SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: Folic acid NAME OF ACTIVE INGREDIENT(S): Folic acid	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: NRGMON-CON-1004 CR002386 **Title of Study:** A Randomized, Open-Label, Absolute Bioavailability Study of Folic Acid		
Principal Investigator: Maria Gutierrez, M.D. Comprehensive NeuroScience, Inc., Ft. Lauderdale, FL, USA		
Publication (Reference): None		
Studied Period (years): Clinical Conduct: 26 October 2004 to 04 December 2004 Sample Analysis: 29 November 2004 to 14 January 2005		**Phase of development:** 1
Objectives: This was a pilot study to determine the absolute bioavailability of orally administered folic acid, to estimate intrasubject variance, and to use the samples collected to validate analytical methods. Safety was also assessed.		
Methodology: This was a randomized, open-label, 3-way crossover, single-center trial, consisting of a prerandomization phase, an open-label treatment phase (3 single doses separated by washouts of 7 days each), and a posttreatment phase. Subjects were randomly assigned to 1 of 6 treatment sequences (2 subjects per sequence). All subjects received a single dose of folic acid in each treatment period (400-µg oral solution, 400-µg intravenous [i.v.] infusion, and a 1-mg oral tablet). Blood samples for pharmacokinetic analysis were collected at specified times following each dose. Blood samples for measurement of red cell folate were collected prior to dosing on Day 1 of Period 1. For each period, subjects were confined to the study unit from the evening before Day 1 through the completion of the Day 2 assessments (24-hour pharmacokinetic blood sample collection). End-of-study assessments took place on Day 17 or at the time of early withdrawal.		
Number of Subjects (planned and analyzed): The planned total sample size was 12 subjects. A total of 12 subjects were enrolled; all 12 completed all aspects of the study and were analyzed for safety and pharmacokinetics.		
Diagnosis and Main Criteria for Inclusion: Healthy, nonsmoking women between the ages of 18 and 45 years, inclusive, who were not pregnant or lactating, were enrolled in the study.		
Test Product, Dose and Mode of Administration, Batch No.: Commercially-available folic acid solution (manufacturer lot number 140133) for both oral solution and i.v. infusion doses was supplied in 10-mL vials, contained folic acid at a concentration of 5 mg/mL, and was administered as a 400-µg oral solution or a 400-µg intravenous (i.v.) infusion. Folic acid tablets for oral consumption were supplied as commercially-available tablets (manufacturer lot number C4B0264) containing 1 mg of folic acid.		
Reference Therapy, Dose and Mode of Administration, Batch No.: None		
Duration of Treatment: Single dose on Day 1 of each of 3 treatment periods with a 7-day washout between doses.		
Criteria for Evaluation: Pharmacokinetics: Observed plasma folate concentrations, as well as baseline-corrected folate levels, were used to estimate the following pharmacokinetic parameters after oral administration: C_{max}, t_{max}, AUC_{48}, AUC_{∞}, F_{abs}, $t_{1/2}$, and CL following i.v. infusion. Safety: Safety was assessed through the monitoring of adverse events, vital signs, physical examinations, and clinical laboratory tests (hematology, chemistry, and urinalysis). Pregnancy tests were done at screening, before each dose, and at poststudy to verify eligibility for continued participation in the study.		

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Statistical Methods:

Pharmacokinetics: Mean plasma concentration-time profiles were plotted for each treatment group. The plasma concentration data and the estimates of pharmacokinetic parameters were summarized using mean, standard deviation, and coefficient of variation for each treatment group. The primary parameter of interest for the evaluation of absolute bioavailability was area under the plasma concentration-time curve (AUC). The analyses were carried out on log-transformed, dose-normalized (to 400 μg) parameter values. Bioavailability of folic acid 400-μg oral solution and 1-mg tablet with respect to the 400-μg i.v. infusion was estimated using 90% confidence intervals for the ratio of mean AUCs from: 1) 400-μg oral solution versus 400-μg i.v. infusion and 2) 1-mg tablet versus 400-μg i.v. infusion.

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, and physical examinations.

SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS: The liquid chromatography coupled to mass spectrometry/mass spectrometry (LC/MS/MS) method could not be validated. The validated microbiological assay will be used to determine plasma and whole blood folate concentrations in the oral contraceptive-folic acid program. The peak plasma folate levels following single-dose administration of all 3 folic acid treatments (i.v. infusion, oral solution, and tablet dosage) postdose were approximately two- to three-fold higher than the baseline folate levels. The pharmacokinetic parameters of folic acid from the oral solution were similar to those of the infusion. Peak plasma folate concentrations following tablet administration were observed an hour later than those seen with the solution. The interindividual variability of the baseline corrected folate AUC values appeared modestly higher than the corresponding total AUC values obtained from the uncorrected folate concentration. Apparent half-life following tablet administration was substantially shorter than either i.v. or oral administration. However, in a significant number of subjects, the apparent half-life could not be estimated due to the interference of the endogenous folate level. Therefore, the differences in the apparent half-life may not be reliable.

Based on the statistical analysis, absolute bioavailability of the oral solution and the tablet using observed (uncorrected) data was approximately 104% and 62%, respectively. Relative bioavailability of the tablet to solution dosage was approximately 59%. Absolute bioavailability of the oral solution and the tablet using baseline corrected data was approximately 125% and 101%, respectively. Relative bioavailability of the tablet to solution was approximately 80%.

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Mean (SD) folate plasma pharmacokinetic parameters using observed concentrations are presented below.

Parameters	400-µg i.v. Infusion (N=12)	400-µg Oral Solution (N=12)	1-mg Tablet (N=12)
C_{max} (ng/mL)	37.9 (13.1)	30.4 (9.78)	22.5 (5.58)[d]
t_{max}[a] (h)	0.25 (0.25-0.25)	1.00 (0.50-1.00)	2.00 (1.00-3.00)
$t_{1/2}$[b] (h)	9.3 (2.7)[f]	9.8 (3.3)[g]	3.4 (0.9)[h]
λ_z[b] (h^{-1})	0.0812 (0.0281)[f]	0.0781 (0.0250)[g]	0.2127 (0.0500)[h]
AUC_{last*}[c] (ng.h/mL)	177 (101)	182 (54.2)	106 (24.9)[d]
AUC_{12} (ng.h/mL)	223 (73.9)	229 (69.7)	134 (32.2)[d]
AUC_{24} (ng.h/mL)	380 (117)	394 (117)	207 (53.1)[d]
AUC_{48} (ng.h/mL)	706 (202)	722 (214)	344 (100)[d]
CL (mL/min)	33.8 (13.5)	--	--
F_{abs}[e]	--	1.05 (0.131)	0.624 (0.106)[d]

[a] t_{max} represented by median (range)
[b] Parameter estimated using the concentration-time points in the terminal phase prior to the folate concentration dropping below the individual's baseline folate level for the first time
[c] Parameter equal to AUC of the interval: 0 to the time point at which the subsequent folate concentration drop below the individual's baseline folate level for the first time
[d] Parameters have been dose normalized to 400 µg
[e] Parameter is equal to (AUC_{12} oral) / (AUC_{12} i.v. infusion)
[f] n=5 [g] n=6 [h] n=9

Mean (SD) folate plasma pharmacokinetic parameters using baseline-corrected concentrations are presented below.

Parameters	400-µg i.v. Infusion (N=12)	400-µg Oral Solution (N=12)	1-mg Tablet (N=12)
C_{max} (ng/mL)	23.8 (9.71)	17.7 (6.06)	16.3 (5.26)[d]
t_{max}[a] (h)	0.25 (0.25-0.25)	1.00 (0.50-1.00)	2.00 (1.00-3.00)
$t_{1/2}$[b] (h)	2.0 (0.87)[f]	2.6 (1.0)[g]	1.37 (0.43)[h]
λ_z[b] (h^{-1})	0.3998 (0.1958)[f]	0.3017 (0.1031)[g]	0.5404 (0.1486)[h]
AUC_{last*}[c] (ng.h/mL)	60.5 (22.7)	75.1 (27.1)	61.5 (18.8)[d]
AUC_{12} (ng.h/mL)	64.2 (21.5)	79.7 (27.0)	63.0 (17.7)[d]
AUC_{24} (ng.h/mL)	81.8 (27.1)	103 (38.3)	72.1 (20.3)[d]
AUC_{48} (ng.h/mL)	127 (60.8)	155 (75.1)	87.9 (25.1)[d]
CL (mL/min)	122 (59.4)	--	--
F_{abs}[e]	--	1.31 (0.429)	1.09 (0.436)[d]

[a] t_{max} represented by median (range)
[b] Parameter estimated using the concentration-time points in the terminal phase prior to the baseline corrected folate concentration dropping below 0 for the first time
[c] Parameter equal to AUC of the interval: 0 to the time point at which the subsequent baseline corrected folate concentration drop below zero for the first time
[d] Parameters have been dose normalized to 400 µg
[e] Parameter is equal to (AUC_{12} oral) / (AUC_{12} i.v. onfusion)
[f] n=5 [g] n=7 [h] n=10

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SAFETY RESULTS: In general, all 3 folic acid treatments were safe and well tolerated. No deaths or serious adverse events occurred during the study; no subject discontinued because of an adverse event. A total of 3 (25%) subjects reported 4 treatment-emergent adverse events during the course of the study. The events reported were dizziness, abdominal pain, upper respiratory tract infection, and flushing. All 4 adverse events were considered mild in severity and resolved spontaneously. The dizziness, upper respiratory tract infection, and flushing were assessed as possibly related to study medication, whereas the abdominal pain was of doubtful relationship to study treatment.

There were no clinically significant changes noted in clinical laboratory testing or in other safety data (vital signs or physical examinations) for any subject during the course of the study.

CONCLUSIONS:

- The LC/MS/MS method could not be validated. The validated microbiological assay will be used to determine plasma and whole blood folate concentrations in the oral contraceptive-folic acid program.
- The peak plasma folate levels following single dose administration of all 3 folic acid treatments (i.v., oral solution, and tablet dosage) postdose were approximately two- to three-fold higher than the baseline folate levels.
- The absolute bioavailability of the oral solution estimated using baseline corrected and uncorrected methods were 125% and 104% respectively.
- The absolute bioavailability of the tablet estimated using baseline corrected and uncorrected methods were 101% and 62% respectively.
- The differences in absolute bioavailability estimates obtained from the observed and the baseline corrected approach reflects the complexity of assessing folate pharmacokinetics (viz., assay limitation to discriminate between different types of folates, endogenous substrate influence, etc.).
- The intraindividual variability of the baseline corrected folate AUC values appeared modestly higher than the corresponding total AUC values obtained from uncorrected folate concentrations.
- We plan to characterize the pharmacokinetics of folates in future studies using both an observed and a baseline corrected approach.
- All 3 folic acid treatments were safe and well tolerated.

Date of the report: 16 September 2005

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