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-1002 CR002203

Title of Study: A Pivotal Bioequivalence Study of 250 µg Norgestimate/25 µg Ethinyl Estradiol With or Without Folic Acid in Healthy Female Subjects

Principal Investigator: William Garland, M.D. (from 9 May to 10 July 2005) and Dane Ship, M.D. (from 11 July to 16 August 2005) - Radiant Research, San Diego, CA; USA

Publication (Reference): None

Studied Period (years): Clinical Conduct: 9 May to 16 August 2005 Sample Analysis: 11 August and 21 October 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/25 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/25 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/25 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/25 µg EE; Treatment B: 250 µg NGM/25 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-four subjects were enrolled; 53 were analyzed for safety, and 48 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/25 µg EE) was administered as a single tablet corresponding to Days 15 to 21 in the commercial dialpak of ORTHO TRI-CYCLEN LO® (lot number: R13257, expiration date: May 2006); Treatment B (250 µg NGM/25 µg EE plus 400 µg of folic acid) was administered as a single tablet (lot number: R13255, expiration date: January 2006); and Treatment C (400 µg of folic acid) was administered as single United States Pharmacopoeia (USP) tablet (lot number: R13256, expiration date: January 2006)

Reference Therapy, Dose and Mode of Administration, Batch No.: None

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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)

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/25 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_{∞}, 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 and were not applied 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/25 µg EE (ORTHO TRI-CYCLEN LO) or a single oral dose of 250 µg NGM/25 µg EE plus folic acid 400 µg (combined formulation) are summarized below:

	NGMN		NG		EE*	
Parameter	250 µg NGM/25 µg EE (ORTHO TRI-CYCLEN LO) (N=45)	250 µg NGM/25 µg EE Plus Folic Acid 400 µg (N=45)	250 µg NGM/25 µg EE (ORTHO TRI-CYCLEN LO) (N=45)	250 µg NGM/25 µg EE Plus Folic Acid 400 µg (N=45)	250 µg NGM/25 µg EE (ORTHO TRI-CYCLEN LO) (N=44)	250 µg NGM/25 µg EE Plus Folic Acid 400 µg (N=45)
C_{max} (ng/mL)	1.39 (0.365)	1.41 (0.361)	0.473 (0.212)	0.451 (0.168)	70.3 (15.1)	71.4 (16.7)
t_{max}[a] (h)	1.50 (1.00-3.00)	1.50 (1.00-5.00)	2.00 (1.00-5.00)	2.00 (1.00-5.02)	1.50 (1.00-3.00)	1.50 (1.00-3.00)
AUC_{24} (ng.h/mL)	8.46 (1.94)[b]	8.78 (2.06)[b]	5.90 (2.50)[e]	5.67 (1.98)[h]	472 (94.3)	472 (109)
AUC_{72} (ng.h/mL)	12.9 (3.10)[c]	13.3 (3.21)[d]	16.0 (4.70)[f]	15.7 (4.76)[f]	941 (407)[j]	903 (170)[k]
AUC_{last} (ng.h/mL)	12.4 (3.53)	12.9 (3.61)	7.79 (6.37)	7.97 (5.94)[b]	641 (240)	592 (170)
AUC_{∞} (ng.h/mL)	14.3 (4.21)	14.9 (4.25)	NAs	NAs	711 (145)[i]	666 (187)[b]
$t_{1/2}$ (h)	26.4 (6.95)	26.8 (6.79)	36.3 (30.1)[g]	30.3 (25.9)[g]	20.5 (7.57)[i]	17.0 (4.63)[b]

[*] Units for EE are in pg
[a] Median (minimum-maximum)
[b] n=44 [c] n=40 [d] n=41 [e] n=32 [f] n=11 [g] n=13 [h] n=34 [i] n=43 [j] n=8 [k] n=4
NAs - not assessable

Mean C_{max}, AUC_{last}, and AUC_{∞} of NGMN and EE were similar between single oral doses of ORTHO TRI-CYCLEN LO and 250 µg NGM/25 µg EE plus folic acid. Mean terminal half-life estimates of NGMN was 26.4 hours and 26.8 hours for subjects dosed with ORTHO TRI-CYCLEN LO and 250 µg NGM/25 µg EE plus folic acid 400 µg, respectively. Mean $t_{1/2}$ estimates of EE decreased by approximately 17% in the presence of folic acid (20.5 hours versus 17.0 hours for ORTHO TRI-CYCLEN LO and 250 µg NGM/25 µg EE with folic acid, respectively). The differences for other exposure parameters, such as AUC_{24} and AUC_{72}, between the 2 treatments for both NGMN and EE were approximately less than 10%.

Mean C_{max} and AUC_{last} of NG were similar between single oral doses of ORTHO TRI-CYCLEN LO and 250 µg NGM/25 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. Mean terminal half-life of NG for ORTHO TRI-CYCLEN LO was approximately 17% higher compared to 250 µg NGM/25 µg EE with folic acid (36.3 hours versus 30.3 hours for ORTHO TRI-CYCLEN LO and 250 µg NGM/25 µg EE with folic acid, respectively). The differences for other exposure parameters such as AUC_{24} and AUC_{72} between the 2 treatments were less than 10% for NG.

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, NG, and EE) following a single dose of 250 µg NGM/25 µg EE plus folic acid 400 µg with reference to a single dose of ORTHO TRI-CYCLEN LO are summarized below:

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Analyte	Parameter	N	Intra-Subject CV (%)	250 µg NGM/25 µg EE Plus Folic Acid 400 µg (Test)	ORTHO TRI-CYCLEN LO (Reference)	Ratio (%) Test/ Reference	90% CI for Ratio (%)
NGMN	AUC_{∞}	44	9.81	13.91	13.40	103.80	100.15 - 107.58
	AUC_{last}	44	9.64	12.14	11.65	104.22	100.61 - 107.95
	C_{max}	44	18.07	1.37	1.33	103.12	96.61 - 110.07
NG	AUC_{last}	43	29.56	5.86	5.12	114.41	102.60 - 127.59
	C_{max}	44	18.94	0.43	0.43	100.84	94.24 - 107.90
EE	AUC_{∞}	41	16.66	658.75	702.00	93.84	88.17 - 99.88
	AUC_{last}	43	20.49	579.28	618.08	93.72	86.96 - 101.01
	C_{max}	43	14.02	70.63	69.21	102.05	97.00 - 107.37

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/25 µg EE plus folic acid 400 µg with reference to a single dose of ORTHO TRI-CYCLEN LO were contained within the bioequivalence limits of 80% to 125%. The 90% confidence intervals for the ratio of means for C_{max} of NG were contained within the bioequivalence range of 80% to 125%. However, the 90% confidence intervals for the ratio of means for AUC_{last} of NG were not contained within the bioequivalence limits of 80% to 125%; a slightly higher AUC_{last} for 250 µg NGM/25 µg EE plus folic acid 400 µg compared to 250 µg NGM/25 µg EE was observed. Based on the primary analytes, NGMN and EE in the 2 formulations of 250 µg NGM/25 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	
Parameters	Folic Acid 400 µg (N=48)	250 µg NGM/25 µg EE Plus Folic Acid 400 µg (N=46)	Folic Acid 400 µg (N=48)	250 µg NGM/25 µg EE Plus Folic Acid 400 µg (N=46)
C_{max} (ng/mL)	30.0 (7.31)	30.1 (8.07)	14.6 (4.09)	14.4 (3.56)
t_{max}[a] (h)	1.75 (0.50-12.03)	2.00 (1.00-5.00)	1.75 (0.50-12.03)	2.00 (1.00-5.00)
AUC_{last} (ng.h/mL)	476 (127)	495 (144)	112 (61.3)	119 (55.8)
AUC_{last*}[b] (ng.h/mL)	369 (155)	393 (159)	111 (61.5)	119 (56.1)
AUC_{12} (ng.h/mL)	267 (69.2)	276 (77.1)	89.2 (26.6)[f]	90.3 (24.9)[f]
$t_{1/2}$ (h)	42.7 (48.5)[d]	30.4 (30.0)[c]	10.5 (10.4)[c]	9.91 (13.1)[e]

[a] Median (minimum-maximum)
[b] AUC of the interval: 0 to the time point at which the subsequent folate concentration in the terminal phase dropped below baseline folate level for the first time
[c] n=20 [d] n=18 [e] n=25 [f] n=41

For observed (uncorrected) and baseline corrected plasma folate data, mean C_{max}, AUC_{last}, and AUC_{last*} were similar when folic acid was dosed with and without 250 µg NGM/35 µg EE. Mean terminal half-life ($t_{1/2}$) of folates for using the observed method decreased by 29% when folic acid was coadministered with 250 µg NGM/35 µg EE as compared to folic acid administered alone**,** while the $t_{1/2}$ estimates from the baseline corrected method remained similar between the two formulations.

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/25 µg EE plus folic acid 400 µg with reference to a single dose of folic acid 400 µg are summarized below:

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Folate	Parameter	N	Intra-subject CV (%)	250 µg NGM/ 25 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}	46	47.16	108.77	97.01	112.12	95.05 - 132.25
	AUC_{last*}[a]	46	47.74	108.19	96.31	112.33	95.06 - 132.74
	C_{max}	46	19.36	13.98	14.04	99.59	93.00 - 106.66
Observed	AUC_{12}	46	14.38	263.67	257.12	102.55	97.45 - 107.91
	AUC_{last}	46	14.22	473.34	457.19	103.53	98.44 - 108.89
	AUC_{last*}[a]	46	41.74	364.30	332.23	109.65	94.88 - 126.73
	C_{max}	46	14.90	28.92	29.05	99.54	94.43 - 104.93

[a] Parameter equal to AUC of the interval: time 0 to the time point at which the subsequent baseline corrected folate concentration dropped below baseline folate level for the first time

Folate C_{max} values obtained from both observed and baseline corrected plasma folate concentrations were similar between folic acid 400 µg and 250 µg NGM/25 µg EE with folic acid 400 µg (combined formulation), with the 90% confidence intervals for the ratio of means (250 µg NGM/25 µg EE plus folic acid 400 µg with reference to folic acid 400 µg) falling within the bioequivalence range of 80% to 125%. AUC_{12} and AUC_{last} for the observed method were also within the bioequivalence range of 80 to 125%. AUC_{last} (baseline corrected) and AUC_{last*} (observed and baseline corrected methods) fell outside the 90 % confidence intervals showing a slightly higher exposure of plasma folate in the combined formulation.

SAFETY RESULTS: In general, all 3 treatments were safe and well tolerated. No deaths or serious adverse events occurred during the study, and only 1 subject discontinued treatment because of an adverse event (urticaria) 16 days after receiving Treatment C (folic acid 400 µg). Headache, venipuncture site pain, dizziness, upper abdominal pain, and nausea were the most common adverse events.

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 3 subjects who became pregnant during the study (2 after receiving Treatment A [250 µg NGM/25 µg EE] and 1 after receiving Treatment C [folic acid 400 µg]).

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/25 µg EE, 1 without folic acid and 1 containing 400 µg folic acid, were bioequivalent. In general, plasma folate pharmacokinetics were comparable between folic acid 400 µg alone and 250 µg NGM/25 µg EE plus folic acid 400 µg. Overall, all 3 treatments administered during this study were safe and well tolerated. No deaths or serious adverse events occurred, and 1 subject discontinued treatment because of an adverse event (urticaria).

Date of the report: 31 May 2006

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