SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: ORTHO-CYCLEN®+ Folic Acid NAME OF ACTIVE INGREDIENT(S): Norgestimate-Ethinyl Estradiol + Folic Acid	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: NRGMON-CON-1001 CR002206

Title of Study: An Open-Label Pharmacokinetic Drug Interaction Study of Folic Acid and 250 μg Norgestimate/35 μg Ethinyl Estradiol (ORTHO-CYCLEN®) in Healthy Women

Principal Investigator: Daniel Freeland, D.O. - CEDRA Clinical Research, L.L.C., Austin, Texas; USA

Publication (Reference): None

Studied Period (years): Clinical Conduct: 20 Jan 2005 to 24 Feb 2005 Sample Analysis: Not performed.	**Phase of development**: 1

Objectives: The primary objective of this study was to evaluate the pharmacokinetic drug interaction between folic acid and 250 μg norgestimate (NGM), the active metabolites norelgestromin (NGMN) and norgestrel (NG), and 35 μg ethinyl estradiol (EE). Safety was also assessed.

Methodology: This was an open-label, randomized, single-center, pharmacokinetic interaction study. Healthy adult female subjects who met the prestudy eligibility criteria were randomized to 1 of 2 treatment groups. The randomization was balanced using permuted blocks. Subjects in Group 1 were to receive a single oral dose of 250 μg NGM/35 μg EE (1 tablet of ORTHO-CYCLEN) on Days 1 and 17, and 1 mg of folic acid on Days 4 through 18. Subjects in Group 2 were to receive a single, oral 1-mg dose of folic acid on Days 1 and 17, and 1 ORTHO-CYCLEN tablet on Days 2 through 17. Serial blood samples were to be collected from each subject on Days 1 and 17 before dosing and at specified times for up to 72 hours after dosing for pharmacokinetic evaluation. Subjects were to be confined overnight at the study unit on Days –1 and 16 for an overnight fast of at least 8 hours before dosing on Days 1 and 17. Subjects were to remain confined at the study unit until the 24-hour blood samples were collected on Days 2 and 18. Safety was based on the incidence of adverse events, and on changes in clinical laboratory values (hematology, chemistry, and urinalysis), vital signs, electrocardiograms (ECGs), and physical and gynecological examination findings.

The Sponsor prematurely terminated this study on 14 February 2005 because of errors made at the study site in subject randomization, the timing of blood draws, and handling of laboratory samples. As a result of these errors, the pharmacokinetic samples collected were not analyzed, and a new study was initiated (NRGMON-CON-1006). Due to the premature termination of the study, no subject received more than 9 days of therapy. Most subjects completed the screening and premature termination procedures.

Number of Subjects (planned and analyzed): 48 subjects planned; 48 randomized (24 Group 1, 24 Group 2); 0 evaluable for pharmacokinetics; 48 evaluable for safety.

Diagnosis and Main Criteria for Inclusion: Healthy female subjects, 18 to 45 years of age inclusive.

Test Products, Doses and Mode of Administration, Batch Nos.:

- ORTHO-CYCLEN tablet (250 μg NGM/35 μg EE); Manufacturer (Ortho-McNeil) Lot: 4EM766; Bulk Lot D04LL1397; Package Lot: R12961 (NDC 0062-1901-15)
- Folic acid tablet (1 mg); Manufacturer (Watson Laboratories) Lot: C4B0264; Bulk Lot D04LL1390; Package Lot: R12960 (NDC 0591-5216-01)

Group 1: Single ORTHO-CYCLEN tablet on Days 1 and 17, 1 folic acid tablet on Days 4 to 18

Group 2: Single folic acid tablet on Days 1 and 17, 1 ORTHO-CYCLEN tablet on Days 2 to 17

The study drugs were to be taken with 240 mL (8 oz) of water at approximately 8:00 a.m. Subjects were required to fast for a minimum of 8 hours before dosing on Days 1 and 17.

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

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: ORTHO-CYCLEN®+ Folic Acid NAME OF ACTIVE INGREDIENT(S): Norgestimate-Ethinyl Estradiol + Folic Acid	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Duration of Treatment: 18 days Group 1; 17 days Group 2

Criteria for Evaluation:

Pharmacokinetics: Mean concentrations of NGMN, NG, EE, and folic acid were to be determined from blood samples collected predose and up to 72 hours postdose. The pharmacokinetic parameters to be determined included C_{max}, t_{max}, AUC_{24}, AUC_{72}, AUC_{last}, AUC_{∞}, C_{last}, $\lambda_{z,}$ and $t_{½}$.

Safety: Safety was evaluated by monitoring adverse events and changes in clinical laboratory values (hematology, serum chemistry, and urinalysis), vital sign measurements, ECGs, and physical and gynecological examination findings.

Statistical Methods:

Pharmacokinetics: Concentration vs. time profiles for NGMN, NG, EE, and folic acid were to be plotted for each subject and by treatment group (i.e., Group 1: ORTHO-CYCLEN alone, ORTHO-CYCLEN + folic acid; Group 2: folic acid alone, folic acid + ORTHO-CYCLEN). Descriptive statistics (mean, median, geometric mean, SD, CV, and range) were to be summarized by treatment group.

Safety: The incidence of adverse events was summarized for each treatment group using a standard adverse event dictionary (Medical Dictionary for Regulatory Activities [MedDRA]). Laboratory, vital signs, and physical and gynecological examination results were listed.

SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS: The pharmacokinetic analyses were not performed.

SAFETY RESULTS: ORTHO-CYCLEN (250 µg NGM/35 µg EE) in combination with folic acid (1 mg) was well tolerated in healthy adult females 19 to 45 years of age. Of the 48 subjects enrolled, 20 (41.7%) reported 1 or more adverse event. The most common events, dysmenorrhea and metrorrhagia, were each reported in 3 (6.3%) subjects. All adverse events were mild to moderate in severity except for 1 case of severe dysmenorrhea, and the majority of events were considered by the investigator to be possibly related to study medication. There were no deaths, serious adverse events, or adverse events leading to premature treatment discontinuation. There were no treatment-related trends or clinically relevant changes in laboratory values (serum chemistry, hematology, and urinalysis), vital signs, ECG assessments, physical examination, or gynecological examination findings. Two subjects became pregnant during the conduct of this study. One of these subjects chose to terminate her pregnancy. The other subject chose to continue the pregnancy. Her expected date of delivery is October 28, 2005.

CONCLUSION: Concomitant administration of folic acid with ORTHO-CYCLEN was well tolerated in healthy adult women. There were no significant safety findings.

Date of the report: 16 August 2005

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