabolites of avanafil is catalyzed by cytochrome P450 (CYP)3A4. It is possible that the pharmacokinetics (PK) of avanafil may be modified by drugs that block the CYP enzyme pathways, resulting in significant changes in its PK, efficacy, and AE profiles.

PURPOSE:

- CYP3A4 catalyzes formation of the main metabolites of avanafil. This study assessed the effect of coadministration of strong (ketoconazole, ritonavir) and moderate (erythromycin) CYP3A4 inhibitors on the PK of avanafil.

METHODS:

- An open-label, randomized, one-sequence, 3-parallel group study was conducted at a single center.
- A total of 44 subjects were enrolled with 41 subjects completing the study. Data from all 44 subjects who were enrolled in the study were included in the analyses, where applicable.
- Subjects were randomized into one of the following 3 groups:
  - Group 1: Ketoconazole 400 mg once daily (QD) for five days (Days 2 - 6) plus a single dose of 50 mg avanafil on Days 1 and 6 (N = 15)
  - Group 2: Erythromycin 500 mg every 12 hours for five days (Days 2 - 6) plus a single dose of 200 mg avanafil on Days 1 and 6 (N = 15)
  - Group 3: Ritonavir 300 mg twice daily (BID) for one day (Day 2), 400 mg BID for one day (Day 3), 600 mg BID for five days (Day 4 - 8) plus a single dose of 50 mg avanafil on Days 1 and 8 (N = 14)
- Single oral doses of avanafil were received following an overnight fast.
- Serial blood samples drawn on avanafil administration days were quantified for plasma avanafil using a validated LC-MS/MS method.
- Noncompartmental analysis was performed on the plasma concentrations versus time profiles to derive the PK parameters of interest (maximum plasma concentration [C_{max}], area under the curve from time 0 to the last measurable concentration [AUC_{0-t}], area under the curve from time 0 to infinity [$AUC_{0-\infty}$], time to reach C_{max} [t_{max}], apparent elimination rate constant [k_{el}], and apparent elimination half-life [$t_{½}$]) using WinNonlin® Professional (Version 5.0.1, Pharsight Corporation, Cary, North Carolina).
- Analysis of variance was performed on the ln-transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ using the SAS® Proc Mixed procedure (SAS® Version 8.2, SAS Institute, Cary, North Carolina). Nonparametric comparisons of t_{max} and $t_{½}$ were conducted using the Wilcoxon Signed Ranks Test.
- The median and 95% confidence intervals (CIs) of the differences between treatments for t_{max} and $t_{½}$ values were constructed using Walsh Averages and appropriate quantile of the Wilcoxon Signed Rank Test. Significant differences in t_{max} and $t_{½}$ values for the treatment comparisons were concluded if the resulting p-value was < 0.05.

RESULTS:

- The geometric mean plasma avanafil concentrations following avanafil alone and avanafil + ketoconazole (Group 1), avanafil + erythromycin (Group 2), and avanafil + ritonavir (Group 3) are presented in **Figures 1, 2,** and **3,** respectively.
  - Geometric mean plasma avanafil concentrations were higher following the coadministration of avanafil + CYP3A4 inhibitors (ketoconazole, erythromycin, and ritonavir) compared to administration of avanafil alone.
- The statistical comparisons of plasma avanafil PK parameters following avanafil + ketoconazole, avanafil + erythromycin, and avanafil + ritonavir versus avanafil alone are presented in **Tables 1, 2,** and **3,** respectively.
  - The statistical comparisons of plasma avanafil PK parameters demonstrated peak and overall avanafil exposures, as measured by C_{max} and $AUC_{0-\infty}$, increased by approximately 3-fold and 14-fold, respectively, following avanafil + ketoconazole compared to avanafil alone.
  - The statistical comparisons of plasma avanafil PK parameters demonstrated peak and overall avanafil exposures, as measured by C_{max} and $AUC_{0-\infty}$, increased by approximately 2-fold and 3-fold, respectively, following avanafil + erythromycin compared to avanafil alone.
  - The statistical comparisons of plasma avanafil PK parameters demonstrated peak mean and overall avanafil exposures, as measured by C_{max} and AUC_{0-t}, increased by 2.5-fold and 13-fold, respectively, following avanafil + ritonavir compared to avanafil alone.
  - Nonparametric statistical comparisons demonstrated statistically significant differences (p-values < 0.05) in t_{max} following avanafil + ketoconazole or ritonavir, but not following avanafil + erythromycin, compared to avanafil alone (p-value > 0.05).
  - Nonparametric statistical comparisons demonstrated statistically significant differences (p-values < 0.05) in $t_{½}$ following avanafil + ketoconazole or erythromycin compared to avanafil alone. Ritonavir $t_{½}$ values were not compared, due to small N.

Figure 1. Geometric Mean Plasma Avanafil Concentrations Versus Time on Day 1 Following Avanafil and Day 6 Following Avanafil + Ketoconazole (Group 1) (Linear Scale)

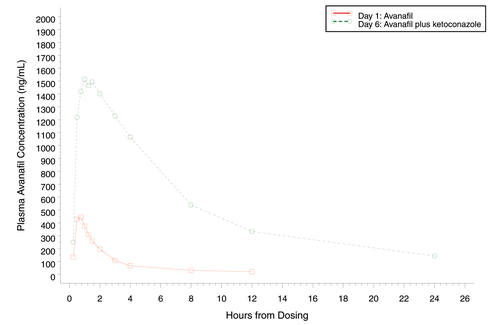

Figure 2. Geometric Mean Plasma Avanafil Concentrations Versus Time on Day 1 Following Avanafil and Day 6 Following Avanafil + Erythromycin (Group 2) (Linear Scale)

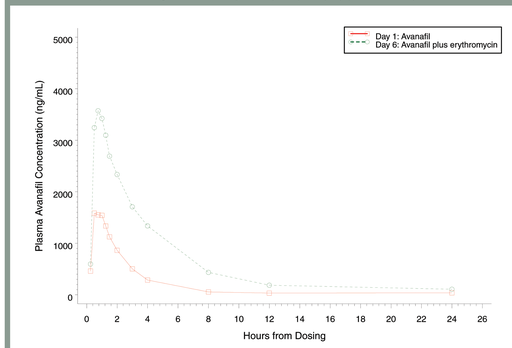

Figure 3. Geometric Mean Plasma Avanafil Concentrations Versus Time on Day 1 Following Avanafil and Day 8 Following Avanafil + Ritonavir (Group 3) (Linear Scale)

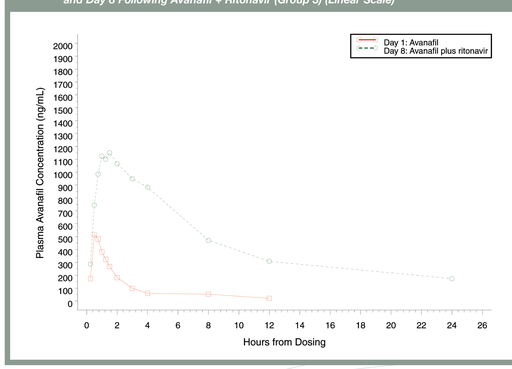

Table 1. Statistical Comparisons of Plasma Avanafil Pharmacokinetic Parameters Following Avanafil + Ketoconazole Versus Avanafil Alone (Group 1)

Pharmacokinetic Parameter	Geometric LS Means		Avanafil + Ketoconazole (Test) vs. Avanafil (Reference)		
	Avanafil + Ketoconazole	Avanafil	90% CI	% Mean Ratio	Fold Change
C_{max} (ng/mL)	1630	506	274.50 - 378.17	322.20	3.22
AUC_{0-t} (ng·hr/mL)	12800	952	1138.27 - 1593.66	1346.85	13.5
$AUC_{0-\infty}$ (ng·hr/mL)[a]	14500	1040	1168.42 - 1652.70	1389.62	13.9
	Treatment Median		95% CI	Median Difference	P-Value
t_{max} (hr)	1.00	0.516	0.24 - 0.75	0.497	0.0052
$t_{½}$ (hr)	8.50	1.39	5.84 - 7.95	6.90	0.0002

Group 1: Ketoconazole 400 mg QD for 5 days (Days 2-6) plus a single dose of 50 mg avanafil on Days 1 and 6
CI = Confidence interval

Table 2. Statistical Comparisons of Plasma Avanafil Pharmacokinetic Parameters Following Avanafil + Erythromycin Versus Avanafil Alone (Group 2)

Pharmacokinetic Parameter	Geometric LS Means		Avanafil + Erythromycin (Test) vs. Avanafil (Reference)		
	Avanafil + Erythromycin	Avanafil	90% CI	% Mean Ratio	Fold Change
C_{max} (ng/mL)	4010	1880	170.55 - 266.96	213.38	2.13
AUC_{0-t} (ng·hr/mL)	15700	4510	285.65 - 425.94	348.81	3.49
$AUC_{0-\infty}$ (ng·hr/mL)	16200	5230	270.53 - 356.44	310.53	3.11
	Treatment Median		95% CI	Median Difference	P-Value
t_{max} (hr)	0.749	0.505	-0.14 - 0.26	0.001	0.6698
$t_{½}$ (hr)	7.81	2.22	4.51 - 6.35	5.57	0.0078

Group 2: Erythromycin 500 mg BID for 5 days (Days 2-6) plus a single dose of 200 mg avanafil on Days 1 and 6
CI = Confidence interval

Table 3. Statistical Comparisons of Plasma Avanafil Pharmacokinetic Parameters Following Avanafil + Ritonavir Versus Avanafil Alone (Group 3)

Pharmacokinetic Parameter	Geometric LS Means		Avanafil + Ritonavir (Test) vs. Avanafil (Reference)		
	Avanafil + Ritonavir	Avanafil	90% CI	% Mean Ratio	Fold Change
C_{max} (ng/mL)	1340	548	211.24 - 283.18	244.58	2.45
AUC_{0-t} (ng·hr/mL)	11100	873	1023.93 - 1567.43	1266.86	12.7
	Treatment Median		95% CI	Median Difference	P-Value
t_{max} (hr)	1.50	0.502	0.37 - 1.25	0.747	0.0005

Group 3: Ritonavir 300 mg BID for 1 day (Day 2), 400 mg BID for 1 day (Day 3),
600 mg BID for 5 days (Days 4-8) plus a single dose of 50 mg avanafil on Days 1 and 8
$AUC_{0-\infty}$ and $t_{½}$ were not included in the statistical comparison because the sample size was too small (N = 4 on Day 8).
CI = Confidence interval

CONCLUSION:

- Coadministration of moderate or strong CYP3A4 inhibitors results in increased maximum and overall plasma avanafil exposure and appears to decrease the plasma elimination rate of avanafil. A slight, but statistically significant, delay in the median time of maximum plasma avanafil concentration is observed following the coadministration of strong CYP3A4 inhibitors. For subjects taking known CYP3A4 inhibitors, avanafil dose-adjustment is recommended.