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Drug product:	NEXIUM™	**SYNOPSIS**	
Drug substance(s):	Esomeprazole magnesium		
Document No.:			
Edition No.:			
Study code:	D9612L00057 (316)		
Date:	20 December 2004		

A Multicenter, Open-label, Four-way Crossover Study of the Effects of Esomeprazole, Aspirin and Rofecoxib on Prostaglandin (PGE2) Production, Cyclooxygenase-2 Enzyme Activity and PCNA Expression in Patients with Barrett's Esophagus

Study center(s)

This study was conducted at 10 centers in the US (a total of 13 sites were initiated; 12 sites received study drug, and 10 sites enrolled patients).

Publications

Triadafilopoulos G, Kaur B, Traxler B, Chu N, Levine D, Weston A: The effects of esomeprazole combined with aspirin or rofecoxib on steady state prostaglandin E2 production in patients with Barrett's esophagus. Gastroenterology 2004; 126(suppl 2, abstr):A-617.

Triadafilopoulos G, Kaur B, Sood S, Traxler B, Chu N, Levine D, Weston A. Effects of esomeprazole combined with aspirin or rofecoxib on steady state prostaglandin E_2 (PGE_2) production in patients with Barrett's oesophagus (BE). Gut 2004;53(Suppl VI):A62, Abs OP-G-293

Study dates		**Phase of development**
First patient enrolled	26 April 2002	Therapeutic exploratory (II)
Last patient completed	16 June 2003	

Objectives

The primary objective of this study was to determine if the reduction from baseline of PGE_2 production in Barrett's esophagus metaplastic tissue from patients with documented Barrett's esophagus, would be equivalent at steady-state (Day 10) in the esomeprazole 40 mg bid and

aspirin treatment group [ie, E40 bid & A325 qd treatment regimen] compared to the esomeprazole 40 mg bid and rofecoxib 25 mg qd treatment group [ie, E40 bid & R25 qd treatment regimen].

The secondary objective was to determine if the reduction from baseline in PGE_2 production, COX-2 enzyme activity and PCNA expression in Barrett's esophagus metaplastic tissue from patients with documented Barrett's esophagus would be greatest at steady-state (Day 10) in either the esomeprazole 40 mg bid plus aspirin treatment group [ie, E40 bid & A325 qd treatment regimen] or esomeprazole 40 mg bid plus rofecoxib 25 mg treatment group [ie, E40 bid & R25 qd treatment regimen] compared to the esomeprazole 40 mg bid alone treatment group [ie, E40 bid treatment regimen] or rofecoxib 25 mg qd alone treatment group [ie, R25 qd treatment regimen].

Study design

This Phase II, multicenter, randomized, multiple-dose, open-label, 4-way crossover, pharmacodynamic study in patients with Barrett's esophagus was designed to evaluate prostaglandin E_2 (PGE_2) content, cyclooxygenase-2 (COX-2) expression, and proliferating cell nuclear antigen (PCNA) expression in Barrett's esophagus metaplastic tissue following 10 days of treatment with each of the following:

- Treatment A: Esomeprazole 40 mg bid (E40 bid)
- Treatment B: Esomeprazole 40 mg bid plus aspirin 325 mg qd (E40 bid & A325 qd)
- Treatment C: Esomeprazole 40 mg bid plus rofecoxib 25 mg qd (E40 bid & R25 qd)
- Treatment D: Rofecoxib 25 mg qd (R25 qd).

Based on the treatment designations above, results tables of treatment group comparisons are reported as follows: A – B, A – C, A – D, B – C, B – D, and C – D.

Target patient population and sample size

A total of 32 adult, male or female, patients with documented, biopsy-proven Barrett's esophagus (columnar-lined epithelium ≥2 cm) and no evidence of dysplasia or adenocarcinoma were to complete the study. It was estimated that 32 completed patients would provide 83% power to detect a difference of 3 pg/mg in mean PGE_2 content among the treatments, and that approximately 50 patients would need to be screened to reach this target.

Investigational product and comparator(s): dosage, mode of administration, and batch numbers

Esomeprazole magnesium (NEXIUM®) 40 mg delayed-release capsules (batch numbers L5598 and L6352).

Aspirin 325 mg tablets (batch numbers P24566 and P25868).

Rofecoxib 25 mg tablet (batch numbers L3055 and M2354).

All study medication was to be taken orally with water 30 minutes before breakfast and (for bid dosing) 30 minutes before dinner.

Duration of treatment

There were four 10-day treatment periods, with a 10- to 14-day washout period between treatments. Each patient was to complete all four 10-day treatments, in the order assigned at randomization.

Criteria for evaluation (main variables)

Pharmacodynamic variables

- Primary variable: Mean difference from baseline to steady state (Day 10) in PGE_2 content for each treatment.
- Secondary variables: Mean difference from baseline to steady state (Day 10) in COX-2 and PCNA expression for each treatment.

Safety variables

Standard safety assessments included adverse event reports, clinical laboratory data (hematology, serum chemistry, and urinalysis), vital signs, and physical examination.

Statistical methods

For the All Available and Evaluable datasets, PGE_2 content, COX-2 expression, and PCNA expression were summarized at baseline and on Day 10 of each treatment, and were analyzed using an analysis of variance (ANOVA) model with effects for sequence, patient within sequence, period, and treatment.

All patients who took at least 1 dose of study medication were included in the descriptive summary of safety results. No formal treatment comparisons were made.

Patient population

As shown in Table S1, the patients were predominantly male (92%) and Caucasian (98%), with a mean age of 60 years. Most of the patients were overweight (mean height and weight approximately 69 inches and 204 pounds, respectively); these characteristics have been shown to be associated with gastroesophageal reflux disease and Barrett's esophagus.

Two patients were enrolled into the study twice (Patient 011 001/002 and Patient 018-001/002) because they had no immunoassay data for their first enrollment due to site error and only Patient 018-002 had evaluable immunoassay data for the second enrollment. Both patients did however, provide safety data for both enrollment periods, all of which are included in the data listings and summary tables.

In addition, 4 patients each were allowed to repeat 1 treatment regimen. Immunoassay data from the repeated regimens were available for analysis for 2 of these patients. The immunoassay data for these visits were entered into the analysis model according to the patients' original randomized sequence. Safety data were recorded for both the initial and repeated treatment regimens.

Table S1 Patient disposition, demographics, and baseline characteristics

		All patients
Disposition:		
N screened		59
N randomized		47
N (%) of patients who[a]:	Completed	36 (76.6%)
	Discontinued[b]	11 (23.4%)
N with data from at least 1 immunoassay (All Available dataset) [c]		38
N with evaluable data from at least 1 immunoassay data (Evaluable dataset)[d]		36
N analyzed for safety[e]		47
Demographics (N=47):		
Gender, n (%):	Male	43 (91.5%)
	Female	4 (8.5%)
Age (years):	Mean (SD)	60.1 (11.1)
	Range	37.0 - 79.0
Race, n (%):	Caucasian	46 (97.9%)
	Black	1 (2.1%)
Weight (lbs)	Mean (SD)	204.4 (36.0)
	Range	151.0 – 296.0
Height (in)	Mean (SD)	69.4 (3.7)
	Range	61.5 – 78.0
Baseline characteristics (all available data, N=47):		
Erosive esophagitis, n (%)	No	25 (53.2%)
	Yes	22 (46.8%)
LA Classification of Esophagitis, n (% of N=47)	Grade A	8 (17.0%)
	Grade B	14 (29.8%)
	Grade C or D	0
Length of Barrett's esophagus tissue (cm)	Mean (SD)	5.5 (3.1)
	Range	2.0 – 14.0

[a] For Site 011, Patient 001 and 002 are the same individual. For Site 018, Patient 001 and 002 are the same individual. Patients 011-001, 011-002, and 018-001 are included in the number of patients who discontinued. Patient 018-002 is included in the number of patients who completed. These patients are included in all other categories above and are counted twice. Detailed information is presented in Section 6.1.

[b] If a patient completed at least 1 treatment arm, any evaluable data were included in the pharmacodynamic analysis.

[c] Number of all randomized patients who had a biopsy-proven diagnosis of Barrett's esophagus and who completed 1 treatment arm with resulting data from at least 1 immunoassay.

[d] Number of patients with data that met the criteria for the All Available dataset as well as certain predefined measures of compliance with respect to the conduct of the study.

[e] Number of patients who took at least 1 dose of study treatment and provided post-baseline safety data.

Pharmacodynamic results

The primary objective of this study was to determine whether the E40 bid & A325 qd treatment regimen provided an equivalent reduction in the PGE_2 content of Barrett's esophagus tissue compared to the E40 bid & R25 qd treatment regimen. The 2 regimens were not equivalent in reducing PGE_2 content. The E40 bid & A325 qd regimen provided a significantly greater reduction in PGE_2 content compared to the E40 bid & R25 qd regimen. The estimated difference between the 2 regimens was –21.6 pg/mg (p=0.0062, 95% CI -36.8 to -6.3, see Table S2).

Additionally, the E40 bid & A325 qd treatment resulted in a significantly greater reduction in PGE_2 content compared to the other 2 treatments (p=0.0012 when compared to E40 bid alone, and p=0.0195 when compared to R25 qd alone). The other treatments were not statistically different from one another.

The estimated mean within-treatment change from baseline for all patients who had valid baseline values for the E40 bid & A325 qd treatment was –22.9 pg/mg PGE_2 content (see Table S3). This represented a significant decrease from baseline; no significant changes were observed for the other treatments.

No significant differences were observed among the 4 treatment regimens or in the mean within-treatment changes from baseline for COX-2 expression in Barrett's esophagus tissue.

No significant differences were observed among the 4 treatment regimens for PCNA expression in Barrett's esophagus tissue; however, mean within-treatment changes from baseline were observed. PCNA expression was significantly reduced from baseline by all treatment regimens except R25 qd alone, ie, by all treatment regimens containing E40.

The post-treatment immunoassay results are summarized by treatment in Tables S2 and S3.

Table S2 Summary of treatment differences, Barrett's esophagus tissue (Evaluable data)

Treatment comparison	Difference[a]			
	LS mean	SEM	95% CI	p-value
	PGE_2 content (pg/mg of tissue)			
E40 bid - E40 bid & A325 qd	27.2	8.2	(11.0, 43.4)	0.0012
E40 bid - E40 bid & R25 qd	5.7	8.0	(-10.2, 21.5)	0.4782
E40 bid - R25 qd	9.1	7.9	(-6.6, 24.8)	0.2517
E40 bid & A325 qd - E40 bid & R25 qd	-21.6	7.7	(-36.8, -6.3)	0.0062
E40 bid & A325 qd - R25 qd	-18.1	7.6	(-33.3, -3.0)	0.0195
E40 bid & R25 qd - R25 qd	3.4	7.5	(-11.5, 18.4)	0.6478
	COX-2 expression (μg/mg of protein)			
E40 bid - E40 bid & A325 qd	0.04	0.05	(-0.07, 0.15)	0.4840
E40 bid - E40 bid & R25 qd	-0.01	0.05	(-0.12, 0.10)	0.8621
E40 bid - R25 qd	0.03	0.05	(-0.08, 0.13)	0.6247
E40 bid & A325 qd - E40 bid & R25 qd	-0.05	0.05	(-0.15, 0.06)	0.3706
E40 bid & A325 qd - R25 qd	-0.01	0.05	(-0.11, 0.09)	0.8093
E40 bid & R25 qd - R25 qd	0.04	0.05	(-0.07, 0.14)	0.4941
	PCNA expression (μg/mg of protein)			
E40 bid - E40 bid & A325 qd	9.2	18.4	(-27.4, 45.9)	0.6184
E40 bid - E40 bid & R25 qd	12.4	18.1	(-23.7, 48.4)	0.4967
E40 bid - R25 qd	-14.2	17.5	(-49.0, 20.7)	0.4216
E40 bid & A325 qd - E40 bid & R25 qd	3.2	17.7	(-32.1, 38.4)	0.8593
E40 bid & A325 qd - R25 qd	-23.4	17.2	(-57.5, 10.8)	0.1776
E40 bid & R25 qd - R25 qd	-26.5	16.9	(-60.1, 7.1)	0.1204

[a] All evaluable data were included in this analysis whether or not a patient had data for both of the treatments being compared.

E40=esomeprazole 40 mg; A325=aspirin 325 mg; R25=rofecoxib 25 mg.

Table S3 Summary of within-treatment changes from baseline, Barrett's esophagus tissue (Evaluable data)

Treatment	N	LS mean	SEM	95% CI	p-value
			PGE_2 content (pg/mg of tissue)		
E40 bid	35	4.3	5.9	(-7.4, 16.0)	0.4684
E40 bid & A325 qd	37	-22.9	5.6	(-34.1, -11.8)	0.0001
E40 bid & R25 qd	38	-1.4	5.3	(-11.9, 9.1)	0.7955
R25 qd	38	-4.8	5.3	(-15.4, 5.8)	0.3688
			COX-2 expression (µg/mg of protein)		
E40 bid	26	0.00	0.04	(-0.08, 0.08)	0.9575
E40 bid & A325 qd	27	-0.04	0.04	(-0.11, 0.04)	0.3421
E40 bid & R25 qd	28	0.01	0.04	(-0.06, 0.09)	0.7605
R25 qd	29	-0.02	0.04	(-0.09, 0.05)	0.5008
			PCNA expression (µg/mg of protein)		
E40 bid	35	-28.6	13.3	(-55.1, -2.2)	0.0341
E40 bid & A325 qd	37	-37.8	12.9	(-63.5, -12.2)	0.0043
E40 bid & R25 qd	38	-41.0	12.2	(-65.2, -16.8)	0.0011
R25 qd	38	-14.5	11.7	(-37.8, 8.9)	0.2209

E40=esomeprazole 40 mg; A325=aspirin 325 mg; R25=rofecoxib 25 mg.

Safety results

There were no deaths in this study. Overall, the 4 treatment regimens were well tolerated and had a similar incidence of treatment-related adverse events. The highest percentage of adverse events was reported during treatment with R25 qd (38.5%, Table S4). Vomiting was the most commonly reported AE and occurred most frequently in the R25 qd alone treatment regimen (Table S5). Three randomized patients experienced a total of 5 SAEs. One non-enrolled patient, who did not receive any study medication, also experienced an SAE. Of these 3 randomized patients, 1 discontinued as a result of the events (peripheral ischemia and deep vein thrombosis); at the time of these events, the patient was receiving E40 bid alone treatment. None of the SAEs was attributed to study drug. Two patients discontinued due to adverse events. One of these adverse events, erosive esophagitis, was attributed to study drug (R25 qd). In addition, 1 patient discontinued due to adverse events that started prior to receiving the first dose of study drug (the patient discontinued treatment on Study Day 9); the adverse events for this patient are included in the patient listings, but not in the adverse event summary tables. These findings did not raise any safety concerns.

Regarding the other safety parameters, review of the clinical laboratory, physical examination, and vital sign data did not reveal any trends or other issues with any of the 4 treatment regimens.

The safety data for this study were consistent with the known safety profile of esomeprazole.

Table S4 Number (%) of patients who had at least 1 adverse event in any category, and total numbers of adverse events (Safety population[a])

Category of adverse event (AE)	E40 bid (N=47)		E40 bid & A325 qd (N=44)		E40 bid & R25 qd (N=41)		R25 qd (N=39)	
	Number (%) of patients who had an adverse event in each category[b]							
Any AEs	9	(19.2)	9	(25.0)	9	(22.0)	15	(38.5)
Serious AE (SAE)	1	(2.1)	1	(2.3)	1	(2.4)	0	
Discontinuations of study treatment due to AEs[c]	1	(2.1)	0		0		1	(2.6)
Treatment-related AEs	3	(6.4)	1	(2.3)	4	(9.8)	5	(12.8)
	Total number of adverse events[d]							
Any AEs	16		17		15		23	
SAEs	2		1		2		0	
Discontinuations of study treatment due to AEs	2		0		0		1	
Treatment-related AEs	7		1		5		8	

[a] For Site 011, Patient 001 and 002 are the same individual. For Site 018, Patient 001 and 002 are the same individual. These patients are included in all categories above and are counted twice. Detailed information is presented in Section 6.1.

[b] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

[c] Patient 015-003 discontinued due to adverse events that started prior to receiving the first dose of study drug (E40 bid & R25 qd). The adverse events for this patient are included in the patient listings, but are not included in the adverse event summary tables (see Section 8.4.3).

[d] Events are counted by preferred term; ie, for patients with multiple events falling under the same preferred term, only 1 occurrence of the event is counted.

E40=esomeprazole 40 mg; A325=aspirin 325 mg; R25=rofecoxib 25 mg.

Table S5 **Number (%) of patients with the most commonly reported[a] adverse events, sorted by decreasing order of frequency as summarized over all treatments (Safety dataset)**

	Number (%) of patients who had a post-treatment adverse event [b]				
Adverse event (preferred term)	**E40 bid (N=47)**	**E40 bid & A325 qd (N=44)**	**E40 bid & R25 qd (N=41)**	**R25 qd (N=39)**	**Total[c] (N=47)**
Vomiting NOS	1 (2.1%)	1 (2.3%)	1 (2.4%)	3 (7.7)%)	5 (10.6%)
Diarrhea NOS	1 (2.1%)	0	2 (4.9%)	0	3 (6.4%)
Nausea	0	1 (2.3%)	0	2 (5.1%)	3 (6.4%)
Abdominal pain upper	0	1 (2.3%)	0	1 (2.6%)	2 (4.3%)
Constipation	0	1 (2.3%)	1 (2.4%)	0	2 (4.3%)
Cough	0	0	0	2 (5.1%)	2 (4.3%)
Dyspepsia	0	1 (2.3%)	1 (2.4%)	1 (2.6%)	2 (4.3%)
Esophageal ulcer	0	0	0	2 (5.1%)	2 (4.3%)
Gastroesophageal reflux disease	0	0	1 (2.4%)	2 (5.1%)	2 (4.3%)
Nasopharyngitis	0	1 (2.3%)	1 (2.4%)	0	2 (4.3%)
Pharyngolaryngeal pain	0	1 (2.3%)	0	1 (2.6%)	2 (4.3%)
Tooth carries NOS	0	1 (2.3%)	1 (2.4%)	0	2 (4.3%)
Tooth injury	0	0	0	2 (5.1%)	2 (4.3%)

[a] Events that occurred post-baseline in at least 2 patients are included in this table.

[b] For Site 011, Patient 001 and 002 are the same individual. For Site 018, Patient 001 and 002 are the same individual. These patients are included in all categories above and are counted twice. Detailed information is presented in Section 6.1.

[c] Patients are counted once whether the event occurred during 1 or multiple treatments.

E40=esomeprazole 40 mg; A325=aspirin 325 mg; R25=rofecoxib 25 mg.

Date of the report

20 December 2004