PI-114

THE CONTRACEPTIVE VAGINAL RING, NUVARING, SHOWS NO INTERACTION WITH BROAD SPECTRUM ORAL ANTIBIOTICS. P. Dogterom, PhD, M. van den Heuvel, MSc, T. Thomsen, MD, NV Organon, Pharm PlanNet Contract Research GmbH, Oss, Netherlands.

Two studies were performed to investigate whether ethinylestradiol (EE) and etonogestrel (ENG) released from NuvaRing (NR) are affected by concomitant treatment with the antibiotics amoxicillin (A) and doxycycline (D).

Sixteen healthy women per study (age: 18 to 40 yrs.) were randomised to 21 days of treatment with NuvaRing, either alone (control) or concomitantly with amoxicillin (875 mg twice daily for 10 days, study I) or doxycycline (100 mg once daily for 10 days, study II). After a 7-days washout they were crossed over to the alternate treatment. Based on serum EE and ENG levels, area under the curve (AUC) values over 12 hours (amoxicillin) or 24 hours (doxycycline) on days 1 and 10 and for the whole of days 1-11 and days 1-22 were calculated and tested for interactions based on FDA guidance.

Geometric mean results of the various AUCs ($ng.h.mL^{-1}$) are presented in the following table.

study I		AUC_{day1}	AUC_{day10}	$AUC_{day1-11}$	$AUC_{day1-22}$
EE	NR	0.32	0.25	5.58	11.1
	NR + A	0.32	0.24	5.30	10.9
ENG	NR	11.1	24.4	427	950
	NR + A	10.2	24.9	427	959
study II		AUC_{day1}	AUC_{day10}	$AUC_{day1-11}$	$AUC_{day1-22}$
EE	NR	0.61	0.51	5.28	10.8
	NR + D	0.58	0.48	5.02	10.3
ENG	NR	19.9	42.7	363	811
	NR + D	21.0	43.1	371	827

Calculation of EE and ENG interaction/control ratios plus 90% confidence intervals confirmed the absence of PK interactions for both antibiotics. In both studies, NuvaRing with or without concomitant antibiotic therapy was well tolerated. These studies show an absence of PK interactions between NuvaRing and concomitant broad-spectrum antibiotics and indicate that NuvaRing is a reliable contraceptive option even in situations where users may require antibiotic treatment.

PI-115

AN OPEN-LABEL STUDY ON THE PHARMACOKINETICS (PK) OF PITAVASTATIN (NK-104) WHEN ADMINISTERED CONCOMITANTLY WITH FENOFIBRATE OR GEMFIBROZIL IN HEALTHY VOLUNTEERS. P. Mathew, T. Cuddy, MS, W. G. Tracewell, PhD, D. Salazar, PhD, MDS Pharma Services, Sankyo Pharma Development, Neptune, NJ.

The objective of this study was to compare the steady state (SS) PK of Pitavastatin (NK-104) before and after coadministration with either fenofibrate or gemfibrozil as interactive agents for 7 days. In this single-center, open-label, one-sequence, crossover study, 24 healthy subjects aged 18 to 45 years who met qualifying criteria were enrolled. PK of NK-104 and its lactone at SS were assessed after administration of NK-104 (4mg QD) for Days 1 through 6 and after coadministration with either fenofibrate (160mg QD) or gemfibrozil (600mg BID) on Days 8 through 14. Differences in log transformed PK parameters between the two treatments were estimated using ANOVA and their associated 90% confidence intervals (CI) were inversely transformed to obtain the ratios. No drug-drug interaction was claimed if the 90% CI fell entirely within the range of 80%-125%. Fenofibrate coadministration showed equivalence in the $Cmax_{SS}$ of NK-104, NK-104 lactone and $AUC(0\text{-}24)_{SS}$ of NK-104 lactone and increased the NK-104 $AUC(0\text{-}24)_{SS}$ by 18%. Gemfibrozil coadministration increased the $Cmax_{SS}$ of NK-104 by 31%, $AUC(0\text{-}24)_{SS}$ by 45% and decreased the $Cmax_{SS}$ of NK-104 lactone by 28% and $AUC(0\text{-}24)_{SS}$ by 15%. Both fenofibrate and gemfibrozil were observed to lower the amount of NK-104 lactone excreted in urine and NK-104 lactone renal clearance. The coadministration of either fenofibrate or gemfibrozil with NK-104 for 7 days was found to be safe, well tolerated and without clinically significant PK interactions.

PI-116

PHARMACOKINETIC (PK) INTERACTION STUDY OF SIROLIMUS (SRL) AND CYCLOSPORINE (CSA). A. Patat, MD, J. J. Zimmerman, PhD, V. Parks, BSc, J. Richards, MD, Wyeth Research, DDS, Paris La Defense, France.

SRL (Rapamune®) is an effective immunosuppressant currently marketed worldwide for the prophylaxis of renal allograft rejection. The interaction between SRL 5 mg (oral solution) and CsA 300 mg (Neoral® capsules) when administered simultaneously and 2 hours apart was assessed in a randomized, open-label, 5-period crossover study in 33 healthy male subjects (age 19-43 years, weight 58-89 kg). The subjects received a single oral dose of SRL alone (A), CsA alone (B), SRL and CsA together (C), SRL 2 hours after CsA (D), or SRL 2 hours before CsA (E). Whole blood SRL was assayed by HPLC with mass spectrometric detection (HPLC/MS/MS), and whole blood CsA by immunoassay. Geometric least-squares (GLS) mean ratios and 90% confidence intervals (CIs) were computed for treatment comparisons. Reference treatments for equivalence tests were either A (SRL alone) or B (CsA alone). A GLS mean ratio between 80% to 125% showed equivalence.

CsA significantly increased SRL Cmax and AUC during simultaneous administration (by 117% and 183%, respectively) and when SRL was administrated 2 hours after CsA (by 126% and 141%, respectively). CsA did not affect SRL PK when SRL was administrated 2 hours before CsA. SRL did not affect the PK of CsA, regardless of the timing of administration.

GLS mean ratios (90% CI)* for whole blood SRL and CsA PK parameters

	SRL			**CsA**		
	C vs A	D vs A	E vs A	C vs B	D vs B	E vs B
Cmax	217 (196-241)	226 (204-251)	98 (88-109)	105 (96-115)	97 (89-116)	93 (86-102)
AUC	283 (257-311)	241 (219-265)	99 (90-109)	105 (100-110)	101 (96-106)	94 (89-99)
t1/2	87 (82-91)	87 (83-92)	97 (92-103)	95 (90-100)	104 (99-109)	99 (94-104)

*Equivalence Window = 80% to 125%.

In conclusion, CsA significantly increased SRL whole blood exposure when SRL and CsA were administered simultaneously and when SRL was given 2 hours after CsA. However, no significant PK interaction was observed when SRL was administered 2 hours before CsA.