Assessment of Effect of Age on the Pharmacokinetics of Avanafil, a New, Potent, Selective PDE-5 inhibitor, in Male Subjects

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PURPOSE:

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, a potent and highly specific PDE-5 inhibitor (IC50 value for PDE-5 = 0.0043 – 0.0052 µM), has been developed and recently approved for the treatment of ED. Results of clinical studies conducted to date indicate the potential of avanafil to provide rapid onset of action, improvement in erectile function comparable to other marketed PDE-5 inhibitors, rapid elimination, the potential for twice-daily dosing if needed, greater specificity for the PDE-5 isoenzyme, and the possibility of reduced risk of nitrate interaction. Because avanafil is likely to be used primarily in elderly males, one of the primary objectives of this study was to assess the effects of age on the pharmacokinetics (PK) of avanafil following a single oral 200 mg dose of avanafil.

METHODS:

- An open-label, non-randomized, two-cohort, and single-dose study was conducted at a single site.
- Data from 32 male subjects, assigned according to age (18-45 years, Cohort A, N = 18; ≥ 65 years, N = 14, Cohort B), were included in the analysis.
- Subjects in each of the 2 cohorts received a single 200 mg oral dose of avanafil following a 10-hour overnight fast.
- Serial blood samples drawn from predose through 24 hours postdose 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 concentration-time curve from time 0 to the last measureable concentration [AUC_{0-t}], area under the concentration-time 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 states C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ using the SAS® Proc Mixed procedure (SAS® Version 9.1, SAS Institute, Cary, North Carolina).
- Nonparametric comparisons of t_{max} and $t_{½}$ were conducted using the Wilcoxon Rank Sum Test. The median and 95% confidence intervals (CIs) of the differences between cohorts for t_{max} and $t_{½}$ values were constructed using Hodges-Lehmann estimate. Significant differences in t_{max} and $t_{½}$ values for the treatment comparisons were concluded if the resulting p-value was < 0.05.
- Blood samples for the determination of plasma protein binding of avanafil were obtained from six young subjects (Cohort A) and six elderly subjects (Cohort B) at predose (fortified with 500 ng/mL or 5000 ng/mL avanafil) and 0.75 hour postdose on Day 1.

RESULTS:

- The geometric mean plasma avanafil concentrations in young and elderly subjects are presented in **Figure 1**.
  - Administration of one 200 mg avanafil tablet to young and elderly subjects resulted in similar shapes of the plasma avanafil concentration-time profile.
- Summaries and the statistical comparisons of plasma avanafil PK parameters following the administration of a single 200 mg dose in young and elderly subjects are presented in **Table 1** and **Table 2**, respectively.
- The statistical comparisons of avanafil PK parameters, C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, between elderly and young subjects showed that the 90% CIs of the mean ratios were outside the 80% to 125% range. Probably the high inter-subject variability has contributed to the wider CIs for the PK parameters.
  - Peak and total exposure to avanafil, as measured by C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, were similar between elderly and young subjects. The differences in geometric mean ratios were 0.38% to 12.4%.
- The nonparametric statistical comparisons of plasma avanafil t_{max} and $t_{½}$ between elderly and young subjects are summarized in **Table 3**.
  - The nonparametric statistical comparison of plasma avanafil t_{max} and $t_{½}$ between elderly and young subjects showed that the 95% CIs of differences in median values contained the value of zero, and the p-values were > 0.05 suggesting that the differences in median t_{max} and $t_{½}$ values were not significantly different.
- Plasma protein binding of avanafil is presented in **Table 4**.
  - Plasma protein binding of avanafil was high (~99%), and it was age and concentration independent.

Figure 1. Geometric Mean Plasma Avanafil Concentrations Versus Time Following a Single 200 mg Oral Dose of Avanafil in Young Subjects (Cohort A) and Elderly Subjects (Cohort B) - (Linear Scale)

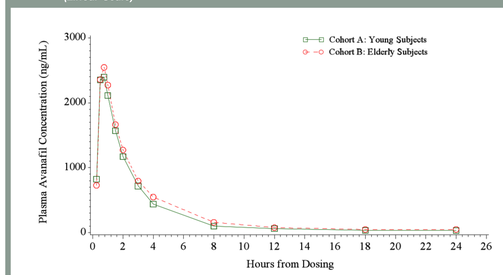

Table 1. Arithmetic Mean (SD)[‡] and Geometric Mean Pharmacokinetic Parameters for Plasma Avanafil in Young Subjects (Cohort A) and Elderly Subjects (Cohort B)

Pharmacokinetic Parameters	Young Subjects Cohort A		Elderly Subjects Cohort B	
	Mean ± SD (N)	Geometric Mean	Mean ± SD (N)	Geometric Mean
C_{max} (ng/mL)	2850 ± 887	2670	2790 ± 837	2680
	(18)		(14)	
AUC_{0-t} (ng*hr/mL)	7200 ± 2210	6810	8540 ± 4220	7650
	(18)		(14)	
$AUC_{0-\infty}$ (ng*hr/mL)	7970 ± 1960	7750	8510 ± 4330	7630
	(15)		(13)	
t_{max} (hr)	0.56 (0.25, 1.0)	.	0.75 (0.50, 0.78)	.
	(18)		(14)	
$t_{½}$ (hr)	6.5 ± 2.9	.	5.6 ± 3.1	.
	(15)		(13)	
k_{el} (1/hr)	0.144 ± 0.0998	.	0.169 ± 0.0941	.
	(15)		(13)	

Cohort A: one 200 mg avanafil tablet in male subjects 18 to 45 years of age, inclusive
Cohort B: one 200 mg avanafil tablet in male subjects at least 65 years of age
[*]t_{max} is presented as median (minimum, maximum) and is presented with two significant figures.
‡SD = Standard Deviations
. = not calculated.

Table 2. Statistical Comparisons of Plasma Avanafil Pharmacokinetic Parameters: Elderly Subjects (Cohort B) Versus Young Subjects (Cohort A)

Pharmacokinetic Parameters	Geometric LS Means				Cohort B Versus Cohort A	
	Elderly Subjects (Cohort B)	N	Young Subjects (Cohort A)	N	90% CI	% Mean Ratio
C_{max} (ng/mL)[a]	2680	14	2670	18	(80.42,125.29)	100.38
AUC_{0-t} (ng*hr/mL)[a]	7650	14	6810	18	(86.81, 145.53)	112.40
$AUC_{0-\infty}$ (ng*hr/mL)[a]	7630	13	7750	15	(77.46, 125.18)	98.47

Cohort A: one 200 mg avanafil tablet in male subjects 18 to 45 years of age, inclusive (reference)
Cohort B: one 200 mg avanafil tablet in male subjects at least 65 years of age (test)
The data for four subjects (Subjects 11, 15, 18 [Cohort A], and 113 [Cohort B]) were not included in the statistical analysis of $AUC_{0-\infty}$ because the coefficient of determination (R^2 value) for the k_{el} calculation was < 0.8 or the slope was undefined.
Parameters were log-transformed prior to analysis. % Mean Ratio = 100*(test/reference).
[a] C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ are presented with three significant figures.
CI = confidence interval.

Table 3. Nonparametric Statistical Comparisons of Plasma Avanafil Pharmacokinetic Parameters t_{max} and $t_{½}$: Elderly Subjects (Cohort B) Versus Young Subjects (Cohort A)

Parameter	Cohort B		Cohort A		Difference Cohort B -Cohort A		
	Median[b]	N	Median[b]	N	95% CI[a]	Median	P-value
t_{max} (hr)	0.75	14	0.56	18	(-0.02 , 0.24)	0.016	0.1899
$t_{½}$ (hr)	4.7	13	6.7	15	(-3.78 , 1.43)	-1.089	0.5190

Cohort A: one 200 mg avanafil tablet in male subjects 18 to 45 years of age, inclusive (reference)
Cohort B: one 200 mg avanafil tablet in male subjects at least 65 years of age (test)
The data for four subjects (Subjects 11, 15, 18 [Cohort A] and 113 [Cohort B]) were not included in the statistical analysis of $t_{½}$ because the coefficient of determination (R^2 value) for the k_{el} calculation was < 0.8 or the slope was undefined.
The comparison was conducted using the Wilcoxon Rank Sum test.
[a] Confidence interval (CI) for the difference between two medians was calculated using the Hodges-Lehmann estimate.
[b] t_{max} and $t_{½}$ are presented with two significant figures.

Table 4. Mean (±SD) Human Plasma Protein Binding of Avanafil in Six Young and Elderly Male Subjects

		Protein Binding (%)	Recovery (%)
0.75 hour Post-dose	Young	99.2 ± 0.08	91.6 ± 2.5
	Elderly	99.1 ± 0.09	92.9 ± 3.5
Pre-dose (500 ng/mL)	Young	99.3 ± 0.03	98.9 ± 1.6
	Elderly	99.2 ± 0.07	97.3 ± 3.0
Pre-dose (5000 ng/mL)	Young	98.9 ± 0.05	97.7 ± 1.8
	Elderly	98.8 ± 0.03	100.8 ± 3.7
Warfarin	Positive Control	99.2 ± 0.07	100.2 ± 5.7

CONCLUSION:

- Total and peak exposures to avanafil were similar between elderly and young subjects. Plasma protein binding of avanafil was high (~99%), and was independent of age and concentration. Avanafil dose adjustments are not recommended for elderly subjects.