APPENDIX 2
SINGLE-DOSE RELIEF TRIALS

Introduction

As noted in the Program Overview (Section 4), three additional trials investigating Ome-Mg's efficacy after a single treated episode were completed subsequent to filing the NDA. The protocol for two of these trials (Trials 018 and 019) instructed subjects to take a single dose of medication upon moderate or greater heartburn severity using an in-clinic, meal-induced heartburn model. The other study (Study 017) followed a design similar to Studies 092 and 095, except only a single heartburn episode was evaluated. Other differences from the 092/095 trials included:

- taking a single blinded tablet of study medication rather than using a double-dummy (two-tablet) design;
- defining Sustained Adequate Relief as the primary variable;
- allowing 2 hours for development of Adequate Relief.

These criteria were incorporated in an attempt to minimize/reduce the response within the placebo arm.

Other aspects of these trials are as described for the clinical program in Section 5.

Subjects who participated in these trials are characterized by the following (reference Table 5.1 in Section 5 for similar characteristics in the other trials):

TABLE A1 DEMOGRAPHIC AND ANTHROPOMETRIC CHARACTERISTICS (ITT SUBJECTS)			
Characteristic	# 017 (2172)	# 018 (2138)	# 019 (2312)
Gender (% female)	60	59	60
Race (% Caucasian)	72	80	69
Age (years)	41	43	42
Weight (kg)	84	87	85
Height (cm)	169	170	170
Smoker (%)	25	29	28
Alcohol Use (%)	43	41	46
Caffeine Use (%)	87	88	90

In addition, subjects were asked to indicate factors they associated with their heartburn during the 30 days preceding study entry. Table A2 shows the percent of subjects who associated these common factors with their heartburn experience. [Note: subjects could mark as many factors as applied to their condition.]

TABLE A2 FACTORS ASSOCIATED WITH HEARTBURN			
	# 017 (2172)	# 018 (2138)	# 019 (2313)
Factor	% of subjects who indicated that factor contributed to heartburn		
Food/Beverage	99	100	100
Stress	51	52	55
Lying Down	35	50	51
Hectic Lifestyle	27	32	36
Physical Activity	16	24	24
Medications	4	9	8
Subjects may indicate more than one factor that contributes to heartburn.			

Study Design and Clinical Methodology

Both studies were randomized, parallel, double-blind, and placebo-controlled. A 1-week single-blind, placebo run-in phase preceded the double-blind, randomized treatment phase.

The primary efficacy variable was the occurrence of Sustained Adequate Relief (i.e., Adequate Relief within the second hour after dosing [inclusive] and sustaining the Adequate rating through [and including] the third hour after dosing). Secondary efficacy variables included:

Overall Assessment of Study Medication,
Time to Sustained Complete Relief (defined analogously to Sustained Adequate Relief),
Backup Medication (Gelusil®) Use.

Baseline heartburn severity was rated according to the scale in Section 5.

Subjects recorded relief scores at 15-minute intervals for 3 hours following consumption of their dose of study medication using the relief scale given in Section 5. Subjects were instructed not to eat or drink anything for the evaluation period. Use of heartburn medications other than the study medications and Gelusil was not permitted during the study. Use of Gelusil as backup medication was discouraged for 2 hours after taking the study medication. If Gelusil was taken, relief scoring was discontinued for the remainder of the evaluation period.

Subjects gave an Overall Assessment of the study drug at the end of the evaluation period, or upon taking Gelusil, by responding to the question, "Overall, how would you rate the study medication?" Subjects responded using the five-point scale in Section 5.

Statistical Methods

A Cochran-Mantel-Haenszel test was used to assess treatment differences for Sustained Adequate Relief, Sustained Complete Relief, and Backup Medication Use. An Extended Mantel-Haenszel test was used to assess treatment differences for the Overall Assessment.

Demographics and Other Baseline Characteristics

Collectively, 6,728 subjects were randomized to treatment in 68 clinical study centers across Trials 017, 018 and 019. A total of 6,622 subjects were included in the ITT dataset for statistical analysis: 4,411 to active medication and 2,211 to placebo. The 70 randomized subjects excluded from the ITT dataset either did not dose with the study medication, recorded no efficacy data, or were previously enrolled in the study.

For the ITT population, the Ome-Mg and placebo groups were generally comparable in demographic and baseline characteristics in both trials (Table A3a and A3b).

TABLE A3A		
DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS (STUDY 017)		
Study	**017**	
Characteristic	**Ome-Mg 20 (N=723)**	**Ome-Mg 10 (N=726)**	**Placebo (N=723)**
Gender			
Female	434 (60.0%)	433 (59.6%)	426 (58.9%)
Male	289 (40.0%)	293 (40.4%)	297 (41.1%)
Race			
Asian	10 (1.4%)	5 (0.7%)	8 (1.1%)
Black	116 (16.0%)	111 (15.3%)	99 (13.7%)
Caucasian	499 (69.0%)	542 (74.7%)	516 (71.4%)
Hispanic	94 (13.0%)	63 (8.7%)	88 (12.2%)
Other	4 (0.6%)	5 (0.7%)	12 (1.6%)
Age (Years)			
Mean (SD)	41.5 (13.46)	40.7 (14.00)	41.4 (13.95)
Min–Max	18–79	18–81	18–81
Current Smoker			
Yes	178 (24.6%)	175 (24.1%)	187 (25.9%)
Other Current Nicotine Use			
Yes	10 (1.4%)	16 (2.2%)	10 (1.4%)
Currently Consume Alcohol			
Yes	301 (41.6%)	340 (46.8%)	303 (41.9%)
Currently Consume Caffeine-Containing Beverages			
Yes	620 (85.8%)	650 (89.5%)	616 (85.2%)
Currently Consume Other Caffeine-Containing Products			
Yes	416 (57.5%)	415 (57.2%)	427 (59.1%)
Heartburn Frequency % of days During Placebo Run-in Phase			
Mean (SD)	61.6 (19.88)	59.1 (19.15)	59.5 (19.20)
≥50%	498 (68.9%)	487 (67.1%)	489 (67.6%)

TABLE A3B DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS (STUDIES 018 AND 019)						
Study	018			019		
Characteristic	Ome-Mg 20 (N=711)	Ome-Mg 10 (N=712)	Placebo (N=715)	Ome-Mg 20 (N=773)	Ome-Mg 10 (N=766)	Placebo (N=773)
Gender						
Female	414 (58.2%)	431 (60.5%)	425 (59.4%)	461 (59.6%)	460 (60.1%)	470 (60.8%)
Male	297 (41.8%)	281 (39.5%)	290 (40.6%)	312 (40.4%)	306 (39.9%)	303 (39.2%)
Race						
Asian	2 (0.3%)	5 (0.7%)	2 (0.3%)	4 (0.5%)	3 (0.4%)	1 (0.1%)
Black	72 (10.1%)	68 (9.6%)	80 (11.2%)	142 (18.4%)	134 (17.5%)	143 (18.5%)
Caucasian	560 (78.8%)	572 (80.3%)	575 (80.4%)	531 (68.7%)	540 (70.5%)	520 (67.3%)
Hispanic	68 (9.6%)	58 (8.1%)	53 (7.4%)	91 (11.8%)	78 (10.2%)	91 (11.8%)
Other	9 (1.3%)	9 (1.3%)	5 (0.7%)	5 (0.6%)	11 (1.4%)	18 (2.3%)
Age (Years)						
Mean (SD)	41.8 (13.52)	43.4 (13.68)	43.4 (13.99)	41.0 (12.39)	41.6 (12.78)	42.4 (12.80)
Min–Max	18–85	18–91	18–82	18–79	18–81	18–82
Current Smoker						
Yes	203 (28.6%)	206 (28.9%)	205 (28.7%)	208 (26.9%)	206 (26.9%)	225 (29.1%)
Other Current Nicotine Use						
Yes	23 (3.2%)	17 (2.4%)	19 (2.7%)	13 (1.7%)	20 (2.6%)	24 (3.1%)
Currently Consume Alcohol						
Yes	295 (41.5%)	289 (40.6%)	310 (43.4%)	360 (46.6%)	356 (46.5%)	355 (45.9%)
Currently Consume Caffeine-Containing Beverages						
Yes	627 (88.2%)	637 (89.5%)	626 (87.6%)	689 (89.1%)	684 (89.3%)	697 (90.2%)
Currently Consume Other Caffeine-Containing Products						
Yes	412 (57.9%)	416 (58.4%)	421 (58.9%)	452 (58.5%)	427 (55.7%)	435 (56.3%)
Heartburn Frequency % of days During Placebo Run-in Phase						
Mean (SD)	66.1 (20.01)	67.2 (19.51)	68.1 (19.49)	71.9 (21.27)	72.6 (20.67)	72.2 (20.24)
≥50%	553 (77.8%)	565 (79.4%)	586 (82.0%)	632 (81.8%)	644 (84.1%)	646 (83.6%)

Efficacy Results

Primary Efficacy Parameter

Table A4 displays results of the analyses of the efficacy parameters. No statistically significant differences in efficacy among the treatments were observed.

TABLE A4 ANALYSIS OF EFFICACY VARIABLES PERCENTAGE OF SUBJECTS WITH INDICATED OUTCOME SINGLE DOSE TREATMENT STUDIES INTENT-TO-TREAT SUBJECTS			
	OME-MG 20	**OME-MG 10**	**PLACEBO**
SUSTAINED ADEQUATE RELIEF[a]			
Study 017	74.3% (N=723)	75.4% (N=726)	72.9% (N=723)
Study 018	63.2% (N=711)	57.7% (N=712)	60.7% (N=715)
Study 019	64.0% (N=773)	61.9% (N=766)	63.9% (N=773)
SUSTAINED COMPLETE RELIEF[a]			
Study 017	46.2% (N=723)	49.0% (N=726)	45.2% (N=723)
Study 018	31.1% (N=711)	30.6% (N=712)	29.2% (N=715)
Study 019	33.2% (N=773)	29.5% (N=766)	31.0% (N=773)
BACKUP MEDICATION USE[a]			
Study 017	1.7% (N=723)	1.2% (N=726)	1.1% (N=723)
Study 018	18.1% (N=711)	23.6% (N=712)	18.2% (N=715)
Study 019	17.1% (N=773)	17.0% (N=766)	18.8% (N=773)
OVERALL ASSESSMENT OF STUDY MEDICATION[b]			
Study 017	60.2% (N=711)	63.2% (N=715)	59.0% (N=714)
Study 018	49.4% (N=710)	45.2% (N=712)	47.4% (N=711)
Study 019	49.3% (N=761)	47.4% (N=756)	48.0% (N=760)
[a] Percentage of subjects with indicated outcome. Treatment difference was tested using Cochran-Mantel Haenszel chi-square test with Investigator as a stratification variable. [b] Percentage of subjects with Good, Very Good, and Excellent ratings on Overall Assessment of Study Medication. All levels of this variable were utilized for test of treatment difference using Extended-Mantel Haenszel chi-square test with Investigator as a stratification variable.			