

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-229

STATISTICAL REVIEW(S)

NDA #21-229

Name of the Drug: Prilosec (Omeprazole Magnesium) Delayed-Release Tablets

Sponsor: The Proctor and Gamble Company

Submission: OTC Switch, Study #22103

Biostatistics Reviewer: M. Atiar Rahman, Ph.D.

Background: In this submission the sponsor included report of a study, conducted as follow-up of previously conducted label comprehension studies on omeprazole magnesium tablets. This study evaluated consumer comprehension and appropriate self-selection of three labeling options for OTC omeprazole magnesium tablets, so that an optimal labeling could be determined.

There were four cohorts of subjects, namely frequent/literate, frequent/low literate, infrequent/literate, infrequent/low literate. For each label, the percentage of correct/acceptable responses was estimated for each of the 4 cohorts for each communication objectives.

In order to evaluate the labels the following analyses were carried out on the above endpoints.

1) A logistic regression was run to see the impact of literacy (Literate vs. Low Literate) and frequency (Frequent vs. Infrequent) on each label understanding. The analysis was based on the percentage of consumers who provided a correct or acceptable response. The logistic model included LABEL (A, B, or C), FREQUENCY (frequent or infrequent sufferer), LITERACY (literate or low literate sufferer), FREQUENCY*LITERACY, LABEL*FREQUENCY, and LABEL*LITERACY. If the LABEL*FREQUENCY and LABEL*LITERACY terms were not significant ($p > 0.10$) in the above model, then the analysis in #2 below was carried out.

2) A Cochran-Mantel-Haenszel chi-square test with FREQUENCY and LITERACY as the stratification variables was carried out on each question/set of questions to determine which label was best understood (across both literacy and frequency groups) for each section of the label. Hypotheses were tested separately on each label pair.

Dr. Karen Lechter of HFD-410 sent this consult to this Division to response to her following questions.

1. Is label B really better than the other labels? At first glance, there appear to be few statistically significant differences.
2. Are the sample sizes appropriate for the types of analyses they are doing?
3. Was logistic regression appropriate for this analysis?
4. On p. 35 of Vol 5, is the Kappa statistic of 0.9 adequate for interrater reliability? Should they have used a larger sample of questions to test interrater reliability? See p.19 for a description of the coding process—only 3 questions were coded by both coders.

5. On p.36, under "Review of Statistical Plan," was the procedure for looking at interactions appropriate in terms of using 0.10 for the first screen and then running pairwise comparisons at $p < 0.05$ if the interaction was not significant?

This reviewer's response

1. Is label B really better than the other labels? At first glance, there appear to be few statistically significant differences.

Reviewer's response: Results in Sponsor's Tables D and D1 (also results in other tables) showed that in general Label B might have done better than Labels A or C. However, in many component Label A or C did better than Label B.

The sponsor performed many tests. For a proper statistical interpretation the sponsor needed to adjust for the multiple testing. Due to lack of a pre-specified multiple testing adjustment procedure, the statistical significance found in sponsor's analysis was not statistically rigorous.

2. Are the sample sizes appropriate for the types of analyses they are doing?

Reviewer's response: Sample size was calculated based on the precision of estimate (95% confidence interval) of percentage of subjects with correct self-selection. For precise estimation of sample size, the knowledge of true target comprehension rate and a threshold value were needed. Since such values were not specified in this report, this reviewer can not response to this question.

3. Was logistic regression appropriate for this analysis?

Reviewer's response: The logistic regression was basically used to test the interaction of literacy and frequency of heartburn with labels. The actual pairwise comparisons were performed using the Cochran-Mantel-Haenszel test. This was done following the original protocol. The method is acceptable.

4. On p. 35 of Vol 5, is the Kappa statistic of 0.9 adequate for interrater reliability? Should they have used a larger sample of questions to test interrater reliability?

Reviewer's response: Kappa value can go up to 1. Higher value of Kappa indicates interrater reliability. The 0.9 value of Kappa seems to be quite large. However, the sponsor should have reported the confidence interval for better interpretation. For the Kappa statistic, use of more number of questions might give higher reliability. However, introduction of too many questions may also introduce undesirable inter and intra rater variations in the data. A proper method would be to pre-specify some important key issues on which the raters should be judged for agreement. In this case the related 3 questions were agreed upon by the sponsor and the FDA.

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5. On p.36, under "Review of Statistical Plan," was the procedure for looking at interactions appropriate in terms of using 0.10 for the first screen and then running pairwise comparisons at $p < 0.05$ if the interaction was not significant?

Reviewer's response: There is no hard and fast rule for the choice of p-value for testing significance of an interaction term. Generally test level for interaction terms are pre-specified in the protocol. For this study, test level of 0.10 was pre-specified in the protocol. For comments on the rest of the question, please see this reviewer's response to Questions #1 and #3.

/S/

M. Atiar Rahman, Ph.D.

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Statistical Review and Evaluation

IND: 54,307
Applicant: Procter & Gamble
 8700 Mason-Montgomery Road,
 Mason, Ohio 45040-9462
Name of Drug: Prilosec 1TM (Omeprazole Magnesium) Tablets
Rout of Administration: Oral
Documents Reviewed: Paper submissions of September 5, 13, 17 and 19, 2002
Reviewing Medical Officer: Daiva Shetty, M.D.
Reviewing Statistician: M. Atiar Rahman, Ph.D.
Project Manager: Walter Ellenberg, Ph.D.

1. Background: In this submission the sponsor included a draft protocol (#22103, Draft 9-5-02) for a new label comprehension study. The title of the protocol is "A Multi-Center Label Comprehension Study to Evaluate Consumer Comprehension of OTC Labeling Options for Omeprazole Magnesium Tablets".

The objective of this study is to evaluate how well consumers with heartburn understand the conditions (i.e. uses, warnings, and directions) in which they can use OTC omeprazole magnesium tablets based on their reading the carton label. There will be three labeling options to test in this labeling comprehension study to determine optimal labeling that best conveys the concepts outlined in the action letter of August 8, 2002.

This will be a 3-arm (3 label versions) study. Qualified consumers will be asked to read one of the three package labels for omeprazole magnesium tablets. Respondents will be asked questions about the label to determine if they appropriately self-select the product, comprehend the product label warnings, and comprehend the product directions to use. Comprehension scores across the three alternative package labels will be compared to determine which is the most effective in communicating key product information.

There will be four cohorts of population, namely

- 1) Literate¹ frequent heartburn sufferers (Experiencing heartburn 2 or more days per week. Score 61 or higher on the REALM test).
- 2) Low-literate¹ frequent heartburn sufferers (Experiencing heartburn 2 or more days per week. Score 60 or lower on the REALM test)
- 3) Literate¹ infrequent heartburn sufferers (Experiencing heartburn less often than 2 days a week. Score 61 or higher on REALM test), and
- 4) Low-literate¹ infrequent heartburn sufferers (Experiencing heartburn less often than 2 days a week. Score 60 or lower on the REALM test)

Subjects will be adult males and females, 18 years of age or older.

The key communication objectives to be evaluated include the following:

- 1) Consumers with heartburn understand that:
 - a. Omeprazole magnesium tablets are for adults who have frequent heartburn
 - b. Omeprazole magnesium tablets are not intended for relief/prevention of episodic heartburn.

¹ As determined by the Rapid Estimate of Adult Literacy in Medicine (REALM).

- 2) Consumers with heartburn understand when to see their doctor before and after starting treatment.
- 3) Consumers with heartburn understand to ask doctor before use if they have any of the label warning symptoms.
- 4) Consumers with heartburn understand the label directions and when they can take an additional course of treatment without physician intervention.

Qualified consumers will be randomized to one of the three labels. Each center (shopping facility) will receive a randomization schedule from the sponsor, which will be used to randomly assign consumers sequentially as they enroll.

Subjects will be asked questions about the label to determine if they appropriately self-select the product, recognize the product is only for frequent heartburn, and comprehend the product label warnings and directions. Comprehension scores across three alternative package labels will be compared to determine which is most effective in communication key product information.

Recruitment for this study will take place in approximately 40 facilities located in the shopping malls and approximately 12 off-site locations targeted to obtain the majority of the low literacy population.

2. Sample size: The sponsor proposed a sample size of 150 per arm within each cohort (450 per cohort, 1800 total subjects for the study). The sponsor did not provide any formal sample size calculation methodology for this study

Reviewer's comment: The following is the FDA draft guidance² recommendation for sample size calculation for label comprehension study:

"As indicated above, labeling comprehension studies are designed to assess the extent to which proposed OTC labeling communicates important information to potential users of a drug product. Sample size calculations may be derived on the basis of the key communication objectives. For planning purposes, these studies should be designed with (1) an *a priori* target comprehension rate (P) for the key communication objective(s), and (2) a specified threshold comprehension rate (P-) defined as the lower acceptable bounds. Statistically, this is accomplished through the use of a one-sided confidence interval. The following table provides minimum sample sizes for a range of target comprehension rates and threshold levels:

Table 1. Sample Size Determination

Target Comprehension Rate (P)	Threshold Level (P-)	Sample Size ^{1,2}
0.75	0.65	150
	0.70	590
0.80	0.70	130
	0.75	510
0.85	0.75	110
	0.80	410
0.90	0.80	90
	0.85	290

¹Probability is 80% that the 97.5% lower one-sided confidence limit is (P-).

²Numbers rounded up to the nearest 10.

² Guidance for Industry, Labeling Comprehension Studies for OTC Drug Products (Draft Guidance) USDHHS, FDA, CDER, March 2002.

As these studies are observational, and not randomized trials, the sample size has to be adequately large to reflect the target population as far as demographics, comprehension level, and interpretability of the instrument. Every effort is to be made to reach the sample size planned and continuous enrollment (to maintain exchangeability of the respondents) is to be done until the planned sample size is reached. -

For key communication objectives, the goal would be to aim for the highest comprehension rate and the narrowest threshold range possible, such as a P of 90 to 95% and a P- no more than 5% away from P. For the secondary communication objectives, a cutoff rate of comprehension can also be set if desired. The goal is to use the results to develop the best label; so that the areas of low comprehension should be improved."

Therefore, for sample size calculation it is important to know the target comprehension and threshold rates. This reviewer recommends first determining the target comprehension and threshold rates for these labels through a pilot study. Calculate the sample size for the main study later on based on the results of the pilot study.

3. Statistical analysis plan:

A respondent would be considered to have successfully met a particular communication objective if, after probing he/she presents a correct/acceptable response to the questions(s) related to that objective.

Reviewer's comment: For the evaluation of correct/acceptable response, the sponsor needs to develop a suitable questionnaire, which can produce unbiased and unambiguous responses. In Attachment-I (Submission date September 17), the sponsor submitted an outline of such a questionnaire. The sponsor should submit their final version for review. The sponsor should also clearly describe the scoring system to questions in the questionnaire and algorithm of converting the scores to meeting/not meeting the key communication objectives.

For a suitable questionnaire the FDA draft guidance describes "The questionnaire design should (1) clearly reflect the communication objectives of the study; and (2) optimize the validity and interpretability of the information collected. Wording, question structure and question sequences significantly affect the validity and interpretability of the data collected. A detailed discussion of questionnaire development is beyond the scope of this guidance. However, the following points merit particular consideration:

- Questions should be pegged to the specific communication objective.
- The vocabulary used should be simple. If participants are to read the questionnaire themselves, the text should be at a minimum of an eighth grade reading level.
- Questions should be direct, specific, unambiguous, and address a single item or issue.
- Questions may be designed to address different levels of communication or information processing. In addition, some questions should test whether participants can apply the information on the label to hypothetical situations.
 - Different types of questions may be used, such as open-ended (prompted or unprompted), closed-ended and a combination of these is encouraged. Scenarios or branching questions that are based on response algorithms can be used.
 - Care should be taken to avoid the many potential sources of question bias such as leading questions and acquiescence bias.
 - In listing response categories, all answers should be captured, including "don't know."
- Response choices in multiple-choice questions should be mutually exclusive and independent.

- In most cases, a self-selection question should be included.
 - Responses to questions intended to measure behavioral intent may be unreliable with respect to actual behavior. Information about how subjects would behave under OTC conditions should be obtained in an actual-use trial.
- Pre-testing the questionnaire with a sample of respondents similar to the target population to ascertain that it is eliciting the intended information is standard practice and provides an extremely useful validation procedure.

Two general approaches (alone or in combination) that might be considered are (1) using a self-administered instrument, and (2) a trained interviewer. In some instances, an interviewer may lessen the dependence of the questionnaire on the literacy level, educational level, or visual acuity of the respondent. Using an interviewer, however, may contribute to the loss of privacy and is open to interviewer influence particularly if the interviewer leads the participant in order to elicit a response. Interviewers involved in the study should be adequately trained, and have standard protocols and/or scripts to adhere to, especially regarding questions that participant might ask.

THE QUESTIONNAIRE SHOULD ELICIT INFORMATION ABOUT THE PARTICIPANTS SUCH AS THE FOLLOWING:

- demographics
- medical condition for wanting to take drug product
- medical history
- concomitant medications.

Of note, unless there is a self-selection question, there is no need obtain information about medical condition, medical history, or concomitant medications."

The protocol described the primary endpoint as the percentage of responders who provide a correct/acceptable response based on reading the label for the following criteria:

- 1) **Product use:** Omeprazole magnesium tablets are for the treatment of frequent heartburn.
- 2) **Self-selection:** Omeprazole magnesium tablets are for frequent heartburn sufferers (experience heartburn 2 or more days a week) and not for infrequent heartburn sufferers (experience heartburn less often than 2 days a week).
- 3) **Episodic/Frequent use scenarios:** Omeprazole magnesium tablets are for frequent heartburn sufferers and not for episodic use (i.e., not for relief/prevention of episodic heartburn).
- 4) **Label warning scenarios:**
 - a. Respondents know when to see their doctors before and after starting treatment.
 - b. Respondents understand to ask a doctor before use if they have any of the label warning symptoms, as demonstrated through direct scenarios.
- 5) **Direction for use scenarios:**
 - a. User should take 1 pill each day in the morning before breakfast for 14 consecutive days.
 - b. User should not use more than one 14-day course of therapy every 4 months unless directed by their doctor.
 - c. User can take another course of therapy at 4-months intervals.
 - d. User should notify their doctor if heartburn returns within 4 months of using omeprazole magnesium tablets for 14 days.
 - e. User knows not to chew or crush tablets before swallowing, or crushes tablets in food.

For each label, the percentage of correct/acceptable responses will be presented for each of the 4 cohorts for the above responses within each of the 3 labels. In order to determine which sections of the label are best

understood, the following analysis will be carried out on the above endpoints.

The protocol proposed that a logistic regression will be run to see the impact of literacy (literate vs. low literate) and frequency (frequent vs. infrequent) on which label is best understood. The logistic model that determines this will include the following independent factors. LABEL, FREQUENCY, LITERACY, FREQUENCY*LITERACY, LABEL*FREQUENCY, and LABEL*LIERACY.

The 2 interaction terms with LABEL will be investigated from this model, and the by-cohort percentages from each label will be uses to explain any differences that may occur.

If the LABEL*FREQUENCY, and LABEL*LIERACY terms are not significant ($p > 0.10$) in the above model, a Cochran-Mantel-Haenszel chi-square test with FREQUENCY and LITERACY as the stratification variables will be carried out to determine which version of the label are best understood. The by label percentages of correct/acceptable will be used to prioritize the labels and/or label sections.

Reviewer's comments: Following the FDA draft guidance, the sponsor should present both percentages of correct responses and their corresponding 95% confidence intervals. The guidance recommends presenting the results as follows:

Table 2. Decision Making by Participants' Responses

		Information provided by Subject	
		No contraindication to use	Contraindication to use
Subjects' Responses	Can use product	% correct chose to use appropriately	% incorrect should not use but thought they could
	Cannot use product	% incorrect can use but thought they could not	% correct should not use and chose not to use appropriately

The sponsor need to make suitable modification of the above table template to accommodate the four cohorts and three arms. The sponsor then should test if each version met the threshold level. This will be achieved if the lower limit of 95% confidence limit of percentage of correct response exceeds the threshold.

Since the three versions of the label have very little variation, it is very unlikely to see statistically significant differences among them. Therefore, it is recommended to decide optimality of a label based on the estimates and confidence intervals, rather than a formal test of hypothesis. Since the sample size was not estimated to power the tests based on the proposed logistic model, the conclusions may not be very meaningful. However, the results may be used for additional analysis. The sponsor should explain what are they going to do if the interaction terms turn out to be significant.

4. Comment which can be communicate to the sponsor:

- This reviewer recommends first determining the target comprehension and threshold rates for the three labels, through a pilot study. Calculate the sample size for the main study based on the results of the pilot study using the methodology given in the guidance.
- The sponsor should present both percentages of correct responses and their corresponding 95% confidence intervals. The sponsor should test if each version met the threshold level. This will be achieved if the lower limit of 95% confidence limit of percentage of correct response exceeds the threshold.
- This reviewer recommends that the results be submitted following the template given in the guidance.

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- Conclude the optimality of labels based on percentages and confidence intervals, rather than a formal test of hypothesis.
- Since the sample size was not estimated to power the tests based on the proposed logistic model, the conclusions may not be very meaningful. However, the results may be used as additional analysis. The sponsor should explain what are they going to do if the interaction terms turn out to be significant.

• M. Atiar Rahman, Ph.D.
Mathematical Statistician

Concur: Stan Lin, Ph.D.
Team Leader, Biometrics III

cc:

Archival NDA 21-229
HFD-560/ Dr. Ganley
HFD-560/ Dr. Shetty
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HFD-700/ Dr. Anello

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Statistical Review and Evaluation

NDA: 21-229
Applicant: Procter & Gamble
 8700 Mason-Montgomery Road,
 Mason, Ohio 45040-9462
Name of Drug: Prilosec 1TM(Omeprazole Magnesium) Tablets
Rout of Administration: Oral
Documents Reviewed: Electronic submission, Final report, Dated January 2002
Reviewing Medical Officer: Daiva Shetty, M.D.
 M. Atiar Rahman, Ph.D.
Reviewing Statistician:

1. Introduction: In this submission the sponsor included the final report of Study #2001007. The objective of this study was to investigate how consumers use Prilosec (Omeprazole Magnesium) tablets under the proposed label instructions in naturalistic over-the-counter conditions.

2. Design

2.1 Title: "A Multi-Center, Open-Label, Actual-Use Study to Investigate How OTC Consumers Use Omeprazole Magnesium, 20.6 mg".

2.2 Design and Endpoints: This was a one-arm, multi-center, multi-dose, open-label, observational, actual-use study of free-living OTC consumers ("all-comers"). The study was conducted at five retail sites in five cities in the United States.

The following indication of consumer behaviors were examined: 1) the percentage of subjects who correctly self-selected that the study medication was a drug they could or could not use, 2) the percentage of doses where no more than one tablet of study medication was taken per dose, 3) the percentage of dosing days where no more than one dose and no more than one tablet of study medication was taken per day, 4) the percentage of subjects who took between 11-14 doses of study medication in an 11-17 day period (80%-120% of dosing directions).

If the subject reported that the medication was one they could use for their heartburn, then they were considered correct if they:

- 1) Reported a history of two or more days of heartburn per week or reported taking heartburn medications two or more days per week.
- 2) Were at least 18 years of age.
- 3) Were not pregnant or nursing.
- 4) Were not allergic to omeprazole.
- 5) Did not report any alarm symptoms*
- 6) Were not taking any contraindicated medication*

* If a subject had consulted a physician about the alarm symptoms or taking any contraindicated medications with prilosec then the subject was considered as having correctly self-selected.

In addition, a) the percentage of subjects who took no more than one tablet per dose on all doses, and b) the percentage of subjects who took no more than one doses and no more than one tablet on all days were also analyzed.

There were three scheduled visits. In Visit-1 the subject was asked if he/she got heartburn. If the subject replied "yes", the subject was asked to read the study drug package and determine if he/she could use the product for his/her symptoms. If the subject replied "yes", he/she was offered to participate in the study. If willing to participate, the subject was recruited. After the recruitment subject's demographic, heartburn and medication history, and other related data were collected. In the same visit patient's literacy level test and pregnancy test were also done. A diary was dispensed to all subjects eligible for actual-use phase of the study to record the date and time of the dose, and number of tablets taken. Diaries also provided the history of concomitant medications and adverse experiences. In visit 2 (end-of-study) the diary was reviewed to address any missing, incomplete, inconsistent, or confusing entries. Visit-3 was a 3-month follow-up. The follow-up questionnaire was an effort to learn as much as possible about the OTC self-treatment of heartburn and consumer's interactions with physicians relative to their heartburn.

3. Sample size: Choice of sample size and sites for recruiting consumers were made to provide sufficient information about different demographic and clinical subgroups. Of particular note, the sample size was estimated to be sufficient to identify a sufficient number of consumers with frequent heartburn, whose heartburn may have relapsed within 30-60 days. To meet the above requirement a sample of 750 subjects was targeted. However, in practice, 758 subjects were recruited. The sponsor stated that with this sample size, the estimate of complying percentage with the dosing direction would not differ from the true value by more than 3.6% with probability more than 95%.

Reviewer's comment: This reviewer calculated the 95% confidence interval with $p=0.5$, and $n=758$. The length of the 95% confidence interval was found to be 7.2%. The half of this length is 3.6%, which is the same as the sponsor reported.

4. Statistical analysis plan: The demographic parameters and heartburn history information were summarized using descriptive statistics. This summaries were carried out for 3 populations: 1) those who took the study medication, 2) all those who participated in the self-selection interview and selected the drug as appropriate to use, and 3) those who stated an intent to purchase the study medication.

The percentage of subjects (and 95% confidence interval), who correctly self-selected that the study medication was one they could use, was computed separately for each self-selection criterion. In addition, an overall correct self-selection was computed that utilized all self-selection criteria. Correct self-selection was computed for two populations: 1) All subjects who used study medication plus all the available information from the 12 subjects who were precluded (see Table 1 below) from participation. This was referred by the sponsor as the primary analysis data (N=770), 2) All those subjects who participated in the self-selection process and selected the drug as appropriate to use. This was referred by the sponsor as the secondary analysis data (N=1251). The overall correct self-selection was also summarized by demographic characteristics such as gender

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(male vs. female), race (Caucasian vs. non-Caucasian), age, (<65 years vs. ≥ 65 years) study center and literacy level (REALM). Elements of consumer dosing behavior relevant to the dosing directions were summarized in tabular and/or graphical form. Subjects who agreed to participate in the study and returned a diary but decided not to use the study medication, were not included in the analyses of dosing behavior, since no drug usage behavior was available. According to the protocol the following separate elements of consumer behavior relevant to the dosing directions were summarized.

- The percentages of doses (and 95% confidence interval) where no more than one tablet of study medication was taken per dose.
- The percentage of dosing days (and 95% confidence interval) where no more than one dose and no more than one tablet of study medication was taken per day.
- The percentages of subjects (and 95% confidence interval) who took between 11-14 doses of study medication in an 11-17 day period (80%-120% of dosing directions). If a subject took more than 14 doses of study medication, they must have consulted a healthcare provider within the study period to be considered compliant with dosing directions.
- The percentage of subjects who took no more than one tablet per dose on all doses
- The percentage of subjects who took no more than one dose and no more than one tablet on all days.

In order to obtain a more accurate measure of the subject's heartburn frequency of taking heartburn medication was utilized in addition to the subject's reported heartburn frequency. This was done because some subjects take heartburn medications in a preventive manner, and thus, do not report an accurate measure of heartburn frequency.

Reviewer's comment: For self-selection the subject's reported heartburn frequency should be used.

In the actual data analysis there was a change from the original analysis plan in the secondary population for measuring self-selection. Those subjects who selected the drug "not-appropriate" to use were not included in the secondary population (as was originally planned), because this group of subjects would never have purchased or used the study medication.

Reviewer's comment: For self-selection it should not matter if the subject really purchase or use the product. Therefore, such patients should have been included.

Summary of information from the 3-month questionnaire regarding the return of heartburn was performed. Safety was investigated by evaluating all reported AEs.

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5. Results from Sponsor's Analyses

5.1 Disposition: The following table (Table 1) shows patients disposition.

Table 1: Disposition of "All comers"

Status	Number of subjects
Total contacts	5060
Do get heartburn	1999
Agreed to participate	1301
Selected as appropriate to use	1251
Decided to participate in the study	863
Purchased study medication	854
Completed the study (return diary)	762
Submitted blank diary	4
Submitted completed diary	758
Withdrawal from total participants (1301) before purchasing study medication	447
Answer to product "appropriate" not available	1
Self-selected product "not appropriate" to use	49
Answer to study participation not available	1
Subjects who later decided not to participate	384
Subject < 18 years of age	3
Did not meet study criteria	9

Source: Table 2 – page 20, Section 4.1.3 – page 21, Table 8.1.1 - page 49.

Of the 92 subjects who did not return Diaries, 82 were lost to follow-up, 8 reconsidered or withdrew consent, 1 experienced adverse experience, and 1 was withdrawn by the investigator.

Among the 758 subjects, who returned the completed diary, 449 (59.2%) were female and 309 (40.8%) were male, 530 (69.9%) were Caucasian, 105 (13.9%) were black, 7 (0.9%) had up to 8th grade of education, 186 (24.5%) had high school or equivalent diploma, 593 (77.1%) were <65 years old and 176 (22.9%) was ≥65 years old (note that the number of subjects <65 years and ≥65 years add up to 769). The mean age was 49.1 years. Most of them had heartburn problem for more than one year.

5.2 Analysis population: For determination of appropriateness of use, the primary analysis data set consists of those subjects who used study medication and returned completed diary, plus those who did not participate based on study related criteria (Subject < 18 years of age, and did not meet study criteria). Therefore, the size of the primary analysis data set is 758+12=770. The secondary analysis data set is comprised of all subjects who participated in the self-selection interview and selected the drug as appropriate to use, whether or not they purchased the study medication. Therefore, the size of the secondary analysis data set is 1251.

For determination of dosing behavior the analysis data set consists of all subjects who used at least one dose of study medication and returned completed diary. Therefore, the size of this analysis data set is 758.

Reviewer's comment: Since the process of self-selection involves only selection of the study drug as appropriate or not, irrespective of its real use, the appropriate population for determination of self-selection should be all subjects who participated in this self-selection process i.e. N=1251.

5.3 Correctness of self-selection: The following table displays the consumers criteria for self-selecting the study medication.

Table 2: Correct Self-Selection of Study Medication

Self-Selection Criteria	Self-Selection					
	Primary population			Secondary population		
	N	n	% (95% C.I.)	N	n	% (95% C.I.)
Heartburn > 2 Days/Week	770	699	90.8% (88.7%-92.8%)	1251	1078	86.2% (84.3%-88.1%)
> 18 years of age	770	767	99.6% (99.2%-100%)	1250	1247	99.8% (99.5%-100%)
Not pregnant or nursing	764	763	99.9% (99.6%-100%)	866	864	99.8% (99.4%-100%)
Not allergic to Omeprazole	764	764	100.0% (100%-100%)	866	866	100.0% (100%-100%)
No contraindicated symptoms	767	703	91.7% (89.7%-93.6%)	1247	1112	89.2% (87.4%-90.9%)
Not taking contraindicated medication	770	762	99.0% (98.2%-99.7%)	1251	1236	98.8% (98.2%-99.4%)
Over all self-selection criteria	770	642	83.4% (80.7%-86.0%)	1251	961	76.3% (74.5%-79.2%)

Source: Sponsor's Table 8.2.1 and 1.9.2.5

Reviewer's comments:

- 1) This reviewer recalculated the percentage of self-selection in different self-selection criteria and their respective 95% C.I. Reviewer's results confirmed the sponsor's results.
- 2) Sponsor's Table 8.2.8 (not reproduced here) shows that percentage of correct self-selection are 78.5%, 69.8, 89.8, 84.8, and 91.0 in Centers 1, 2, 3, 4, and 5, respectively. It can be noted that Center 2 (Atlanta, GA) had statistically significantly less percentage of correct self-selection compared to any other center, except compared to Center 1 (Vernon, CT).

5.4 Compliance to dosing directions and associated behaviors: Following table shows sponsor's results:

**Table 3: Consumer's Behavior Measures Relative to Dosing Directions
All Subjects Who Used Study Medication.**

Factor	% (95% C.I.)
Dosing Occasions (N=10830)	
Doses where one tablet not exceeded	99.1% (98.9%-99.2%)
Dosing Days (N=10743)	
Days where one dose and one tablet not exceeded	98.3% (98.0%-98.5%)
Subjects (N=758)	
Subjects who took no more than one tablet/dose	95.9% (94.5%-97.3%)
Subjects who took no more than one dose and no more than one tablet on all occasions	90.9% (88.8%-92.9%)
Subjects who dosed 11-14 doses in an 11-17 day period	
Used period	79.2% (76.3%-82.0%)
Total experience	81.1% (78.3%-83.9%)

Source: Table 8.2.2

Sponsor's analysis shows that 99.1% dosing occasions, and 98.3% of dosing days consisted of only

Prilosec

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1 tablet. Sponsor's results given in Appendix 1.9.2.14 (not reproduced here) shows that about 63% of subjects took exactly 14 dose in 14 days.

Reviewer's comment: It is not clear if all these 14 doses were in 14 consecutive days or consisted of only one tablet per dose.

Most frequent adverse experience was headache (136 subjects), followed by diarrhea (29 subjects) and abdominal pain (24 subjects).

Reviewer's Comments on sponsor's findings:

- 1) *Use of subjects who dosed 11-14 doses in an 11-17 day period may overestimate the percentage of compliance.*
- 2) *Results from sponsor's Table 8.2.5 shows (not reproduced here), only 64.4% of subjects took study medication for a minimum of 14 sequential days. However, it is not clear from this table if all these subjects took only one tablet per dose.*
- 3) *It could be very informative to know the percentage of subjects who dosed exactly 14 doses with one tablet per dose and treated exactly 14 sequential days.*
- 4) *All subjects, who used the study medication more than 14 days, were supposed to consult their physicians. Sponsor's results in text Table 3 (not reproduced here), shows that during 2-months study, 14 out of 34 (41%) subjects who used the study medication more than 14 days, consulted their physicians. This shows non-compliance by 20 (59%) subjects.*
- 5) *In overall assessment about 82% of the subjects, who used the study medication, rated the study medication as very good or excellent.*

6. Conclusion:

- **Self-selection:** Using all subjects who participated in the self-selection process, irrespective of its actual use, 76.3% of the subjects made overall correct selection.
- **Compliance:** Sixty four point four percent (64.4%) of subjects took study medication for a minimum of 14 sequential days. About 63% of subjects took exactly 14 dose in 14 days. Fifty nine percent (59%) of subjects who used the study medication more than 14 days did not consult their physicians in two months.

M. Atiar Rahman, Ph.D.
Mathematical Statistician

Concur: Stan Lin, Ph.D.
Team Leader, Biometrics III

cc:

Archival NDA 21-229
HFD-560/ Dr. Ganley
HFD-560/ Dr. Shetty
HFD-560/ Ms. Frazier
HFD-560/ Mr. Ellenberg

HFD-725/ Dr. Huque
HFD-725/ Dr. Lin
HFD-725/ Dr. Rahman
HFD-700/ Dr. Anello

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Atiar Rahman
5/8/02 01:00:22 PM
BIOMETRICS

Stan Lin
5/8/02 02:30:42 PM
UNKNOWN

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Welsh

STATISTICAL REVIEW AND EVALUATION --- STABILITY

NDA #: 21-229

FEB 21 2001

Drug Class: 2S

Applicant: AstraZeneca

Name of Drug: Prilosec 1 (omeprazole magnesium) Tablets

**Documents Reviewed: DMF Amendment dated July 6, 2000
Date File ome-mg stability.**

Statistical Reviewer: Milton C. Fan, Ph.D.

Review Chemist: Arthur Shaw, Ph.D.

Key Words: stability

A. Introduction

Per the request from reviewing chemist, Dr. Arthur Shaw, this reviewer has performed a statistical review and evaluation of the sponsor's stability data analyses.

B. Sponsor's Analysis

Results from long term stability studies with up to 24 months data on six drug product batches (1503, 1506, 1507, 7006, 7026, and 7030) packaged in both blisters and pouches and stored at 25°C/ RH were used for a statistical stability analysis to estimate an expiry dating period for omeprazole magnesium tablets. The batches evaluated were:

10 mg, batches 1503, 1506 and 1507
20 mg, batches 7006, 7026 and 7030.

Data were analyzed in a mixed effect ANCOVA. The mixed effect approach was adopted in order to generalize the results to be valid for batches in general, not only those used in the study. The model assumed included fixed effects for intercept and slope as well as random batch effects for each combination of strength and package type.

For each combination of strength and package type estimates of intercept and slope as well as the 95% confidence intervals were calculated from the ANCOV.

For a decreasing (increasing) drug characteristic the shelf life is estimated by the intersection between the specification limit and the 95% one-sided lower (upper) confidence limit of the mean regression curve of the drug characteristic. In the case of a drug characteristic that may increase or decrease the intersection between the

specification line and either of the limits of a two-sided 95% interval is taken for an estimate. For each drug characteristics the shortest shelf life obtained from any combination of strength and package type is taken as an estimate of the overall shelf life.

The specifications for:

Omeprazole Content: _____ of label claim

Related substances: Single known NMT _____, Single unknown NMT _____, Total NMT _____

Omeprazole (drug release buffer stage): NLT _____ in minutes.

The statistical analysis of 24 months data at 25°C / _____ RH on these batches supports the proposed period of _____

C. Reviewer's Evaluation

1. Reviewer's Comments on Sponsor's Statistical Stability Analysis

The sponsor used its statistical stability program in its analyses. PROC MIXED of SAS used to fit the stability data. In the sponsor's statistical stability analysis, the hypothesis of common intercept and common slope was not tested. So, batches were not pooled.

2. Reviewer's Stability Analysis of Contents

This reviewer ran the Division E-Review/Stability Web stability program on contents for each package type stored at 25°C / _____ RH. The specifications used were _____ Detailed results of analyses are given in Appendix I. Below is a summary of the estimated extrapolated expiration dating period based on contents for 25°C / _____ RH.

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Estimated Expiration Dating Periods Based on
Contents
25°C/ RH

Package	Batch	(month)
10 mg Blister	1503	
	1506	—
	1507	
10 mg Pouch	1503	—
	1506	—
	1507	
20 mg Blister	All	—
20 mg Pouch	All	—

Based on the specification , the estimated expiration dating periods based on contents for 10 mg blister, 10 mg pouch, 20 mg blister and 20 mg pouch were respectively.

3. Reviewer's Stability Analysis of Total Related Substances

This reviewer ran the Division E-Review/Stability Web stability program on total related substances for each package type stored at 25°C/ RH. As suggested by the review chemist, Dr. Shaw, the upper specifications used were instead of used by the sponsor. Additional analyses were performed for the upper specifications (and). Detailed results of analyses for upper specification of are given in Appendix II. Below is a summary of the estimated extrapolated expiration dating period based on total related substances for 25°C/ RH.

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Estimated Expiration Dating Periods Based on
Total Related Substances
25°C/60%RH

Package	Batch	(month)	(month)	(month)	(month)
10 mg Blister	1503	_____	_____	_____	_____
	1506				
	1507				
10 mg Pouch	1503	_____	_____	_____	_____
	1506				
	1507				
20 mg Blister	7006	_____	_____	_____	_____
	7026				
	7030				
20 mg Pouch	7006	_____	_____	_____	_____
	7026				
	7030				

With the specification of NMT _____ (suggested by Dr. Shaw), the estimated expiration dating periods based on total unrelated substances for 10 mg blister, 10 mg pouch, 20 mg blister and 20 mg pouch were _____ respectively.

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Milton C. Fan, Ph.D.

[*ISJ*]
Mathematical Statistician

This review consists of 5 pages of text and 8 pages of tables.

concur: Dr. Lin [*ISJ*] 2/29/01

cc:

- Archival NDA 21-229
- HFD-180
- HFD-180/Dr. Talarico
- HFD-180/Dr. Zhou
- HFD-180/Dr. Shaw
- HFD-180/Ms. Walsh
- HFD-700/Dr. Anello

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HFD-715/Dr. Nevius
HFD-715/Dr. Lin
HFD-715/Dr. Permutt
HFD-715/Dr. Fan
Dr. Fan/x73088/mcf/2/21/01

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Appendix I

Estimation of Expiry Dating Period

Analysis variable: CNT1_10_BLISTER [11111]

Confidence limit(s) selected (L-Lower, U-Upper, B-Both): B	Each-side significance level: 0.050
Lower specification limit: _____	Upper specification limit: _____

Test of Batch Poolability (p-value cutpoint used: 0.25)

Variable Analyzed: CNT1_10_BLISTER [11111]

Poolability	Pr(C)<0.25	Pr(C)>=0.25
Pr(B)<0.25	MODEL 3	MODEL 2
Pr(B)>=0.25	MODEL 3	MODEL 1

Model Determined: MODEL2
 Poolability: The regression lines are parallel.

Source	SS	DF	MS	F-Statistic	P-Value
A					0.3139
B					0.1323
C					0.7235
RESIDUAL					

C: Ho: sep. intercept com. slope, Ha: sep. intercept sep. slope
 B: Ho: com. Intercept com. slope, Ha: sep. intercept com. slope
 A: Ho: com. Intercept com. slope, Ha: sep. intercept sep. slope

Fitted Line	Batch	Estimated Expiry Period
	1503	
	1506	
	1507	
	~MIN	

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Appendix I (Continued)

Estimation of Expiry Dating Period

Analysis variable: _CNT1_10_POUCH_ [11211]

Confidence limit(s) selected (L-Lower, U-Upper, B-Both): B	Each-side significance level: 0.050
Lower specification limit: _____	Upper specification limit: _____

Test of Batch Poolability (p-value cutpoint used: 0.25)

Variable Analyzed: _CNT1_10_POUCH_ [11211]

Poolability	Pr(C)<0.25	Pr(C)>=0.25
Pr(B)<0.25	MODEL 3	MODEL 2
Pr(B)>=0.25	MODEL 3	MODEL 1

Model Determined: MODEL2
 Poolability: The regression lines are parallel.

Source	SS	DF	MS	F-Statistic	P-Value
A					0.5200
B					0.2251
C					0.9156
RESIDUAL					

C: Ho: sep. intercept com. slope, Ha: sep. intercept sep. slope
 B: Ho: com. Intercept com. slope, Ha: sep. intercept com. slope
 A: Ho: com. Intercept com. slope, Ha: sep. intercept sep. slope

Fitted Line	Batch	Estimated Expiry Period
	1503	
	1506	
	1507	
	~MIN	

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Appendix I (Continued)

Estimation of Expiry Dating Period

Analysis variable: CNT1_20_BLISTER_ [12111]

Confidence limit(s) selected (L-Lower, U-Upper, B-Both): B	Each-side significance level: 0.050
Lower specification limit: _____	Upper specification limit: _____

Test of Batch Poolability (p-value cutpoint used: 0.25)

Variable Analyzed: CNT1_20_BLISTER_ [12111]

Poolability	Pr(C)<0.25	Pr(C)>=0.25
Pr(B)<0.25	MODEL 3	MODEL 2
Pr(B)>=0.25	MODEL 3	MODEL 1

Model Determined: MODEL1
Poolability: All batches are pooled.

Source	SS	DF	MS	F-Statistic	P-Value
A					0.7143
B					0.5761
C					0.6105
RESIDUAL					

C: Ho: sep. intercept com. slope, Ha: sep. intercept sep. slope
 B: Ho: com. Intercept com. slope, Ha: sep. intercept com. slope
 A: Ho: com. Intercept com. slope, Ha: sep. intercept sep. slope

Fitted Line	Batch	Estimated Expiry Period
← _____	POOL	← _____
	~MIN	← _____

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Appendix I (Continued)

Estimation of Expiry Dating Period

Analysis variable: CNT1_20_POUCH_ [12211]

Confidence limit(s) selected (L-Lower, U-Upper, B-Both): B	Each-side significance level: 0.050
Lower specification limit: <u> </u>	Upper specification limit: <u> </u>

Test of Batch Poolability (p-value cutpoint used: 0.25)

Variable Analyzed: CNT1_20_POUCH_ [12211]

Poolability	Pr(C)<0.25	Pr(C)>=0.25
Pr(B)<0.25	MODEL 3	MODEL 2
Pr(B)>=0.25	MODEL 3	MODEL 1

Model Determined: MODEL1
Poolability: All batches are pooled.

Source	SS	DF	MS	F-Statistic	P-Value
A					0.9554
B					0.8821
C					0.8184
RESIDUAL					

- C: Ho: sep. intercept com. slope, Ha: sep. intercept sep. slope
- B: Ho: com. Intercept com. slope, Ha: sep. intercept com. slope
- A: Ho: com. Intercept com. slope, Ha: sep. intercept sep. slope

Fitted Line	Batch	Estimated Expiry Period
<u> </u>	POOL	<u> </u>
<u> </u>	~MIN	<u> </u>

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Appendix II

Estimation of Expiry Dating Period

Analysis variable: REL1_10_BLISTER [21111]

Confidence limit(s) selected (L-Lower, U-Upper, B-Both): U	Each-side significance level: 0.050
Lower specification limit: .	Upper specification limit: —

Test of Batch Poolability (p-value cutpoint used: 0.25)

Variable Analyzed: REL1_10_BLISTER [21111]

Poolability	Pr(C)<0.25	Pr(C)>=0.25
Pr(B)<0.25	MODEL 3	MODEL 2
Pr(B)>=0.25	MODEL 3	MODEL 1

Model Determined: MODEL2
 Poolability: The regression lines are parallel.

Source	SS	DF	MS	F-Statistic	P-Value
A					0.1438
B					0.0538
C					0.6416
RESIDUAL					

C: Ho: sep. intercept com. slope, Ha: sep. intercept sep. slope
 B: Ho: com. Intercept com. slope, Ha: sep. intercept com. slope
 A: Ho: com. Intercept com. slope, Ha: sep. intercept sep. slope

Fitted Line	Batch	Estimated Expiry Period.
	1503	
	1506	
	1507	
	~MIN	

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Appendix II (Continued)

Estimation of Expiry Dating Period

Analysis variable: REL1_10_POUCH_ [21211]

Confidence limit(s) selected (L-Lower, U-Upper, B-Both): U	Each-side significance level: 0.050
Lower specification limit: .	Upper specification limit: _____

Test of Batch Poolability (p-value cutpoint used: 0.25)

Variable Analyzed: REL1_10_POUCH_ [21211]

Poolability	Pr(C)<0.25	Pr(C)>=0.25
Pr(B)<0.25	MODEL 3	MODEL 2
Pr(B)>=0.25	MODEL 3	MODEL 1

Model Determined: MODEL3
 Poolability: The regression lines have separate slopes & intercepts.

Source	SS	DF	MS	F-Statistic	P-Value
A					0.0180
B					0.0138
C					0.1078
RESIDUAL					

C: Ho: sep. intercept com. slope, Ha: sep. intercept sep. slope
 B: Ho: com. intercept com. slope, Ha: sep. intercept com. slope
 A: Ho: com. intercept com. slope, Ha: sep. intercept sep. slope

Fitted Line	Batch	Estimated Expiry Period
_____	1503	_____
	1506	_____
	1507	_____
	~MIN	_____

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Appendix II (Continued)

Estimation of Expiry Dating Period

Analysis variable: _REL1_20_BLISTER_ [22111]

Confidence limit(s) selected (L-Lower, U-Upper, B-Both): U	Each-side significance level: 0.050
Lower specification limit: .	Upper specification limit: —

Test of Batch Poolability (p-value cutpoint used: 0.25)

Variable Analyzed: _REL1_20_BLISTER_ [22111]

Poolability	Pr(C)<0.25	Pr(C)>=0.25
Pr(B)<0.25	MODEL 3	MODEL 2
Pr(B)>=0.25	MODEL 3	MODEL 1

Model Determined: MODEL3
 Poolability: The regression lines have separate slopes & intercepts.

Source	SS	DF	MS	F-Statistic	P-Value
A					0.0250
B					0.0145
C					0.1820
RESIDUAL					

C: Ho: sep. intercept com. slope, Ha: sep. intercept sep. slope
 B: Ho: com. intercept com. slope, Ha: sep. intercept com. slope
 A: Ho: com. intercept com. slope, Ha: sep. intercept sep. slope

Fitted Line	Batch	Estimated Expiry Period
	7006	
	7026	
	7030	
	~MIN	

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Appendix II (Continued)

Estimation of Expiry Dating Period

Analysis variable: REL1_20_POUCH_ [22211]

Confidence limit(s) selected (L-Lower, U-Upper, B-Both): U	Each-side significance level: 0.050
Lower specification limit: .	Upper specification limit: /

Test of Batch Poolability (p-value cutpoint used: 0.25)

Variable Analyzed: REL1_20_POUCH_ [22211]

Poolability	Pr(C)<0.25	Pr(C)>=0.25
Pr(B)<0.25	MODEL 3	MODEL 2
Pr(B)>=0.25	MODEL 3	MODEL 1

Model Determined: MODEL3
 Poolability: The regression lines have separate slopes & intercepts.

Source	SS	DF	MS	F-Statistic	P-Value
A					0.0200
B					0.0226
C					0.0703
RESIDUAL					

C: Ho: sep. intercept com. slope, Ha: sep. intercept sep. slope
 B: Ho: com. intercept com. slope, Ha: sep. intercept com. slope
 A: Ho: com. intercept com. slope, Ha: sep. intercept sep. slope

Fitted Line	Batch	Estimated Expiry Period
	7006	
	7026	
	7030	
	~MIN	

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Statistical Consult for NDA 21-229

NDA 21-229

Name of Drug: Prilosec (omeprazole)

Applicant: Proctor and Gamble Co.

Indication: Treatment of Heartburn

Documents Reviewed: Electronic documents for use studies (003, 014, 022, 067, 091) submitted by sponsor on 1/27/00 and 4/25/00.

Medical Reviewer: Dr. Ling Chin and Dr. Daiva Shetty

Statistical Consultant: Laura Lu, Ph.D.

Date of Review: 9/11/00

I. Introduction

The sponsor conducted a total of 5 OTC use studies (Studies 003, 014, 022, 067, 091) to assess consumer compliance. These are uncontrolled studies with one-arm (omeprazol). Study 003 was the primary actual use study with 1514 patients recruited and 1093 patients participated. The primary objective of these studies was to characterize the usage patterns/dosing compliance of omeprazole magnesium when used according to proposed label instructions under naturalistic OTC conditions. Per Dr. Ling Chin's request, this statistical consult provides comments for Study 003. Comment #3 also applies to Studies 022 and 067.

II. Statistical Comments

1. Confidence Intervals

The primary information for compliance provided by the sponsor was the consistency (with label in terms of dosing compliance) rates among the patients who took at least one dose of medication and had complete data. Confidence intervals are more informative than the a single rate estimation by providing a range for the estimation rate based on estimation error. Therefore, this reviewer presents the 95% confidence intervals for the consistency rate in overall and prevention/relief patient populations for the actual use study 003 in Table 1 below. According to the company, a total of 815 patients had compliance status (consistent or inconsistent) with 812 of these from the completer's group and 3 of these from the incompleter's group. But it is not sure how these 815 patients were associated with the detailed patient disposition groups presented in Table 1a in Appendix A.

Table 1. Point Estimation and Confidence Intervals for Consistency Rate (Study 003)

	Prevention Any Time (N = 36)	Prevention 1 hr Before (N = 28)	Dual Prevention (N = 13)	Relief (N = 316)	Prevention And Relief (N = 422)	Overall (N = 815)
Consistency (n (%))	9 (25%)	9 (32%)	7 (54%)	254(80%)	228 (54%)	507 (62%)
95% Confidence Interval	(11%, 39%)	(15%, 49%)	(27%, 81%)	(76%, 84%)	(49%, 59%)	(59%, 65%)

3861 B1-10-C - ACTUAL USE

2. Lost-to-Follow-up Patients

In Study 003, a total of 210 patients were lost to follow-up (see Table 1a in Appendix A) without returning the product use journal, so no information was available in actual use pattern. Among the baseline characteristics, frequency of heartburn during day time in the past, frequency of heartburn during night time in the past, Rx medication use (whether Rx medication was used for heartburn before), and medication factor (whether medication was a factor contributing to heartburn in the past) were strongly associated with consistency rate ($p=0.001$). Detailed results presented in Tables a2-a5 in Appendix A show that consistency rate decreases as the frequency of heartburn increases, and the consistency rate is lower among patients who used Rx heartburn medication before and among patients whose heartburn was contributed by use of medication. To assess the potential difference in consistency rates among the lost-to-follow-up patients and the completers, the distribution of heartburn frequency, Rx medication use and medication factor among the completers and lost-to-follow-up patients were compared in Tables 2-5 below. Tables 2 and 3 below show that the lost-to-follow-up patients tend to have heartburn less frequently compared with the completer group. Tables 4-5 show that the proportion of patients who used Rx medication before and the proportion of patients whose heartburn was contributed by use of medication were less among lost-to-follow-up patients than that of the completer group. So based on association between baseline characteristic and consistency rate, there is no evidence showing that the consistency rate in the lost-to-follow-up patients were lower than that in the completer group. However, since the consistency rate could be influenced by unobserved factors such as reason for taking the medication, there is still chance that the consistency rate in the lost-to-follow-up group is lower than that in the completer's group.

Table 2. Distribution of Frequency of Heartburn During Daytime (Study 003)

Patient Population	Frequency of Heartburn During Daytime				
	Rarely	1	2-3	4-5	≥ 6
Completer (N=874)	170 (19.5%)	174 (19.9%)	319 (36.5%)	101 (11.6%)	110 (12.6%)
L-T-F-U (N=210)	83 (39.5%)	52 (24.8%)	57 (27.1%)	11 (5.2%)	7 (3.3%)

*: Lost-to-follow-up patients

Table 3. Distribution of Frequency of Heartburn During Nighttime (Study 003)

Patient Population	Frequency of Heartburn During Nighttime				
	Rarely	1	2-3	4-5	≥ 6
Completer (N=874)	298 (34.1%)	160 (18.3%)	267 (30.6%)	77 (8.8%)	72 (8.2%)
L-T-F-U (N=210)	103 (49.1%)	47 (22.4%)	40 (19.1%)	15 (7.1%)	5 (2.4%)

*: Lost-to-follow-up patients

Table 4. Distribution of Rx Medication Use (Study 003)

Patient Population	Rx Medication Use	
	Yes	No
Completer (N=874)	95 (10.9%)	779 (89.1%)
L-T-F-U (N=210)	8 (3.8%)	202 (96.2%)

*: Lost-to-follow-up patients

Table 5. Distribution of Medication Factor (Study 003)

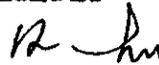
Patient Population	Medication Factor	
	Yes	No
Completer (N=874)	26 (3.0%)	848 (97.0%)
L-T-F-U (N=210)	0 (0.0%)	210 (100.0%)

*: Lost-to-follow-up patients

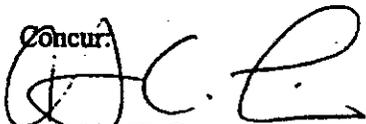
3. Analyses Based on Predominant Use Groups

Consistency rates were also provided by predominant use groups (where predominant use is defined as using the study medication more than 50% of the time for anyone of the three reasons for use: 1) predominant Prevention-Any-Time users, 2) predominant Prevention-1-Hour-Before users, 3) predominant Relief users, and 4) no predominant use (includes those subjects who did not use the study medication more than 50% of the time for any one of the three reasons for use)). Since the analyses based on predominant use groups were not prespecified and there is no clear rationale for this reclassification, judgement should be based on the results from the prespecified analyses based on strict prevention/relief groups.

Laura Lu



Mathematical Statistician

Concur.

 Stan Lin, Ph.D.
 Team Leader

9/13/00

CC:
 HFD-180/Walsh
 HFD-560/Keravich
 HFD-560/Chin/Shetty/Katz/Ganley
 HFD-660/Div. File
 HFD-725/Lu/Lin ST./Huque
 HFD-725/Div. File

Appendix A

Table 1a. Patient Disposition in Study 003

Reason for Discontinuation	N
Received Study Medication and Product Use Journal	1093
Completed Study	874
Took at Least 1-Dose Medication	822
Did Not Take Medication	52
Did Not Complete Study	219
Adverse Event	4
Subject Reconsidered/Withdrew Consent	4
Lost to Follow-Up	210

Table 2a. Frequency (Daytime) BY Consistency Status

Heartburn History: Frequency During Daytime
Consistency (Y=Yes, N=No)

Frequency			Total
	N	Y	
Percent			
Row Pct			
Col Pct			
2-3	109	202	311
	13.37	24.79	38.16
	35.05	64.95	
	35.39	39.84	
4-5	50	50	100
	6.13	6.13	12.27
	50.00	50.00	
	16.23	9.86	
>=6	75	32	107
	9.20	3.93	13.13
	70.09	29.91	
	24.35	6.31	
ONCE	37	118	155
	4.54	14.48	19.02
	23.87	76.13	
	12.01	23.27	
RARELY	37	105	142
	4.54	12.88	17.42
	26.06	73.94	
	12.01	20.71	
Total	308	507	815
	37.79	62.21	100.00

P-value from Chi-Square Test: 0.001

Table 3a. Frequency (Night) BY Consistency Status

Heartburn History: Frequency During Night
Consistency (Y=Yes, N=No)

Frequency			
Percent			
Row Pct			
Col Pct	N	Y	Total
2-3	110	145	255
	13.50	17.79	31.29
	43.14	56.86	
	35.71	28.60	
4-5	32	44	76
	3.93	5.40	9.33
	42.11	57.89	
	10.39	8.68	
>=6	47	25	72
	5.77	3.07	8.83
	65.28	34.72	
	15.26	4.93	
ONCE	38	109	147
	4.66	13.37	18.04
	25.85	74.15	
	12.34	21.50	
RARELY	81	184	265
	9.94	22.58	32.52
	30.57	69.43	
	26.30	36.29	
Total	308	507	815
	37.79	62.21	100.00

P-value from Chi-Square Test: 0.001

Table 4a. Rx Medication Use By Consistency Status

Heartburn History: Rx Medication Use (Y=Yes, N=No)
 Consistency (Y=Yes, N=No)

Frequency Percent Row Pct Col Pct			Total
	N	Y	
N	253 31.04 34.94 82.14	471 57.79 65.06 92.90	724 88.83
Y	55 6.75 60.44 17.86	36 4.42 39.56 7.10	91 11.17
Total	308 37.79	507 62.21	815 100.00

P-value from Chi-Square Test: 0.001

Table 5a. Medication Factor By Consistency Status

MEDICAT(Heartburn Factor: Medication, 1=Yes, 2=No)
 Consistency (Y=Yes, N=No)

Frequency Percent Row Pct Col Pct	Consistency		Total
	N	Y	
1	18 2.21 72.00 5.84	7 0.86 28.00 1.38	25 3.07
2	290 35.58 36.71 94.16	500 61.35 63.29 98.62	790 96.93
Total	308 37.79	507 62.21	815 100.00

P-value from Chi-Square Test: 0.001

NDA 21-229
HFD-560 Division Files
HFD-180 Division Files
HFD-560 Ganley/Katz/ Shetty/Chin/Cothran
HFD-180 Walsh

STATISTICAL NDA REVIEW AND EVALUATION

Date: **November 9, 2000**

NDA: 21-229

APPLICANT: AstraZeneca LP

NAME OF DRUG: Prilosec 1 (omeprazole magnesium) 20 mg Tablets.

INDICATION: 1. 4-hour prevention of heartburn; 2. Two-week prevention of heartburn; and 3. treatment of heartburn.

USER FEE DUE DATE: 1/27/01.

DRUG CLASSIFICATION: 1S.

DOCUMENT REVIEWED: Volumes 1.001 – 1.003, 1.027 – 1.153; dated 1/27/2000.

MEDICAL REVIEWER: L. Goldkind, M.D.

STATISTICAL REVIEWER: Wen-Jen Chen, Ph.D.

STATISTICAL ISSUES:

- Neither Study 1997092 nor Study 1997095 shows the superiority of Ome-Mg 20 mg to placebo in the treatment of heartburn.
- Only one study (171) shows the superiority of Omeprazole 20 mg to placebo in the prevention of nocturnal heartburn on the 2-week prevention of heartburn.

KEYWORDS: Clinical studies; NDA review.

1.0 . INTRODUCTION

In the submitted Volume 29, the sponsor indicated that Omeprazole is a highly specific and effective inhibitor of gastric acid secretion and belongs to the class of proton pump inhibitor (PPI). Omeprazole suppresses gastric acid secretion by specific inhibition of the H⁺/K⁺ ATPase enzyme system at the secretory surface of the gastric parietal cell. Because it blocks the final step of acid production, the effect leads to inhibition of both basal and stimulated acid secretion. This class of drugs is used in the treatment of gastric acid-related symptoms and pathology, such as

Gastroesophageal Reflux Disease (GERD) and the erosive esophagitis (EE) that generally accompanies GERD.

This submission consists of six studies, 1998005, 1998006, 171, 183, 1997092, and 1997095 to acquire the approval for over-the-counter marketing of omeprazole magnesium tablets in the use of prevention and treatment of heartburn. Currently, Prilosec Delayed-Release Capsules are approved for short-term treatments of active duodenal ulcer and active benign gastric ulcer, the treatment of symptomatic Gastroesophageal Reflux Disease, the short-term treatment and maintenance of healing of Erosive Esophagitis, and the long-term treatment of pathological hypersecretory conditions. The prevention and treatment of heartburn for over the counter use are new indications for Prilosec.

Of the above six studies, the four studies, 1998005, 1998006, 171, and 183, were submitted to support the efficacy claim on the prevention of heartburn while the other two studies, 1997092 and 1997095, were for the treatment of heartburn. Of these four studies submitted for the prevention indication, the two studies, 1998005 and 1998006, were to support the efficacy claim on the 4-hour prevention of heartburn and the other two studies, 171 and 183, were to support the efficacy claim on the two-week prevention of heartburn.

2.0 Studies 1998005 and 1998006 - prevention indication on 4-hour treatment phase

2.1.0 Background Information for Studies 1998005 and 1998006

Objectives: The primary objective of this study was to assess the efficacy of pre-prandial dosing with omeprazole magnesium 20.6 mg (Ome-Mg 20) versus placebo in preventing the occurrence of heartburn over a 4-hour period following a provocative meal. The secondary objective was to expand the comparisons of the effectiveness for omeprazole magnesium 10.3 mg (Ome-Mg 10) versus placebo and Ome-Mg 20 versus placebo in preventing the occurrence of heartburn over a 4-hour period following a provocative meal.

Study Design: This study was a multi-center, single-dose, randomized, double-blind, double-dummy, parallel, placebo-controlled study with an initial target population of approximately 1242 completed subjects. The study consisted of four visits: two visits during the Screening period, a Baseline meal visit, and a Randomization meal visit. All subjects agreeing to participate were required to provide written informed consent and underwent eligibility screening period, which included a physical exam and a medical/medication history. To be eligible for randomization to treatment, subjects must have experienced Moderate or Severe heartburn following the Baseline meal.

Subjects who met all Continuance criteria and continued to meet inclusion/exclusion criteria were randomly assigned (in a 1:1:1 ratio) to one of the following treatment groups at each study center, according to a randomization schedule provided by Procter & Gamble: Ome-Mg 20, Ome-Mg 10, and Placebo. At the Randomization meal, subjects received two bottles of study

medication each containing one tablet. In the presence of study staff, subjects consumed both of their allocated tablets. Subjects consumed the tablets with water 1-hour prior to the Randomization meal. Subjects remained at the study center to evaluate their heartburn for 4 hours after the randomization meal commenced.

Study medication safety was evaluated from the self-reported adverse events (AEs) experienced by subjects after dosing and through the 4-hour evaluation period and from self-reported AEs experienced by subjects for the 48 hours following the Randomization meal. All AEs were tracked until resolution or until it was determined by a study physician that an ongoing AE was stable. Figure 2.1.0.1 displays the study procedures.

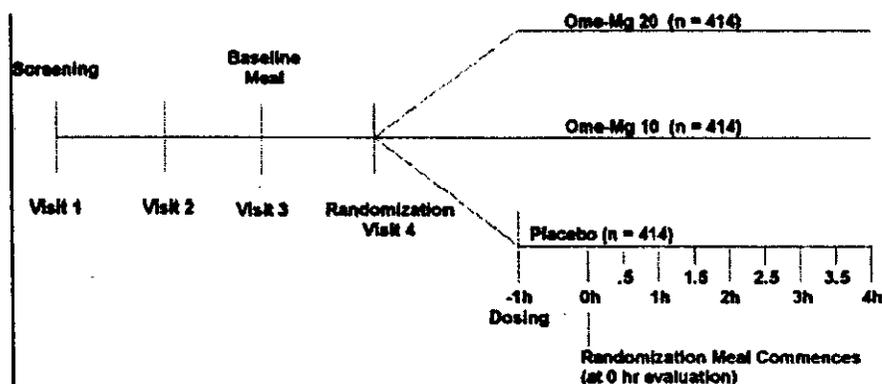


Figure 2.1.0.1 Clinical Study Diagram

Efficacy and Safety Measurements: Efficacy measurements on heartburn symptoms were collected from subjects at the beginning of the provocative meals and every 30 minutes for 4 hours after the beginning of the provocative meals. Subjects evaluated their heartburn symptoms using the following categorical scale:

- None (0) - No heartburn is present;
- Mild (1) - Heartburn is present but easily tolerated;
- Moderate (2) - Heartburn is sufficient to cause interference with normal daily activities or sleep;
- Severe (3): Heartburn is incapacitating subject from performing normal daily activities or sleep.

In addition, safety was assessed by the collection of voluntarily reported AEs after dosing with study medication at Visit 4.

Determination of Sample Size: Sample size estimates for this study were determined based on a 95% power using a two-tailed chi-square test of difference in two probabilities at significance level of .05. A sample size of 414 per treatment was calculated to be appropriate to detect a difference between 25% and 15% in the percentages of Heartburn-Free (the primary efficacy

measure) subjects between the Ome-Mg 20 and placebo groups. This difference of 10% was determined based on a pilot study.

Study Population: The inclusion criteria for the study population included patients

- having a history of developing at least Moderate heartburn within 1-hour after provocative meals and the ability to identify foods/beverages that produced these heartburn symptoms;
- having a history of developing heartburn which responded, to some degree, to antacids or OTC H2RA treatment;
- for male or non-pregnant, non-lactating female (women of child-bearing potential must have used an acceptable form of contraception as determined by the Investigator), in good general health, any race, and at least 18 years of age; etc.

Patients were excluded from the study population if they had

- a history (past or present) of erosive esophagitis verified by endoscopy;
- a history (past or present) of GERD diagnosed by a physician;
- a history (past or present) of pathologic intraesophageal pH monitoring;
- any medical condition or concomitant therapy which may interfere with the evaluation of heartburn treatment;
- a history of lactose intolerance; etc.

[For the detail of patient selection, refer to sponsor's Volume 1.029].

Study Hypothesis: The efficacy of Ome-Mg 20 is superior to placebo in preventing the occurrence of heartburn over a 4-hour period following a provocative meal.

Primary and Secondary Efficacy Variables: The primary efficacy endpoint was the percentage of subjects Heartburn-Free over the entire 4-hour period after the Randomization meal (i.e., severity score is 0 at all time points). The secondary efficacy endpoints were i.) Overall Assessment (poor, fair, good, very good, and excellent) of the study medication at the end of the 4-hour measurement period, ii.) Average Symptom Severity Score across the 4-hour measurement period, iii.) Maximum Symptom Severity Score over the 4-hour measurement period, iv.) Reduction of Maximum Symptom Severity Score of the Randomization meal from the Maximum Symptom Severity Score of the Baseline meal, v.) Percentage of subjects taking backup medication (Backup Medication Use), and vi.) Time to Backup medication use.

Efficacy analyses

The efficacy endpoints were analyzed for the following two groups of patients:

- Intent-to-treat (ITT) population – All randomized subjects who dosed with study medication and had at least one efficacy evaluation following the randomization meal.
- Per- Protocol (PP) population – A sub-population of ITT population excluding those subjects who did not satisfy the Evaluable criteria.

A Cochran-Mantel-Haenszel (CMH) test stratified by Investigator was performed for the primary endpoint (heartburn-free or not) to compare treatment effects. For the secondary efficacy endpoints, Extended Mantel-Haenszel test was applied to compare the treatment effects on the overall assessment and Maximum Symptom Severity Score while analysis of variance model was used to analyze the average symptom severity score, the percentage of subjects taking backup medication, and reduction of maximum severity score. Finally, the time to backup medication use was analyzed by the Cox proportional hazard model, adjusting for investigator.

The primary statistical analyses were performed on the ITT population while the secondary statistical analyses were on the PP population.

Disposition of Patients for Study 1998005: Of the 1382 subjects scheduled for the Randomization meal, 1287 subjects (93.1%) were randomized to treatment. Ninety-five subjects (6.9%) did not show for the Randomization meal (e.g., lost to follow-up) or failed the Visit 4 Randomization meal Continuance criteria. The randomized subjects were allocated to treatments in the following manner: 433 in the Ome-Mg 20 group, 430 in the Ome-Mg 10 group, and 424 in the placebo group. Table 2.1.0.1 summarizes patient disposition among three treatment groups for the 4-hour treatment phase: Ome-Mg 20, Ome-Mg 10, and placebo.

Table 2.1.0.1 Patient disposition among three treatment groups (Study 1998005)

Disposition	Ome-Mg 20	Ome-Mg 10	Placebo	Overall
Total Randomized	433	430	424	1287
Intent-to-Treat	433	428	423	1284
Per-Protocol	406	398	400	1204

Disposition of Patients for Study 1998006: Of the 1274 subjects scheduled for the Randomization meal, 1171 subjects (91.9%) were randomized to treatment. Ninety-three subjects (7.3% of those scheduled) did not show for the Randomization meal (e.g., lost to follow-up), 11 subjects (0.86% of those scheduled) failed the Visit 4 Randomization meal Continuance criteria, and 1 subject (0.08% of those scheduled) was inadvertently randomized and allowed to dose with study medication. The randomized subjects were allocated to treatments in the following manner: 394 in the Ome-Mg 20 group, 387 in the Ome-Mg 10 group, and 390 in the placebo group. Table 2.1.0.2 summarizes patient disposition among three treatment groups for the 4-hour treatment phase: Ome-Mg 20, Ome-Mg 10, and placebo.

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Table 2.1.0.2 Patient disposition among three treatment groups (Study 1998006)

Disposition	Ome-Mg 20	Ome-Mg 10	Placebo	Overall
Total Randomized	394	387	390	1171
Intent-to-Treat	393	387	390	1170
Per-Protocol	389	380	380	1149

Premature Discontinuations for Study 1998005: Sixteen randomized subjects (1.2%) did not complete the 4-hour treatment phase: 5 subjects in the Ome-Mg 20 group, 8 subjects in the Ome-Mg 10 group, and 3 subjects in the placebo group. Among those subjects that did not complete the treatment phase, 7 subjects had AEs, 5 subjects withdrew consent, 2 subjects failed the Continuance criteria, and 2 subjects discontinued due to Investigator and Sponsor's decision.

Premature Discontinuations for Study 1998006: Seven randomized subjects (0.6%) did not complete the 4-hour treatment phase: 2 subjects in the Ome-Mg 20 group, 1 subjects in the Ome-Mg 10 group, and 4 subjects in the placebo group. Among those subjects that did not complete the treatment phase, 1 subjects had AEs, 5 subjects withdrew consent, and 1 subjects discontinued due to Investigator and Sponsor's decision.

2.2.0 Sponsor's Analysis Results and Reviewer's Comments for Study 1998005

2.2.1 Sponsor's Statistical Analysis Results

Demographics and Baseline Characteristics

The demographic variables and baseline characteristics analyzed by the sponsor for the three treatment groups, Ome-Mg 20, Ome-Mg 10, and placebo were gender, race, age, current smoker, current use of other nicotine products, alcohol consumption, currently consume caffeine-containing beverage, currently consume other caffeine-containing products, average symptom severity score following baseline meal, and maximum symptom severity score following baseline meal for all randomized, ITT, and PP patients.

For ITT patients, the analyzed demographic and baseline characteristics were comparable among the three treatment groups, with the exception of alcohol consumption per week ($p=0.033$), where the placebo group appeared to have a larger percentage of non-drinkers (61%) when compared to the two omeprazole groups (56% for Ome-Mg 20 and 20% for Ome-Mg 10). The results from all randomized and PP patient populations were found similar to those of ITT population.

Summary of Sponsor's Efficacy Analysis Results

i.) Primary Efficacy Endpoint Analyses

Table 2.2.1.1 (extracted from sponsor's Table F in Volume 29) summarizes the results for the primary efficacy analysis on heartburn-free during the 4-hour evaluation period (primary efficacy endpoint) from the start of the Randomization meal for intent-to-treat patient population.

Table 2.2.1.1 (Sponsor's) Primary efficacy analysis on 4-hour Heartburn-Free evaluation for intent-to-treat patients

TREATMENT GROUP	HEARTBURN-FREE RATE	P-VALUE VS. PLACEBO ¹	P-VALUE FOR HOMOGENEITY ²
Placebo (N=423)	20.1% (85/423)		
Ome-Mg 10 (428)	24.3% (104/428)	0.139	0.624
Ome-Mg 20 (N=433)	25.4% (110/433)	0.057	0.94

¹: Cochran-Mantel-Haenszel test for a treatment vs. placebo using investigator as a stratification factor;

²: Breslow-Day test for homogeneity between a treatment vs. placebo across investigators performed by this reviewer using sponsor's SAS program.

Table 2.2.1.1 indicated that at significance level of .05, the heartburn-free rate for Ome-Mg 20 ($p=0.057$) was borderline significantly higher than that of placebo ($p=0.057$); however, the heartburn-free rate of Ome-Mg 10 was not significantly better than that of placebo ($p=0.14$) for intent-to-treat patients.

The results on the heartburn-free rate analysis for the per-protocol patients were found similar to those of intent-to-treat patients.

ii.) Secondary Efficacy Endpoint Analyses

Table 2.2.1.2 (extracted from sponsor's Table 8.2.2, Table 8.2.5, and Table 8.2.7 in Volume 29) summarizes the analysis results on the secondary efficacy endpoints classified as categorical variables and continuous variables for ITT population. The categorical secondary endpoints were overall assessment, maximum symptom severity score, and backup medication (use or not-use) while the continuous secondary endpoints were average symptom severity score, reduction of maximum symptom severity scores (randomization meal score minus baseline meal score), and time to backup medication use.

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Table 2.2.1.2 (Sponsor's) Analysis Results for the Secondary Efficacy endpoints

TREATMENT COMPARISON	P-VALUE
Overall Assessment (Poor to excellent)	
Ome-Mg 20 vs. Placebo	0.002*
Ome-Mg 10 vs. Placebo	0.175
Maximum Symptom Severity Score (None to Severe)	
Ome-Mg 20 vs. Placebo	0.001*
Ome-Mg 10 vs. Placebo	0.027*
Backup Medication Use (within 4 hours)	
Ome-Mg 20 vs. Placebo	0.015*
Ome-Mg 10 vs. Placebo	0.48
Average symptom Severity Score	
Ome-Mg 20 vs. Placebo	0.024*
Ome-Mg 10 vs. Placebo	0.059
Reduction of Maximum Symptom Severity Scores	
Ome-Mg 20 vs. Placebo	0.001*
Ome-Mg 10 vs. Placebo	0.095
Time to Backup Medication Use	
Ome-Mg 20 vs. Placebo	0.158
Ome-Mg 10 vs. Placebo	0.701

*: Significant at .05 significance level.

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Based on the results of the secondary endpoint analyses, Table 2.2.1.2 showed that except for time to backup medication, the effect of Ome-Mg 20, when dosed 1-hour prior to a provocative meal, is superior to placebo evaluated by the other five secondary variables ($p \leq 0.015$). On the contrary, except for the maximum symptom severity score showing the superiority of Ome-Mg 10 to placebo ($p=0.027$), the efficacy of Ome-Mg 10 was only numerically better than that of placebo assessed by the rest of five variables.

Adverse Events

Overall, 85 of the subjects reported 108 adverse events (AEs). Twenty-four (6%) of the subjects on Ome-Mg 20 reported 28 AEs; 34 of the subjects (8%) on Ome-Mg 10 reported 44 AEs; and 27 of the subjects (6%) on placebo reported 36 AEs. The percentage of AEs that were considered to be Mild to Moderate in intensity was 86%, 80%, and 81% of subjects on Ome-Mg 20, Ome-Mg 10, and placebo, respectively. The percentage of AEs that were considered to be Severe in intensity was 14% for Ome-Mg 20 and Ome-Mg 10 and 19% for the placebo treatment groups. The percentage of AEs that were considered possibly or probably due to study medication was 61%, 68%, and 64% for subjects on Ome-Mg 20, Ome-Mg 10, and placebo, respectively.

During the study, no subject experienced a serious adverse events (SAE). Seven subjects discontinued study medication because of an AE. The discontinuations due to AEs were reported by 3 subjects on Ome-Mg 20, 3 subjects on Ome-Mg 10, and 1 subject on placebo.

2.2.2 Reviewer's Comments and Conclusions for Study 1998005

It is noted that the efficacy of Ome-Mg 20 is shown borderline significantly better than that of placebo ($p=0.057$) on 4-hour heartburn-free evaluation by the sponsor's analysis, reported in Table 2.2.1.1. However, the efficacy of Ome-Mg 10 is not statistically significantly better than that of placebo assessed by 4-hour heartburn-free rates ($p=0.14$).

To validate the borderline superiority of Ome-Mg 20 to placebo, this reviewer performed the following two analyses using intent-to-treat patients: 1.) P-value multiplicity adjustment analysis for the secondary endpoints and 2.) subgroup analysis on 4-hour heartburn-free evaluation.

Data used in this reviewer's analysis was submitted by the sponsor, dated January 29, 2000.

1.) P-value multiplicity adjustment analysis

Since the treatment effects of Ome-Mg 20 versus placebo were assessed using six secondary endpoints: overall assessment, maximum symptom severity score, backup medication use, average symptom severity score, reduction of maximum symptom severity score, and time to backup medication, this reviewer applies the Hochberg step-up procedure to adjust the multiplicity induced by the six multiple comparisons by ITT patient population. Table 2.2.2.1 presents the results of the Hochberg multiplicity adjustments on the p-values for comparing the effects of Ome-Mg 20 versus placebo using above six secondary endpoints by ITT patient population.

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Table 2.2.2.1 (Reviewer's) Hochberg multiplicity adjustments on the p-values for comparing the effects of Ome-Mg 20 versus placebo by the secondary endpoints using ITT patients

SECONDARY ENSPOINT	Raw-p ¹	Adj.-p ²
Overall Assessment (Poor to excellent)	0.002	0.008*
Maximum Symptom Severity Score (None to Severe)	0.001	0.005*
Backup Medication Use (within 4 hours)	0.015	0.045*
Average symptom Severity Score	0.024	0.048*
Reduction of Maximum Symptom Severity Scores	0.001	0.006*
Time to Backup Medication	0.158	0.158

*: Significance at significance level of 0.05 determined by Hochberg procedure.

¹: Original p-value; ²: P-value adjusted by Hochberg procedure;

Table 2.2.2.1 shows that after Hochberg multiplicity adjustments, the treatment effects of Ome-Mg 20 superior to placebo are found for overall assessment, maximum symptom severity score, backup medication use, average symptom severity score, and reduction of maximum symptom severity score using ITT patient population.

Similar results are found for per-protocol patients.

2. Subgroup Analysis

To assess the consistency of results on 4-hour heartburn-free evaluation across subgroups, this reviewer also performed some subgroup analyses for the subgroups listed below for ITT patient population.

Gender

This reviewer's gender group (Female and Male) analysis results for the comparisons of treatment effects are presented by Table A.1.1 in Appendix I. The results are briefly summarized below:

- The subgroup analysis results indicate that the 4-hour heartburn-free rate of Ome-Mg 10 is significantly higher than that of placebo for female patients.
- To compare with placebo, it is noted that at least a positive trend favors omeprazole for both male and female groups.

Age

This reviewer's age group (≤ 65 and > 65) analysis results for the comparisons of treatment effects are presented by Table A.1.2 in Appendix I.

- The subgroup analysis results indicate that the 4-hour heartburn-free rate of Ome-Mg 20 is significantly higher than that of placebo for patients with age less than or equal to 65.
- To compare with placebo, it is noted that in general, there is a positive trend in favor of omeprazole for both age groups with the exception of Ome-Mg 20 versus placebo using senior age group (age > 65).

Race

This reviewer's race group (Caucasian and Non-Caucasian) analysis results for the comparisons of treatment effects are presented by Table A.1.3 in Appendix I.

- The subgroup analysis results indicate that the 4-hour heartburn-free rates of omeprazole are numerically higher than those of placebo for both Caucasian and Non-Caucasian groups with the exception of Ome-Mg 10 versus placebo using Non-Caucasian group.

2.2.3 Recommendations/Conclusions of the treatment effects for Study 1998005

- ◆ From the results of the sponsor's and this reviewer's analyses, it can be concluded that the effect of Ome-Mg 20 is borderline significantly better than that of placebo in the 4-hour prevention of heartburn.
- ◆ However, by Table 2.2.1.1, the efficacy of Ome-Mg 10 is not superior to that of placebo in the 4-hour prevention of heartburn ($p=0.14$).

2.3.0 Sponsor's Analysis Results and Reviewer's Comments for Study 1998006

2.3.1 Sponsor's Statistical Analysis Results

Demographics and Baseline Characteristics

The demographic variables and baseline characteristics analyzed by the sponsor for the three treatment groups, Ome-Mg 20, Ome-Mg 10, and placebo were gender, race, age, current smoker, current use of other nicotine products, alcohol consumption, currently consume caffeine-containing beverage, currently consume other caffeine-containing products, average heartburn severity following baseline meal, and maximum heartburn severity following baseline meal for ITT and PP patients.

For ITT patients, the analyzed demographic and baseline characteristics were comparable among the three treatment groups, with the exception of race ($p=0.004$) and age ($p=0.04$). There were

more Caucasians in the Ome-Mg 10 group than in the other two treatment groups, and those subjects in the Ome-Mg 10 group were also slightly older than those in the other two treatment groups.

The analysis results on demographic and baseline characteristics from the per-protocol population were found to be similar to those of ITT population.

Summary of Sponsor's Efficacy Analysis Results

i.) Primary Efficacy Endpoint Analyses

Table 2.3.1.1 (extracted from sponsor's Table F in Volume 38) summarizes the results for the primary efficacy analysis on heartburn-free during the 4-hour evaluation period (primary efficacy endpoint) from the start of the Randomization meal for intent-to-treat patient population.

Table 2.3.1.1 (Sponsor's) Primary efficacy analysis on 4-hour Heartburn-Free evaluation for intent-to-treat patients

TREATMENT GROUP	HEARTBURN-FREE RATE	P-VALUE VS. PLACEBO ¹	P-VALUE FOR HOMOG ²
Placebo (N=390)	17.2% (67/390)		
Ome-Mg 10 (387)	25.3% (98/387)	0.005	0.16
Ome-Mg 20 (N=393)	25.7% (101/393)	0.004	0.044

¹: Significant at .05 for treatment comparisons and at 0.10 for odds homogeneity test;

¹: Cochran-Mantel-Haenszel test for a treatment vs. placebo using investigator as a stratification factor;

²: Breslow-Day test for odds homogeneity between a treatment vs. placebo across investigators performed by this reviewer using sponsor's SAS program.

Table 2.3.1.1 indicated that at significance level of .05, the heartburn-free rate for both Ome-Mg 20 (p=0.004) and Ome-Mg 10 (p=0.005) were significantly higher than that of placebo, after controlling investigator effect, for intent-to-treat patients. However, a statistically significant lack of homogeneity across investigators in heartburn-free rates was found by Breslow-Day test for Ome-Mg 20 versus placebo (p=0.044). The effect of investigators on the heartburn-free rates will be discussed later in section 2.3.2 – Reviewer's Analysis and Comments.

The results on the heartburn-free rate analysis for per-protocol patients were found similar to those of intent-to-treat patients.

ii.) Secondary Efficacy Endpoint Analyses

Table 2.3.1.2 (extracted from sponsor's Table 8.2.2, Table 8.2.5, and Table 8.2.7 in Volume 38) summarizes the analysis results on the secondary efficacy endpoints classified as categorical

variables and continuous variables for ITT population. The analyzed categorical secondary endpoints were overall assessment, maximum symptom severity score, and backup medication (use or not-use) while the continuous secondary endpoints were average symptom severity score and reduction of maximum symptom severity scores (randomization meal score minus baseline meal score).

Table 2.3.1.2 (Sponsor's) Analysis Results for the Secondary Efficacy endpoints

TREATMENT COMPARISON	P-VALUE
Overall Assessment (Poor to excellent)	
Ome-Mg 20 vs. Placebo	< 0.001*
Ome-Mg 10 vs. Placebo	0.016
Maximum Symptom Severity Score (None to Severe)	
Ome-Mg 20 vs. Placebo	< 0.001*
Ome-Mg 10 vs. Placebo	< 0.001*
Backup Medication Use (within 4 hours)	
Ome-Mg 20 vs. Placebo	< 0.001*
Ome-Mg 10 vs. Placebo	0.049*
Average symptom Severity Score	
Ome-Mg 20 vs. Placebo	< 0.001*
Ome-Mg 10 vs. Placebo	< 0.001*
Reduction of Maximum Symptom Severity Scores	
Ome-Mg 20 vs. Placebo	< 0.001*
Ome-Mg 10 vs. Placebo	0.001*
Time to Backup Medication Use	
Ome-Mg 20 vs. Placebo	0.210
Ome-Mg 10 vs. Placebo	0.237

*: Significant at .05 significance level.

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Based on the results of Table 2.3.1.2, the sponsor claimed that the effects of Ome-Mg 20 and Ome-Mg 10, when dosed 1-hour prior to a provocative meal, were superior to placebo in five secondary efficacy endpoints: overall assessment, maximum symptom severity score, back-up medication use, average symptom severity score, and reduction of maximum symptom severity scores.

Adverse Events

Overall, 35 of the subjects reported 45 adverse events (AEs). Eleven of the subjects (3%) on Ome-Mg 20 reported 16 AEs; 15 of the subjects (4%) on Ome-Mg 10 reported 20 AEs; and 9 of the subjects (2%) on placebo reported 9 AEs. The percentage of AEs that were considered to be Mild to Moderate in intensity was 100%, 95%, and 100% for subjects on Ome-Mg 20, Ome-Mg 10, and placebo, respectively. The percentage of AEs that were considered possibly or probably

due to study medication was 75%, 50%, and 67% for subjects on Ome-Mg 20, Ome-Mg 10, and placebo, respectively. During the study, no subject experienced a serious adverse events (SAE). Only one subject who dosed with Ome-Mg 20 discontinued study medication due to an AE.

2.3.2 Reviewer's Analyses and Comments for Study 1998006

Since the primary objective of the study is to compare the efficacy of Ome-Mg 20 versus placebo, this reviewer first validates the efficacy of Ome-Mg 20 superior to placebo claimed by the sponsor. After validating the efficacy of Ome-Mg 20 superior to placebo, the efficacy comparison of Ome-Mg 10 versus placebo is then pursued.

To validate the efficacy of Ome-Mg 20 superior to placebo, this reviewer performs the following three analyses using intent-to-treat patients: 1.) Sensitivity analysis to inspect the effect of investigator on the 4-hour heartburn-free evaluation, 2.) P-value multiplicity adjustment analysis for the secondary endpoints and 3.) Subgroup analysis on 4-hour heartburn-free evaluation.

Data used in this reviewer's analysis was submitted by the sponsor, dated January 29, 2000.

1.) Sensitivity analysis

As shown by Table 2.3.1.1, at significance level of .10, a significant lack of homogeneity on odds ratio of 4-hour heartburn-free evaluation between Ome-Mg 20 and placebo across investigators was found by Breslow-Day test ($p=0.044$) for ITT patient population.

In order to assess the effect of the investigators on the differences of 4-hour heartburn-free rates between Ome-Mg 20 and placebo, this reviewer performs the following two analyses using ITT patient population:

- i. Cochran-Mantel-Haenszel test using center (investigator) group (Centerg) with four levels as a stratification factor: level 1 for center size ≤ 50 ; level 2 for $50 < \text{center size} \leq 80$; level 3 for $80 < \text{center size} \leq 100$; and level 4 for center size > 100 .
- ii. Two-sided Fisher Exact test to compare the overall 4-hour heartburn-free rates between Ome-Mg 20 and placebo without using any stratification factors.

In the sensitivity analysis i., since the numbers of patients enrolled by centers (investigators) in each level were close among one another, the effects of investigators in each level on the heartburn-free rates are likely to be similar and the patients in each level are pooled. If the effect of investigator on the heartburn-free rates is critical, the results (p-values) of the sensitivity analysis i., ii., and the sponsor's analysis on the treatment efficacy comparisons for Ome-Mg 20 versus placebo on heartburn-free rates are expected to be very different.

Table 2.3.2.1 summarizes the effect of Centerg on the comparison of two treatment effects (Ome-Mg 20 versus placebo) assessed by 4-hour heartburn-free rates for ITT patient population. In

addition, the result for the overall comparisons on the two treatment effects without using any stratification factors is also discussed.

Table 2.3.2.1 (Reviewers) The sensitivity analysis result for the effect of Centerg on the comparison of two treatment effects assessed by 4-hour heartburn-free rates

TREATMENT COMPARISON	P-VALUE FOR CMH ¹	P-VALUE FOR HOMOG ²
Ome-Mg 20 vs. Placebo	0.003*	0.688

¹: Treatment comparison using Cochran-Mantel-Haenszel test with Centerg as a stratification factor;

²: Homogeneity test using Breslow-Day method to assess homogeneity of treatment effects across the levels of Centerg. *: Significant at .05 level.

Table 2.3.2 indicates that with Centerg as a stratification factor, the treatment effect of Ome-Mg 20 is superior to that of placebo ($p=0.003$) evaluated by 4-hour heartburn-free rate using ITT patient population. In addition, the result from the two-sided Fisher Exact test on the overall 4-hour heartburn-free rates using ITT patient population is also in favor of Ome-Mg 20 ($p=0.004$). Since the results (p-values) of the three analyses (two sensitivity analyses and the sponsor's analysis) to compare the heartburn-free rates between Ome-Mg 20 and placebo are similar, the superiority of Ome-Mg 20 to placebo is persuaded.

2. P-value multiplicity adjustment analysis

Refer to the section 2.2.2 on the reason applying the Hochberg step-up procedure for the p-value multiplicity adjustment when the treatment effects are assessed by the six secondary endpoints: overall assessment, maximum symptom severity score, backup medication use, average symptom severity score, reduction of maximum symptom severity score, and time to backup medication.

Table 2.3.2.2 presents the results for the Hochberg multiplicity adjustments on the p-values when comparing the effects of Ome-Mg 20 versus placebo by the six secondary endpoints using ITT patient population.

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Table 2.3.2.2 (Reviewer's) Hochberg multiplicity adjustments on the p-values for comparing the effects of Ome-Mg 20 versus placebo by the secondary endpoints using ITT patients

SECONDARY ENSPOINT	Raw-p ¹	Adj.-p ²
Overall Assessment (Poor to excellent)	<0.001*	<0.001*
Maximum Symptom Severity Score (None to Severe)	<0.001*	<0.001*
Backup Medication Use (within 4 hours)	<0.001*	<0.001*
Average symptom Severity Score	<0.001*	<0.001*
Reduction of Maximum Symptom Severity Scores	<0.001*	<0.001*
Time to Backup Medication	0.210	0.210

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*: Significance at significance level of 0.05 determined by Hochberg procedure.

¹: Original p-value; ²: P-value adjusted by Hochberg procedure;

Table 2.3.2.2 shows that after Hochberg multiplicity adjustments, the treatment effects of Ome-Mg 20 superior to placebo are found for overall assessment, maximum symptom severity score, backup medication use, average symptom severity score, and reduction of maximum symptom severity score using ITT patient population.

3. Subgroup Analysis

To assess the consistency of results on 4-hour heartburn-free evaluation across subgroups, this reviewer also performed some subgroup analyses for the subgroups listed below for ITT patient population.

Gender

This reviewer's gender group (Female and Male) analysis results for the comparisons of treatment effects are presented by Table A.2.1 in Appendix II. The results are briefly summarized below:

- The subgroup analysis results indicate that the 4-hour heartburn-free rates of Ome-Mg 20 are significantly higher than those of placebo for both female and male patients while the 4-hour heartburn-free rate of Ome-Mg 10 is significantly higher than that of placebo only for male patient.
- To compare with placebo, it is noted that at least a positive trend favors omeprazole for both male and female groups.

Age

This reviewer's age group (≤ 65 and > 65) analysis results for the comparisons of treatment effects are presented by Table A.2.2 in Appendix II.

- The subgroup analysis results indicate that for 4-hour heartburn-free rates, both Ome-Mg 20 and Ome-Mg 10 are significantly higher than those of placebo for patients with age less than or equal to 65.
- To compare with placebo, it is noted that in general, there is a positive trend in favor of omeprazole for both age groups.

Race

Most of the patients were Caucasian (80%), so no subgroup analysis was performed.

2.3.3 Conclusions/Recommendations of the treatment effects for Study 1998006

From the results of the sponsor's and this reviewer's analyses, it can be concluded that the effect of Ome-Mg 20 is significantly better than that of placebo in the 4-hour prevention of heartburn. Since the primary objective of this Study is achieved, the efficacy of Ome-Mg 10 versus placebo is then pursued.

Based on Table 2.3.1.1, the efficacy of Ome-Mg 10 is superior to that of placebo ($p=0.005$) on 4-hour heartburn-free evaluation (the primary efficacy endpoint). In addition, following the Hochberg P-value multiplicity adjustment analysis on overall assessment, maximum symptom severity score, backup medication use, average symptom severity score, reduction of maximum symptom severity scores, and time to backup medication use, the superiority of Ome-Mg 10 to placebo in the 4-hour prevention of heartburn is supported.

2.4.0 Reviewer's Conclusions and Recommendations for Studies 1998005 and 1998006

- ❖ The superiority of Ome-Mg 20 mg to placebo on 4-hour heartburn-free evaluation (the primary efficacy endpoint) is supported by Study 1998006 ($p=0.004$).
- ❖ The result of Ome-Mg 20 significantly better than that of placebo on 4-hour heartburn-free evaluation, shown by Study 1998006, is not replicated by that of Study 1998005.
- ❖ The superiority of Ome-Mg 10 to placebo on 4-hour prevention of heartburn is supported only by one study, Study 1998006.

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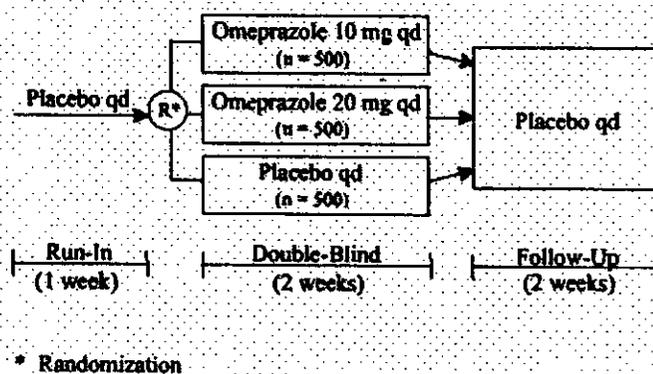
3.0 Studies 171 and 183 - Prevention indication for two-week treatment phase

3.1.0 Background Information for Studies 171 and 183

Objectives: The primary objective of the study was to demonstrate that a single dose of omeprazole magnesium 20 mg (Ome-Mg 20) (versus placebo) is effective in completely preventing the occurrence of heartburn over a full day. The secondary objectives were to 1.) compare the treatment groups with regard to the maximum severity of heartburn and the occurrence of nocturnal heartburn after a single dose, 2.) compare the treatment groups with regard to complete prevention of heartburn over a full day, the maximum severity of heartburn and the occurrence of nocturnal heartburn over repeated daily doses, 3.) describe the incidence of heartburn for each treatment group during the follow-up phase, and 4.) assess the safety and tolerability of omeprazole magnesium when used in preventing heartburn.

Study Design: This study was a multicenter, double-blind, randomized, parallel, placebo-controlled study to investigate the safety and efficacy of omeprazole magnesium, 10 mg qd and 20 mg qd, in preventing heartburn. The five-week study had the following three phases: 1.) Single-Blind placebo Run-In (one week), 2.) Double-Blind randomized treatment (two weeks), and 3.) Single-Blind placebo Follow-Up (two weeks).

During each study phase the blinded nature of the study was preserved using double dummy packaging. The subject was always dispensed two bottles of medication: bottle A contained active Ome-Mg 10 or placebo, bottle B contained active Ome-Mg 20 or placebo. Both bottles contained placebo for the placebo arm of the treatment phase and during the Run-In and Follow-Up phases. Subjects were also dispensed GELUSIL at every visit but encouraged not to use it unless absolutely necessary for the relief of heartburn. Figure 3.1.0.1 displays the process of the clinical study.



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Figure 3.1.0.1 Clinical Study Diagram

Study Procedures: This study consisted of four visits: Visit 1 (Screening), Visit 2(baseline/Randomization), Visit 3, and Visit 4.

At Visit 1, informed consent was obtained, a complete medical history was obtained, physical exam performed, and routine laboratory samples collected. Consented subjects who satisfied enrollment criteria were entered into the Run-In phase and dispensed single-blind placebo kits and heartburn diaries. GELUSIL tablets were also supplied to the subjects to use throughout the study, if necessary.

At Visit 2, seven to nine days following Visit 1, the Run-In phase diaries were reviewed to determine if subjects satisfied the following criteria for randomization: 1.) at least two days with heartburn, 2.) no more than two days with missed doses, and 3.) no more than two days with incomplete or inconsistent diary entries. Compliance with study medication and safety were also monitored at this visit. Approximately 1500 eligible subjects were to be randomized to receive one of the following medications: Ome-Mg 20, qd, Ome-Mg 10, qd, and placebo qd according to a randomization schedule generated by Biostatistics, Astra Pharmaceuticals. GELUSIL tablets were also supplied to the subjects to use throughout the study, if necessary. One week following Visit 2 subjects were contacted by telephone to monitor safety, encourage diary and medication compliance and confirm the date of Visit 3.

At Visit 3, 14 days (+ 2 days) following randomization, the diaries from the Double-Blind phase were collected and reviewed. Subjects were evaluated for adverse events and blood specimens were drawn at this visit for laboratory analysis. Subjects were dispensed a diary and single-blind placebo to be used over the next 14 days. A new supply of GELUSIL was also supplied. One week following Visit 3 subjects were contacted by telephone to monitor safety, encourage diary and medication compliance and confirm the date of Visit 4.

At Visit 4, 15 days (+ 2 days) following Visit 3, subjects returned for their final visit where Visit 3 diaries were reviewed and adverse events were recorded.

Determination of Sample Size: The primary study question was whether there was a difference on Day 1 between Ome-Mg 20 and placebo in the probability of having no heartburn. The study intended to detect an arithmetic difference of 10 percentage points between Ome-Mg 20 and placebo with 95% power using a two-sided $\alpha = 0.05$ level test. If in the current experimental setting the true placebo rate is 20% and 500 subjects were available for analysis, then this study had just over 95% power to detect the targeted difference, assuming the use of a Chi-square test. If the placebo rate is 40% then the study had 89% power.

Study Population: The inclusion criteria for the study population included heartburn on at least two days per week over the past month, heartburn which responds to antacids or OTC H2-receptor antagonist treatment, and presence of heartburn on at least two days during the Run-In phase, etc.

Patients were excluded from the study population if they demonstrated history of erosive esophagitis verified by endoscopy, history of gastroesophageal reflux disease (GERD) diagnosed by a physician, and history of pathologic intraesophageal pH monitoring, etc.

[For the detail of patient selection, refer to sponsor's Volume 1.046].

Efficacy and Safety Measurements: Every morning during the five week study, each subject completed his or her diary by answering the following questions:

- Over the last 24 hours (yesterday and last night), what was the severity of your most intense episode of heartburn (No Heartburn, Mild, Moderate, Severe)?
- Did you experience heartburn during the night (from going to bed last night to getting out of bed this morning) - Yes, No?
- Over the last 24 hours, how many GELUSIL tablets did you take?

Subjects were instructed to complete their diary and take their dose of study medication each morning prior to breakfast. All measures of efficacy were derived from data recorded in the subject diaries after daily self-assessment. Prevention of heartburn after the first dose was of principal interest, although the overall benefit of subsequent doses was evaluated.

Safety was assessed with a physical exam at the screening visit; adverse events captured throughout the study and laboratory specimens drawn at the screening visit and at the end of the treatment phase.

Primary and Secondary Efficacy Variables: The primary efficacy variable was no heartburn between consecutive daily doses (ie. no heartburn over 24 hours) and the primary evaluation was the period between the first and second daily dose following randomization (Day 1).

The secondary efficacy endpoints were:

- the complete prevention of nocturnal heartburn (no nocturnal heartburn) on Day 1;
- the occurrence of no more than mild heartburn over 24 hours on Day 1;
- the percentage of days with the outcome of no heartburn over 24 hours over the two week double-blind phase;
- the percentage of days with the outcome of no nocturnal heartburn over the two week double-blind phase;
- the percentage of days with the outcome of no more than mild heartburn over 24 hours over the two week double-blind phase;

Efficacy analyses

The efficacy endpoints were analyzed for the following two groups of patients:

Intent-to-treat (ITT) population – All randomized subjects for whom at least one efficacy evaluation was available following first dose.

Per- Protocol (PP) population – A sub-set of ITT population excluding those subjects with major protocol violations.

The heartburn rates for the three treatment groups on Day 1 were compared using the Cochran-Mantel-Haenszel (CMH) test statistic, with investigator as a stratification variable. P-values were calculated for all comparisons between treatment groups. In the ITT analysis, subjects with missing responses were assumed to have heartburn.

In addition, odds ratio estimates with 95% confidence intervals for each treatment pair were calculated using logistic regression with treatment, center, and interaction between treatment and center as model parameters. A center was consisted of patients either recruited from an investigator who at least recruited forty-five subjects, or combined from investigators who recruited less than forty-five subjects. A significant level of .10 was used to assess the interaction between treatment and center.

For the Double-Blind phase, the percentage of days with no heartburn over 24 hours was calculated for each subject and the treatment means compared using two-way ANOVA with treatment and investigator as model parameters.

All statistical tests were two-sided. Unless otherwise noted, statistical significance was defined as a p-value less than or equal to .05. The primary statistical analyses were performed on the ITT population, and the secondary statistical analyses were performed on the PP population.

Disposition of Patients for Study 171: A total of 1817 subjects enrolled in the study. Of this number, 1775 (97.7%) met enrollment criteria and entered the Run-In phase. However, of the 1775 subjects, 1582 subjects (87.1% of all enrolled) had a sufficient number of days of heartburn and satisfactory diary entries to qualify them to be randomized to treatment at Visit 2. The randomized subjects were allocated to treatments in the following manner: 529 (33.4%) to Ome-Mg 20, 527 (33.3%) to Ome-Mg 10, and 526 (33.2%) to placebo. Table 3.1.0.1 summarizes patient disposition among three treatment groups for the two-week treatment phase: Ome-Mg 20, Ome-Mg 10, and placebo.

Table 3.1.0.1 Patient disposition for two-week double blind treatment phase (Study 171)

Disposition	Ome-Mg 20	Ome-Mg 10	Placebo	Overall
Total Randomized	529	527	526	1582
Intent-to-Treat	523	518	519	1560
Per-Protocol	519	514	515	1548

In addition, Table 3.1.0.2 presented the subject disposition among the three treatment groups for two-week follow-up period.

Table 3.1.0.2 Patient disposition for two-week follow-up phase (Study 171)

	Ome-Mg 20	Ome-Mg 10	Placebo	Overall
Number entering Follow-Up Phase	506	513	501	1520
Number completing Follow-Up Phase	496	508	498	1502

Disposition of Patients for Study 183: A total of 1850 subjects enrolled in the study. Of this number, 1782 (96.3%) met enrollment criteria and entered the Run-In phase. However, of the 1782 subjects, 1580 subjects (85.4% of all enrolled) had a sufficient number of days of heartburn and satisfactory diary entries to qualify them to be randomized to treatment at Visit 2. The randomized subjects were allocated to treatments in the following manner: 526 (33.3%) to Ome-Mg 20, 527 (33.4%) to Ome-Mg 10, and 527 (33.4%) to placebo. Table 3.1.0.3 summarizes patient disposition among three treatment groups for the two-week treatment phase: Ome-Mg 20, Ome-Mg 10, and placebo.

Table 3.1.0.3 Patient disposition for two-week double blind treatment phase (Study 183)

Disposition	Ome-Mg 20	Ome-Mg 10	Placebo	Overall
Total Randomized	526	527	527	1580
Intent-to-Treat	524	520	520	1564
Per-Protocol	514	515	511	1540

In addition, Table 3.1.0.4 presented the subject disposition among the three treatment groups for two-week follow-up period.

Table 3.1.0.4 Patient disposition for two-week follow-up phase (Study 183)

	Ome-Mg 20	Ome-Mg 10	Placebo	Overall
Number entering Follow-Up Phase	512	513	506	1531
Number completing Follow-Up Phase	509	508	504	1521

Discontinuations for Study 171: Of 1582 randomized subjects, 37 subjects discontinued during the Double-Blind phase: 15 from the Ome-Mg 20 group, 9 from the Ome-Mg 10 group, and 13 from the placebo group. The reasons for withdrawal were: 1 subject lacked a therapeutic response, 6 subjects discontinued due to an adverse, 11 subjects withdrew consent, 14 subjects were lost to follow-up, and 5 subjects discontinued due to a decision by the investigator or sponsor.

In addition, a total of 18 subjects discontinued during the Follow-Up phase: 4 lacked a therapeutic response, 5 had an adverse event causing discontinuation, 4 withdrew consent, 4 were lost to follow-up, and 1 discontinued due to a decision by the investigator or sponsor.

Discontinuations for Study 183: Of 1580 randomized subjects, 34 subjects discontinued during the Double-Blind phase: 11 from the Ome-Mg 20 group, 11 from the Ome-Mg 10 group, and 12 from the placebo group. The reasons for withdrawal were: 1 subject was found not to have met enrollment criteria, 1 subject was found not to have met randomization criteria, 1 subject lacked a therapeutic response, 6 subjects discontinued due to an adverse event, 12 subjects withdrew consent, 8 subjects were lost to follow-up, and 5 subjects discontinued due to a decision by the investigator or sponsor.

In addition, a total of 10 subjects discontinued during the Follow-Up phase: A total of 10 subjects discontinued during the Follow-Up phase: 4 had an adverse event causing discontinuation, 2 withdrew consent, 2 were lost to follow-up, and 2 discontinued due to a decision by the investigator or sponsor.

3.2.0 Sponsor's Analysis Results and Reviewer's Comments for Study 171

3.2.1 Sponsor's Statistical Analysis and Results

Demographics and Baseline Characteristics

The demographic variables and baseline characteristics analyzed by the sponsor for the three treatment groups, Ome-Mg 20, Ome-Mg 10, and placebo were gender, race, age, current smoker, other current nicotine use, alcohol consumption, consume caffeine-containing beverage, consume other caffeine-containing products, heartburn frequency (% of days) during Run-In, and average heartburn severity score during Run-In for ITT, PP, and all randomized patients.

The treatment groups were compared with respect to the demographic and baseline variables mentioned above. One-way ANOVA was performed on continuous variables and a simple chi-square test was applied to categorical variables. The sponsor indicated that at significance level of .05, no significant differences were found on the analyzed demographic and baseline variables among the three treatment groups for all randomized, ITT and PP patient populations.

Summary of Sponsor's Efficacy Analysis Results

i.) The results for the primary evaluation analysis

Table 3.2.1.1 (extracted from sponsor's Table 8.2.2 in Volume 46) summarizes the results of the primary efficacy analysis on heartburn-free over 24 hours on Day 1 (the primary evaluation) following the first dose of double-blind medication using ITT patient population.

Table 3.2.1.1 (Sponsor's) Primary efficacy analysis on Day 1 Heartburn-Free evaluation during the two-week double-blind phase using intent-to-treat patients

TREATMENT GROUP	HTBN-FR RT ^a	P-VALUE VS. PLACEBO ^c	P-VALUE VS. OME-MG10 ^b
Placebo (N=519)	32.6% (169/519)		
Ome-Mg 10 (518)	41.5% (215/518)	p=0.003 [*]	
Ome-Mg 20 (N=523)	49.7% (260/523)	p < 0.001 [*]	p=0.008 [*]

^a: Heartburn-Free rate; ^{*}: Significant at .05 for treatment comparisons and at 0.10 for odds homogeneity test;
^c: Cochran-Mantel-Haenszel test for a treatment vs. placebo using investigator as a stratification factor;
^b: Cochran-Mantel-Haenszel test for Ome-Mg 20 vs. Ome-Mg 10 using investigator as a stratification factor;
 Note: P-values for Breslow-Day test on odds ratios across investigators were greater than .5 for above pairwise comparisons.

Table 3.2.1.1 indicated that both Ome-Mg 20 and Ome-Mg 10 had significantly higher prevention rates on Day 1 than placebo (P < 0.001 and 0.003 respectively for Ome-Mg 20 and Ome-Mg 10 versus placebo) for ITT population. The increase over placebo for Ome-Mg 20 was 17.1 percent (49.7% - 32.6%) and for Ome-Mg 10 was 8.9 percent (41.5% - 32.6%). In addition, the prevention rate on Day 1 for Ome-Mg 20 was also found significantly higher than that of Ome-Mg 10 (p=0.008).

The results on the heartburn-free rate analysis for per-protocol patients were found not substantively different from those of ITT population.

ii.) The results for the secondary endpoint analyses

Day 1

Table 3.2.1.2 (extracted from sponsor's Table 8.2.2 in Volume 46) summarizes the analysis results on the two secondary efficacy variables, no nocturnal heartburn (NNOTUNHB) and no more than mild heartburn (NMMHB) over 24 hour following the first dose of double-blind medication for ITT population.

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Table 3.2.1.2 (Sponsor's) Analysis results for the secondary efficacy endpoints for Day 1 of double-blind phase using ITT population

OUTCOME/ TREATMENT COMPARISON	P-VALUE ¹	P-VLU FOR HOMO ²
No nocturnal heartburn		
Ome-Mg 20 vs. Placebo	0.004*	0.667
Ome-Mg 10 vs. Placebo	0.001*	0.496
No more than mild heartburn		
Ome-Mg 20 vs. Placebo	0.001*	0.154
Ome-Mg 10 vs. Placebo	0.007*	0.603

*: Significant at .05 significance level .

¹: Cochran-Mantel-Haenszel test for a treatment vs. placebo using investigator as a stratification factor;

²: Breslow-Day test for homogeneity between a treatment vs. placebo across investigators performed by this reviewer using sponsor's SAS program.

Table 3.2.1.2 indicated that patients in both Ome-Mg 20 and Ome-Mg 10 groups had a significantly greater proportions without nocturnal heartburn on Day 1 than that in the placebo group ($p \leq 0.004$ by CMH test). Similarly, the proportions of no more than mild heartburn on Day 1 for both Ome-Mg treatment groups were significantly higher than that of placebo group ($p \leq 0.007$ by CMH test).

The results from PP analyses were similar to those of ITT analyses.

Double-Blind Phase

The subject-specific percents of days without heartburn (PDNHB) over 24 hours, percents of days without nocturnal heartburn (PDNNTNHB), and percents of days for no more than mild heartburn (PDNMMHB) over 24 hours during the two-week double-blind phase were analyzed using analysis of covariance method, which included treatment and investigator as factors. The analysis results were summarized by Table 3.2.1.3 (extracted from the sponsor's Table 8.2.6 in Volume 46).

Table 3.2.1.3 (Sponsor's) Analysis Results for the Secondary Efficacy endpoints over two-week double-blind phase for ITT population

OUTCOME/ TREATMENT COMPARISON	P-VALUE for Ome-Mg 20 vs. Placebo	P-VALUE for Ome-Mg 10 vs. Placebo
PDNHB	< 0.001*	< 0.001*
PDNNTNHB	< 0.001*	< 0.001*
PDNMMHB	< 0.001*	< 0.001*

*: Significant at .05 significance level .

Table 3.2.1.3 indicated that the mean percents of days without heartburn, mean percents of days without nocturnal heartburn, and mean percents of days with no more than mild heartburn over

24 hours during the two-week double-blind phase for both Ome-Mg groups were significantly higher than those of placebo ($p < 0.001$) for ITT population.

The results from PP analyses were similar to those of ITT analyses.

Results of Adverse Events

The most common events ($\geq 1\%$) observed during the placebo Run-In phase were diarrhea, headache, and nausea. The most common events ($\geq 1\%$) during the Combined phase (Double-Blind and Follow-Up Phases) included events such as diarrhea, headache, nausea, infection, abdominal pain, flu syndrome and rhinitis. The sponsor emphasized that these events occurred at a low frequency and were similar to those reported for placebo.

There were seven serious adverse events noted during the conduct of the study, one in the Run-In phase and six during the Double-Blind and Follow-Up phases. The sponsor pronounced that none were identified as treatment related.

3.2.2 Reviewer's Analyses and Comments

It is noted that the efficacy of Ome-Mg 20 is shown significantly better than that of placebo ($p < 0.001$) on Day 1 heartburn-free evaluation (the primary evaluation of the primary endpoint) by the sponsor's analysis, reported in Table 3.2.1.1.

Since the primary objective of the study is to compare the efficacy of Ome-Mg 20 versus placebo, this reviewer first validates the robustness on the superiority of Ome-Mg 20 to placebo. After validating the efficacy of Ome-Mg 20 superior to placebo claimed by the sponsor, the superiority of Ome-Mg 10 to placebo is then pursued.

To validate the robustness of the Ome-Mg 20 superior to placebo, this reviewer performs the following two analyses using intent-to-treat patients: 1.) P-value multiplicity adjustment analysis on the secondary endpoints and 2.) Subgroup analysis on Day 1 heartburn-free evaluation.

Data used in this reviewer's analysis was submitted by the sponsor, dated January 29, 2000.

1.) P-value multiplicity adjustment analysis

Since the treatment effects of Ome-Mg 20 versus placebo were compared using five secondary endpoints: no nocturnal heartburn (NNOTUNHB) and no more than mild heartburn (NMMHB) over 24 hour following the first dose of the two-week double-blind phase, percents of days without heartburn (PDNHB) over 24 hours, percents of days without nocturnal heartburn (PDNNTNHB), and percents of days for no more than mild heartburn (PDNMMHB) over 24 hours during the two-week double-blind phase, this reviewer applies the Hochberg step-up procedure to adjust the multiplicity effect induced by the five multiple comparisons based on ITT

patient population.

Table 3.2.2.1 presents the results for the Hochberg multiplicity adjustments on the p-values for the above five secondary endpoints when comparing the effects of Ome-Mg 20 versus placebo using ITT patient population.

Table 3.2.2.1 (Reviewer's) Hochberg multiplicity adjustments on the p-values for the multiple comparisons using ITT patients

OUTCOME/ TREATMENT COMPARISON	RAW_P ¹ for Ome-Mg 20 vs. Placebo	ADJ_P ² for Ome-Mg 20 vs. Placebo
NNOTUNHB	0.004	0.004*
NMMHB	0.001	0.002*
PDNHB	< 0.001	< 0.001*
PDNNTNHB	< 0.001	< 0.001*
PDNMMHB	< 0.001	< 0.001*

*: Significance at significance level of 0.05 determined by Hochberg procedure.

¹: Original p-value; ²: P-value adjusted by Hochberg procedure;

Table 3.2.2.1 indicates that after Hochberg adjustment, Ome-Mg 20 is superior to placebo when assessed by NNOTUNHB, NMMHB, PDNHB, PDNNTNHB, and PDNMMHB using ITT patient population.

2.) Subgroup Analysis

To assess the consistency of results for the rates of on heartburn-free across subgroups, this reviewer also performed some subgroup analyses for the subgroups listed below for ITT patient population.

Gender

This reviewer's gender group (Female and Male) analysis results for the comparisons of treatment effects are presented by Table A.3.1 in Appendix III. The results are briefly summarized below:

- The subgroup analysis results indicate that Day 1 heartburn-free rates of Ome-Mg 20 are significantly higher than those of placebo for both female and male patients while only for male patients, Day 1 heartburn-free rate of Ome-Mg 10 is significantly higher than that of placebo.
- To compare with placebo, it is noted that at least a positive trend favors omeprazole for both male and female groups.

Age

This reviewer's age group (≤ 65 and > 65) analysis results for the comparisons of treatment effects are presented by Table A.3.2 in Appendix III.

- The subgroup analysis results indicate that Day 1 heartburn-free rates of Ome-Mg 20 are significantly higher than those of placebo for patients in both age groups.
- To compare with placebo, it is noted that in general, there is a positive trend in favor of omeprazole for both age groups.

Race

This reviewer's race group (Caucasian and Non-Caucasian) analysis results for the comparisons of treatment effects are presented by Table A.3.3 in Appendix III.

- The subgroup analysis results indicate that Day 1 heartburn-free rates of Ome-Mg 20 are significantly higher than those of placebo for both Caucasian and Non-Caucasian patients while only for Caucasian patients, Day 1 heartburn-free rate of Ome-Mg 10 is significantly higher than that of placebo.
- The subgroup analysis results indicate that Day 1 heartburn-free rates of omeprazole are numerically higher than that of placebo for both Caucasian and Non-Caucasian groups.

3.2.3 Comments/Conclusions of treatment effects for Study 171

From the results of the sponsor's and this reviewer's analyses, it can be concluded that the effects of Ome-Mg 20 is significantly better than placebo in the prevention of heartburn. Since the primary objective of this Study is achieved, the efficacy of Ome-Mg 10 versus placebo is then pursued.

By Table 3.2.1.1, the efficacy of Ome-Mg 10 is superior to that of placebo ($p=0.003$) on Day 1 heartburn-free evaluation (the primary evaluation of the primary efficacy endpoint) using ITT population. In addition, following the P-value multiplicity adjustment analysis on the same five secondary endpoints as those performed for comparing the efficacy of Ome-Mg 20 versus placebo, the superiority of Ome-Mg 10 to placebo in the prevention of heartburn is supported.

3.3.0 Sponsor's Analysis Results and Reviewer's Comments for Study 183

3.3.1 Sponsor's Statistical Analysis and Results

Demographics and Baseline Characteristics

The demographic variables and baseline characteristics analyzed by the sponsor for the three treatment groups, Ome-Mg 20, Ome-Mg 10, and placebo were gender, race, age, current smoker, other current nicotine use, alcohol consumption, consume caffeine-containing beverage, consume

other caffeine-containing products, heartburn frequency (% of days) during Run-In, and average heartburn severity score during Run-In for ITT, PP, and all randomized patients.

The treatment groups were compared with respect to the demographic and baseline variables mentioned above. One-way ANOVA was performed on continuous variables and a simple chi-square test was applied to categorical variables. The results indicated that at significance level of .05, no significant differences were found on the analyzed demographic and baseline variables among the three treatment groups for all randomized, ITT and PP patient populations.

Summary of Sponsor's Efficacy Analysis Results

i.) The results for the primary evaluation analysis

Table 3.3.1.1 (extracted from sponsor's Table 8.2.2 in Volume 57) summarizes the results of the primary efficacy analysis on heartburn-free over 24 hours on Day 1 (the primary evaluation) following the first dose of double-blind medication for ITT patient population.

Table 3.3.1.1 (Sponsor's) Primary efficacy analysis on Day 1 Heartburn-Free evaluation during the two-week double-blind phase using intent-to-treat patients

TREATMENT GROUP	HTBN-FR RT ^a	P-VALUE VS. PLACEBO	P-VALUE VS. OME-MG10
Placebo (N=520)	32.1% (167/520)		
Ome-Mg 10 (520)	45.2% (235/520)	p ^c < 0.001 [*] ; p ^b =0.85.	
Ome-Mg 20 (N=524)	46.8% (245/524)	p ^c < 0.001 [*] ; p ^b =0.35.	p ^c =0.57; p ^b =0.07 [*] .

^a: Heartburn-Free rate; ^{*}: Significant at .05 for treatment comparisons and at 0.10 for odds homogeneity test;

^c: Cochran-Mantel-Haenszel test for a treatment vs. placebo using investigator as a stratification factor;

^b: Breslow-Day test for odds homogeneity between a treatment vs. placebo across investigators.

Table 3.3.1.1 indicated that both Ome-Mg 20 and Ome-Mg 10 had significantly higher heartburn prevention rates on Day 1 than placebo (P < 0.001 for both Ome-Mg 20 and Ome-Mg 10 versus placebo) for ITT population. The increase over placebo for Ome-Mg 20 was 14.7 percent (46.8% - 32.1%) and for Ome-Mg 10 was 13.1 percent (45.2% - 32.1%).

The results on the heartburn-free rate analysis for per-protocol patients were found not substantively different from those of ITT population.

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ii.) The results for the secondary Efficacy Endpoint Analyses

Day 1

Table 3.3.1.2 (extracted from sponsor's Table 8.2.2 in Volume 57) summarizes the analysis results on the two secondary efficacy variables, no nocturnal heartburn (NNOTUNHB) and no more than mild heartburn (NMMHB) over 24 hour following the first dose of double-blind medication for ITT population.

Table 3.3.1.2 (Sponsor's) Analysis Results for the Secondary Efficacy endpoints for Day 1 of double-blind phase using ITT population

OUTCOME/ TREATMENT COMPARISON	P-VALUE ¹	P-VLU FOR HOMO ²
No nocturnal heartburn		
Ome-Mg 20 vs. Placebo	0.141	0.09
Ome-Mg 10 vs. Placebo	0.502	0.007*
No more than mild heartburn		
Ome-Mg 20 vs. Placebo	< 0.001*	0.444
Ome-Mg 10 vs. Placebo	0.008*	0.626

*: Significant at .05 significance level.

¹: Cochran-Mantel-Haenszel test for a treatment vs. placebo using investigator as a stratification factor;

²: Breslow-Day test for homogeneity between a treatment vs. placebo across investigators performed by this reviewer using sponsor's SAS program.

Table 3.3.1.2 indicated that the proportions of no more than mild heartburn on Day 1 for both Ome-Mg treatment groups were significantly higher than that of placebo group ($p \leq 0.008$ by CMH test). However the proportions without nocturnal heartburn on Day 1 for both Ome-Mg 20 and Ome-Mg 10 were not significantly greater than that of placebo.

The results from PP analyses were similar to those of ITT analyses.

Double-Blind Phase

The subject-specific percents of days without heartburn (PDNHB), percents of days without nocturnal heartburn (PDNNTNHB), and percents of days for no more than mild heartburn (PDNMMHB) over 24 hours during the two-week double-blind phase were analyzed using analysis of covariance method, which included treatment and investigator as factors. The analysis results were summarized by Table 3.3.1.3 (extracted from the sponsor's Table 8.2.6 in Volume 57).

Table 3.3.1.3 (Sponsor's) Analysis Results for the Secondary Efficacy endpoints over two-week double-blind phase for ITT population

OUTCOME/ TREATMENT COMPARISON	P-VALUE for Ome-Mg 20 vs. Placebo	P-VALUE for Ome-Mg 10 vs. Placebo
PDNHB	< 0.001*	< 0.001*
PDNNTNHB	< 0.001*	< 0.001*
PDNMMHB	< 0.001*	< 0.001*

*: Significant at .05 significance level .

Table 3.3.1.3 indicated that the mean percents of days without heartburn, mean percents of days without nocturnal heartburn, and mean percents of days with no more than mild heartburn over 24 hours during the two-week double-blind phase for both Ome-Mg groups were significantly higher than those of placebo ($p < 0.001$) for ITT population.

The results from PP analyses were similar to those of ITT analyses.

Results of Adverse Events

The most common events ($\geq 1\%$) observed during the placebo Run-In phase included events such as diarrhea, headache, nausea, and abdominal pain. The most common events ($\geq 1\%$) during the Combined phase (Double-Blind and Follow-Up Phases) included infection, diarrhea, headache abdominal pain, flatulence, flu syndrome, pharyngitis, constipation and vomiting. The sponsor emphasized that these events occurred at a low frequency and were similar to those reported for placebo.

There were five serious adverse events noted during the conduct of the study, one in the Run-In phase and four during the Double-Blind treatment phase. The sponsor pronounced that none were identified as treatment related.

3.3.2 Reviewer's Analyses and Comments

It is noted that the efficacy of Ome-Mg 20 is shown significantly better than that of placebo ($p < 0.001$) on Day 1 heartburn-free evaluation (the primary evaluation of the primary endpoint) by the sponsor's analysis, reported in Table 3.3.1.1.

To validate the robustness of Ome-Mg 20 superior to placebo, this reviewer performed the following two analyses using intent-to-treat patients: 1.) P-value multiplicity adjustment analysis on the secondary endpoints and 2.) Subgroup analysis on Day 1 heartburn-free evaluation. After validating the efficacy of Ome-Mg 20 superior to placebo, the superiority of Ome-Mg 10 to placebo is then pursued.

Data used in this reviewer's analysis was submitted by the sponsor, dated January 29, 2000.

1.) P-value multiplicity adjustment analysis

As the reason stated in the section 3.2.2, this reviewer applies the Hochberg step-up procedure to adjust the multiplicity effect for the efficacy comparisons between Ome-Mg 20 and placebo when assessed by the five secondary endpoints: no nocturnal heartburn (NNOTUNHB) and no more than mild heartburn (NMMHB) over 24 hour following the first dose of the two-week double-blind phase, percents of days without heartburn (PDNHB) over 24 hours, percents of days without nocturnal heartburn (PDNNTNHB), and percents of days for no more than mild heartburn (PDNMMHB) over 24 hours during the two-week double-blind phase.

Table 3.3.2.1 presents the results for the Hochberg multiplicity adjustments on the p-values for the above five secondary endpoints when comparing the effects of Ome-Mg 20 versus placebo using ITT patient population.

Table 3.3.2.1 (Reviewer's) Hochberg multiplicity adjustments on the p-values for the multiple comparisons using ITT patients

OUTCOME/ TREATMENT COMPARISON	RAW_P ¹ for Ome-Mg 20 vs. Placebo	ADJ_P ² for Ome-Mg 20 vs. Placebo
NNOTUNHB	0.14	0.14
NMMHB	< 0.001	<0.001*
PDNHB	< 0.001	< 0.001*
PDNNTNHB	< 0.001	< 0.001*
PDNMMHB	< 0.001	< 0.001*

*: Significance at significance level of 0.05 determined by Hochberg procedure.

¹: Original p-value; ²: P-value adjusted by Hochberg procedure;

Table 3.3.2.1 indicates that except for NNOTUNHB, after Hochberg adjustment, Ome-Mg 20 is superior to placebo when assessed by NMMHB, PDNHB, PDNNTNHB, and PDNMMHB using ITT patient population.

2.) Subgroup Analysis

To assess the consistency of results for the rates of on heartburn-free across subgroups, this reviewer also performed some subgroup analyses for the subgroups listed below for ITT patient population.

Gender

This reviewer's gender group (Female and Male) analysis results for the comparisons of treatment effects are presented by Table A.4.1 in Appendix IV. The results indicate that the Day 1 heartburn-free rates for both Ome-Mg 20 and Ome-Mg 10 are significantly higher than those of placebo for female and male patients.

Age

This reviewer's age group (≤ 65 and > 65) analysis results for the comparisons of treatment effects are presented by Table A.4.2 in Appendix IV. The results indicate that the Day 1 heartburn-free rates for both Ome-Mg 20 and Ome-Mg 10 are significantly higher than those of placebo for patients in both age groups.

Race

This reviewer's race group (Caucasian and Non-Caucasian) analysis results for the comparisons of treatment effects are presented by Table A.4.3 in Appendix IV. The results indicate that the Day 1 heartburn-free rates for both Ome-Mg 20 and Ome-Mg 10 are significantly higher than those of placebo for Caucasian patients. However, for Non-Caucasian patients, Day 1 heartburn-free rates for both Ome-Mg 20 and Ome-Mg 10 are numerically lower than those of placebo.

3.3.3 Comments/Conclusions of treatment effects for Study 183

From the results of the sponsor's and this reviewer's analyses, it can be concluded that the effects of Ome-Mg 20 is significantly better than that of placebo in the two-week prevention of heartburn. However, Ome-Mg 20 is not superior to placebo in the two-week prevention of nocturnal heartburn.

Since the primary objective of this Study is achieved, the efficacy of Ome-Mg 10 versus placebo is then pursued. By Table 3.3.1.1, the efficacy of Ome-Mg 10 is superior to that of placebo ($p=0.001$) on Day 1 heartburn-free evaluation (the primary evaluation of the primary efficacy endpoint) using ITT population. In addition, following Hochberg step-up multiplicity adjustment analysis on the same five secondary endpoints as those performed for comparing the efficacy of Ome-Mg 20 versus placebo, the superiority of Ome-Mg 10 to placebo in the prevention of heartburn is supported.

3.4.0 Reviewer's Conclusions and Recommendations for Studies 171 and 183

- ◆ The effects of Ome-Mg 20 and Ome-Mg 10 are both significantly better than that of placebo in the two-week prevention of heartburn. However, only one study, Study 171, shows the superiority of omeprazole to placebo in the two-week prevention of nocturnal heartburn.

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4.0 Studies 1997092 and 1997095 - Treatment indication

4.1.0 Background Information for Studies 1997092 and 1997095

Objectives: The primary objective of this study was to compare a single dose of omeprazole magnesium 20.6 mg (Ome-Mg 20) vs. placebo in providing Sustained Complete Relief of episodic heartburn for the first episode. Secondary objectives included the comparison of omeprazole magnesium 10.3 mg (Ome-Mg 10) vs. Ome-Mg 20 and placebo for effectiveness in the treatment of episodic heartburn following repeated dosing (daily, as needed) over a 2-week interval.

Study Design: This study was a multi-center, single- and repeated-dose, randomized, double-blind, double-dummy, parallel, placebo-controlled study with a 7-day placebo run-in phase and a 14-day active treatment phase.

Subjects went to the study center for 3 visits. At Visit 1 (Screening visit), the subject was given double-dummy placebo treatment and a placebo Run-in Diary to record heartburn episodes, relief assessments, and backup medication (Gelusil) use. During Visit 1, the following screen procedures were performed: collecting informed consent from elected subjects, reviewing inclusion/exclusion criteria with each subject, collecting information on demographics, medical history, medication history, and performing physical examination on vital sign, height, weight, heart, lungs, and abdomen.

Within 7 days (± 2) of completing Visit 1, subjects returned for Visit 2 (Baseline visit). Following the placebo run-in phase, the subject's compliance with placebo Run-in Diary completion, study medication dosing, and any Gelusil use were evaluated. Subjects who satisfied the Continuance criteria were randomized in a 1:1:1 ratio to receive one of the following study treatments to be used over the next 14 days: Ome-Mg 20, Ome-Mg 10, or Placebo. At Visit 2, subjects were given study medication, Heartburn Symptom Diary, and backup medication Gelusil for the 2-week treatment period.

Visit 3 was the final visit, which occurred 14 days (± 2) after Visit 2. The study procedures described for medication accountability, concomitant medication, and AE evaluation were repeated at this visit. After accountability, subjects were permitted to keep their remaining supply of Gelusil. Heartburn Symptom Diaries were reviewed by study staff to address all missing, inconsistent, or confusing Heartburn Symptom Diary entries with the subject. Figure 4.1.0.1 displays the process of the clinical study.

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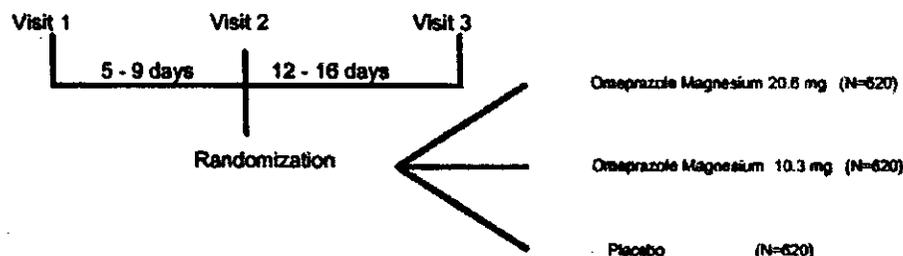


Figure 4.1.0.1 Clinical Study Diagram

Determination of Sample Size: Based on the data from a previous study run by AstraZeneca LP under a similar protocol, the proportion of subjects with Sustained Complete Relief from the first-treated episode of heartburn in this study was expected to be 30% in the placebo group. In order to detect a difference of 10% between an Ome-Mg group and the placebo group, a sample size of approximately 620 subjects was to be randomized to each treatment group to provide a 95% power with a type I error rate equal to .05.

Study Population: The inclusion criteria for the study population included

- a history of heartburn occurring at least 2 days per week during the 30 days prior to the study;
- heartburn being able to be partially relieved from antacids or H2RA treatments;
- male or non-pregnant, non-lactating female, in good general health, of any race, and at least 18 years of age;
- Continuance Criteria - presence of heartburn on at least 2 days during the placebo run-in phase and at least 5 out of 7 days with satisfactory entries in the Placebo Run-in Diary.

The exclusion criteria for the study population included

- a history (past or present) of erosive esophagitis verified by endoscopy,
- a history (past or present) of GERD as diagnosed by a physician,
- a history (past or present) of pathologic intraesophageal pH level monitoring,
- any medical condition or concomitant therapy which may have interfered with the evaluation of heartburn treatment, etc.

[For the detail of patient selection, refer to sponsor's Volume 1.067].

Efficacy and Safety Measurements: During the 2-week treatment phase, subjects were to record a maximum of one heartburn episode per day in their Heartburn Symptom Diary. Once heartburn symptoms reached a level, subjects would normally treat with study medication. Just prior to dosing, patients were to record their baseline severity: Mild (Heartburn present but easily tolerated), Moderate (Heartburn causing interference with normal daily activities or sleep), or Severe (Heartburn incapacitating subjects from normal daily activities or sleep).

To evaluate the efficacy of the study drug, the patient recorded a heartburn symptom relief score from the following scale every 10 minutes for the first hour and hourly thereafter for a total of 3 hours after dosing: Complete relief (no heartburn), Adequate relief (satisfactory), and Inadequate relief (including no relief).

In addition, the patient was also asked to rate the Overall Assessment of Study Medication at the end of the evaluation period using the following scales: poor, fair, good, very good, and excellent.

Finally, safety was assessed by the collection of voluntarily reported adverse events.

Study Hypotheses: The efficacy of Ome-Mg 20 is superior to placebo in the treatment of episodic heartburn for the first episode.

Primary and Secondary Efficacy Variables: The primary efficacy variable was the occurrence of sustained complete relief after the first-treated episode of heartburn. Sustained complete relief was defined as achieving complete relief within the first hour (inclusive) and sustaining the complete rating through (and including) the third hour after dosing with study medication.

The following secondary efficacy variables were analyzed for the first-treated and last-treated episodes of heartburn within the 2-week treatment period: occurrence of complete relief within the first hour, occurrence of sustained adequate relief, occurrence of adequate relief within the first hour, occurrence of backup medication (Gelusil) use, time to sustained complete relief, time to complete relief (within 3 hours), time to backup medication use, and overall assessment of study medication. In addition, statistical analyses were also performed on the following secondary efficacy endpoints: occurrence of sustained complete relief for the last treated episode of heartburn, occurrence of sustained complete relief over all-treated episodes of heartburn, occurrence of complete relief within the first hour over all-treated episodes of heartburn, occurrence of sustained adequate relief over all-treated episodes of heartburn, occurrence of adequate relief within the first hour over all-treated episodes of heartburn, occurrence of backup medication (Gelusil) use over all-treated episodes of heartburn, and overall assessment of the study medication over all-treated episodes of heartburn.

Efficacy analyses

The efficacy endpoints were analyzed for the following two groups of patients:

Intent-to-treat (ITT) population – All randomized subjects who took at least one dose of the study medication during the active treatment phase and had efficacy data available following dosing.

Per- Protocol (PP) population – A sub-set of ITT population excluding those subjects who did not satisfy the Evaluable criteria.

A Cochran-Mantel-Haenszel (CMH) test with Investigator as the stratification variable was performed on the sustained complete relief to compare the treatment effects. In addition, a logistic regression analysis with treatment and investigator as factors was also performed on the occurrence of sustained complete relief for the first episode. The estimated odds ratios (the ratios of the odds of having sustained complete relief in one treatment group relative to another treatment group) and their 95% confidence intervals (CIs) were calculated from the logistic regression model.

The primary statistical analyses were performed on the ITT population, and the secondary statistical analyses were performed on the PP population. In addition, the primary comparison was between Ome-Mg 20 and placebo. All other comparisons were considered secondary.

Disposition of Patients for Study 1997092: A total of 2447 subjects were screened. Among them, 2395 subjects (97.9%) entered the placebo run-in phase by passing all Inclusion and Exclusion criteria, while 52 subjects failed the screening. Among those who entered the placebo run-in phase, 1899 subjects (79.3%) with a sufficient number of days for heartburn and satisfactory Placebo Run-in Diary entries were randomized into the three treatment groups, Ome-Mg 20, Ome-Mg 10, and placebo, at Visit 2.

A total of 1869 (98.4% of all randomized) subjects were included in the ITT analyses. Of the 30 randomized subjects who were excluded from the ITT analyses, 26 subjects did not take a dose of study medication, 1 subject had no efficacy data following any dose, and 3 subjects enrolled in this study more than once. Table 4.1.0.1 summarizes patient disposition among three treatment groups for the active treatment phase.

Table 4.1.0.1 Patient disposition among three treatment groups

Disposition	Ome-Mg 20	Ome-Mg 10	Placebo	Overall
Total Randomized	628	636	635	1899
Intent-to-Treat	621	621	627	1869
Per-Protocol	586	583	589	1758

Disposition of Patients for Study 1997095: A total of 2501 subjects were screened. Among them, 2395 subjects (95.8%) entered the placebo run-in phase by passing all Inclusion and Exclusion criteria, while 106 subjects failed the screening. Among those who entered the placebo run-in phase, 1892 subjects (79.0%) with a sufficient number of days for heartburn and satisfactory Placebo Run-in Diary entries were to be randomized into the three treatment groups, Ome-Mg 20, Ome-Mg 10, and placebo, at Visit 2.

A total of 1852 (97.9% of all randomized) subjects were included in the ITT analyses. Of the 40 randomized subjects who were excluded from the ITT analyses, 30 subjects did not take a dose

of study medication and 10 subjects enrolled in this study more than once. Table 4.1.0.2 summarizes patient disposition among three treatment groups for the active treatment phase.

Table 4.1.0.2 Patient disposition among three treatment groups

Disposition	Ome-Mg 20	Ome-Mg 10	Placebo	Overall
Total Randomized	638	633	621	1892
Intent-to-Treat	627	623	602	1852
Per-Protocol	607	612	584	1803

Premature Discontinuations for Study 1997092: A total of 1869 subjects (98.4% of all randomized) completed the 14-day active treatment phase and returned for Visit 3. The 30 (1.6%) randomized subjects who discontinued during the active treatment phase consisted of 6 subjects from the Ome-Mg 20 group and 12 subjects from each of the other two groups: Ome-Mg 10 and placebo. Among those who discontinued, 3 subjects had AEs, 4 subjects withdrew voluntarily, 17 subjects were lost to follow-up, and 6 subjects discontinued due to investigator's or Sponsor's decisions.

Premature Discontinuations for Study 1997095: A total of 1850 subjects (97.8% of all randomized) completed the 14-day active treatment phase and returned for Visit 3. The 42 (2.2%) randomized subjects who discontinued during the active treatment phase consisted of 11 subjects from each of the Ome-Mg groups and 20 from placebo group. Among those who discontinued, 1 subject in the placebo group was found to fail the Inclusion/Exclusion criteria, 10 subjects withdrew due to an AE, 3 subjects in the placebo group withdrew voluntarily, 19 subjects were lost to follow-up, and 9 subjects discontinued due to Investigator's and Sponsor's decision.

4.2.0 Sponsor's Statistical Analysis Results and Reviewer's Comments for Study 1997092

4.2.1 Sponsor's Statistical Analysis Results

Demographics and Baseline Characteristics

The demographic variables and baseline characteristics analyzed by the sponsor for the three treatment groups, Ome-Mg 20, Ome-Mg 10, and placebo were gender, race, age, current smoker, other current nicotine use, current alcohol consumption, currently consume caffeine-containing beverage, currently consume other caffeine-containing products, heartburn frequency (% of days) during placebo run-in phase, and average heartburn severity during placebo run-in phase for all randomized, ITT, and PP patients.

For all randomized and ITT patients, the analyzed demographic and baseline characteristics were balanced in the 3 treatment groups with the exception of current smoking status. The differences on the rates of current smokers were found significant among the three treatment groups for all randomized ($p = 0.038$) and ITT patients ($p = 0.029$). The placebo group had more current smokers (31%) than the Ome-Mg 20 group (27%) followed by the Ome-Mg 10 group (25%). The larger proportion of smokers in the placebo group may be in favor of the tested drugs for the treatment efficacy comparisons.

For PP patients, the analyzed demographic and baseline characteristics were balanced in the 3 treatment groups based on chi-square test for categorical variables and analysis of variance method for continuous variables.

Summary of Sponsor's Efficacy Analysis Results

i.) Primary Efficacy Endpoint Analyses

The primary variable is the occurrence of Sustained Complete Relief for the subjects' first-treated episode of heartburn. Table 4.2.1.1 (extracted from sponsor's Table 8.2.3 in Volume 67) summarizes the results of the primary efficacy analysis for the first treated episodes of heartburn for ITT patient population.

Table 4.2.1.1 Primary efficacy analysis on SCR for the first treated episode of heartburn using intent-to-treat patients

TREATMENT GROUP	HTBN-FR RT [*]	P-VALUE VS. PLACEBO ¹	P-VALUE FOR HOMOG ²
Placebo (N=627)	29.5% (185/627)		
Ome-Mg 10 (621)	31.5% (195/620)	0.503	0.541
Ome-Mg 20 (N=621)	30.2% (187/620)	0.822	0.386

^{*}: Heartburn-Free rate;

¹: Cochran-Mantel-Haenszel test for a treatment vs. placebo using investigator as a stratification factor;

²: Breslow-Day test for odds homogeneity across investigators between a treatment vs. placebo.

*: Significant at .05 significance level for treatment efficacy comparison while .10 for odds homogeneity test.

Table 4.2.1.1 showed that neither Ome-Mg 20 (30.2%) nor Ome-Mg 10 (31.5%) was found superior to placebo (29.5%) when assessed by SCR on the first treated episode of heartburn after adjusting for Investigator.

The results from the per-protocol patient analysis were similar to those of the intent-to-treat patient analysis.

ii.) Secondary Efficacy Endpoint Analyses

Analysis results for first- and last-treated episodes of heartburn

Table 4.2.1.2 (extracted from sponsor's Table 8.2.3 and 8.2.24 in Volume 67) summarizes the analysis results on the following secondary efficacy variables for the first- and last-treated episodes of heartburn using ITT population: sustained complete relief (SCR) (last-treated episode only), complete relief within the first hour (CR), sustained adequate relief (SAR), adequate relief within the first hour (AR), backup medication (Gelusil) use (BU), and overall assessment of study medication (OE).

Table 4.2.1.2 (Sponsor's) P-Values for the secondary efficacy endpoints using ITT population

OUTCOME/TREATMENT COMPARISON	FIRST-TREATED EPISODE OF HEARTBURN	LAST-TREATED EPISODE OF HEARTBURN
Sustained Complete Relief		
Ome-Mg 20 vs. Placebo	Not applicable for secondary Endpoint analysis	$p^c = 0.035^*$; $p^b = 0.51$.
Ome-Mg 10 vs. Placebo		$p^c = 0.054$; $p^b = 0.840$.
Ome-Mg 20 vs. Ome-Mg 10		$p^c = 0.886$; $p^b = 0.901$.
Complete Relief within the First Hour		
Ome-Mg 20 vs. Placebo	$p^c = 0.94$; $p^b = 0.440$.	$P^c = 0.026^*$; $p^b = 0.640^*$.
Ome-Mg 10 vs. Placebo	$p^c = 0.58$; $p^b = 0.62$.	$P^c = 0.023^*$; $p^b = 0.714$.
Ome-Mg 20 vs. Ome-Mg 10	$p^c = 0.569$; $p^b = 0.162$.	$p^c = 0.939$; $p^b = 0.940$.
Sustained Adequate Relief		
Ome-Mg 20 vs. Placebo	$p^c = 0.27$; $p^b = 0.190$.	$P^c = 0.14$; $p^b = 0.560$.
Ome-Mg 10 vs. Placebo	$p^c = 0.10$; $p^b = 0.278$.	$P^c = 0.069$; $p^b = 0.304$.
Ome-Mg 20 vs. Ome-Mg 10	$p^c = 0.531$; $p^b = 0.51$.	$p^c = 0.718$; $p^b = 0.912$.
Adequate Relief within the First Hour		
Ome-Mg 20 vs. Placebo	$p^c = 0.59$; $p^b = 0.210$.	$p^c = 0.185$; $p^b = 0.867$.
Ome-Mg 10 vs. Placebo	$p^c = 0.09$; $p^b = 0.140$.	$p^c = 0.213$; $p^b = 0.32$.
Ome-Mg 20 vs. Ome-Mg 10	$p^c = 0.215$; $p^b = 0.743$.	$p^c = 0.946$; $p^b = 0.605$.
Backup Medication (Gelusil) Use		
Ome-Mg 20 vs. Placebo	$p^c = 0.10$; $p^b = 0.142$.	$p^c = 0.269$; $p^b = 0.713$.
Ome-Mg 10 vs. Placebo	$p^c = 0.150$; $p^b = 0.630$.	$p^c = 0.006^*$; $p^b = 0.363$.
Ome-Mg 20 vs. Ome-Mg 10	$p^c = 0.833$; $p^b = 0.620$.	$p^c = 0.098$; $p^b = 0.621$.
Overall Assessment of Study Medication		
Ome-Mg 20 vs. Placebo	$p^c = 0.083$; $p^b = NA$.	$p^c = 0.009^*$; $p^b = NA$.
Ome-Mg 10 vs. Placebo	$p^c = 0.093$; $p^b = NA$.	$p^c = 0.001^*$; $p^b = NA$.
Ome-Mg 20 vs. Ome-Mg 10	$p^c = 0.96$; $p^b = NA$.	$p^c = 0.354$; $p^b = NA$.

*: Significant at .05 significance level for treatment efficacy comparison while .10 for odds homogeneity test.

^c: Treatment efficacy was compared by Cochran-Mantel-Haenszel test using investigator as a stratification factor; NA: Breslow-Day test is not applicable for polytomous response.

^b: Breslow-Day test for homogeneity of odds ratio between a treatment vs. placebo across investigators.

Table 4.2.1.2 indicated that at significance level of .05, as to the first-treated episode of heartburn, no statistically significant differences were found for all paired treatment comparisons when assessed by complete relief within the first hour, sustained adequate relief, adequate relief within the first hour, and backup medication (Gelusil) use.

For the last-treated episode of heartburn, the effect of Ome-Mg 20 was significantly better than that of placebo on sustained complete relief ($p = 0.035$), complete relief within the first hour ($p = 0.026$), and overall assessment of study medication ($p = 0.009$) using ITT population. Similarly, the effect of Ome-Mg 10 was significantly better than that of placebo on complete relief within the first hour ($p = 0.023$), backup medication (Gelusil) use ($p = 0.006$), and overall assessment of study medication ($p = 0.001$) than the placebo group.

Analysis results for all-treated episodes of heartburn

Table 4.2.1.3 (extracted from sponsor's Table 8.2.20 and 8.2.24 in Volume 67) summarizes the analysis results on the following secondary efficacy variables for the all-treated episodes of heartburn using ITT population: sustained complete relief (last-treated episode only), complete relief within the first hour, sustained adequate relief, adequate relief within the first hour, backup medication use, and overall assessment of study medication.

Table 4.2.1.3 (Sponsor's) P-Values on the secondary efficacy endpoints using all-treated episodes of heartburn for ITT population

INDICATED OUTCOME	OME-20 MG VS. PLACEBO ^g	OME-10 MG VS. PLACEBO ^g	OME-20 MG VS. OME-10 MG ^g
Sustained Complete Relief	0.032*	0.102	0.59
Complete Relief within the First Hour	0.064	0.11	0.80
Sustained Adequate Relief	0.014*	0.031*	0.73
Adequate Relief within The First Hour	0.073	0.122	0.79
Backup Medication (Gelusil) Use	0.03*	0.001*	0.28
Overall Assessment of Study Medication	0.0005*	0.0004*	0.98

*: Significant at .05 significance level for treatment efficacy comparison .

^g: Treatment efficacy was compared by GEE method.

Table 4.2.1.3 indicated that at significance level of .05, for the all-treated episodes of heartburn, the effect of Ome-Mg 20 was significantly better than that of placebo when assessed by sustained complete relief ($p = 0.032$), sustained adequate relief ($p = 0.014$), backup medication (Gelusil) use ($p = 0.03$), and overall assessment of study medication ($p = 0.005$) using ITT population.

Similarly, the effect of Ome-Mg 10 was significantly better than that of placebo on sustained adequate relief ($p = 0.031$), backup medication (Gelusil) Use ($p=0.001$), and overall assessment of study medication ($p=0.004$).

Results of Adverse Events

Table 4.2.1.4 presents an overall summary of adverse events (Aes) by treatment group for the active treatment phase.

Table 4.2.1.4 (Sponsor's) Adverse events by treatment groups for active treatment phase

	ACTIVE TREATMENT PHASE						OVERALL	
	Ome-Mg 20 (N = 628)		Ome-Mg 10 (N = 636)		PLACEBO (N = 635)		(N = 1899)	
	n	%	n	%	N	%	n	%
Subjects								
With Any AEs	82	13%	72	11%	71	11%	225	12%
With Serious AEs	0	0%	3	< 1%	0	0%	3	< 1%
Withdrawals Due to AEs	1	< 1%	0	0%	2	< 1%	3	< 1%
Deaths	0	0%	0	0%	0	0%	0	0%
Subjects								
Reporting 0 AE	546	87%	564	89%	564	89%	1674	88%
Reporting 1 AE	57	9%	51	8%	50	8%	158	8%
Reporting > 1 AEs	25	4%	21	3%	21	3%	67	4%
Overall	628	100%	636	100%	635	100%	1899	100%
Adverse Event Intensity								
Unknown	0	0%	0	0%	1	1%	1	< 1%
Mild	55	44%	50	48%	45	42%	150	45%
Moderate	54	43%	42	40%	46	43%	142	42%
Severe	17	13%	13	12%	14	13%	44	13%
Overall	126	100%	105	100%	106	100%	337	100%

Table 4.2.1.4 indicated that a total of 337 AEs were reported by 225 subjects. There were 126 AEs reported by 82 subjects in the Ome-Mg 20 group, 105 AEs reported by 72 subjects in the Ome-Mg 10 group, and 106 AEs reported by 71 subjects in the placebo group. Three serious adverse events (SAEs) were reported in the Ome-Mg 10 group in the active treatment phase. There were 3 subjects discontinued due to AEs, with 2 in the placebo group and 1 in the Ome-Mg 20 group. There were 45%, 42%, and 13% of the AEs in each of the Mild, Moderate, and Severe categories. There was a lower percentage of Moderate or Severe AEs in the Ome-Mg 10 group (52%) as compared to the 2 other groups (56% in each group).

Finally, there were 71%, 27%, and 3% of the AEs determined to be Unlikely, Possibly, and Probably related to study medication, respectively. The subjects on placebo had 25% of AEs considered Possibly or Probably related to study medication, compared to 31% for Ome-Mg 20 and 33% for Ome-Mg 10.

4.2.2 Reviewer's Analyses and Comments

From Table 4.2.1.1, it is noted that the primary objective, Ome-Mg 20 superior to placebo in providing sustained complete relief of episodic heartburn for the first treated episode (the primary efficacy endpoint), is not supported by the sponsor's primary efficacy analysis on the first episode ($p=0.822$). Since the significance level of .05 was spent for the primary objective and the superiority of Ome-Mg 20 mg to placebo is not established by the primary efficacy endpoint analysis, the indication of heartburn treatment is not supported. In order to further corroborate the non-superiority of Ome-Mg 20 mg over placebo in the treatment of heartburn through a single dose of Ome-Mg 20 mg, this reviewer i.) performs GEE analysis on SCR (the primary efficacy endpoint) for testing the interaction between treatment and day (treatment*day) using all treated episodes and ii.) employs the sponsor's GEE analysis on SCR using treatment, investigator, and episode as model parameters for treated episodes separated at least 3 and 5 days from the most recent episode.

Data used in this reviewer's analysis i.) was submitted by the sponsor, dated January 29, 2000 while the results of analyses ii.) were submitted by the sponsor dated 7/20/2000.

i.) GEE analysis on SCR for testing treatment*day using all treated episodes

Since the sponsor performed GEE method to analyze all treated episodes, to validate the carryover effect of Ome-Mg 20 over time, this reviewer applies GEE method to SCR using treatment, pooled investigator, day, and treatment*day as model parameters for all treated episodes. Here, day 1 was defined as the day when the first heartburn episode was treated while day2 is the day following day 1, etc.

As noted in the paper of Liang and Zeger (1986) entitled "Longitudinal data analysis using generalized linear models" published by Biometrika, the consistent estimates of the model parameters and its covariance matrix depend on the correct specification of the mean. Since it is very hard to identify the correct GEE model function, this analysis is considered as a reference only. The results are presented in Table 4.2.2.1.

Table 4.2.2.1(Reviewer's) Results of GEE method on SCR to compare the efficacy between Ome-Mg 20 and placebo using all treated episodes

PARAMETER	ESTIMATE	P-VALUE
Treatment	0.050	0.66
Pooled Investigator	----- [#]	-----
Day	-0.004	0.58
Treatment*Day	0.024	0.009 [*]

[#]: Not important for this analysis; ^{*}: Significant at .05 level.

Table 4.2.2.1 shows that the parameter estimate (0.024) of treatment*day is significantly different from zero ($p=0.009$), indicating the log odds of SCR for OME-Mg 20 is a positive trend

in favor of the later treatment period. The carryover effect of Ome-Mg 20 is thus identified.

- ii.) Sponsor's GEE analysis on SCR using treated episodes separated at least 3 and 5 days from the most recent episode.

As noted by the medical reviewer, L. Goldkind, M.D., the duration of gastric acid inhibition associated with the use of Prilosec is about 5 days. In order to avoid the carryover effect of Ome-Mg 20 from the previous treated episode, Table 4.2.2.2 presents the sponsor's GEE analysis on SCR with treatment, investigator, and episode as model parameters to compare the efficacy of Ome-Mg 20 versus placebo by two sets of episode groups: EPISD1 and EPISD2. Groups EPISD1 and EPISD2 respectively consist of treated episodes separated at least 3 and 5 days from the most recent episode.

Table 4.2.2.2 (Sponsor's) GEE method on SCR with treatment, investigator, and episode as model parameter to compare treatment effects of Ome-Mg 20 vs. Placebo

EPISODE GROUP	ODDS RATIO	95% C.I.	P-VALUE
EPISD1 [#]	1.15	(0.93, 1.4)	0.21
EPISD2 ^{&}	1.04	(0.82, 1.3)	0.78

[#]: EPISD1 consists of episodes separated at least 3 days from the most recent episode.

[&]: EPISD2 consists of episodes separated at least 5 days from the most recent episode.

Table 4.2.2.2 show that after eliminating the carryover effect, a single dose effect of Ome-Mg 20 tested by groups EPISD1 ($p=0.21$) and EPISD2 ($p=0.78$) is not superior to that of placebo.

It is noted that the primary objective, Ome-Mg 20 superior to placebo in providing sustained complete relief of episodic heartburn for the first treated episode, uses up .05 significance level and is not supported by the sponsor's primary efficacy endpoint analysis. Therefore, no significance level left to assess the secondary objective or any other secondary endpoints.

4.2.3 Conclusions of treatment effects

From the results of the sponsor's and this reviewer's analyses, it can be concluded that the effect of Ome-Mg 20 is not significantly better than that of placebo in the treatment of heartburn through a single dose.

4.3.0 Sponsor's Statistical Analyses and Reviewer's Comments for Study 1997095

4.3.1 Sponsor's Statistical Analysis Results

Demographics and Baseline Characteristics

The demographic variables and baseline characteristics analyzed by the sponsor for the three treatment groups, Ome-Mg 20, Ome-Mg 10, and placebo were gender, race, age, current smoker, other current nicotine use, current alcohol consumption, currently consume caffeine-containing

beverage, currently consume other caffeine-containing products, heartburn frequency (% of days) during placebo run-in phase, and average heartburn severity during placebo run-in phase for all randomized, ITT, and PP patients.

For all randomized, ITT, and per-protocol patients, the analyzed demographic and baseline characteristics were balanced in the 3 treatment groups ($p > .05$).

Summary of Sponsor's Efficacy Analysis Results

i.) Primary Efficacy Endpoint Analysis

The primary variable is the occurrence of Sustained Complete Relief for the subjects' first-treated episode of heartburn. Table 4.3.1.1 (extracted from sponsor's Table 8.2.3 in Volume 94) summarizes the results of the primary efficacy analysis for the first treated episodes of heartburn for ITT patient population.

Table 4.3.1.1 Primary efficacy analysis on SCR for the first treated episode of heartburn using intent-to-treat patients

TREATMENT GROUP	HTBN-FR RT [#]	P-VALUE VS. PLACEBO ¹	P-VALUE FOR HOMOG ²
Placebo (N=602)	29.4% (177/602) [*]		
Ome-Mg 10 (623)	29.9% (186/623) [*]	0.810	0.111
Ome-Mg 20 (N=627)	29.2 (183/627) [*]	0.934	0.001 [*]

[#]: Number of subjects with indicated outcome/number of subjects having treated heartburn episodes with non-missing efficacy values included in analysis; [#]: Heartburn-Free rate;

¹: Cochran-Mantel-Haenszel test for a treatment vs. placebo using investigator as a stratification factor;

²: Breslow-Day test for odds homogeneity across investigators between a treatment vs. placebo.

^{*}: Significant at .05 significance level for treatment efficacy comparison while .10 for odds homogeneity test.

Table 4.3.1.1 showed that at significant level of .05, neither Ome-Mg 20 (29.2%) nor Ome-Mg 10 (29.9%) was found superior to placebo (29.4%) when assessed by SCR on the first treated episode of heartburn after adjusting for Investigator.

The results from the per-protocol patient analysis were similar to those of the intent-to-treat patient analysis.

ii.) Secondary Efficacy Endpoint Analyses

Analysis results for first- and last-treated episodes of heartburn

Table 4.3.1.2 (extracted from sponsor's Table 8.2.3 and 8.2.24 in Volume 94) summarizes the analysis results on the following secondary efficacy variables for the first- and last-treated

episodes of heartburn using ITT population: sustained complete relief (last-treated episode only), complete relief within the first hour, sustained adequate relief, adequate relief within the first hour, backup medication (Gelusil) use, and overall assessment of study medication.

Table 4.3.1.2 (Sponsor's) P-Values for the secondary efficacy endpoints using ITT population

OUTCOME/TREATMENT COMPARISON	FIRST-TREATED EPISODE OF HEARTBURN	LAST-TREATED EPISODE OF HEARTBURN
Sustained Complete Relief		
Ome-Mg 20 vs. Placebo	Not applicable for secondary endpoint analysis	$p^c = 0.001^*$; $p^b = 0.01^*$
Ome-Mg 10 vs. Placebo		$p^c = 0.068$; $p^b = 0.355$
Ome-Mg 20 vs. Ome-Mg 10		$p^c = 0.08$; $p^b = 0.72$
Complete Relief within the First Hour		
Ome-Mg 20 vs. Placebo	$p^c = 0.899$; $p^b = 0.002^*$	$p^c = 0.001^*$; $p^b = 0.013^*$
Ome-Mg 10 vs. Placebo	$p^c = 0.394$; $p^b = 0.23$	$p^c = 0.065$; $p^b = 0.445$
Ome-Mg 20 vs. Ome-Mg 10	$p^c = 0.526$; $p^b = 0.76$	$p^c = 0.111$; $p^b = 0.77$
Sustained Adequate Relief		
Ome-Mg 20 vs. Placebo	$p^c = 0.003^*$; $p^b = 0.034^*$	$p^c = 0.001^*$; $p^b = 0.125$
Ome-Mg 10 vs. Placebo	$p^c = 0.326$; $p^b = 0.222$	$p^c = 0.065$; $p^b = 0.341$
Ome-Mg 20 vs. Ome-Mg 10	$p^c = 0.036^*$; $p^b = 0.73$	$p^c = 0.046^*$; $p^b = 0.54$
Adequate Relief within the First Hour		
Ome-Mg 20 vs. Placebo	$p^c = 0.017^*$; $p^b = 0.023^*$	$p^c = .001^*$; $p^b = 0.017^*$
Ome-Mg 10 vs. Placebo	$p^c = 0.194$; $p^b = 0.545$	$p^c = 0.012^*$; $p^b = 0.422$
Ome-Mg 20 vs. Ome-Mg 10	$p^c = 0.230$; $p^b = 0.54$	$p^c = 0.113$; $p^b = 0.52$
Backup Medication (Gelusil) Use		
Ome-Mg 20 vs. Placebo	$p^c = 0.035^*$; $p^b = 0.094$	$p^c = 0.050$; $p^b = 0.698$
Ome-Mg 10 vs. Placebo	$p^c = 0.529$; $p^b = 0.316$	$p^c = 0.603$; $p^b = 0.525$
Ome-Mg 20 vs. Ome-Mg 10	$p^c = 0.111$; $p^b = 0.07$	$p^c = 0.142$; $p^b = 0.66$
Overall Assessment of Study Medication		
Ome-Mg 20 vs. Placebo	$p^c = 0.017^*$; $p^b = NA$	$p^c = 0.001^*$; $p^b = NA$
Ome-Mg 10 vs. Placebo	$p^c = 0.019^*$; $p^b = NA$	$p^c = 0.001^*$; $p^b = NA$
Ome-Mg 20 vs. Ome-Mg 10	$p^c = 0.72$; $p^b = NA$	$p^c = 0.177$; $p^b = NA$

*: Significant at .05 significance level for treatment efficacy comparison while .10 for odds homogeneity test.

c: Treatment efficacy was compared by Cochran-Mantel-Haenszel test using investigator as a stratification factor;

b: Breslow-Day test for homogeneity of odds ratio between a treatment vs. placebo across investigators.

NA: Breslow-Day test is not applicable for polytomous response.

Table 4.3.1.2 indicated that at significance level of 0.05, for the first-treated episode of heartburn, the treatment effect of Ome-Mg 20 was significantly better than that of placebo when assessed by sustained adequate relief ($p=0.003$), adequate relief within the first hour (0.017), backup medication (Gelusil) use (0.035), and overall assessment of study medication ($p=0.017$).

complete relief ($p = 0.002$), complete relief within the first hour ($p=0.002$), sustained adequate relief ($p < 0.001$), adequate relief within the first hour ($p < 0.001$), backup medication (Gelusil) use ($p=0.018$), and overall assessment of study medication ($p < 0.001$) using ITT subjects.

In addition, the effect of Ome-Mg 10 was superior to that of placebo when assessed by complete relief within the first hour ($p=0.029$), sustained adequate relief ($p= 0.006$), adequate relief within the first hour ($p=0.009$), and overall assessment of study medication ($p<0.001$). Finally, the Ome-Mg 20 group had significantly higher percentage of subjects on sustained adequate relief ($p= 0.017$) than that of Ome-Mg 10 group.

Results of Adverse Events

Table 4.3.1.4 (Extracted from sponsor's Table 8.3.8 in Volume 94) presents an overall summary of adverse events (AEs) by treatment group for the active treatment phase.

Table 4.3.1.4 (Sponsor's) Adverse events by treatment groups for active treatment phase

	ACTIVE TREATMENT PHASE							
	Ome-Mg 20 (N = 638)		Ome-Mg 10 (N = 633)		PLACEBO (N = 621)		OVERALL (N = 1892)	
	n	%	n	%	N	%	n	%
Subjects								
With Any Aes	82	13	85	13	93	15	260	14
With Serious Aes	2	<1	3	<1	3	<1	8	<1
Withdrawals Due to Aes	1	<1	3	<1	5	1	9	<1
Deaths	0	0	0	0	0	0	0	0
Subjects								
Reporting 0 AE	556	87	548	87	528	85	1632	86
Reporting 1 AE	63	10	67	11	67	11	197	10
Reporting > 1 AEs	19	3	18	3	26	4	63	3
Overall	638	100	633	100	621	100	1892	100
Adverse Event Intensity								
Mild	57	50	61	53	47	35	165	45
Moderate	43	38	36	31	62	46	141	39
Severe	13	12	19	16	26	19	58	16
Overall	113	100	116	100	135	100	364	100

Table 4.3.1.4 summarizes the adverse events (AEs) reported for each treatment group. Overall, 260 (14%) of the subjects reported 364 AEs. Eighty-two (13%) of the subjects on Ome-Mg 20 reported 113 AEs; 85 (13%) of the subjects on Ome-Mg 10 reported 116 AEs; and 93 (15%) of the subjects on placebo reported 135 AEs. The percentage of AEs that were considered to be Mild to Moderate in intensity was 88%, 84%, and 81% for subjects on Ome-Mg 20, Ome-Mg 10, and placebo, respectively. The percentage of AEs that were considered to be Severe was 12% for Ome-Mg 20, 16% for Ome-Mg 10, and 19% for the placebo treatment groups.

Finally, the percentage of AEs that were considered to be possibly or probably due to study medication was 32%, 41%, and 33% for subjects on Ome-Mg 20, Ome-Mg 10, and placebo, respectively.

4.3.2 Reviewer's Analyses and Comments

Table 4.3.1.1 indicates that the primary objective, Ome-Mg 20 superior to placebo in providing sustained complete relief of episodic heartburn for the first treated episode (the primary efficacy endpoint analysis), is not supported by the sponsor's primary efficacy analysis on the first episode ($p=0.934$). Since the significance level of .05 was spent for the primary objective and the superiority of Ome-Mg 20 mg to placebo is not established by the primary efficacy endpoint analysis, the indication of heartburn treatment is not supported. In order to further corroborate the non-superiority of Ome-Mg 20 mg over placebo in the treatment of heartburn through a single dose of Ome-Mg 20 mg, this reviewer i.) performs GEE analysis on SCR (the primary efficacy endpoint) for testing the interaction between treatment and day (treatment*day) using all treated episodes and ii.) employs the sponsor's GEE analysis on SCR using treatment, investigator, and episode as model parameters for treated episodes separated at least 3 and 5 days from the most recent episode.

Data used in this reviewer's analysis i.) was submitted by the sponsor, dated January 29, 2000 while the results of analyses ii.) were submitted by the sponsor dated 7/20/2000.

ii.) GEE analysis on SCR for testing treatment*day using all treated episodes

Following the reason and caution stated in subsection 4.2.2, this reviewer applies GEE method to SCR using treatment, pooled investigator, day, and treatment*day as model parameters for all treated episodes. Here, day 1 was defined as the day when the first heartburn episode was treated while day2 is the day following day 1, etc. The results are presented in Table 4.3.2.1.

Table 4.3.2.1(Reviewer's) Results of GEE method on SCR to compare the efficacy between Ome-Mg 20 and placebo using all treated episodes

PARAMETER	ESTIMATE	P-VALUE
Treatment	0.13	0.27
Pooled Investigator	-----#	-----
Day	-0.004	0.55
Treatment*Day	0.026	0.014*

#: Not important for this analysis; *: Significant at .05 level.

Table 4.3.2.1 shows that the parameter estimate (0.026) of treatment*day is significantly different from zero ($p=0.014$), indicating the log odds of SCR for OME-Mg 20 is a positive trend in favor of the later treatment period. The carryover effect of Ome-Mg 20 is thus identified.

- ii.) Sponsor's GEE analysis on SCR using treated episodes separated at least 3 and 5 days from most recent episode.

As noted by the medical reviewer, L. Goldkind, M.D., the duration of gastric acid inhibition associated with the use of Prilosec is about 5 days. In order to avoid the carryover effect of Ome-Mg 20 from the previous treated episode, Table 4.3.2.2 presents the sponsor's GEE analysis on SCR with treatment, investigator, and episode as model parameters to compare the efficacy of Ome-Mg 20 versus placebo by two sets of episode groups: EPISD1 and EPISD2. Groups EPISD1 and EPISD2 respectively consist of episodes separated at least 3 and 5 days from the most recent episode.

Table 4.3.2.2 (Sponsor's) GEE method on SCR with treatment, investigator, and episode as model parameter to compare treatment effects of Ome-Mg 20 vs. Placebo

EPISODE GROUP	ODDS RATIO	95% C.I.	P-VALUE
EPISD1 ^a	1.07	(0.86, 1.33)	0.535
EPISD2 ^a	0.98	(0.77, 1.25)	0.85

^a: EPISD1 consists of episodes separated at least 3 days from the most recent episode.

^a: EPISD2 consists of episodes separated at least 5 days from the most recent episode.

Table 4.3.2.2 show that after eliminating the carryover effect, a single dose effect of Ome-Mg 20 tested by groups EPISD1 (p=0.535) and EPISD2 (p=0.85) is not superior to that of placebo.

It is noted that the primary objective, Ome-Mg 20 superior to placebo in providing sustained complete relief of episodic heartburn for the first episode, uses up .05 significance level and is not supported by the sponsor's primary efficacy endpoint analysis. Therefore, no significance level left to assess the secondary objective or any other secondary endpoints.

4.3.3 Conclusions of treatment effects

From the results of the sponsor's and this reviewer's analyses, it can be concluded that the effect of Ome-Mg 20 is not significantly better than that of placebo in the treatment of heartburn through a single dose.

4.4.0 Reviewer's Analyses and Comments for Studies 1997092 and 1997095

From the results of the sponsor's and this reviewer's analyses, it can be concluded that the effect of Ome-Mg 20 is not significantly better than that of placebo in the treatment of heartburn through a single dose.

5.0 Overall Conclusions/Recommendations

For the indication of 4-hour prevention of heartburn:

- The superiority of Ome-Mg 20 mg to placebo on 4-hour heartburn-free evaluation (the primary efficacy endpoint) is supported by Study 1998006 ($p=0.004$).
- The result of Ome-Mg 20 significantly better than that of placebo on 4-hour heartburn-free evaluation, shown by Study 1998006, is not replicated by that of Study 1998005.
- The superiority of Ome-Mg 10 to placebo on 4-hour prevention of heartburn is supported only by one study, Study 1998006.

For the indication of 2-week prevention of heartburn:

- The effects of Ome-Mg 20 and Ome-Mg 10 are both significantly better than that of placebo in the two-week prevention of heartburn. However, only one study, Study 171, shows the superiority of omeprazole to placebo in the two-week prevention of nocturnal heartburn.

For the indication of treatment of heartburn:

- The effect of Ome-Mg 20 is not significantly better than that of placebo in the treatment of heartburn through a single dose.

[151]

Wen-Jen Chen Ph.D.,
Mathematical Statistician

[151] 11/9/00
Concur: Dr. Permutt

cc: Archival NDA# 21-229
HFD-180 Div File
HFD-180/Dr. Talarico
HFD-180/Dr. Gallo-Torres
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HFD-715/Dr. Nevius
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Appendix I

Table A.1.1 (Reviewer's) Fisher exact tests on 4-hour Heartburn-Free to compare treatment effects by Gender (ITT Patients)

	Ome-Mg 20 Vs. Placebo	Ome-Mg 10 Vs. Placebo
Female	21% (56/273) versus 18% (46/260); p=0.44.	25% (70/283) versus 18% (46/260); p=0.047*.
Male	34% (54/160) versus 24% (39/163); p=0.065.	24.1% (35/145) versus 23.9% (39/163); p=1.0.

*: Significance at significant level of .05 .

Table A.1.2 (Reviewer's) Fisher exact tests on 4-hour Heartburn-Free to compare treatment effects by Age group (ITT Patients)

	Ome-Mg 20 Vs. Placebo	Ome-Mg 10 Vs. Placebo
Age > 65	9.5% (2/21) versus 22.2% (4/18); p=0.40.	28% (7/25) versus 22% (4/18); p=0.74.
Age ≤ 65	26% (108/412) versus 20% (81/405); p=0.038*.	24.3% (98/403) versus 20% (81/405); p=0.15.

*: Significance at significant level of .05 .

Table A.1.3 (Reviewer's) Fisher exact tests on 4-hour Heartburn-Free to compare treatment effects by Race (ITT Patients)

	Ome-Mg 20 Vs. Placebo	Ome-Mg 10 Vs. Placebo
Caucasian	24.6% (83/337) versus 19.9% (64/322); p=0.16.	26.3% (88/335) versus 19.9% (64/322); p=0.064.
Non-Caucasian	28.1% (21/96) versus 20.8% (21/101); p=0.250.	18.3% (17/93) versus 20.8% (21/101); p=0.72.

*: Significance at significant level of .05 .

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Appendix II

Table A.2.1 (Reviewer's) Fisher exact tests on 4-hour Heartburn-Free to compare treatment effects by Gender (ITT Patients)

	Ome-Mg 20 Vs. Placebo	Ome-Mg 10 Vs. Placebo
Female	23.6% (55/233) versus 15.2% (35/231); p=0.025*	21.7% (49/226) versus 15.2% (35/231); p=0.09.
Male	29.4% (47/160) versus 20.1% (32/159); p=0.037*	30.4% (49/161) versus 20.1% (32/159); p=0.04*

*: Significance at significant level of .05 .

Table A.2.2 (Reviewer's) Fisher exact tests on 4-hour Heartburn-Free to compare treatment effects by Age (ITT Patients)

	Ome-Mg 20 Vs. Placebo	Ome-Mg 10 Vs. Placebo
Age > 65	20.0% (4/20) versus 16.1% (5/31); p=0.724.	18.52% (5/27) versus 16.13% (5/31); p=1.0.
Age ≤ 65	26.27% (98/373) versus 17.30% (62/359); p=0.004*	25.83% (93/360) versus 17.3% (62/359); p=0.006*

*: Significance at significant level of .05 .

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Appendix III

Table A.3.1 (Reviewer's) Fisher exact tests on Day 1 Heartburn-Free rate to compare treatment effects by Gender (ITT Patients)

	Ome-Mg 20 Vs. Placebo	Ome-Mg 10 Vs. Placebo
Female	50.5% (150/297) versus 33.5% (96/287); p< 0.001*.	41.2% (117/284) versus 33.5% (96/287); p=0.06.
Male	48.7% (110/226) versus 31.5% (73/232); p<0.001*.	41.9% (98/234) versus 31.5% (73/232); p=0.02*.

*: Significance at significant level of .05.

Table A.3.2 (Reviewer's) Fisher exact tests on Day 1 Heartburn-Free rate to compare treatment effects by Age group (ITT Patients)

	Ome-Mg 20 Vs. Placebo	Ome-Mg 10 Vs. Placebo
Age > 65	55.6% (25/45) versus 27.0% (10/37); p=0.013*.	50% (17/34) versus 27.0% (10/37); p=0.74.
Age ≤ 65	49.2% (235/478) versus 33.0% (159/482); p < 0.001*.	40.9% (198/484) versus 33.0% (159/482); p=0.06.

*: Significance at significant level of .05 .

Table A.3.3 (Reviewer's) Fisher exact tests on Day 1 Heartburn-Free rate to compare treatment effects by Race (ITT Patients)

	Ome-Mg 20 Vs. Placebo	Ome-Mg 10 Vs. Placebo
Caucasian	51.9% (208/401) versus 33.6% (134/399); p < 0.001*.	42.8% (175/409) versus 33.6% (134/399); p=0.007*.
Non-Caucasian	42.6% (52/122) versus 29.2% (35/120); p=0.03*.	36.7% (40/109) versus 29.2% (35/120); p=0.23.

*: Significance at significant level of .05 .

Appendix IV

Table A.4.1 (Reviewer's) Fisher exact tests on Day 1 Heartburn-Free rate to compare treatment effects by Gender (ITT Patients)

	Ome-Mg 20 Vs. Placebo	Ome-Mg 10 Vs. Placebo
Female	46.3% (131/283) versus 33.8% (99/293); p= 0.003*	45.6% (131/287) versus 33.8% (99/293); p=0.004*
Male	47.3% (114/241) versus 30.0% (68/227); p<0.001*	44.64% (104/233) versus 30.0% (68/227); p=0.001*

*: Significance at significant level of .05.

Table A.4.2 (Reviewer's) Fisher exact tests on Day 1 Heartburn-Free rate to compare treatment effects by Age group (ITT Patients)

	Ome-Mg 20 Vs. Placebo	Ome-Mg 10 Vs. Placebo
Age > 65	48.6% (34/70) versus 21.5% (14/65); p=0.001*	43.9% (29/66) versus 21.5% (14/65); p= 0.009*
Age ≤ 65	46.5% (211/454) versus 33.6% (153/455); p < 0.001*	45.4% (206/454) versus 33.6% (153/455); p < 0.001*

*: Significance at significant level of .05 .

Table A.4.3 (Reviewer's) Fisher exact tests on Day 1 Heartburn-Free rate to compare treatment effects by Race (ITT Patients)

	Ome-Mg 20 Vs. Placebo	Ome-Mg 10 Vs. Placebo
Caucasian	47.9% (212/443) versus 29.2% (130/445); p < 0.001*	45.33% (204/450) versus 29.2% (130/445); p < 0.001*
Non-Caucasian	40.7% (33/81) Versus 49.3% (37/75); p = 0.3.	44.3% (31/70) versus 49.3% (37/75); p=0.62.

*: Significance at significant level of .05 .