SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: Norgestimate/Ethinyl Estradiol/Folic Acid NAME OF ACTIVE INGREDIENT(S): Norgestimate/Ethinyl Estradiol	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: NRGMON-CON-1003 CR002200 **Title of Study:** A Pivotal Bioequivalence Study of 250 µg Norgestimate/35 µg Ethinyl Estradiol With or Without Folic Acid in Healthy Female Subjects		
Principal Investigator: Dennis Morison, D.O. - Bio-Kinetic Clinical Applications, Inc., Springfield, MO; USA		
Publication (Reference): None		
Studied Period (years): Clinical Conduct: 9 May to 19 August 2005 Sample Analysis: 1 August to 30 September 2005		**Phase of development:** 1
Objectives: The primary objective of this study was to determine the bioequivalence of norgestimate (NGM) as measured by the pharmacokinetics of the active metabolite norelgestromin (NGMN) and ethinyl estradiol (EE) in 2 formulations of 250 µg NGM/35 µg EE, 1 without folic acid and 1 containing 400 µg folic acid. The secondary objective of this study was to determine the bioequivalence of NGM as measured by the pharmacokinetics of the active metabolite NG in these 2 formulations and to characterize the pharmacokinetics of plasma folate from the formulation of 250 µg NGM/35 µg EE containing 400 µg folic acid and from 400 µg folic acid administered alone. Safety also was assessed.		
Methodology: This was a single-center, open-label, randomized, 3-way crossover bioequivalence study of a single dose of 250 µg NGM/35 µg EE with or without folic acid. The study consisted of a pretreatment phase (a screening period lasting up to 21 days), an open-label treatment phase (consisting of 3 periods during which a single dose of study drug was administered followed by up to 72 hours of serial blood sample collections for pharmacokinetic analysis), and a posttreatment phase (consisting of safety evaluations at the completion of the third open-label treatment period or at early withdrawal). All subjects received the following treatments (1 during each period): Treatment A: 250 µg NGM/35 µg EE; Treatment B: 250 µg NGM/35 µg EE plus folic acid 400 µg (combined formulation); Treatment C: folic acid 400 µg. Subjects were randomly assigned to 1 of 6 treatment sequence groups (ABC, ACB, BAC, BCA, CAB, or CBA) on Day 1 of the first open-label treatment period. Subjects received a single dose of study drug on Day 1 in each period according to their assigned treatment sequence. There was a washout period between treatments of at least 4 weeks. Subjects were confined to the study unit from the evening before dosing (Day –1) until after vital signs were measured following collection of the 24-hour (Treatment C) or 48-hour (Treatments A or B) postdose blood sample. Serial blood samples were collected at specified times for 24 hours after dosing for the determination of plasma concentrations of folate and for 72 hours after dosing for the determination of serum concentrations of NGMN, NG, and EE. The total duration of the study, not including the pretreatment phase, was approximately 9 weeks.		
Number of Subjects (planned and analyzed): The planned total sample size was 54 subjects to ensure the completion of 43 subjects. Fifty-three subjects were enrolled; 53 were analyzed for safety, and 50 were analyzed for pharmacokinetics.		
Diagnosis and Main Criteria for Inclusion: Healthy, nonpregnant, nonlactating, nonsmoking women, aged 18 to 45 years, weighing at least 110 pounds, with regular menstrual cycles, a body mass index between 16 and 29.9 kg/m^2, and a hematocrit of at least 36% were enrolled in the study.		
Test Product, Dose and Mode of Administration, Batch No.: Treatment A (250 µg NGM/35 µg EE) was administered as a single tablet corresponding to Days 15 to 21 in the commercial dialpak of ORTHO-CYCLEN® (lot number: R13260, expiration date: October 2006); Treatment B (250 µg NGM/35 µg EE plus 400 µg of folic acid) was administered as a single tablet (lot number: R13258, expiration date: January 2006); and Treatment C (400 µg of folic acid) was administered as single United States Pharmacopoeia (USP) tablet (lot number: R13259, expiration date: January 2006)		
Reference Therapy, Dose and Mode of Administration, Batch No.: None		
Duration of Treatment: A single dose on the first day of each of 3 treatment periods with a 28-day washout between doses (approximately 9 weeks)		

SYNOPSIS (CONTINUED)

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Criteria for Evaluation:

Pharmacokinetics: The following pharmacokinetic parameters were estimated by non-compartmental methods for serum NGMN, NG, and EE and plasma folate for each subject: C_{max}, t_{max}, AUC_{12} (folate only), AUC_{24} (NGMN, NG, and EE only), AUC_{72} (NGMN, NG, and EE only), AUC_{last}, AUC_{last*} (folate only), AUC_{∞} (NGMN and EE only), λ_z, and $t_{½}$. The pharmacokinetic parameters of contraceptive steroids (NGMN, NG, EE) were determined to evaluate the bioequivalence of the formulation of 250 µg NGM/35 µg EE containing folic acid 400 µg (Treatment B) to the one not containing folic acid (Treatment A). Additionally, folate pharmacokinetic parameters obtained from baseline corrected and uncorrected folate concentration-time data, with and without coadministration of 250 µg NGM/35 µg EE were determined. For each subject, the mean of the 2 predose baseline values collected for plasma folate concentrations was used to determine baseline folate levels.

Safety: Safety was assessed through the monitoring of adverse events, vital sign and electrocardiogram (ECG) measurements, physical and gynecological (including breast) examinations, and clinical laboratory tests (hematology, chemistry, and urinalysis). Pregnancy tests were done at screening, before each dose, and at poststudy to establish continued eligibility.

Statistical Methods:

Pharmacokinetics: To determine the bioequivalence of the formulation of 250 µg NGM/35 µg EE containing folic acid 400 µg (Treatment B) to the one not containing folic acid (Treatment A), the analysis was performed on log-transformed estimated pharmacokinetic parameters (AUC_{last}, $AUC\infty$, and C_{max}) of NGMN, NG, and EE obtained from Treatments B and A. The analysis was done for each analyte separately. Only the data from subjects who completed Treatments A and B were included in the statistical analysis of NGMN, NG, and EE. Mixed-effects models were fit to the data with one of the estimated pharmacokinetic parameters of interest as the dependent variable; treatment sequence group, period, and treatment as fixed effects; and subject as a random effect. Testing for the treatment sequence group and period effects was carried out at the 10% and 5% levels of significance, respectively, using the appropriate error terms. The estimated least square means and intrasubject variability from the mixed-effects model were used to construct 90% confidence intervals for the difference in means on the log scale between the 2 treatments. The limits of the confidence intervals were retransformed using antilogarithms to obtain 90% confidence intervals for the ratio of the mean pharmacokinetic parameters for Treatment B to A. The 2 treatments were to have been considered bioequivalent if the 90% confidence intervals for the ratio of the means fell within 80% to 125%.

To characterize the pharmacokinetics of plasma folate from Treatments B and C (folic acid 400 µg), a similar analysis was performed on log transformed estimated pharmacokinetic parameters (AUC_{last} and C_{max}). Only the data from subjects who completed Treatments B and C were included in the statistical analysis of folate. Mixed-effects models were fit to the data with one of the estimated pharmacokinetic parameters of interest as the dependent variable; treatment sequence group, period, and treatment as fixed effects; and subject as a random effect. Testing for the treatment sequence group and period effects was carried out at the 10% and 5% levels of significance, respectively, using the appropriate error terms. The estimated least square means and intrasubject variability from the mixed-effects model was used to construct 90% confidence intervals for the difference in means on the log scale between the 2 treatments. The limits of the confidence intervals were retransformed using antilogarithms to obtain 90% confidence intervals for the ratio of the mean pharmacokinetic parameters of plasma folate for Treatment B to C. Standard bioequivalence criteria were not necessary for plasma folate.

Safety: Safety evaluations were based upon the type, incidence, and severity of treatment-emergent adverse events reported throughout the study, and on prestudy to poststudy changes in vital sign measurements, clinical laboratory test results, ECGs, and physical and gynecological (including breast) examinations.

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SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS: Arithmetic mean (SD) of serum pharmacokinetic parameters of NGMN, EE, and NG following a single oral dose of 250 µg NGM/35 µg EE (ORTHO-CYCLEN) or a single oral dose of 250 µg NGM/35 µg EE plus folic acid 400 µg (combined formulation) are summarized below:

	NGMN		NG		EE*	
Parameter	250 µg NGM/35 µg EE (ORTHO-CYCLEN) (N=50)	250 µg NGM/35 µg EE Plus Folic Acid 400 µg (N=48)	250 µg NGM/35 µg EE (ORTHO-CYCLEN) (N=49)	250 µg NGM/35 µg EE Plus Folic Acid 400 µg (N=47)	250 µg NGM/35 µg EE (ORTHO-CYCLEN) (N=50)	250 µg NGM/35 µg EE Plus Folic Acid 400 µg (N=48)
C_{max} (ng/mL)	1.44 (0.408)	1.29 (0.407)	0.370 (0.142)	0.378 (0.160)	84.2 (31.0)	87.3 (35.6)
t_{max}[a] (h)	1.50 (1.00-2.00)	2.00 (1.00-5.00)	2.00 (1.00-3.00)	2.00 (1.50-5.00)	1.50 (1.00-3.00)	1.50 (1.00-3.00)
AUC_{24} (ng.h/mL)	9.13 (2.53)	8.56 (2.39)	5.20 (1.47)[d]	5.07 (1.85)[g]	593 (213)	615 (253)[b]
AUC_{72} (ng.h/mL)	14.2 (3.67)[b]	13.6 (3.64)[c]	14.1 (4.50)[e]	15.4 (5.95)[h]	1201 (367)[k]	1326 (588)[m]
AUC_{last} (ng.h/mL)	13.9 (3.83)	13.3 (3.78)	7.03 (5.57)	7.33 (6.05)[i]	722 (302)	747 (369)
AUC_{∞} (ng.h/mL)	16.3 (4.24)	15.7 (4.50)	NAs	NAs	799 (327)[l]	815 (396)
$t_{1/2}$ (h)	28.4 (7.8)	28.7 (7.4)	56.9 (32.9)[f]	36.9 (24.7)[j]	14.7 (4.0)[l]	14.2 (4.0)

* Units for EE are in pg

[a] Median (range); [b] N=47; [c] N=46; [d] n=33; [e] n=12; [f] n=19; [g] n=31; [h] n=11; [i] n=45; [j] n=15; [k] n=7; [l] n=49; [m] n=6

NAs=not accessible

Mean AUC_{last} and AUC_{∞} of NGMN and EE and mean C_{max} for EE were similar between single oral doses of ORTHO-CYCLEN and 250 µg NGM/35 µg EE plus folic acid. Mean C_{max} of NGMN for 250 µg NGM/35 µg EE plus folic acid was approximately 10% lower compared to ORTHO-CYCLEN alone. Mean $t_{1/2}$ of NGMN was 28.4 hours and 28.7 hours for subjects dosed with ORTHO-CYCLEN and 250 µg NGM/35 µg EE plus folic acid 400 µg, respectively. Mean EE terminal half-life ($t_{1/2}$) was also similar between the 2 formulations (14.7 hours for ORTHO-CYCLEN and 14.2 hours for 250 µg NGM/35 µg EE plus folic acid). The differences for other exposure parameters such as AUC_{24} and AUC_{72} between the 2 treatments for both NGMN and EE were approximately 10% or less.

Mean C_{max} and AUC_{last} of NG, were similar between single oral doses of ORTHO-CYCLEN and 250 µg NGM/35 µg EE plus folic acid 400 µg. AUC_{∞} for NG could not be determined because the terminal log-linear phase could not be reliably characterized within the sampling period in majority of the subjects. The estimated mean terminal half-life of NG for ORTHO-CYCLEN was somewhat shorter compared to 250 µg NGM/35 µg EE plus folic acid 400 µg (56.9 versus 36.9 hours). The differences for other exposure parameters such as AUC_{24} and AUC_{72} between the 2 treatments were less than 10% for NG.

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The statistical results for determining the geometric means of test and reference and their associated 90% confidence intervals of the pharmacokinetic parameters of contraceptive steroids (NGMN, EE and EE) following a single dose of 250 µg NGM/35 µg EE plus folic acid 400 µg with reference to a single dose of ORTHO-CYCLEN are summarized below:

Analyte	Parameter	N	Intra-subject CV (%)	250 µg NGM/ 35 µg EE Plus Folic Acid 400 µg (Test)	ORTHO-CYCLEN (Reference)	Ratio (%) Test/Reference	90% CI for Ratio (%)
NGMN	AUC_{∞}	48	10.09	14.89	15.57	95.60	92.32– 98.99
	AUC_{last}	48	11.06	12.64	13.22	95.62	92.03– 99.35
	C_{max}	48	20.87	1.21	1.35	89.71	83.46– 96.42
NG	AUC_{last}	44	29.18	4.67	4.89	95.45	85.84 – 106.13
	C_{max}	46	20.58	0.34	0.34	99.57	92.60 – 107.06
EE	AUC_{∞}	47	11.19	748.09	725.67	103.09	99.13– 107.21
	AUC_{last}	48	12.85	674.24	659.82	102.18	97.74 – 106.83
	C_{max}	48	12.63	81.09	77.26	104.96	100.48 –109.65

The 90% confidence intervals for the ratio of geometric means of NGMN and EE pharmacokinetic parameters (C_{max}, AUC_{last}, and AUC_{∞}) following a single dose of 250 µg NGM/35µg EE plus folic acid 400 µg with reference to a single dose of ORTHO-CYCLEN were contained within the bioequivalence limits of 80% to 125%. The 90% confidence intervals for the ratio of geometric means of NG pharmacokinetic parameters (C_{max} and AUC_{last}) following a single dose of 250 µg NGM/35µg EE plus folic acid 400 µg with reference to a single dose of ORTHO-CYCLEN were contained within the bioequivalence limits of 80% to 125%. Based on the primary analytes, NGMN and EE in the 2 formulations of 250 µg NGM/35 µg EE, one without folic acid and one containing 400 µg folic acid, were bioequivalent.

Arithmetic mean (SD) of plasma folate pharmacokinetic parameters for observed and baseline corrected plasma folate concentrations following a single oral dose of folic acid 400 µg or a single oral dose of 250 µg NGM/35 µg EE plus folic acid 400 µg (combined formulation) are summarized below:

	Observed Data		Baseline Corrected Data	
Parameter	NGM 250 µg/ EE 35 µg Plus Folic Acid 400 µg (N=48)	Folic Acid 400 µg (N=50)	NGM 250 µg/ EE 35 µg Plus Folic Acid 400 µg (N=48)	Folic Acid 400 µg (N=50)
C_{max} (ng/mL)	23.3 (8.56)	24.5 (8.70)	13.6 (5.09)	14.0 (4.21)
t_{max} [a] (h)	2.00 (1.00-24.00)	2.50 (1.00-8.00)	2.00 (1.00-24.00)	2.50 (1.00-8.00)
AUC_{12} (ng.h/mL)	203 (78.0)	224 (86.9)	86.6 (35.2)	98.6 (36.1)
AUC_{last} (ng.h/mL)	378 (154)	409 (165)	145 (74.9)	157 (65.0)
AUC_{last*} [b] (ng.h/mL)	371 (153)	384 (170)	144 (75.3)	155 (68.3)
$t_{1/2}$ (h)	32.8 (14.7)[c]	39.4 (42.2)[d]	10.6 (5.7)[e]	12.1 (10.8)[f]

[a] Median (range)

[b] AUC of the interval: 0 to the time point at which the individual subject's subsequent folate concentration dropped below the baseline folate level for the first time.

[c] n=9; [d] n=13; [e] n=10; [f] n=15

For observed (uncorrected) and baseline corrected plasma folate data, mean C_{max}, AUC_{last}, and AUC_{last*} and AUC_{12} from uncorrected folate data were similar when folic acid was dosed with and without 250 µg NGM/35 µg EE. AUC_{12} obtained from baseline corrected plasma folate data decreased by approximately 12% when folic acid was administered with NGM 250 µg/ EE 35 µg compared to folic acid alone. Mean terminal half-life ($t_{1/2}$) of folates for both uncorrected and baseline corrected methods decreased by 17% and 12%, respectively, when folic acid was coadministered with 250 µg NGM/35 µg EE as compared to folic acid administered alone.

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The statistical results for determining the geometric means of test and reference and their associated 90% confidence intervals of the pharmacokinetic parameters of plasma folates following a single dose of 250 µg NGM/35 µg EE plus folic acid 400 µg with reference to a single dose of folic acid 400 µg are summarized below:

Folate	Parameter	N	Intra-subject CV (%)	250 µg NGM/ 35 µg EE Plus Folic Acid 400 µg (Test)	Folic Acid 400 µg (Reference)	Ratio (%) Test/ Reference	90% CI for Ratio (%)
Corrected for Baseline	AUC_{last}	48	37.08	127.91	140.41	91.09	80.14–103.54
	AUC_{last*}[a]	48	44.33	127.14	134.51	94.52	81.10–110.16
	C_{max}	48	23.43	12.51	13.05	95.82	88.37–103.90
Observed (uncorrected)	AUC_{12}	48	19.59	187.55	201.76	92.96	86.88–99.46
	AUC_{last}	48	20.46	345.88	366.77	94.30	87.87–101.21
	AUC_{last*}[a]	48	28.93	339.05	336.12	100.87	91.28–111.47
	C_{max}	48	19.62	21.54	22.28	96.67	90.34–103.45

[a] AUC of the interval: 0 to the time point at which the individual subject's subsequent folate concentration dropped below the baseline folate level for the first time.

All the 90% confidence intervals for the ratio of geometric means of folate pharmacokinetic parameters (obtained from baseline corrected as well as uncorrected or observed plasma folate data) following a single dose of 250 µg NGM/35µg EE plus folic acid 400 µg with reference to a single dose of folic acid 400 µg were contained within the bioequivalence range of 80% to 125%.

SAFETY RESULTS: In general, all 3 treatments administered during this study were safe and well tolerated. No deaths or serious adverse events occurred, and no subject discontinued treatment because of an adverse event. Headache, nausea, and vomiting were the most common adverse events, and there was a higher incidence of headache with Treatment A (250 µg NGM/35 µg EE) compared with Treatments B (250 µg NGM/35 µg EE/folic acid 400 µg) and C (folic acid 400 µg).

None of the clinical laboratory values that were outside the normal ranges at the final visit were more than twofold outside the ranges, and none was considered clinically significant. Similarly, changes in vital signs, ECGs, and physical examination results from screening to final visit were slight and not of clinical significance, with the exception of one subject who became pregnant during the study after receiving Treatment C.

CONCLUSION: The conclusion from this pivotal bioequivalence study with respect to the primary objective was that NGMN and EE in the 2 formulations of 250 µg NGM/35 µg EE, one without folic acid and one containing 400 µg folic acid, were bioequivalent. In general, plasma folate pharmacokinetics were similar between folic acid 400 µg alone and 250 µg NGM/35 µg EE plus folic acid 400 µg. Overall, both treatments administered during this study were safe and well tolerated. No deaths or serious adverse events occurred, and no one discontinued treatment because of an adverse event.

Date of the report: 08 June 2006

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