5 Efficacy Summary

This section of the briefing document summarizes the efficacy findings from the six adequate and well-controlled trials filed to the NDA. Three additional single-dose relief trials completed subsequent to filing the NDA are summarized in Appendix 2. Four studies investigated Ome-Mg's effectiveness in preventing heartburn and two studies investigated the effectiveness in relieving heartburn after onset of symptoms. Many elements of study design are common to all six trials.

- Each study was randomized, multi-center, parallel, double-blind/double-dummy, and used no stratification procedures in subject randomization.
- Each study tested Ome-Mg 20 (20.6 mg Ome-Mg), Ome-Mg 10 (10.3 mg Ome-Mg), and placebo in double-dummy fashion.
- Each study used the following definition of heartburn: an upward moving, uncomfortable sensation behind the breastbone, frequently accompanied by a burning or painful feeling.
- Each study enrolled subjects age 18 or older, not previously diagnosed with GERD or erosive esophagitis, and who had a history of symptoms 2 or more days/week that was confirmed during a 1-week lead-in period.
- Common measurement scales were used across all studies in the program as follows:

Heartburn Severity	0 = None; 1 = Mild; 2 = Moderate; 3 = Severe
Heartburn Relief	0 = Inadequate/None; 1 = Adequate; 2 = Complete
Overall Assessment	0 = Poor; 1 = Fair; 2 = Good; 3 = Very Good; 4 = Excellent

These scales are all well-accepted techniques of evaluating efficacy and were widely used in the H_2RA programs and in analgesia trials.

Subjects who participated in these trials are characterized by the following:

TABLE 5.1
DEMOGRAPHIC AND ANTHROPOMETRIC CHARACTERISTICS

Characteristic	# 171 (1,560)	# 183 (1,564)	# 005 (1,284)	# 006 (1,170)	# 092 (1,869)	# 095 (1,852)
Gender (% female)	56	55	64	59	48	54
Race (% Caucasian)	78	86	77	86	83	83
Age (years)[a]	44	47	43	43	45	44
Weight (kg)[a]	86	86	87	88	87	86
Height (cm)[a]	170	169	169	170	171	171
Smoker (%)	25	22	28	31	27	30
Alcohol Use (%)	50	52	43	42	46	47
Caffeine Use (%)	89	89	93	92	88	86

[a] Values for age, weight, and height are mean values.

Table 5.2 illustrates the history of OTC heartburn medication use by subjects in the OTC trials. Over 90% of subjects used an OTC heartburn product within 30 days prior to study participation.

TABLE 5.2
USE OF ANTACIDS AND/OR HISTAMINE H_2-RECEPTOR ANTAGONISTS
30 DAYS PRIOR TO STUDY

Characteristic	# 171 (1,581)	# 183 (1,576)	# 005 (1,286)	# 006 (1,171)	# 092 (1,899)	# 095 (1,892)
Medication	**% of subjects who took the medication indicated – 30 days prior to study**					
Antacid	75%	75%	79%	72%	75%	78%
OTC H_2RA	38%	37%	31%	33%	43%	37%
Either	91%	90%	88%	87%	94%	93%

Values refer to subjects who took at least one dose of medication indicated during the 30-day period prior to study entry.
Sample size reflects subjects in safety database.

In addition, subjects were asked to indicate factors they associated with their heartburn during the 30 days preceding study entry. Table 5.3 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 5.3
FACTORS ASSOCIATED WITH HEARTBURN
30 DAYS PRIOR TO STUDY

	# 171 (1560)	# 183 (1564)	# 005 (1284)	# 006 (1170)	# 092 (1869)	# 095 (1852)
Factor	**% of subjects who indicated that factor contributed to heartburn**					
Food/Beverage	97	97	100	100	97	98
Stress	69	66	63	60	56	59
Lying Down	59	66	53	51	55	55
Hectic Lifestyle	44	45	38	38	26	30
Physical Activity	27	31	23	23	20	20
Medications	12	10	7	8	5	5

Subjects may indicate more than one factor that contributes to heartburn.

5.1 Heartburn Prevention Studies

A total of four trials evaluated the effectiveness of Ome-Mg in preventing the occurrence of heartburn. In two trials (Studies 171 and 183), subjects suffering from heartburn associated with a variety of factors were dosed for 14 consecutive days with Ome-Mg. Two other trials (Studies 005 and 006) evaluated the efficacy of a single-dose of Ome-Mg administered 1 hour prior to a provocative meal. The primary objective of these four trials was to evaluate whether a single dose of Ome-Mg could completely prevent heartburn symptoms when administered 1 hour prior to a provocative meal or up to 24 hours prior to a unspecified precipitating event.

5.1.1 Multiple-Dose Prevention Trials (Studies 171 and 183)

Studies 171 and 183 evaluated the safety and efficacy of Ome-Mg in the prevention of heartburn symptoms over a 24-hour period.

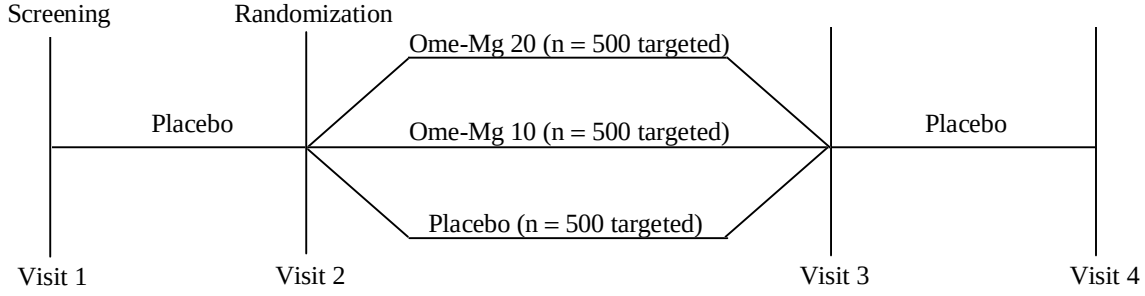
5.1.1.1 Rationale

Omeprazole magnesium's long duration of action and its ability to inhibit all stimuli of gastric acid secretion suggest that Ome-Mg might be particularly effective in preventing heartburn for a full 24 hours. The effectiveness of Ome-Mg was assessed following the first dose and over 2 weeks of consecutive daily dosing. The design of these studies also examines the ability of Ome-Mg to prevent heartburn in a population who had heartburn associated with a variety of conditions that approximate those of daily living.

5.1.1.2 Study Design and Clinical Methods

Both studies were multi-center, double-blind, randomized, double-dummy, parallel, and placebo-controlled. The studies lasted 5 weeks and had three phases: (1) a 1-week, single-blind, placebo run-in phase; (2) a 2-week, double-blind, treatment phase in which patients were randomized to receive a single daily dose of either Ome-Mg 20, Ome-Mg 10, or placebo; and (3) a 2-week, single-blind, placebo, follow-up phase. Subjects took their daily dose of study medication each morning. A schematic of the design follows:

FIGURE 5.1
STUDY SCHEMATIC FOR MULTI-DOSE HEARTBURN PREVENTION TRIALS



Run-in	Double-Blind	Follow-up
(1 week)	(2 weeks)	(2 weeks)

The primary efficacy variable was: No Heartburn over 24 hours on Day 1 (i.e., Complete Prevention of heartburn or Heartburn-Free for a full day). Efficacy was evaluated following the first dose of medication and across all 14 days of dosing during the double-blind phase.

Secondary efficacy variables included:

1. Complete Prevention of Nocturnal Heartburn and Occurrence of No More than Mild Heartburn following the first dose of medication and across all 14 days of dosing during the double-blind phase, and

2. Occurrence of No More than Mild Heartburn following the first dose of medication and across all 14 days of dosing during the double-blind phase.

Occurrence of Heartburn during the 2-week, single-blind placebo, follow-up phase was also investigated.

Each morning subjects (a) rated the most severe episode of heartburn for the previous 24-hour period using the scale given in Section 5, (b) indicated whether or not nocturnal heartburn symptoms were experienced, and (c) recorded information on use of an antacid (Gelusil®), which was provided as a backup medication to be used at the subject's discretion.

5.1.1.3 Statistical Methods

For both studies, a Cochran-Mantel-Haenszel test statistic was used to compare treatment effects on Day 1 for complete prevention of heartburn over 24 hours, complete prevention of nocturnal heartburn, and the occurrence of no more than mild heartburn over 24 hours. A logistic regression analysis was used to compute odds ratios for each treatment comparison and to assess treatment-by-center interaction for the primary efficacy variable. For each endpoint, an analysis of variance (ANOVA) was conducted with each of the three variables to compare treatments with regard to mean percent of days over the 2-week, double-blind phase when an event took place. Generalized Estimating Equations (GEE) were used to assess the same three variables over repeated doses. Time to occurrence of heartburn (following discontinuation of treatment) during the Follow-Up phase was analyzed with survival methods (Kaplan-Meier curves and the Log-Rank test).

5.1.1.4 Demographics and Other Baseline Characteristics

Collectively, 3,162 subjects were randomized to treatment across 49 centers in Trials 171 and 183. A total of 3,124 subjects were included in the ITT dataset for statistical analysis: 2,085 to active medication and 1,039 to placebo. The 38 randomized subjects excluded from the ITT dataset either did not dose with study medication, recorded no efficacy data, or were enrolled previously in the same study.

Table 5.4 provides a summary of demographic and other baseline characteristics by dose group and trial. Baseline characteristics were similar across dose groups and trials with the exception of current tobacco and nicotine use between the 10 mg and 20 mg dose groups in Trial 183. The

10 mg dose group had slightly fewer subjects who were current smokers and users of other nicotine products than did the 20 mg or placebo groups. Covariate interaction analyses show occasional differences in some subgroups, but no clear patterns across indications.

TABLE 5.4
DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS (STUDIES 171 AND 183)

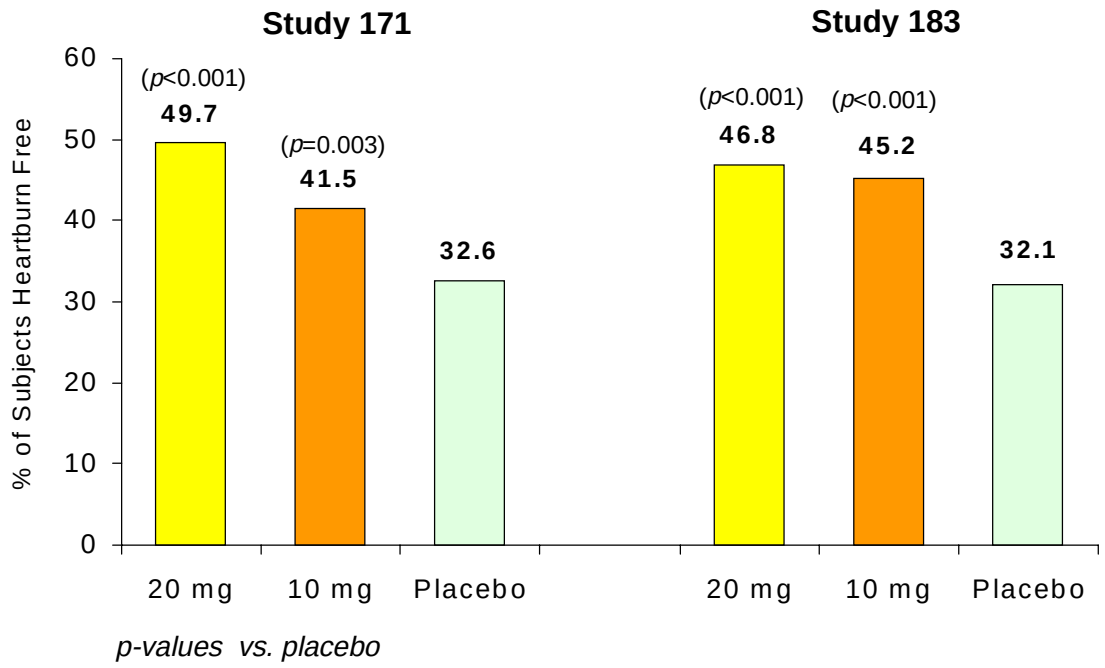
Study	**171**			**183**		
Characteristic	**Ome-Mg 20 N=523**	**Ome-Mg 10 N=518**	**Placebo N=519**	**Ome-Mg 20 N=524**	**Ome-Mg 10 N=520**	**Placebo N=520**
Gender						
Female	297 (56.8%)	284 (54.8%)	287 (55.3%)	283 (54.0%)	287 (55.2%)	293 (56.3%)
Male	226 (43.2%)	234 (45.2%)	232 (44.7%)	241 (46.0%)	233 (44.8%)	227 (43.7%)
Race						
Asian	4 (0.8%)	7 (1.4%)	7 (1.3%)	1 (0.2%)	2 (0.4%)	4 (0.8%)
Black	63 (12.0%)	55 (10.6%)	57 (11.0%)	32 (6.1%)	31 (6.0%)	33 (6.3%)
Caucasian	401 (76.7%)	409 (79.0%)	399 (76.9%)	443 (84.5%)	450 (86.5%)	445 (85.6%)
Hispanic	48 (9.2%)	41 (7.9%)	51 (9.8%)	36 (6.9%)	29 (5.6%)	33 (6.3%)
Other	7 (1.3%)	6 (1.2%)	5 (1.0%)	12 (2.3%)	8 (1.5%)	5 (1.0%)
Age (Years)						
Mean (SD)	44.5 (12.77)	44.1 (13.00)	43.7 (13.22)	46.7 (14.22)	47.3 (14.69)	46.0 (14.14)
Min/Max	18–86	19–86	18–79	20–84	18–84	18–79
Current Smoker						
Yes	120 (22.9%)	126 (24.3%)	136 (26.2%)	133 (25.4%)	101 (19.4%)	116 (22.3%)
Other Current Nicotine Use						
Yes	10 (1.9%)	18 (3.5%)	14 (2.7%)	8 (1.5%)	3 (0.6%)	10 (1.9%)
Alcohol Consumption						
Yes	245 (46.8%)	268 (51.7%)	266 (51.3%)	273 (52.1%)	276 (53.1%)	257 (49.4%)
Consume Caffeine-Containing Beverages						
Yes	462 (88.3%)	468 (90.3%)	460 (88.6%)	471 (89.9%)	461 (88.7%)	453 (87.1%)
Consume Other Caffeine-Containing Products						
Yes	339 (64.8%)	345 (66.6%)	326 (62.8%)	278 (53.1%)	289 (55.6%)	277 (53.3%)
Heartburn Frequency % of Days during Run-In						
Mean (SD)	74.3 (24.39)	73.7 (24.14)	75.2 (24.18)	74.2 (23.57)	74.3 (24.57)	74.2 (24.19)
≥50%	419 (80.1%)	424 (81.9%)	422 (81.3%)	426 (81.3%)	414 (79.6%)	417 (80.2%)

5.1.1.5 Efficacy Results: Day 1

Primary Efficacy Parameter (Heartburn-Free for 24 Hours)

Figure 5.2 displays results of the analyses for the primary efficacy parameter, Heartburn-Free for a Full Day (No Heartburn over 24 Hours) on Day 1. In each study, a significantly greater percentage of subjects in the Ome-Mg 10 and Ome-Mg 20 treatment groups were Heartburn-Free than in the placebo group ($p \leq 0.003$). In Study 171, Ome-Mg 20 had a significantly higher percentage of Heartburn-Free subjects than Ome-Mg 10 ($p = 0.008$), while in Study 183, the two doses produced similar levels of effectiveness.

FIGURE 5.2
PERCENT OF SUBJECTS WITH COMPLETE PREVENTION OF HEARTBURN — DAY 1



Efficacy for the primary variable for both doses was generally consistent across the 49 study centers in both trials. Ome-Mg 20 was numerically superior to placebo at 41 of the 49 study centers across both trials. Similarly, Ome-Mg 10 was numerically superior to placebo in 39 of the 49 study centers across both trials.

Day 1 Secondary Efficacy Parameters

Table 5.5 displays results of the analyses for both secondary efficacy parameters on Day 1. These efficacy results provide further evidence of the effectiveness of Ome-Mg in preventing heartburn. Both Ome-Mg 10 and Ome-Mg 20 were significantly superior to placebo in all analyses, with one exception (No Nocturnal Heartburn in Study 183). Observed differences between Ome-Mg 10 and Ome-Mg 20 were modest.

TABLE 5.5
ANALYSIS OF SECONDARY EFFICACY VARIABLES
PERCENTAGE OF SUBJECTS WITH NO NOCTURNAL AND NO MORE THAN MILD HEARTBURN ON DAY 1

MULTIPLE-DOSE PREVENTION STUDIES: HEARTBURN SYMPTOMS OVER A FULL DAY
INTENT-TO-TREAT SUBJECTS

	Ome-Mg 20	Ome-Mg 10	Placebo
No Nocturnal Heartburn[a]			
Study 171	**78.4%**[b]	**79.1%**[b]	70.4%
Study 183	77.7%	75.6%	73.9%
No More Than Mild Heartburn Over 24 Hours[a]			
Study 171	**81.0%**[b]	**79.0%**[b]	71.6%
Study 183	**81.8%**[b]	**78.0%**[b]	70.8%

[a] Percentage of subjects with indicated outcome. Treatment difference tested using Cochran-Mantel-Haenszel chi-square test with Investigator as a stratification variable.

[b] Comparisons with placebo that resulted in a *p*-values ≤ 0.05 are shaded and bolded in table.

Note: Comparison between Ome-Mg 10 and Ome-Mg 20 resulted in *p*-values > 0.05).

5.1.1.6 Efficacy Results: Across 14 Days

Figure 5.3 and Table 5.6 present a summary of efficacy analyses performed on data collected during the 14-day double-blinded treatment phase for the primary and both secondary parameters.

FIGURE 5.3
PERCENT OF DAYS WITH NO HEARTBURN — OVER 14 DAYS

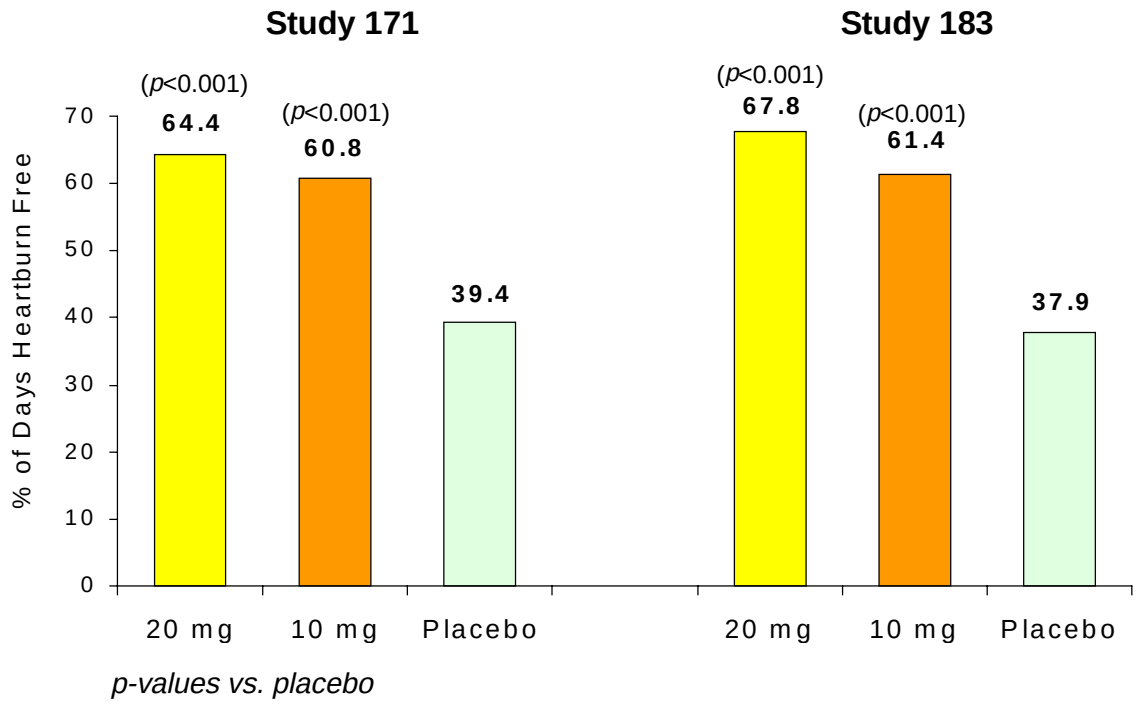


TABLE 5.6
MEAN PERCENTAGE OF DAYS (ADJUSTED) WITH INDICATED OUTCOME OVER 14 DAYS OF DOUBLE-BLIND PHASE[a]

MULTIPLE-DOSE PREVENTION STUDIES: HEARTBURN SYMPTOMS OVER A FULL DAY INTENT-TO-TREAT SUBJECTS

	Ome-Mg 20	Ome-Mg 10	Placebo
No Nocturnal Heartburn[b]			
Study 171	**84.7%[c]**	**83.5%[c]**	74.5%
Study 183	**86.1%[c,d]**	**82.5%[c]**	75.4%
No More Than Mild Heartburn Over 24 Hours[b]			
Study 171	**88.6%[c]**	**86.8%[c]**	75.9%
Study 183	**88.6%[c]**	**86.1%[c]**	73.7%

[a] Percentage based on number of days with valid data. Subjects with less than 5 days of valid data were excluded from this analysis.

[b] Estimated mean percent of days with indicated outcome (least squares mean from ANOVA model with Treatment and Investigator as factors). Treatment difference tested using t-test.

[c] Comparisons with placebo that resulted in *p*-values ≤ 0.05 are shaded and bolded in table.

[d] Comparisons between Ome-Mg 10 and Ome-Mg 20 that resulted in *p*-values ≤ 0.05 are shaded and bolded in table.

With consecutive daily dosing, Ome-Mg-treated subjects had a significantly greater percentage of Heartburn-Free days than did placebo-treated subjects (Figure 5.3). Additionally, Ome-Mg-treated subjects also had a greater percentage of nights with No Nocturnal Heartburn symptoms. Consecutive daily dosing with Ome-Mg also resulted in a greater percentage of days with No More than Mild heartburn versus placebo. For all outcomes, Ome-Mg provided significantly greater protection against heartburn than placebo in both studies. In Study 183, Ome-Mg 20 was significantly more effective than Ome-Mg 10 for percentage of Heartburn-Free days and percentage of nights with No Nocturnal Heartburn.

As seen in Table 5.7, these results are generally corroborated by a GEE analysis of the data across all 14 days.

Outcomes During 2-Week Follow-up Phase

After discontinuation of study medication at the end of the active treatment phase, there was some short-term residual benefit associated with Ome-Mg. In both studies, occurrence of heartburn symptoms for the Ome-Mg 20, Ome-Mg 10, and placebo groups was comparable beyond Day 3 in Study 183 or Day 4 in Study 171 (Figure 5.4).

TABLE 5.7
ANALYSIS OF EFFICACY VARIABLES USING GEE
TREATMENT COMPARISONS BASED ON ALL 14 DAYS OF DOUBLE-BLIND PHASE
MULTIPLE-DOSE PREVENTION STUDIES: HEARTBURN SYMPTOMS OVER A FULL DAY
INTENT-TO-TREAT SUBJECTS

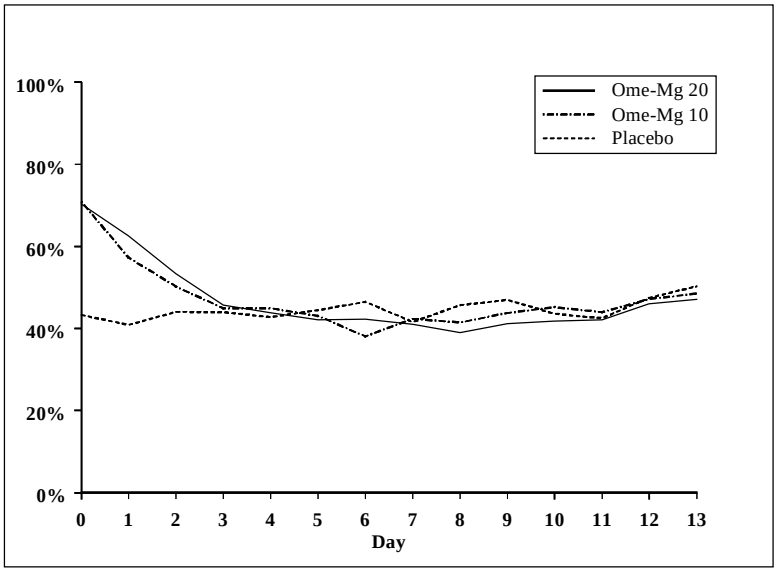
	Ome-Mg 20 vs. Placebo			Ome-Mg 10 vs. Placebo			Ome-Mg 20 vs. Ome-Mg 10		
	Odds Ratio[a]	**95% CI[a]**	***p*-value[b]**	**Odds Ratio[a]**	**95% CI[a]**	***p*-value[b]**	**Odds Ratio[a]**	**95% CI[a]**	***p*-value[b]**
No Heartburn Over 24 Hours									
Study 171	2.90	(2.46, 3.42)	**<0.001**	2.46	(2.09, 2.89)	**<0.001**	1.18	(1.00, 1.40)	**0.050**
Study 183	3.61	(3.06, 4.26)	**<0.001**	2.73	(2.33, 3.21)	**<0.001**	1.32	(1.12, 1.56)	**<0.001**
No Nocturnal Heartburn									
Study 171	1.90	(1.57, 2.30)	**<0.001**	1.69	(1.40, 2.03)	**<0.001**	1.12	(0.92, 1.38)	0.259
Study 183	1.98	(1.64, 2.38)	**<0.001**	1.51	(1.26, 1.82)	**<0.001**	1.30	(1.06, 1.60)	**0.011**
No More Than Mild Heartburn Over 24 Hours									
Study 171	2.40	(1.97, 2.93)	**<0.001**	1.96	(1.62, 2.37)	**<0.001**	1.23	(0.99, 1.51)	0.059
Study 183	2.67	(2.20, 3.24)	**<0.001**	2.13	(1.77, 2.57)	**<0.001**	1.25	(1.01, 1.55)	**0.042**

[a] Estimated odds ratio and 95% confidence interval (CI) obtained from GEE model with Treatment, Center, and Day as categorical explanatory variables (exchangeable correlation assumed). Robust variance estimate used. The odds ratio is the ratio of the estimated odds of having the indicated outcome in the first group relative to the second group shown. See Section 8.7.2.2.8.3 of the NDA for a discussion of significant interactions between Treatment and Day which are not reflected in the models above.

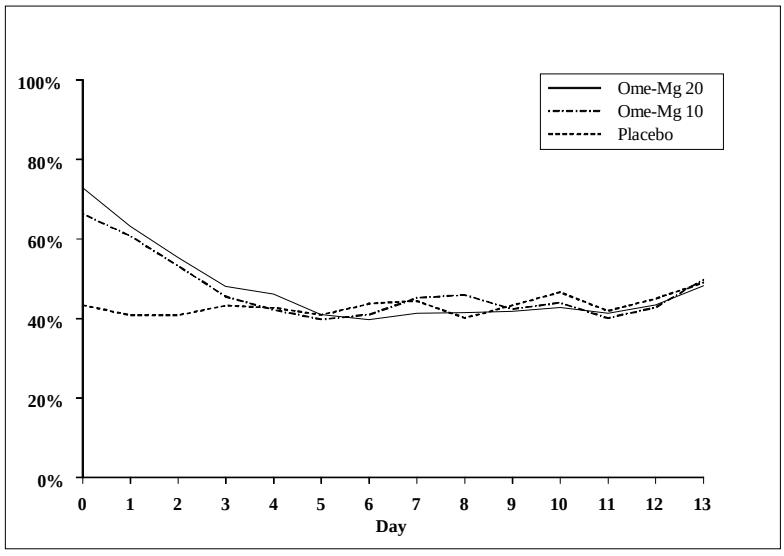
[b] *p*-values for treatment comparisons from Wald chi-square test. *p*-values ≤ 0.05 are shaded and bolded in table.

FIGURE 5.4
PERCENTAGE OF SUBJECTS WITH NO HEARTBURN OVER 24 HOURS
BY DAY AFTER END OF DOUBLE-BLIND PHASE
PER PROTOCOL SUBJECTS WHO ENTER FOLLOW-UP PHASE

STUDY 171



STUDY 183



5.1.2 Single-Dose Prevention Trials (005 and 006)

Studies 005 and 006 evaluated the safety and efficacy of Ome-Mg in the prevention of heartburn symptoms when given 1 hour preceding the ingestion of food and beverage.

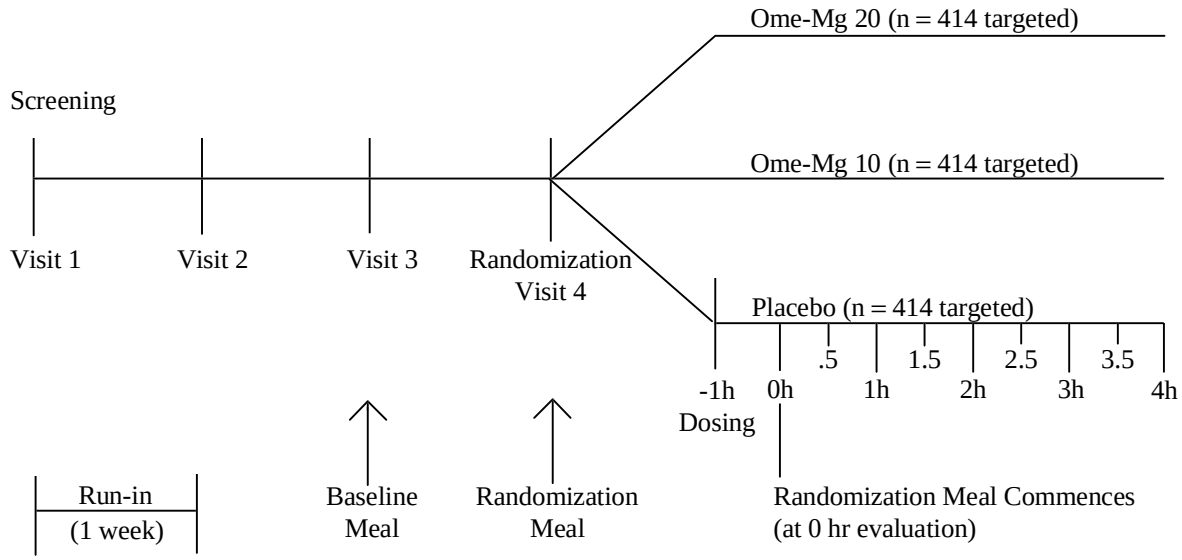
5.1.2.1 Rationale

While Studies 171 and 183 were designed to accommodate Ome-Mg's long duration of action, the drug's pharmacodynamic profile also suggests that acid inhibition begins as early as 1 hour after dosing.[27] The provocative meal model established in the approval programs of the H_2RAs is a suitable method of testing the ability of Ome-Mg to prevent heartburn when dosed 1 hour before an offending event. A rigorous efficacy endpoint, complete prevention of heartburn over the entire 4-hour postprandial period, was chosen as the primary endpoint.

5.1.2.2 Study Design and Considerations

Both Studies 005 and 006 were multi-center, double-blind, randomized, single-dose, placebo-controlled, double-dummy, parallel, in-clinic studies. Figure 5.5 presents a schematic of the study design.

FIGURE 5.5
STUDY SCHEMATIC FOR SINGLE-DOSE HEARTBURN PREVENTION TRIALS



The primary efficacy variable was: Percentage of subjects who were Heartburn-Free over the entire 4-hour period after the meal (i.e., symptom severity score of None at all time points).

Secondary efficacy variables included:

Symptom Amelioration

- Maximum Symptom Severity Score over the 4-hour post-prandial period,
- Reduction of Maximum Severity Score from the analogous score following the Baseline meal, and
- Average Symptom Severity Score over the 4-hour post-prandial period.

Treatment Failure

- Percentage of Subjects who took Backup Medication (Gelusil) during the 4-hour post-prandial period, and
- Time to Backup Medication (Gelusil) use.

Overall Assessment

- Overall Assessment of the study medication at the end of the 4-hour post-prandial period.

Subjects recorded heartburn symptom severity (using the scale described in Section 5) immediately before consuming the provocative meals and at half-hour intervals for 4 hours. The recording of heartburn symptoms was supervised by study center staff.

Subjects also provided an Overall Assessment of the study medication at the end of the 4-hour evaluation period or upon taking Gelusil, a backup medication, by responding to the question, "Overall, how would you rate the study medication?" Subjects responded using the five-point scale in Section 5.

5.1.2.3 Statistical Methods

A Cochran-Mantel-Haenszel test statistic was used to compare treatment effects for the Heartburn-Free variable and incidence of Backup Medication Use. The Overall Assessment and Maximum Symptom Severity Score were analyzed using an Extended-Mantel-Haenszel test. A logistic regression analysis was used to compute odds ratios for treatment comparisons and to assess Treatment-by-Investigator interaction. In addition, an ANOVA was used to assess treatment effects for Average Symptom Severity Score and Reduction of Maximum Symptom Severity Score from the Baseline meal. A Cox proportional hazards model was used to analyze Time to Backup Medication Use.

5.1.2.4 Demographics and Other Baseline Characteristics

Collectively, 2,458 subjects were randomized to treatment across 30 different clinical sites in Trials 005 and 006. A total of 2,454 subjects were included in the ITT dataset for statistical analysis: 1,641 to active medication and 813 to placebo. The four randomized subjects excluded from the ITT dataset either did not dose with study medication or recorded no efficacy data.

Table 5.8 presents a summary of demographic and other baseline characteristics across by treatment group and trial. The distribution of patients for these variables was similar across treatment groups and trials.

TABLE 5.8
DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS (STUDIES 005 AND 006)

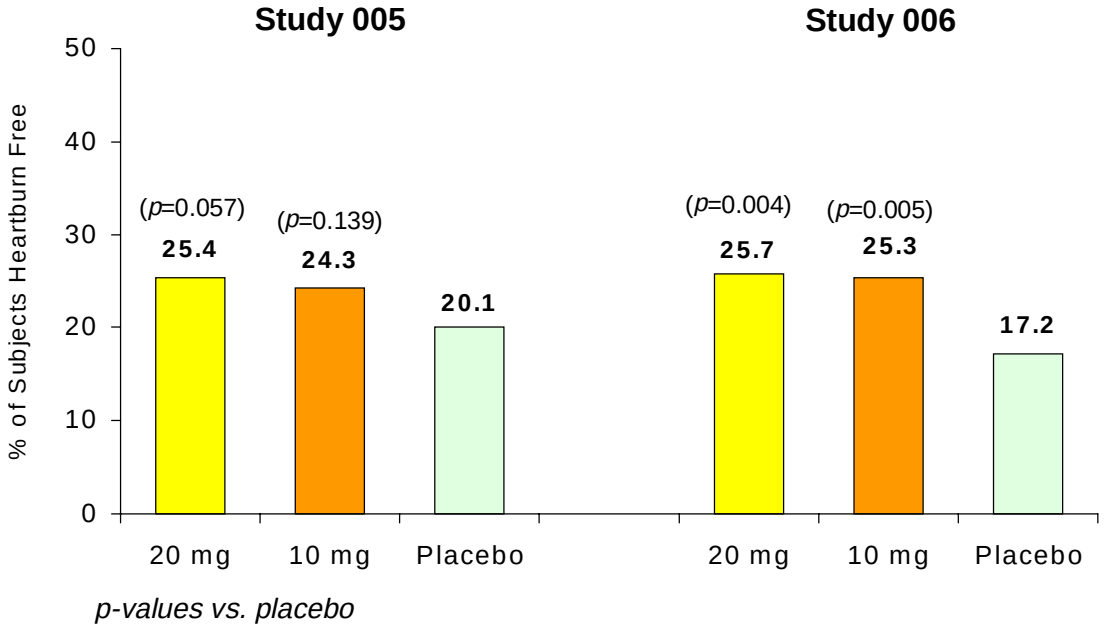
	005			006		
	Ome-Mg 20 (N=433)	**Ome-Mg 10 (N=428)**	**Placebo (N=423)**	**Ome-Mg 20 (N=393)**	**Ome-Mg 10 (N=387)**	**Placebo (N=390)**
Gender						
Female	273 (63.0%)	283 (66.1%)	260 (61.5%)	233 (59.3%)	226 (58.4%)	231 (59.2%)
Male	160 (37.0%)	145 (33.9%)	163 (38.5%)	160 (40.7%)	161 (41.6%)	159 (40.8%)
Race						
Asian	2 (0.5%)	1 (0.2%)	3 (0.7%)	0 (0.0%)	3 (0.8%)	0 (0.0%)
Black	75 (17.3%)	69 (16.1%)	75 (17.7%)	53 (13.5%)	27 (7.0%)	44 (11.3%)
Caucasian	337 (77.8%)	335 (78.3%)	322 (76.1%)	326 (83.0%)	345 (89.1%)	335 (85.9%)
Hispanic	14 (3.2%)	14 (3.3.%)	17 (4.0%)	12 (3.1%)	5 (1.3%)	10 (2.6%)
Other	5 (1.2%)	9 (2.1%)	6 (1.4%)	2 (0.5%)	7 (1.8%)	1 (0.3%)
Age (Years)						
Mean (SD)	42.8 (12.75)	42.7 (12.92)	42.7 (13.27)	42.2 (12.93)	44.6 (13.34)	43.4 (13.55)
Min–Max	18–78	18–86	18–81	18–93	19–80	18–81
Current Smoker						
Yes	126 (29.1%)	119 (27.8%)	118 (27.9%)	118 (30.0%)	131 (33.9%)	113 (29.0%)
Current Use Of Other Nicotine Products						
Yes	10 (2.3%)	9 (2.1%)	8 (1.9%)	8 (2.0%)	6 (1.6%)	5 (1.3%)
Currently Consume Alcohol						
Yes	191 (44.1%)	195 (45.6%)	165 (39%)	168 (42.7%)	157 (40.6)	162 (41.5%)
Currently Consume Caffeine - Containing Beverages						
Yes	397 (91.7%)	406 (94.9%)	393 (92.9%)	361 (91.9%)	355 (91.7%)	356 (91.3%)
Currently Consume Other Caffeine - Containing Products						
Yes	298 (68.8%)	271 (63.3%)	264 (62.4%)	306 (77.9%)	286 (73.9%)	286 (73.3%)

5.1.2.5 Efficacy Results

Primary Parameter

Figure 5.6 displays results of the analyses for the primary efficacy parameter, Complete Prevention of Heartburn (or Heartburn-Free over 4 hours). A significantly ($p \leq 0.005$) greater proportion of subjects on Ome-Mg 20 (25.7%) and Ome-Mg 10 (25.3%) were Heartburn-Free after the meal than placebo-treated subjects (17.2%) in Study 006 but not Study 005 (see *p*-values and treatment differences in Figure 5.6).

FIGURE 5.6
PERCENT OF SUBJECTS WITH COMPLETE PREVENTION OF HEARTBURN



Secondary Parameters

Table 5.9 displays results of the analyses for the secondary efficacy parameters.

TABLE 5.9
ANALYSIS OF SECONDARY EFFICACY VARIABLES

SINGLE DOSE PREVENTION STUDIES: HEARTBURN ASSOCIATED WITH A PROVOCATIVE MEAL
INTENT-TO-TREAT SUBJECTS

	Ome-Mg 20	Ome-Mg 10	Placebo
Maximum Severity Score[b]			
Study 005	**75.3%[e]**	**72.0%[e]**	66.2%
Study 006	**76.6%[e]**	**73.1%[e]**	63.1%
Reduction of Maximum Severity Scores[d]			
Study 005	**-1.31[e]**	-1.20	-1.10
Study 006	**-1.35[e]**	**-1.25[e]**	-1.06
Average Symptom Severity[d]			
Study 005	**0.49[e]**	0.50	0.56
Study 006	**0.44[e]**	**0.47[e]**	0.60
Backup Medication Use (within 4 Hours)[c]			
Study 005	**4.4%[e]**	7.0%	8.3%
Study 006	**1.8%[e]**	**3.6%[e]**	6.4%
Overall Assessment[a]			
Study 005	**77.3%[e]**	70.6%	69.2%
Study 006	**81.1%[e]**	**76.7%[e]**	71.8%

[a] Percentage of subjects with Good, Very Good, and Excellent ratings on Overall Assessment of study medication.
All levels of this variable were utilized for testing for treatment differences using Extended-Mantel-Haenszel chi-square test with Investigator as a stratification variable.

[b] Percentage of subjects with None or Mild scores on maximum severity. All levels of this variable were utilized for testing for treatment differences using Extended-Mantel-Haenszel chi-square test with Investigator as a stratification variable.

[c] Percentage of subjects who took backup medication, treatment difference was tested using Cochran-Mantel Haenszel chi-square test with Investigator as a stratification variable.

[d] Least-square means from ANOVA with Treatment and Investigator as factors.

[e] Comparisons with placebo that resulted in *p*-values of ≤ 0.05 are bolded in table.

Note: Comparisons between Ome-Mg 10 and Ome-Mg 20 resulted in *p*-values > 0.05.

The secondary variables have been grouped into three categories, each of which are discussed below.

Symptom Amelioration: This category contains the variables Maximum Severity Score, Reduction in Maximum Severity Score, and Average Symptom Severity Score over the 4-hour post-prandial period. Table 5.9 shows that Ome-Mg 20 was more effective than placebo for each of these symptom amelioration variables. Ome-Mg 10 was more effective in Study 006 for Reduction of Maximum Severity Score and for Average Symptom Severity Score.

Treatment Failure: This category contains the variables Backup Medication Use and Time to Taking Backup Medication (not shown in Table 5.9). Ome-Mg 20 was more effective than placebo in reducing the need for backup medication in both studies; Ome-Mg 10 was more effective in one study.

Overall Assessment: The Overall Assessment of study medication represents the subjects' assessment of whether the study medication was beneficial for their heartburn. Table 5.9 shows that Ome-Mg 20 was rated significantly higher than placebo in both studies while Ome-Mg 10 was rated higher in only Study 006.

5.1.3 Efficacy Conclusions from Prevention Trials

The following conclusions are supported from the data presented from the four heartburn prevention trials in which approximately 3,700 subjects on active medication were studied.

- Ome-Mg 10 and Ome-Mg 20 are more effective than placebo in prevention for up to a full 24 hours after dosing, including nocturnal HB and as soon as 1 hour before a provocative meal.

- Ome-Mg 10 and Ome-Mg 20 provides a benefit in complete prevention of heartburn in a natural setting.

- With consecutive daily dosing, the incremental benefit over placebo was greater for both Ome-Mg 10 and Ome-Mg 20.

- The clinical benefits were more perceivable to the study subjects who received both Ome-Mg 10 and Ome-Mg 20 than placebo based on Overall Assessment (measured in single-dose studies only).

5.2 Heartburn Treatment Trials (092 and 095)

Studies 092 and 095 were conducted to support labeling for OTC use of Ome-Mg in the relief of occasional, episodic heartburn symptoms of unspecified cause in a naturalistic setting.

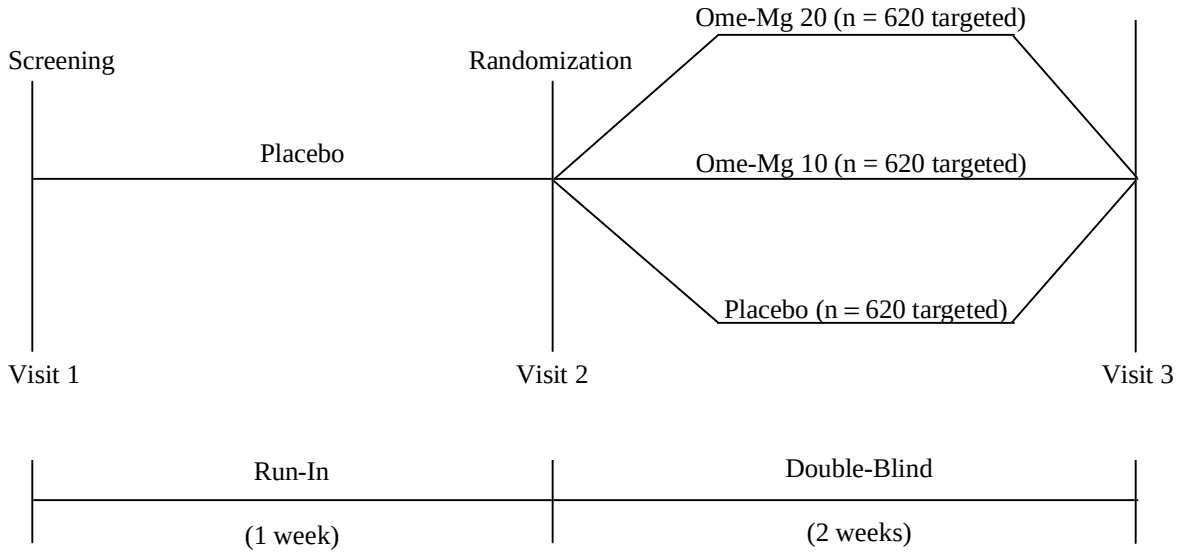
5.2.1 Rationale

The trials undertaken to establish efficacy of Ome-Mg to relieve symptoms after they occur allowed subjects to dose prn, once daily, over a 2-week period so that efficacy could be investigated following the first treated episode as well as with episodic dosing. The same overall design was employed as that used in the repeat dose prevention trial except that subjects were instructed to take medication only after they experienced heartburn.

5.2.2 Study Design and Clinical Methodology

Both studies were randomized, parallel, double-blind, double-dummy, and placebo-controlled. A 1-week single-blind, placebo run-in phase preceded the 2-week double-blind, randomized treatment phase. A schematic of the design follows:

FIGURE 5.7
STUDY SCHEMATIC FOR MULTI-DOSE HEARTBURN TREATMENT TRIALS



The primary efficacy variable was the occurrence of Sustained Complete Relief (i.e., Complete relief within the first hour after dosing [inclusive] and sustaining the Complete rating through [and including] the third hour after dosing). Other endpoints, such as Sustained Adequate Relief, use of Backup Medication, and Overall Assessment, were also measured. Efficacy was evaluated following the first-treated episode, across all treated episodes, and after the last-treated episode.

Secondary efficacy variables included:

Complete Relief
- Occurrence of Complete Relief after the first-treated episode, last-treated episode, and across all treated episodes,
- Time to Sustained Complete Relief after the first-treated episode and last-treated episode, and
- Time to Complete Relief after the first-treated episode and last-treated episode.

Symptom Amelioration
- Occurrence of Sustained Adequate Relief after the first-treated episode, last-treated episode, and across all treated episodes, and
- Occurrence of Adequate Relief after the first-treated episode, last-treated episode, and across all treated episodes.

Treatment Failure

- Backup Medication (Gelusil) Use after the first-treated episode, last-treated episode, and across all treated episodes, and
- Time to Backup Medication (Gelusil) Use after the first-treated episode and last-treated episode.

Overall Assessment

- Overall Assessment of Study Medication after the first-treated episode, last-treated episode, and across all treated episodes.

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

Subjects recorded relief scores at 10-minute intervals for the first hour and then at 2 hours and 3 hours following consumption of each dose of study medication using the relief scale given in Section 5. Subjects were instructed not to eat or drink anything during 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 that heartburn episode.

Subjects gave an Overall Assessment of the study medication 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.

5.2.3 Statistical Methods

A Cochran-Mantel-Haenszel test was used to assess treatment differences for Sustained Complete Relief, Complete Relief within the First Hour, Sustained Adequate Relief, Adequate Relief within the First Hour, and Backup Medication Use for the subjects' first-treated and last-treated heartburn episodes. An Extended Mantel-Haenszel test was used to assess treatment differences for the Overall Assessment after the first-treated and last-treated episodes. Logistic regression analyses were used on the above variables to estimate odds ratios for all treatment comparisons and to assess potential Treatment-by-Covariate interactions. A stratified log rank (or log rank) test was used to analyze the Time-to-Event variables. GEE were used to assess treatment differences for the above variables across all treated heartburn episodes.

5.2.4 Demographics and Other Baseline Characteristics

Collectively, 3,791 subjects were randomized to treatment in 49 clinical study centers across Trials 092 and 095. A total of 3,721 subjects were included in the ITT dataset for statistical analysis: 2,492 to active medication and 1,229 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 5.10).

TABLE 5.10
DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS (STUDIES 092 AND 095)

Study	092			095		
Characteristic	**Ome-Mg 20 (N=621)**	**Ome-Mg 10 (N=621)**	**Placebo (N=627)**	**Ome-Mg 20 (N=627)**	**Ome-Mg 10 (N=623)**	**Placebo (N=602)**
Gender						
Female	306 (49.3%)	304 (49.0%)	295 (47.0%)	329 (52.5%)	326 (52.3%)	337 (56.0%)
Male	315 (50.7%)	317 (51.0%)	332 (53.0%)	298 (47.5%)	297 (47.7%)	265 (44.0%)
Race						
Asian	10 (1.6%)	7 (1.1%)	5 (0.8%)	2 (0.3%)	2 (0.3%)	2 (0.3%)
Black	81 (13.0%)	83 (13.4%)	75 (12.0%)	102 (16.3%)	79 (12.7%)	89 (14.8%)
Caucasian	511 (82.3%)	514 (82.8%)	526 (83.9%)	508 (81.0%)	529 (84.9%)	501 (83.2%)
Hispanic	16 (2.6%)	16 (2.6%)	18 (2.9%)	13 (2.1%)	12 (1.9%)	6 (1.0%)
Other	3 (0.5%)	1 (0.2%)	3 (0.5%)	2 (0.3%)	1 (0.2%)	4 (0.7%)
Age (Years)						
Mean (SD)	44.8 (13.66)	43.9 (13.53)	44.7 (13.41)	44.6 (12.69)	44.4 (12.69)	43.2 (12.60)
Min–Max	18–87	18–89	18–89	18–81	18–77	18–82
Current Smoker						
Yes	166 (26.7%)	152 (24.5%)	195 (31.1%)	195 (31.1%)	197 (31.6%)	161 (26.7%)
Other Current Nicotine Use						
Yes	19 (3.1%)	16 (2.6%)	8 (1.3%)	6 (1.0%)	9 (1.4%)	8 (1.3%)
Current Alcohol Consumption Drinks per Week						
Yes	276 (44.4%)	283 (45.6%)	294 (46.9%)	288 (46.0%)	300 (48.2%)	282 (46.8%)
Currently Consume Caffeine-Containing Beverages						
Yes	553 (89.0%)	548 (88.2%)	548 (87.4%)	536 (85.5%)	543 (87.2%)	506 (84.1%)
Currently Consume Other Caffeine-Containing Products						
Yes	419 (67.5%)	426 (68.6%)	410 (65.4%)	325 (51.8%)	336 (53.9%)	323 (53.7%)
Heartburn Frequency % of days During Placebo Run-in Phase						
Mean (SD)	60.8 (22.96)	59.8 (21.87)	60.5 (22.92)	59.8 (21.97)	59.9 (21.95)	58.6 (21.23)
≥50%	376 (60.5%)	364 (58.6%)	356 (56.8%)	364 (58.1%)	359 (57.6%)	340 (56.5%)

5.2.5 Efficacy Results: Effects Following First-Treated Episode

Sustained Complete Relief and Sustained Adequate Relief

Figures 5.8 and 5.9 display results of the analyses for the primary efficacy parameter following the first dose, Sustained Complete Relief, and for the secondary variable Sustained Adequate Relief. No differences were seen among the three treatment groups for Sustained Complete Relief, but a significantly (p<0.003) greater proportion of subjects for Ome-Mg 20 reported Sustained Adequate Relief after the first-treated episode than placebo-treated subjects in Study 095. Results of the three additional single-dose trials (Appendix 2) did not corroborate this finding.

FIGURE 5.8
PERCENT OF EPISODES WITH SUSTAINED COMPLETE RELIEF — FIRST-TREATED EPISODE

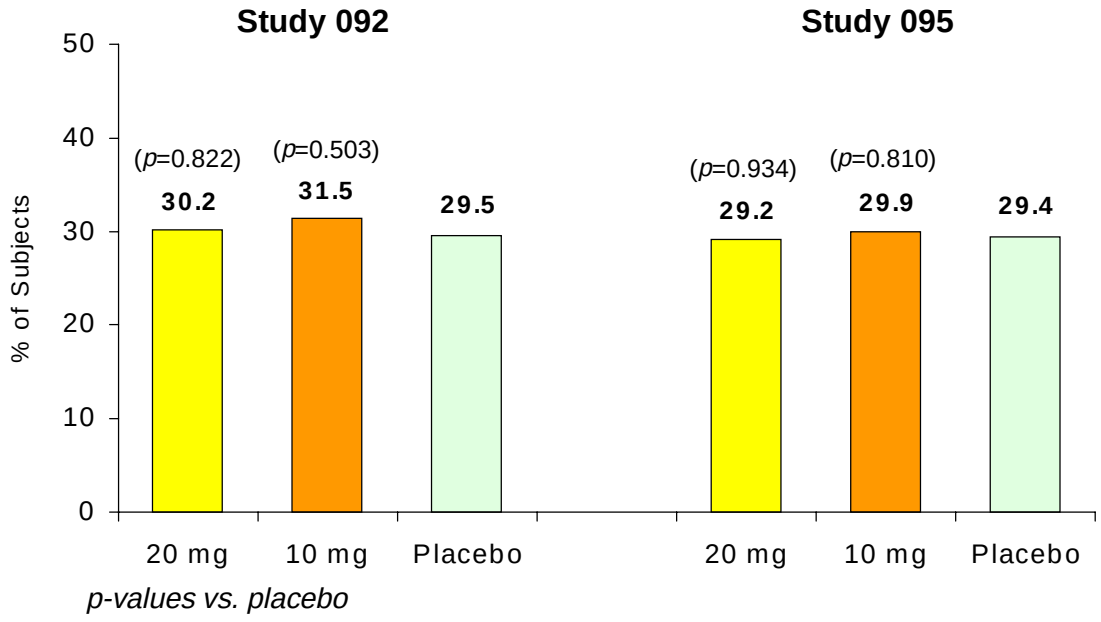
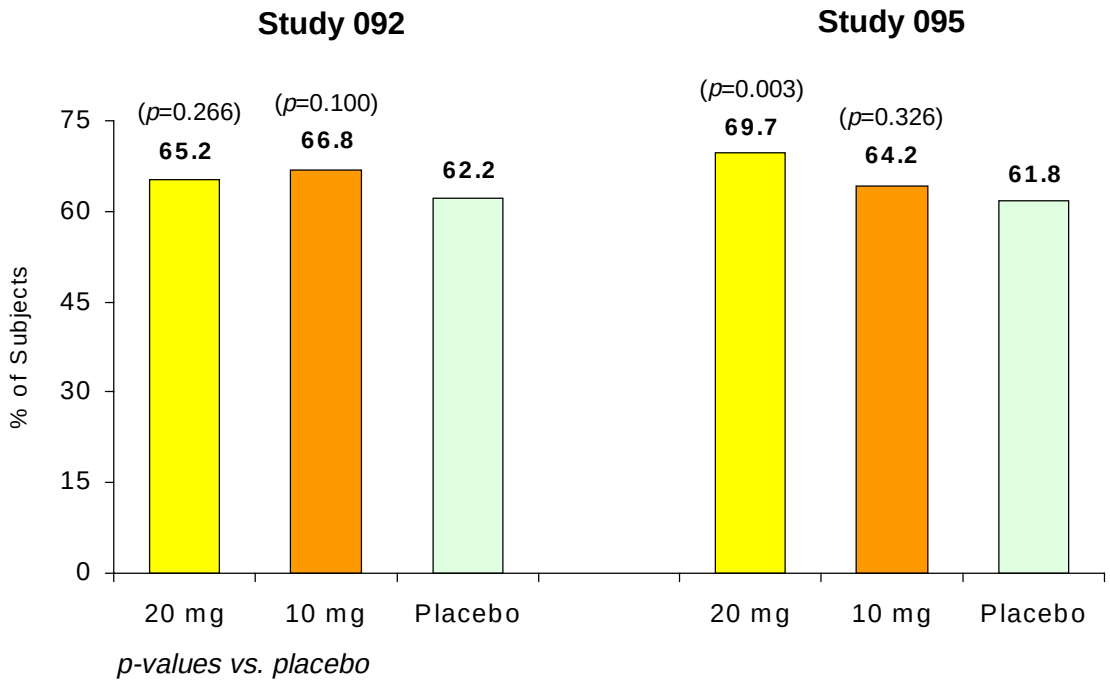


FIGURE 5.9
PERCENT OF EPISODES WITH SUSTAINED ADEQUATE RELIEF — FIRST-TREATED EPISODE



Other Efficacy Parameters

Table 5.11 displays analyses of the remaining efficacy parameters for the first treated episode. Differences in efficacy ($p<0.05$) between either dose level and placebo are shaded and bolded in the table.

TABLE 5.11
ANALYSIS OF SECONDARY EFFICACY VARIABLES
PERCENTAGE OF SUBJECTS WITH INDICATED OUTCOME
FIRST-TREATED EPISODE OF HEARTBURN
MULTIPLE DOSE TREATMENT STUDIES: HEARTBURN OF UNSPECIFIED CAUSE
INTENT-TO-TREAT SUBJECTS

	Ome-Mg 20	Ome-Mg 10	Placebo
Complete Relief within 1 Hour[a]			
Study 092	32.7%	34.2%	32.5%
Study 095	31.9%	33.7%	31.6%
Adequate Relief within 1 Hour[a]			
Study 092	72.3%	75.3%	71.0%
Study 095	**75.6%[c]**	72.7%	69.6%
Backup Medication Use[a]			
Study 092	6.9%	7.2%	9.6%
Study 095	**5.9%[c]**	8.2%	9.1%
Overall Assessment of Study Medication[b]			
Study 092	54.7%	56.3%	50.8%
Study 095	**57.3%[c]**	**56.4%[c]**	47.4%

[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.

[c] Comparisons with placebo that resulted in p-values ≤ 0.05 are bolded in table.

5.2.6 Efficacy Results: Across All Treated Episodes

Figures 5.10 and 5.11 display results of the analyses across all treated episodes for Sustained Complete Relief and Sustained Adequate Relief. Both Ome-Mg 10 and Ome-Mg 20 provided significant Sustained Adequate Relief relative to placebo (Figure 5.11); and Ome-Mg 20 provided the more stringent Sustained Complete Relief (Figure 5.10).

FIGURE 5.10
PERCENT OF EPISODES WITH SUSTAINED COMPLETE RELIEF
ALL TREATED EPISODES (GEE ANALYSES)

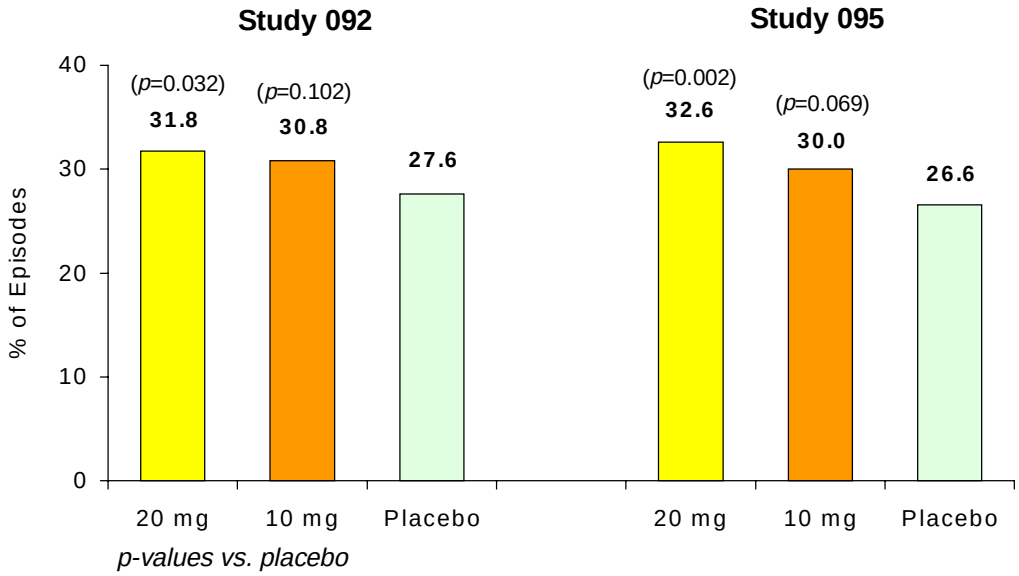


FIGURE 5.11
PERCENT OF EPISODES WITH SUSTAINED ADEQUATE RELIEF
ALL TREATED EPISODES (GEE ANALYSES)

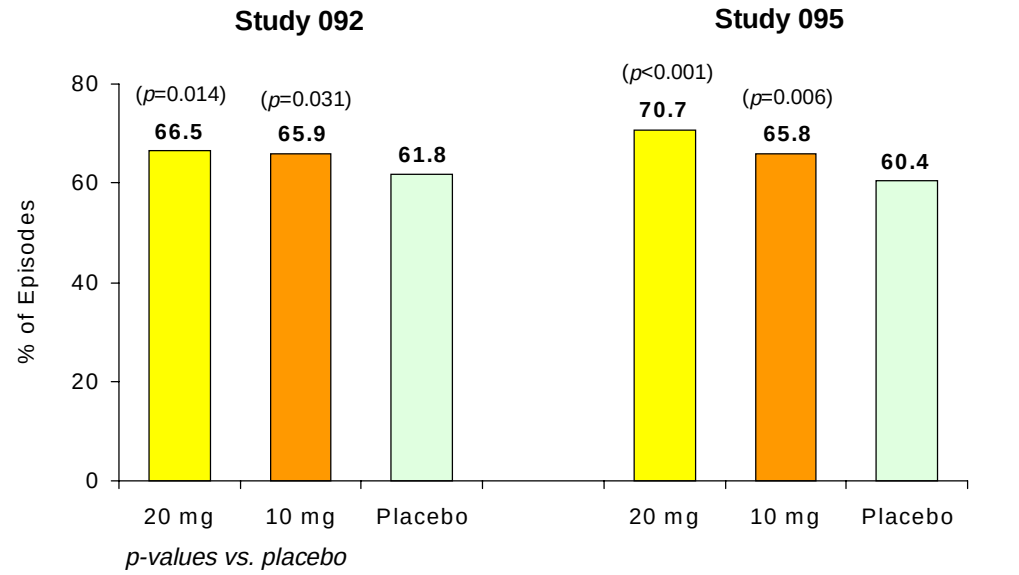


Table 5.12 displays the results for remaining measures. Results are grouped into the four following categories:

Complete Relief of Heartburn (Sustained Complete Relief and Complete Relief within 1 Hour): These variables show that Ome-Mg 20 provides a benefit relative to placebo across all treated episodes for Sustained Complete Relief (Figure 5.10) and Complete Relief within 1 Hour (Table 5.12).

Symptom Amelioration (Sustained Adequate Relief and Adequate Relief): Subjects on either Ome-Mg 20 or Ome-Mg 10 have greater odds of having Sustained Adequate Relief and Adequate Relief within 1 hour across all treated episodes than placebo-treated subjects (Table 5.12).

Treatment Failure (Backup Medication Use): Table 5.12 shows that Ome-Mg 20 was more effective than placebo in reducing the need for backup medication across all treated episodes in both studies. For Ome-Mg 10, the need for backup medications was reduced in Study 092, but not in Study 095.

Overall Assessment of Study Medication: Table 5.12 shows that both Ome-Mg 10 and Ome-Mg 20 were rated higher than placebo by the study subjects for overall beneficial effects in treating heartburn across all treated episodes.

Table 5.12
Analysis of Efficacy Variables Using GEE
Treatment Comparisons Based on All Treated Episodes
During the Active Treatment Phase

Multiple Dose Treatment Studies: Heartburn of Unspecified Cause
Intent-to-Treat Subjects

	Ome-Mg 20 vs. Placebo			Ome-Mg 10 vs. Placebo			Ome-Mg 20 vs. Ome-Mg 10		
	Odds Ratio[a]	**95% CI[a]**	***p*-value[b]**	**Odds Ratio[a]**	**95% CI[a]**	***p*-value[b]**	**Odds Ratio[a]**	**95% CI[a]**	***p*-value[b]**
Complete Relief within 1 Hour									
Study 092	1.19	(0.99, 1.44)	0.064	1.17	(0.97, 1.41)	0.106	1.02	(0.85, 1.23)	0.803
Study 095	1.35	(1.12, 1.62)	**0.002**	1.24	(1.02, 1.50)	**0.029**	1.09	(0.90, 1.31)	0.370
Sustained Adequate Relief									
Study 092	1.25	(1.05, 1.49)	**0.014**	1.21	(1.02, 1.44)	**0.031**	1.03	(0.86, 1.23)	0.732
Study 095	1.58	(1.32, 1.88)	**<0.001**	1.27	(1.07, 1.51)	**0.006**	1.24	(1.04, 1.48)	**0.017**
Adequate Relief within 1 Hour									
Study 092	1.19	(0.98, 1.44)	0.073	1.16	(0.96, 1.40)	0.122	1.03	(0.84, 1.25)	0.792
Study 095	1.54	(1.27, 1.87)	**<0.001**	1.28	(1.06, 1.54)	**0.009**	1.20	(0.99, 1.46)	0.065
Backup Medication Use									
Study 092	0.74	(0.57, 0.97)	**0.030**	0.64	(0.49, 0.83)	**0.001**	1.17	(0.88, 1.55)	0.279
Study 095	0.71	(0.53, 0.94)	**0.018**	0.90	(0.69, 1.17)	0.443	0.79	(0.59, 1.04)	0.095
Overall Assessment of Study Medication									
Study 092	1.38	(1.15, 1.66)	**<0.001**	1.38	(1.15, 1.65)	**<0.001**	1.00	(0.83, 1.20)	0.982
Study 095	1.65	(1.37, 1.98)	**<0.001**	1.42	(1.18, 1.70)	**<0.001**	1.16	(0.97, 1.39)	0.108

[a] Estimated odds ratio and CI obtained from GEE model with Treatment, Investigator, and Episode as categorical explanatory variables (exchangeable 95% correlation assumed). Robust variance estimate used. The odds ratio is the ratio for the estimated odds of having the indicated outcome in the first group relative to the second group shown.

[b] *p*-value for treatment comparisons using Wald chi-square test. *p*-values ≤ 0.05 are shaded and bolded in table.

In the all-episode (GEE) analyses for both studies, a statistically significant Treatment-by-Episode interaction ($p \leq 0.10$ at the significance level $\alpha = 0.1$) was detected for the Sustained Complete Relief. In Study 092, when the first-treated episode was removed from the model, little evidence of Treatment-by-Episode interaction remained for Sustained Complete Relief ($p = 0.170$). In Study 095, when the first-treated episode was removed from the model, the Treatment-by-Episode interaction *p*-value was increased from 0.003 to 0.044; however, the interaction was not completely removed. This suggests that the first-episode results are inconsistent with the results for other treated episodes over the 2-week period.

In each study, after eliminating the first-treated episode from the GEE model, the treatment effect for Ome-Mg 20 versus (vs.) placebo for Sustained Complete Relief remained ($p \leq 0.020$). The Ome-Mg 10 vs. placebo comparison *p*-values for Study 092 remained between 0.05 and 0.10 and the Study 095 treatment effect for Ome-Mg 10 vs. placebo became $p = 0.044$. In addition, small numerical improvements were observed in the estimated treatment effects (expressed as odds ratios relative to placebo).

These analyses show that, relative to placebo, both doses of Ome-Mg are effective on average over the 14-day active treatment period.

5.2.7 Efficacy Results: Last-Treated Episodes

Results of analyses performed on efficacy parameters associated with the last-treated episode were similar to those presented from the all-treated episodes analyses.

5.2.8 Efficacy Conclusions for Relief Trials

The following conclusions are supported from the data presented from the two heartburn relief trials discussed in this section plus the three trials discussed in Appendix 2:

- Ome-Mg 10 and Ome-Mg 20 do not provide Sustained Complete Relief of the first heartburn episode.

- Ome-Mg 10 and Ome-Mg 20 are more effective than placebo in relieving heartburn symptoms across all episodes over a 2-week period in a population of people who suffer from episodic heartburn.

- Sustained Adequate Relief of heartburn symptoms was demonstrated for both Ome-Mg 10 and Ome-Mg 20 across all treated episodes. Ome-Mg 20 provided Sustained Complete Relief across all episodes.

- The clinical effects were more perceivable to the study subjects who received both Ome-Mg 10 and Ome-Mg 20 than placebo based on Overall Assessment after each treated episode (both studies).