tamsulosin, there is the possibility for a pharmacodynamic interaction that may result in clinically significant hypotension.

METHODS: This was a randomized, double-blind, double-dummy, three-period, three-treatment, three-way crossover study. Twenty seven healthy male subjects were hospitalized for measuring baseline blood pressure (BP) from Day 1 to 2 (placebo lead-in period), administration of tamsulosin matching and udenafil matching placebo) at Clinical Trial Center, Seoul National University Hospital. Then they received tamsulosin 0.4 mg or placebo orally according to predefined sequences once daily from Day 2 to 4, Day 9 to 11, and Day 16 to 18. Supine, standing, and ambulatory BP were measured after administration of tamsulosin 0.4 mg or placebo followed by udenafil 200 mg or placebo 3 hours later on Day 5, 12, and 19. The maximal change of standing BP from supine baseline BP at each period was evaluated. In addition, supine BP and ambulatory BP were used for further safety evaluation.

RESULTS: The mean maximal percent change from baseline systolic BP was −14.5% and −11% in subjects receiving tamsulosin with udenafil and tamsulosin alone, respectively. The difference between these treatments was −3.4% (−6.7% − 0.2%, 95% confidence interval), which corresponded to 4 mmHg in absolute values. The mean absolute differences between these treatments in systolic and diastolic BP were 1 and 2 mmHg, respectively, regarding ambulatory and supine BP. Five subjects receiving tamsulosin with udenafil and one subject receiving tamsulosin alone experienced a standing SBP drop of 30 mmHg or more. Three subjects receiving tamsulosin with udenafil and one subject receiving tamsulosin alone exhibited SBP less than 85 mmHg.

CONCLUSION: In healthy subjects, no evidence was found that coadministration of tamsulosin and udenafil show more clinically significant BP decrement than administration of tamsulosin alone.

PII-60
PHARMACOKINETICS AND PHARMACODYNAMICS OF THE DPP-4 INHIBITOR, VILDAGLIPTIN, IN JAPANESE PATIENTS WITH TYPE 2 DIABETES. N. Hayashi, PhD, M. Karube, MD, Y. Kumagai, MD, PhD, Y. Fujita, MD, PhD, S. Irie, MD, Y. Ikeda, MD, Y. L. He, PhD, Novartis Pharma Japan KK, New Medical Research SystemClinic, Kitasato University East Hospital, Kitasato University Hospital, Kyushu Clinical Pharmacology Research Clinic, Novartis Institute and Biomedical Research USA, Tokyo, Japan.

BACKGROUND: Vildaglptin (Vilda) is a potent and selective DPP-4 inhibitor, which is developed as an oral anti-diabetic agent. The objective of this study was to assess the PK/PD in Japanese patients with type 2 diabetes (T2D).

METHODS: Sixty two Japanese patients with T2D were enrolled and completed this study. Each subject was randomly assigned to receive one of the four treatments for 7 days: placebo, 10, 50, or 50 mg of Vilda bid. The correlations between PK and PD parameters were evaluated using AUC<sub>0-12</sub> of plasma Vilda concentration on Day 7, the ratio of AUE<sub>E0-4</sub> of GLP-1 concentration before and after Vilda treatment, and the ratio of breakfast postprandial plasma glucose (PPPG) baseline corrected AUE<sub>E0-4</sub> before and after Vilda treatment.

RESULTS: The GLP-1 levels after breakfast and dinner in Vilda treatment groups were higher than that for placebo group on Day 7. PPPG adjusted AUE<sub>E0-4</sub> showed a decrease after Vilda treatment. The relationship between the exposure to Vilda (AUC<sub>0-12</sub>), and the GLP-1 AUE<sub>E0-4</sub> ratio was evaluated with an Emax model. The E<sub>0</sub>, E<sub>max</sub> and EAUC<sub>50</sub> (AUC<sub>0-12</sub> causing the half-maximum effect) were estimated to be 1.01-fold, 1.98-fold and 223 ng/h/mL. This indicates that GLP-1 AUE<sub>E0-4</sub> did remain unchanged in the absence of Vilda, and the GLP-1 AUE<sub>E0-4</sub> can be increased to a two-fold maximal level. The relationship between the GLP-1 AUE<sub>E0-4</sub> ratio and the PPPG baseline corrected AUE<sub>E0-4</sub> ratio was also analyzed using a model. The relationship was well described with an inhibitory effect E<sub>max</sub> model, indicating that PPPG baseline corrected AUE<sub>E0-4</sub> decreased by 14.6% with no change in GLP-1 (placebo effect), and decreased by 50% with 2.18-fold increase in GLP-1. These Emax models were combined, and PPPG change was predicted for each dose group based on the observed Vilda AUC<sub>0-12</sub>. The predicted PPPG reduction were 14.6, 32.1, 40.0 and 43.1 (% for placebo, 10, 25 and 50 mg group, and the observed were 10.9 ± 7.2, 27.6 ± 5.2, 46.9 ± 7.2 and 38.1 ± 6.2 (%, mean ± SE). The predictability and usefulness of the models were confirmed by the good fitting of model prediction with the observed.

CONCLUSION: The relationship between PK and PD parameters were well described with the Emax models. These results suggest that the mode of action of Vilda on glucose can be primarily explained by the cascade of effects such as PK to GLP-1, and GLP-1 to PPPG.

PII-61
SELECTION AND PHARMACOKINETIC-PHARMACODYNAMIC MODELLING OF A SOLUBLE BIOMARKER FOR A NEUTRAL ENDOPEPTIDASE INHIBITOR. A. C. Heatherington, PhD, S. Sultana, MD, R. Hidi, PhD, M. Boucher, MSC, L. H. Tam, MD, P. Ellis, PhD, O. Petricoul, PhD, J. Grevel, PhD, S. W. Martin, PhD, Pfizer Ltd, Pfizer Ltd, EMF Consulting, Sandwich, Kent, United Kingdom.

BACKGROUND/AIMS: To establish a reliable soluble biomarker for UK447841, a neutral endopeptidase inhibitor (NEPi, IC<sub>50</sub> for human enzyme 9.6 nM), based on knowledge of enzyology, and build a suitable pharmacokinetic-pharmacodynamic model to assist with dose selection in subsequent efficacy studies.

METHODS: In a single dose (SD) study, healthy volunteers (n = 33 males/females) received single escalating oral doses of UK447841 in a cross-over design over 3–800 mg, PK (to 48 hr) and PD (5 analytes, to 8 hr) samples were collected. In a multiple dose (MD) study, healthy volunteers (n = 32 females), resident in a clinical research unit, received daily oral doses of placebo, 100, 400 or 800 mg UK447841 for 7 days in a parallel group design. PK (to 12 hr) and PD (to 12 hr) samples were collected on days 1 and 7.

RESULTS: UK447841 was well tolerated in SD and MD studies. It was rapidly absorbed (median T<sub>max</sub> 0.33–0.75 hr) with dose-proportional exposure increases up to 400 mg. PK profiles were biexponential (terminal half-life −5–9 hr) and time-linear with little accumulation upon MD. Of 5 PD analytes tested in the SD study, big endothelin showed clear dose response for both maximum absolute value [pg/mL, mean (sd), n = 6]: 100 mg 4.27 (0.818), 400 mg 5.76 (1.54), 800 mg: 6.80 (0.727) and area under the effect curve [AUEC<sub>Pg</sub>/hr/mL, mean (sd), n = 6]: 100 mg 35.7 (11.0), 400 mg 48.3 (15.5), 800 mg 64.5 (8.29). Upon MD, stationarity of big endothelin response was confirmed [AUEC 100 mg 33.4 (15.6), 400 mg (47.6 (9.29), 800 mg 63.8 (8.53) pg/hr/mL]. There was no effect of placebo on PD endpoints. A preliminary 2-compartment disposition PK model has been fitted to the data; a full PKPD model has been established using MD data and has been validated using SD data.

CONCLUSIONS: Big endothelin, a substrate for NEP and other metallopeptidases, has demonstrated ideal characteristics of a soluble biomarker. The application of PKPD modelling has quantified the relationship and allowed dose projections for patient studies.

PII-62
POPULATION EXPOSURE-RESPONSE MODEL OF INDIOLON PLASMA CONCENTRATION—DIGIT SYMBOL SUBSTITUTION TEST (DSST) SCORE RELATIONSHIP IN HEALTHY VOLUNTEERS. K. Ito, PhD, B. Frame, MSC, R. Miller, DSc, B. Corrigan, PhD, J. Gründy, PhD, Pfizer Global Research and Development, Pfizer Global Research and Development, Pfizer Global Research and Development, Neurocrine Biosciences, Groton, CT.

BACKGROUND: To develop a population exposure-response model to describe the indiplon plasma concentration-DSST score relationship in healthy volunteers. The DSST is a performance test to evaluate complex psychomotor activity.