**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 currently first-line treatment for men with varied causes of ED such as spinal cord damage, diabetes, hyperlipidemia, cardiovascular disease, or from injuries 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.

- Noncompartmental analysis was performed on the plasma concentrations versus time profiles to derive the PK parameters of interest, including the maximum plasma concentration (Cmax) and the area under the curve from time 0 to the last measurable concentration (AUC). Cmax was the peak plasma concentration, obtained by interpolation using linear trapezoidal summation from the most recent concentration prior to the peak and assuming a 0.5-hour terminal half-life; AUC was the area under the plasma concentration versus time profile on a semi-logarithmic scale from time 0 to infinity.

**METHODS:**

- **PURPOSE:** CYP3A4 catalyzes the formation of the main metabolites of avanafil. This study assessed the effect of coadministration of strong (ketonozonate, ritonavir) and moderate (eritromycin) 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:** Ketonozonate 400 mg once daily (QD) for 5 days (Days 2-6) plus a single dose of 50 mg avanafil on Days 1 and 6 (N = 15)
    - **Group 2:** Eritromycin 500 mg every 12 hours for 5 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 (QID) for one day (Day 1), 400 mg BID for one day (Day 2), 600 mg BID for five days (Days 4-8) plus a single dose of 50 mg avanafil on Days 1, 2, 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.

- The statistical comparisons of plasma avanafil PK parameters following avanafil + ketonozonate (Group 1), avanafil + ritonavir (Group 2), and avanafil + eritromycin (Group 3) are presented in Figures 1, 2, and 3, respectively.

- Geometric LS Means Pharmacokinetic Avanafil + Erythromycin Versus Avanafil Alone (Group 2)

- **RESULTS:**
  - The mean and 95% confidence intervals (CIs) of the differences between treatments for the mean 0-12 h AUC0-12 were constructed using Welch variances and appropriate quantiles of the Wilcoxon Signed Rank Test. Significant differences in mean values for the treatment comparisons were concluded if the resulting p-value was < 0.05.

**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 was observed following the coadministration of strong CYP3A4 inhibitors. For subjects taking known CYP3A4 inhibitors, avanafil close-adjustment is recommended.