Title: Population Pharmacokinetic/Pharmacodynamic Modeling of Two Novel Neutral Endopeptidase Inhibitors in Healthy Subjects

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Objectives: UK-447,841 and UK-505,749 are two selective NEP inhibitors that are being investigated for the 'as required' treatment of the symptoms of Female sexual arousal disorder (FSAD). The objective of this study was to understand the pharmacokinetic characteristics of the two drugs, and develop a PK/PD (biomarker) model to quantitatively assess the relationship between drug concentration and the effects of the two drugs on plasma concentration of big endothelin-1 (big ET-1) and atrial natriuretic peptide (ANP) in healthy subjects.

Methods: Data from 3 phase I studies including a total of 89 (44 male: 55 female) subjects were used to build the population PK/PD model. The sequential PK and PK/PD analyses were performed using NONMEM. The parametercovariate combinations that were considered for inclusion in the model were estimated. A complete battery of diagnostic plots and visual predictive checking were produced to evaluate the models.

Results: The PK for both molecules were described using two-compartment model with zero order and first order absorption processes simultaneously, parameterized in terms of apparent clearance (CL/F) , apparent volume (V/F) zero order absorption duration (D1), and first order absorption rate constant (Ka). A combined big ET-1/ANP indirect response model was developed to describe the relationship between the 2 drugs' concentration and their effect on NEP inhibition. The concentration to achieve half the maximum inhibition effect on big ET-1 and ANP degradation were, respectively, 1.808 and 54.3 mg/L for UK-447,841 and 0.2667 and 5.408 mg/L for UK-505,749. Age was found to be the significant covariate affecting the ANP production rate. In addition, analysis indicated that ANP and big ET-1 enhanced each other's plasma concentrations via big ET-1 stimulating production rate of ANP and ANP slowing down the degradation rate of big ET-1. The goodness-of-fit diagnostic plots showed that the proposed PK/PD model described the PK and two biomarkers data well. Visual predictive checks showed that the model adequately describes the median of the effects but had a slight over predicts the variability especially for ANP.

Conclusions: Two drugs' pharmacokinetic character was well described by proposed model with the physiological values for PK parameters. The drugs' effect was consisted with prior knowledge about UK-505,749 showed 10-fold greater potency than UK-447,841 for both biomarkers.