PI-142

EVALUATION OF THE EFFECT OF LASOFOXIFENE (LASO) ON THE PHARMACOKINETICS (PK) OF DIGOXIN. D. Roman, MD, C. Bramson, MD, D. Ouellet, PhD, E. Randinitis, PhD, M. J. Gardner, PhD, Pfizer, Inc, Ann Arbor, MI.

BACKGROUND: LASO, a next-generation selective estrogen receptor modulator, is in late stage development for the prevention and treatment of osteoporosis. LASO has a long half-life (6 days) and less than 2% of the dose is recovered unchanged in urine. Both oxidative and conjugative metabolism contribute to its elimination. Digoxin is commonly prescribed for arrhythmias and congestive heart failure, has a narrow therapeutic index and may be coadministered with LASO.

OBJECTIVES: To determine the effect of LASO on the steady-state PK of digoxin.

METHODS: This was a 2-period, fixed-sequence study in 12 healthy postmenopausal women. During days 1–20, all subjects received digoxin (0.25 mg/day). On day 11, all subjects received 4 mg loading dose of LASO followed by 0.5 mg/day on days 12–20. On Days 10 and 20, blood and urine samples were collected for up to 24 hours for determination of digoxin concentrations. The 90% CI of least squares mean ratio for Cmax and AUC was calculated.

RESULTS: LASO had no effect on digoxin plasma PK with ratio (90% CI) of 95.4% (84.6% to 107%) and 103% (97.7% to 108%) for Cmax and AUC0-24, respectively. Results were within the 80% to 125% acceptance range. However, the ratio of Ae% was 127% (116% to 142%).

CONCLUSIONS: Coadministration of LASO had no effect on the steady-state pharmacokinetics of digoxin.

PI-143

A PILOT STUDY TO ASSESS SIMULTANEOUS ADMINISTRATION OF ORAL MIDAZOLAM (MDZ) AND FEXOFENADINE (FEX) FOR THE EVALUATION OF CYTOCHROME (CYP) 3A4 AND P-GLYCOPROTEIN (P-GP) ACTIVITIES. M. Garrett, BS, J. Smeraglia, MS, X. Lin, PhD, L. Tan, MD, J. Tran, PharmD, Pfizer Global R & D, Singapore General Hospital, San Diego, CA.

BACKGROUND: Many drug interactions may involve both CYP3A4 and P-gp. Such interactions reflect overlapping substrate specificities and modulators between CYP3A4 and P-gp. MDZ and FEX are ideal in vivo probe substrates for the assessment of CYP3A4 and P-gp mediated interactions, respectively. It is desirable to evaluate the effect of an investigational drug on CYP3A4 and P-gp activities by administering these 2 probe substrates simultaneously. This pilot study was conducted to evaluate the potential interaction between these two probe substrates.

METHOD: Fifteen healthy subjects were randomized to receive the following single-dose regimens separated by a 7-day washout: A) oral MDZ 7.5 mg; B) FEX 120 mg; and C) oral MDZ 7.5 mg + FEX 120 mg. Blood samples were collected for pharmacokinetic (PK) assessments. PK parameters were estimated by standard non-compartmental methods using WinNonlin. Statistical analyses were performed using ANOVA with $\alpha = 0.05$.

RESULTS: No significant differences in drug exposure were observed when MDZ or FEX was given alone and in combination. Preliminary results are shown below.

	AUC_∞ (h · ng/mL) Mean ± SD		
Probe	**Alone**	**Combination**	**P-value**
MDZ	110 ± 33	118 ± 34	0.156
FEX	2020 ± 576	1870 ± 930	0.510

CONCLUSION: Results from this pilot study suggest no significant interaction between oral MDZ and FEX.

PI-144

PHARMACOKINETICS (PK) OF MULTIPLE ORAL DOSES OF DESLORATADINE (DCL) AND FEXOFENADINE (FEX) IN A POPULATION OF HEALTHY ADULTS IDENTIFIED PHENOTYPICALLY AS DESLORATADINE SLOW METABOLIZERS (DSMS). W. Kraft, MD, R. A. Blum, G. S. Frick, C. Vitow, J. A. Stewart, S. J. Kovacs, Thomas Jefferson University, Buffalo Clinical Research Center, CliniQuill Associates, Aventis Pharmaceuticals, Philadelphia, PA.

PURPOSE: To characterize the PK of DCL and FEX in adults identified as DSMs.

METHODS: This was a randomized, double blind, crossover study with a 21-day washout between treatments. DSM subjects received DCL 5 mg or FEX HCl 180 mg QD for 7 days during each treatment period. Serial blood sampling was performed on days 1 and 7, trough samples were collected on Days 5 and 6 and samples were collected 48, 72, 96, 120, and 144 hrs after the Day 7 dose. Plasma was assayed for DCL, 3-OH-DCL, and FEX by LC/MS/MS.

RESULTS: 18 subjects (15 M, 3 F) with a mean (SD) age of 32.2 (±7.33) years and BMI of 27.0 (±3.7) kg/m^2 were enrolled. Exposure to DCL increased 5-fold on Day 7. Relatively low concentrations of 3-OH-DCL were quantifiable more often on Day 7 than Day 1. The disposition of FEX was consistent with previous reports in subjects and patients, with no significant accumulation after 7 days of dosing. Mean (SD) half-lives of 112±56.2 and 17.2±7.3 hrs were estimated for DCL and FEX, respectively, compared with 27 hrs reported for DCL normal metabolizers.

CONCLUSIONS: In DSMs substantial accumulation of DCL was observed; however, steady-state was not reached by Day 7, which suggests continued accumulation with treatment beyond 7 days. There was no apparent alteration of FEX PK in DSMs. The safety of prolonged increased DCL exposure in a variety of clinical settings has not been established. The metabolic pathway responsible for the DSM phenotype remains unknown.

	DCL Day 1	**DCL Day 7**	**FEX Day 1**	**FEX Day 7**
$AUC_{(0-24)}$ (ng · hr/mL) Mean ± SD	40.29 ± 12.62	196.80 ± 53.76	2096 ± 1002	2357 ± 909
C_{max} (ng/mL) Mean ± SD	2.48 ± 0.95	9.84 ± 2.67	367 ± 222	384 ± 180
T_{max} (hrs) Median (Min, Max)	7 (2.5, 12)	7 (6, 12)	2.5 (1, 6)	1.5 (1, 6)
C_{24h} (ng/mL) Mean ± SD	1.62 ± 0.48	7.57 ± 2.26	11.0 ± 3.1	18.4 ± 8.5