

**Title:** PK/PD MODELING OF QTcF DURATION FOR VARDENAFIL & SILDENAFIL FOLLOWING CONCOMITANT ADMINISTRATION WITH GATIFLOXACIN IN HEALTHY VOLUNTEERS

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**Objectives:** To characterize the PK/PD relationship between effect (QTcF) and plasma concentration (Cp) of vardenafil (V), sildenafil (S) and gatifloxacin (G) following single oral administration of V (10 mg), S (50 mg) and G (400 mg) or when V and S were co-administered with G in a placebo-controlled, double-blind, 6-way crossover study on QT/QTcF duration.

**Methods:** 44 healthy men received at least one dose of study medication. Three replicate 12-lead ECGs were recorded at pre-dose (4 time points) and up to 24 hours post-dose (10 time points). S, V and G Cp were measured up to 16 hours post-dose (9 time points). The PK/PD model included a circadian rhythm in QTcF for all treatments defined by two cosine cycles (CC) for PK/PD data obtained up to 0-12 hours and 12-24 hours, respectively. The 2 CC were characterized by amplitudes AMP<sub>1</sub>, AMP<sub>2</sub>, and acrophases t<sub>max1</sub> and t<sub>max2</sub> with CC of 12 and 24 hours, respectively. Various direct effect PK/PD models were investigated to describe the PK/PD relationship for each of the three drugs, and to assess for the presence of a less than additive effect (partial antagonism) or a greater than additive effect (synergy). Interoccasion variability (IOV) in baseline QTcF response (E<sub>0</sub>) and inter-individual variability (IIV) in slopes were included in the model.

**Results:** After accounting for the diurnal variation in QTcF, the PK/PD relationship for V, S and G was described using direct effect slope-intercept models.

Parameter	Population Mean (% CV)	IIV
E <sub>0</sub> (msec)	389 (0.5)	3.18 (24.9)
S <sub>V</sub> (msec mL/ng)	0.552 (21.4)	32.1 (349)
S <sub>S</sub> (msec mL/ng)	0.0165 (26.3)	119.6 (74.8)
S <sub>G</sub> (msec mL/ng)	0.00129 (8.0)	15.5 (121)
AMP <sub>1</sub>	3.96 (12.0)	69.1 (25.7)
AMP <sub>2</sub>	1.88 (27.2)	122.5 (74.0)
t <sub>max1</sub> (hours)	2.07 (7.4)	36.6 (47.8)
t <sub>max2</sub> (hours)	13.0 (3.0)	111.8 (59.4)
IOV on E <sub>0</sub> (%)	0.83 (21.6)	
Residual Variability, (msec)	6.16 (5.4)	

**Conclusions:** According to the PK/PD model, the QTcF prolongation for the combination treatments was explained by an additive effect model. This observation should be considered in the clinical decisions when prescribing V to patients with known history of QT prolongation or patients who are taking medications known to prolong the QT interval.