PIII-17

EFFECT OF A SINGLE CYCLOSPORINE A (NEORAL™) DOSE ON THE SINGLE-DOSE PHARMACOKINETICS (PK) OF SITAGLIPTIN (MK-0431), A DIPEPTIDYL PEPTIDASE-IV INHIBITOR (DPP-IV), IN HEALTHY MALE SUBJECTS. R. Krishna, PhD, FCP, A. J. Bergman, PhD, P. Larson, MS, J. Cote, K. C. Lasseter, MD, M. Pierre, A. Q. Wang, W. Zeng, L. Chen, J. A. Wagner, MD, PhD, G. A. Herman, MD, Merck & Co., Inc., SFBC, Rahway, NJ.

BACKGROUND: Sitagliptin (MK-0431), an orally active, potent and selective DPP-IV inhibitor being developed for Type 2 diabetes mellitus, is a substrate for p-glycoprotein (Pgp). High dose cyclosporine A (CSA) was used as a probe Pgp inhibitor to evaluate the effect of potent Pgp inhibition on sitagliptin PK.

METHODS: 8 healthy young men received Treatments A (single oral 600 mg dose of CSA [NEORAL™] with a single 100 mg oral sitagliptin dose) and B (single oral 100 mg sitagliptin dose alone) in an open-label, randomized, 2-period, crossover study, separated by a 2-week washout. Pre-specified bounds of [0.50, 2.00] were used for AUC GMR whether any alterations in MK-0431 PK was clinically meaningful.

RESULTS: Sitagliptin with or without CSA was generally well tolerated. Sitagliptin $AUC_{0-\infty}$ GMR (1.29) with 90% CI [1.24, 1.34], and C_{max} GMR (1.68) with 90% CI [1.35, 2.08] indicated modest effects by CSA and unlikely to be clinically relevant. There were no meaningful differences in CL_r, apparent $t_{1/2}$ or C_{24hr}.

CONCLUSIONS: This study with high dose CSA confirmed that sitagliptin was a substrate for Pgp. Co-administration of CSA with sitagliptin only modestly increased C_{max} of sitagliptin without a meaningful effect on overall exposure. Given only modest alterations in PK (i.e., on C_{max}) with a highly potent Pgp inhibitor, the magnitude of changes in sitagliptin PK with other medications that are Pgp inhibitors, albeit less potent ones, is unlikely to be clinically meaningful.

PIII-18

VALIDATION OF PHARMACODYNAMIC ASSESSMENT METHOD AFTER ADMINISTRATION OF VOGLIBOSE IN HEALTHY SUBJECTS. Y. M. Tae, J. R. Kim, MD, K. S. Lim, MD, J. W. Kim, MD, B. H. Kim, MD, J. Y. Jeon, O. H. Chung, J. Y. Cho, PhD, K. S. Yu, MD, S. G. Shin, MD, I. J. Jang, Department of Pharmacology and Clinical Pharmacology Unit, Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea.

BACKGROUND: Voglibose is alpha-glucosidase inhibitor. Due to negligible oral absorption, measuring drug concentration in the blood is impractical. So we proposed the pharmacodynamic assessment method to reflect drug effect and this study aimed to validate this method.

METHODS: Placebo-controlled, selective two-period clinical study was conducted in 20 healthy male subjects. Period I: Subjects received a single oral dose of placebo on day 1. After 20 min of dosing, subjects had a 400 kcal sucrose-rich fluid meal. Blood samples for evaluation of serum glucose level were taken during 3 hours. On day 2, all procedures were the same as day 1 except administration of 0.3 mg voglibose instead of placebo. Period II: 9 subjects in whom considerable decreases of serum glucose level were observed in Period I participated in a multiple dose study (placebo: 8, 11 pm on day -1, and 9 am on day 1 / voglibose: 2, 8, 11 pm on day 1, and 9 am on day 2).

RESULTS: AUEC1h (area under the serum glucose level-time curve to 1h) slightly increased by 2.2% and G_{max} (maximum serum glucose level) decreased by 0.5% with large intersubject variability when a single dose was administered. However, after multiple administration, the average percent decreases of AUEC1h and G_{max} were 19.6% ($P<0.001$) and 22.2% ($P<0.001$), respectively.

CONCLUSIONS: Significant drug effects of voglibose in healthy subjects were revealed only after multiple doses. Changes of AUEC1h and G_{max} compared to placebo may be alternative parameters to AUC and C_{max} for equivalence study.

PIII-19

THE INFLUENCE OF AGE, GENDER AND BMI ON THE PHARMACOKINETICS AND PHARMACODYNAMICS OF VILDAGLIPTIN. Y. L. He, PhD, R. Sabo, Y. Wang, J. Campestrini, G. L. Rivere, M. Saltzman, M. Ligueros-Saylan, NIBR, Novartis Pharmaceuticals, Novartis Pharmaceuticals, Parkway Research Center Inc, Cambridge, MA.

OBJECTIVES: Vildagliptin (V) is a potent DPP-4 inhibitor in clinical development for the treatment of type 2 diabetes (T2D). The objective of this study was to investigate the effects of age, gender and body mass index (BMI) on the pharmacokinetics (PK) and DPP-4 activity.

METHODS: This was an open label, single dose study. Forty healthy subjects stratified by age, gender and BMI were enrolled and completed the study. All subjects received a single oral dose of 100 mg vildagliptin. Blood samples were collected for measuring the concentrations V and its major metabolite (LAY151) with LC-MS/MS, and DPP-4 activity with ELISA.

RESULTS: The mean C_{max} and exposure (AUC) of V were higher in elderly ($\geq$70 yr) as compared to the young subjects by 18% and 32%, respectively. The renal and apparent clearance in elderly were lower compared to young subjects by 22% and 31%, respectively. The mean C_{max} and AUC of LAY151 was higher in elderly as compared to young subjects by 62% and 80%, respectively. Gender and BMI ($\leq$25 kg/m^2 and $\geq$29 kg/m^2) did not affect the PK of V and LAY151. DPP-4 activity was significantly inhibited (>90%) in all subjects within 0.5 hours after V administration. The extent and duration of DPP-4 inhibition (>90% for ~12 hours) was not altered by age, gender, or BMI.

CONCLUSIONS: Gender and BMI did not affect the PK of V or DPP-4 inhibition. Changes in the exposure to V (Cmax and AUC) in the elderly did not affect the DPP-4 inhibition, therefore, no dose adjustment of V is necessary in the elderly.

PIII-20

EFFECT OF A NOVEL ACID ANTAGONIST, REVAPRAZAN, ON THE ENDOCRINE FUNCTION IN HEALTHY MALE VOLUNTEERS. E. Kim, MD, J. Shon, MD, J. Ryu, MD, Y. Sunwoo, MD, J. Jang, PhD, K. Song, DVM, B. Moon, DVM, PhD, S. Joo, J. Shin, MD, PhD, Department of Pharmacology and Clinical Trial Cntr Busanpaik Hosp. Inje Univ. Coll of Med, Clinical Trial Cntr Busanpaik Hosp. Inje Univ. Coll of Med, Yuhan Cor. Korea, Busan, Republic of Korea.

AIMS AND METHOD: To evaluate the effect of revaprazan, novel gastric acid antagonist, on human endocrine functions, in randomized, double-blind, crossover design, 200mg revaprazan or placebo were given orally to 13 male volunteers for 1 week with 2-weeks washout. On the days before and after each treatment course, serum concentrations of tri-iodothyronine (T_3), thyroxine (T_4), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) were measured, followed by TSH and LH response tests to thyrotropin releasing hormone (TRH) and luteinizing hormone releasing hormone (LHRH).

RESULTS: There were no differences in basal values for any hormone between placebo and revaprazan phases. For T_3, T_4, TSH, FSH, and LH, the geometric mean ratios (90% confidence interval) for placebo vs revaprazan were 1.04(0.996, 1.081), 1.00(0.947, 1.044), 1.27(0.973, 1.570), 0.92(0.833, 1.009), and 0.97(0.867, 1.075), respectively. The patterns of TSH-LH response to TRH-LHRH were not different between treatments ($p>0.05$, repeated-measures ANOVA).

CONCLUSION: Revaprazan in clinical practice seems not to cause any significant interference in thyroid and gonadal function.