PI-23

PROOF-OF-CONCEPT STUDY OF ICATIBANT (JE 049), A BRADYKININ B2 RECEPTOR ANTAGONIST IN TREATMENT OF HEREDITARY ANGIOEDEMA. B. Rosenkranz, MD, K. Bork, J. Frank, W. Kreuz, L. Dong, J. Knolle, JERINI AG, University Hospital Mainz, University Hospital Aachen, University Hospital Frankfurt/M, Berlin, Germany.

BACKGROUND/AIMS: Bradykinin (BK) is considered to be a key mediator in acute attacks of hereditary angioedema (HAE) due to C1 inhibitor (C1-INH) deficiency. During acute HAE attacks, increased BK plasma levels are detectable. The highly specific BK B2 receptor antagonist Icatibant leads to reduction of fluid extravasation in C1-INH knockout mice. The efficacy and safety of Icatibant in the treatment of acute HAE attacks have been assessed in this study.

METHODS: In the open-label study 20 acute HAE attacks (10 cutaneous, 3 abdominal, 7 combined) in 15 hospitalized patients were treated with Icatibant as follows (n=4 each group): a) 0.4mg/kg body weight (BW) over 2hr i.v.; b) 0.4mg/kg BW over 0.5hr i.v.; c) 0.8mg/kg BW over 0.5hr i.v.; d) 30mg s.c.; and e) 45mg s.c. Evaluation was performed by questionnaires and visual analogue scales. Treatment efficacy was compared to similar, untreated attacks reported previously by the same patients.

RESULTS: Treatment with Icatibant shortened the time to onset of symptom resolution (median time between treatment start and symptom resolution as reported by the patient: 1.5, 1.4, 1.1, 0.5, and 0.6hr respectively, untreated: 48 and 24hr for groups 1 and 2). Upon treatment, duration of the attacks was considerably shorter than that of previous attacks. Icatibant was well tolerated.

CONCLUSIONS: Icatibant has shown to alleviate symptoms of acute cutaneous, abdominal or combined attacks of HAE, thus confirming the key role of BK in this disease.

PI-24

EFFECT OF EXENATIDE ON LISINOPRIL PHARMACODYNAMICS IN PATIENTS TREATED FOR HYPERTENSION. P. Kothare, PhD, H. Linnebjerg, PhD, M. Atkins, PhD, K. Mace, PhD, M. Mitchell, MD, Eli Lilly and Company, Indianapolis, IN.

BACKGROUND/AIMS: Exenatide's antihyperglycemic actions under investigation include slowing gastric emptying, which may affect absorption of co-administered oral drugs. This study evaluated that potential effect with lisinopril, an ACE inhibitor.

METHODS: This double-blind, placebo (PBO)-controlled, crossover study had 19 subjects (11M/8F; 59±6 y; 81.0±14.8 kg; mean±SD) without diabetes, treated with lisinopril for hypertension (5 to 20 mg, 5 min post breakfast, ≥30 d), randomized to subcutaneous doses of exenatide (10 μg) or PBO, 15 min before breakfast and dinner on 1 d separated by ≥2-d washout period. Ambulatory blood pressure (BP) and lisinopril pharmacokinetics were measured for 24-h post dose. The predefined 95% CI limit for no clinically relevant difference in diastolic BP was 8 mmHg.

RESULTS: 24-h diastolic and systolic BP means were not significantly different between exenatide and PBO administered with lisinopril. LSmean (95% CI) for 24-h differences between treatments were 1.38 mmHg (−1.41, 4.17) for diastolic and 1.38 mmHg (−1.95, 4.71) for systolic BP. Exenatide did not alter steady-state lisinopril C_{max} and AUC_{τ} but increased lisinopril T_{max} by 2 h. Mild-to-moderate gastrointestinal disorders were more frequent with exenatide, and no hypoglycemia or hypotension occurred.

CONCLUSIONS: Exenatide was generally well tolerated and did not significantly affect the BP response to lisinopril suggesting exenatide may be co-administered without adjusting lisinopril dosage.

PI-25

LACK OF PHARMACOKINETIC INTERACTION BETWEEN MURAGLITAZAR, A NOVEL DUAL PPAR α/γ AGONIST, AND FENOFIBRATE. R. Mosqueda-Garcia, MD, PhD, D. Reitberg, C. Munsick, R. Darbenzio, S. Nepal, R. Reeves, A. Swaminathan, Bristol-Myers Squibb, Princeton, NJ.

BACKGROUND: Muraglitazar (MURA) is a novel PPAR α/γ dual agonist (nonthiazolidinedione) that reduces glucose and lipid levels in patients with type 2 diabetes. Fenofibrate (FF) is a lipid-lowering agent likely to be co-administered with MURA in diabetic patients. We assessed the potential for pharmacokinetic (PK) interaction between MURA and FF.

METHODS: In an open-label, 3-period, 3-treatment, crossover study, 30 healthy subjects were randomized to sequences that included 7 days administration of MURA (10mg QD), FF (160mg QD), or MURA+FF (10mg/d+160mg/d). Steady state plasma concentrations versus time were used to derive MURA and FF PK profiles.

RESULTS: Administration of MURA with FF was well tolerated with no serious adverse experiences. FF did not affect the PK of MURA: the geometric mean (%CV) Cmax for MURA was 1122 (24), and for MURA+FF, 1202(23) ng/mL. The geometric mean (%CV) AUC(TAU) for MURA was 6994 (25), and for MURA+FF, 7900 (25) ng·h/mL. MURA had no effect on the PK of FF: the geometric mean (%CV) Cmax for FF was 15112 (25), and for FF+MURA, 15418 (26) ng/mL. The geometric mean (%CV) AUC-(TAU) for FF was 235115 (34), and for FF+MURA, 238147 (32) ng·h/mL.

CONCLUSION: There was no PK interaction between FF and MURA based on Cmax and AUC (TAU) under the conditions of this study.

PI-26

EFFECT OF FLUVOXAMINE, PAROXETINE AND KETOCONAZOLE ON THE MULTIPLE DOSE PHARMACOKINETICS OF CILANSETRON IN HEALTHY MALE AND FEMALE VOLUNTEERS. M. deBruijn, PhD, P. Boon, PhD, T. L. ZumBrunnen, PharmD, M. deVries, PhD, PharmD, Solvay Pharmaceuticals, Weesp, The Netherlands.

BACKGROUND/AIMS: To investigate the effects of a CYP1A2 inhibitor (fluvoxamine, FLV), a CYP2D6 inhibitor (paroxetine, PAR), and a CYP3A4 inhibitor (ketoconazole, KET) on the multiple dose pharmacokinetics (PK) of cilansetron(CIL).

METHODS:

DESIGN: Open-label, randomized, parallel-group.

SETTING: This study was conducted in a phase I clinic.

PARTICIPANTS: Three groups of healthy male and female subjects.

INTERVENTION: Each subject received a single oral dose of 2 mg CIL on day 1 followed by CIL 2 mg TID on days 2 to 13 and a single 2 mg CIL dose on day 14. Inhibitors were co-administered on days 8 to 14 (FLV,PAR) and days 12 to 14 (KET), respectively. PK parameters calculated from serial blood samples obtained on Days 7 and 14 were compared using an ANOVA.

RESULTS: Geometric mean and range were as follows:

	Day 7	Day 14		
Parameter	CIL	CIL + FLV (N = 11)	CIL + PAR (N = 12)	CIL + KET (N = 11)
AUC_{0-8} (ng*hr/mL)	21.6 (8.8–52.2)	120.1 (77.5–215.2)	26.2 (12.0–44.7)	27.3 (15.0–60.1)
Cmax (ng/mL)	6.8 (2.5–18.1)	21.7 (15.3–36.0)	9.4 (3.9–14.7)	9.9 (5.3–22.1)
Tmax (h)	1.5 (0.5–4.0)	3.0 (1.75–4.0)	1.5 (0.75–3.0)	1.25 (0.75–2.0)

CONCLUSION: Substantial increases in Cmax, AUC and Tmax of CIL were observed after co-administration with FLV. Small increases in CIL PKs were seen after co-administration of PAR and KET. This data suggests that CIL is partially metabolized by CYP1A2 and that CYP2D6 and CYP3A4 provide a minor contribution to the metabolism of CIL.