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 significant 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 normal 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 1-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 [Cmax], area under the concentration-time curve from time 0 to the last measurable concentration [AUC0-∞], area under the concentration-time curve from time 0 to infinity [AUC0-∞], time to reach Cmax [tmax]), apparent elimination half-life [t1/2], and apparent elimination rate constant [k].
- Analysis of variance was performed on the ln-transformed states Cmax, AUC0-∞, and AUC0-∞ using the SAS Proc Mixed procedure (SAS® Version 9.1, SAS Institute, Cary, North Carolina).
- Nonparametric comparisons of Cmax and t1/2 were conducted using the Wilcoxon Rank Sum Test. The median and 95% confidence intervals (CIs) of the differences between cohorts for Cmax and t1/2 values were constructed using Hodges-Lehmann estimate. Significant differences in Cmax and t1/2 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 a single 200 mg avanafil tablet to young and elderly subjects resulted in similar shapes of the plasma avanafil concentration-time profile.
- The comparison was conducted using the Wilcoxon Rank Sum test.
- The statistical comparisons of 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, Cmax, AUC0-∞, and AUC0-∞, between elderly and young subjects showed that the 95% 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 Cmax, AUC0-∞, and AUC0-∞, 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 t1/2 and t1/2 between elderly and young subjects are summarized in Table 3.
- The nonparametric statistical comparison of plasma avanafil t1/2 and t1/2 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 t1/2 and t1/2 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.

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.