

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**NDA 20-325 / S-015**

**STATISTICAL REVIEW(S)**

**STATISTICAL REVIEW AND EVALUATION --- NDA  
CLINICAL STUDIES**

**Medical Division: Gastrointestinal and Coagulant Drug Product (HFD-180)**  
**Biometrics Division: Division of Biometrics II (HFD-715)**

**STATISTICAL KEY WORDS:** ordered categorical data, logistic regression  
**NDA #:** 20-325

**SERIAL NUMBER:** 015

**DATE RECEIVED BY CENTER:** November 21, 2002

**DRUG NAME:** Pepcid AC (nonprescription famotidine 20 mg)

**INDICATION:** Treatment and Prevention of Heartburn, Acid Indigestion and Sour  
Stomach

**SPONSOR:** Merck & Co.

**DOCUMENTS REVIEWED:** Electronic NDA dated November 21, 2002  
Response to Request for Hardcopy Review Aid for  
Pending Supplement Statistical Documentation Vol. 1-3  
dated December 30, 2002  
Response to FDA Request for Information (Statistical  
Review Aids) dated February 24, 2003  
Response to FDA Request for Information (Additional  
Statistical Information) dated July 25, 2003

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## **1. EXECUTIVE SUMMARY OF STATISTICAL FINDINGS**

### **1.1 Conclusion and Recommendation**

#### **1.1.1 Prevention of Heartburn**

All three studies (114, 117 and 128) showed that famotidine 20 mg was superior to placebo in terms of peak heartburn severity during the 3 hours postmeal. Furthermore, study 117 showed that famotidine 20 mg was statistically significant less severe peak heartburn symptoms than famotidine 10 mg. Study 128 also showed that famotidine 20 mg was marginally significant better than famotidine 10 mg.

Based on this reviewer's subgroup analysis for race, it was found that the statistically significant race by treatment interaction effect was observed in all three studies (114, 117 and 128) (Breslow-Day p-value <0.20). In particular, study 128 revealed that there was no treatment effect for Black; the placebo rate was higher than either famotidine 10 mg or famotidine 20 mg.

#### **1.1.2 Treatment of Heartburn**

In General, the sponsor's analyses were post-hoc re-analyses. Some new analysis results of the efficacy data were based on retrospectively defined endpoints and analyses. These analyses were based on the efficacy data that was used to approve famotidine 10 mg in 1994.

The efficacy data in Study 019 do not provide adequate support for famotidine effectiveness for the treatment of intermittent heartburn. The reported effectiveness results for study #19 regarding the protocol and post-hoc defined primary endpoint proportion of patient-episodes completely relieved is method dependent and reanalysis driven.

From the reviewer's recommendation is that the sponsor should conduct a new study for famotidine 20 mg to provide adequate support for the effectiveness results seen in study #17 regarding the primary endpoint: proportion of patient-episodes completely relieved.

### **1.2 Overview of the Clinical Program and Studies Reviewed**

Pepcid AC (famotidine 10 mg), an OTC H<sub>2</sub>RA, was approved on April 28, 1995 for both the prevention and treatment of heartburn.

In memorandum of meeting minutes dated December 16, 1998, it stated that for the severe heartburn population, famotidine 20 mg must be statistically superior to both famotidine 10 mg and placebo while famotidine 10 mg must be at least numerically better than placebo.

In memorandum of meeting minutes dated August 7, 2002, it stated that FDA agreed that a third study with similar study design that replicated the results of Study 117 is sufficient to

support an NDA filing for famotidine 20 mg OTC for intermittent dosing to prevent frequent and sometime severe heartburn. The proposed target population for the 20 mg product should be separate and distinct from that for the 10 mg product.

In the current NDA, the sponsor seeks approval of a 20-mg nonprescription famotidine for prevention and treatment of heartburn. The proposed product (famotidine 20 mg) is intended to be an extra strength product intended for the severe heartburn sufferers who do not obtain adequate relief from the 10 mg product.

Data from original NDA treatment study (017 and 019) would be used to support a treatment indication for a 20-mg dose. These two studies were included in the original NDA submission. Statistical Review and Evaluation for this original NDA was performed and documented December 16, 1993 and May 13, 1994. The sponsor has submitted the results of supplemental analyses to support a treatment claim for nonprescription famotidine 20 mg.

The sponsor has submitted four new studies (114, 117, 128 and 137) for prevention of heartburn. These new studies include:

Study 114: to compare famotidine 20 mg, famotidine 10 mg, and placebo in preventing heartburn symptoms when administered ten minutes prior to a provocative meal.

Study 117: to compare famotidine 20 mg, famotidine 10 mg, and placebo in preventing heartburn symptoms when administered 10 minutes prior to a provocative meal.

Study 128: to compare famotidine 20 mg, famotidine 10 mg, and placebo in preventing heartburn symptoms when administered prior to a provocative meal.

Study 137: to compare the efficacy of famotidine 20 mg and placebo in preventing heartburn and acid reflux when administered immediately prior to a provocative meal.

Studies 114, 117, 128, and 137 were double-blind, randomized, placebo-controlled, parallel-group multicenter studies.

Study 137 was considered as not a pivotal trial. This study will not statistically reviewed.

#### **1.2.1 Brief Description for Study Design for Study 114**

This study was a multi-center (10 sites), randomized, double-blind, placebo-controlled study to evaluate the efficacy of famotidine 20 mg and famotidine 10 mg in preventing heartburn symptoms when administered ten minutes prior to provocative meal.

The major objective of this study was to assess the ability of famotidine 20 mg and famotidine 10 mg to prevent heartburn in patients treated 10 minutes prior to an evening provocative meal.

To be qualified to participate in the screen session, patients should have a history of food-induced heartburn, of at least 2 months' duration with at least three episodes per week. Patients should consider their symptoms to be of at least moderate to severe intensity. Patients should be able to identify specific foods and beverages that produced symptoms and should use antacids and/or OTC H<sub>2</sub>-receptor antagonists for effective relief of their symptoms. Qualified patients underwent a placebo-treated screening provocative meal consisting of chili and cola to ascertain whether the meal produced a grade 3 (severe) heartburn rating. Eligible patients were randomized into a 4-hour treatment session. Heartburn evaluation performed at 30-minute intervals for 3 hours after the start of a provocative meal. A snack consisting of chocolate brownie and fruit punch, and a diary card and instruction gave to each patient before leave the clinic. Patients recorded any heartburn symptoms that they had experience during the night using three-point scale (1=mild, 2=moderate, and 3= severe). On the morning after the treatment session the patient was asked to rate the overall effect using five point scale (4=excellent, 3=very good, 2=good, 1=fair, and 0=poor). Patients return their diary to the clinic within 72 hours after the treatment meal. Patients with unbearably severe symptoms might take rescue medication, but they were asked to take the rescue until at least 3 hours after the provocative meal. The rescue medication consisted of MYLANTA Double-Strength antacid tablets. Study duration was approximately 8 weeks.

Efficacy measurements were heartburn severity evaluation at 30-minute intervals; heartburn symptoms experienced during the overnight evaluation period; global evaluation of efficacy at the end of the overnight evaluation period.

The primary endpoint was the peak heartburn severity during the 3 hours following the start of the provocative meal.

The secondary endpoints were the proportion of patient with no heartburn during the 3 hours following the start of the meal, mean heartburn severity during the 3 hours following the start of the meal, global assessment of efficacy at the end of the treatment period, and the proportion of patients who did not awaken with heartburn.

Both an all-patients-treated and a per-protocol approach were used for analysis of efficacy. In the all-patients-treated approach, all patients who were randomized and received study medication were included. In the per-protocol approach, serious protocol violators were excluded.

Patient who took rescue at any time following the start of the meal was considered a "treatment failure" for all points subsequent to the use of rescue or to the time of the meal. Prior to analysis, all patients who were considered treatment failure were assigned severity scores of "Severe" for these time points and a global assessment score of Poor (0). Patients who took rescue medication prior to going to bed were counted as if they had awakened with heartburn.

The primary endpoint was the peak heartburn severity during the 3 hours following the start of the provocative meal.

The secondary endpoints were the proportion of patient with no heartburn during the 3 hours following the start of the meal, mean heartburn severity during the 3 hours following the start of the meal, global assessment of efficacy at the end of the treatment period, and the proportion of patients who did not awaken with heartburn.

Both an all-patients-treated and a per-protocol approach were used for analysis of efficacy. In the all-patients-treated approach, all patients who were randomized and received study medication were included. In the per-protocol approach, serious protocol violators were excluded.

Patient who took rescue at any time following the start of the meal was considered a “treatment failure” for all points subsequent to the use of rescue or to the time of the meal. Prior to analysis, all patients who were considered treatment failure were assigned severity scores of “Severe” for these time points and a global assessment score of Poor (0). Patients who took rescue medication prior to going to bed were counted as if they had awakened with heartburn.

Peak heartburn severity in the 3 hours following the start of the provocative meal and global assessment of efficacy measured at the end of the treatment period was analyzed using logistic regression models for ordered categorical data. The proportion of patients who reported no heartburn symptoms during the 3 hours following the start of the meal was analyzed using a logistic regression model for binary data. Mean heartburn severity during the 3 hours following the start of the meal was analyzed using an ANOV model. All models contained factors for treatment group and investigator site.

Because only one treatment comparison was performed for the primary hypothesis, no correction for multiple comparisons was necessary.

It was assumed that between 65% and 71% of the patients given famotidine 20 mg reported none or mild peak heartburn and between 51% and 54% of the patients given famotidine 10 mg reported none or mild peak heartburn. With 260 patients per treatment group, the power to detect difference between famotidine 20 mg and famotidine 10 mg and placebo ranged from 73% to 99%.

### **1.2.2 Brief Description for Study Design for Study 117**

This study was a multi-center (13 sites), randomized, double-blind, placebo-controlled study to evaluate the efficacy of famotidine 20 mg and famotidine 10 mg in preventing heartburn symptoms when administered ten minutes prior to provocative meal.

The design of this study was similar to that of protocol 114.

This study differed from the protocol 114 in the screening criteria used to select the population. Protocol 114 used a placebo-controlled, provocative meal to screen patients where only those patients experiencing severe symptoms during the 3-hour postmeal period were eligible for randomization. This study would screen patients using an observational

baseline run-in week. Patients who treated at least 3 episodes during the run-in week with a least 1 of the episodes being severe would be eligible for randomization. This screening criterion would result in less severe patients than in protocol 114.

Secondary efficacy parameters included the proportion of patients who took rescue medication anytime during the study.

Patients would be randomized 2:2:1 to 1 of 3 treatment groups (famotidine 20 mg; famotidine 10 mg; placebo).

With 500 patients per active treatment groups, the power was at least 89% to detect a difference of 10% between famotidine 20 mg and famotidine 10 mg ( $\alpha=0.05$ , two tailed).

With 500 patients per active treatment groups and 250 patients in the placebo group, the power was at least 73% to detect a difference of 10% between active treatment and placebo ( $\alpha=0.05$ , two tailed).

### **1.2.3 Brief Description for Study Design for Study 128**

This study was a multi-center (15 sites), randomized, double-blind, placebo-controlled study to evaluate the efficacy of famotidine 20 mg and famotidine 10 mg in preventing heartburn symptoms when administered ten minutes prior to provocative meal.

This design of this study was similar to that of protocol 117.

Secondary efficacy parameters included the proportion of patients who took rescue medication during the 3 hours following the start of the meal. The proportion of patients who did not awaken with heartburn was not included as secondary efficacy parameter.

With 500 patients per active treatment groups, the power was at least 89% to detect a difference of 10% between famotidine 20 mg and famotidine 10 mg ( $\alpha=0.05$ , two tailed).

With 500 patients per active treatment groups and 250 patients in the placebo group, the power was at least 73% to detect a difference of 10% between active treatment and placebo ( $\alpha=0.05$ , two tailed).

## **1.3 Principal Findings**

### **1.3.1 Prevention of Heartburn**

Study 114 showed that in term of primary endpoint: the peak heartburn severity during the 3 hours, the difference between famotidine 20 mg and famotidine 10 mg was marginally significant. The difference between famotidine 20 and placebo was statistically significant. The famotidine 10 mg versus placebo difference was not statistically significant.

Superiority of famotidine 20 mg vs. placebo was also observed in the secondary endpoints: the proportion of patients reporting no heartburn and mean heartburn severity during the 3-hour postmeal period, global assessment of efficacy measured at the end of the treatment period and proportion of patients reporting no awakening with heartburn.

Study 117 showed that that in term of primary endpoint: the peak heartburn severity during the 3 hours, the difference between famotidine 20 mg and famotidine 10 mg was statistically significant. The difference between famotidine 20 and placebo was statistically significant. The famotidine 10 mg versus placebo difference was statistically significant.

Superiority of famotidine 20 mg over either placebo or famotidine 10 mg was also observed in the secondary endpoints: proportion of patients reporting no heartburn and mean heartburn severity during the 3-hour postmeal period. Superiority of famotidine 10 mg and famotidine 20 mg over placebo was observed in all secondary endpoints.

Study 128 showed that in term of primary endpoint: the peak heartburn severity during the 3 hours, the difference between famotidine 20 mg and famotidine 10 mg was marginally significant. The difference between famotidine 20 and placebo was statistically significant. The famotidine 10 mg versus placebo difference was statistically significant.

Superiority of famotidine 10 mg and famotidine 20 mg over placebo was also observed in all secondary endpoints. The difference between famotidine 20 mg and famotidine 10 mg was marginally significant for proportion of patients reporting no heartburn during 3 hours postmeal, but were not statistically significant for other secondary endpoints: mean heartburn severity during the 3 hours postmeal and global assessment of efficacy measured at the end of the treatment period.

Based on this reviewer's subgroup analysis for race, it was found that the statistically significant race by treatment interaction effect was observed in all three studies (114, 117 and 128) (Breslow-Day p-value <0.20). In particular, study 128 revealed that there was no treatment effect for Black; the placebo rate was higher than either famotidine 10 mg or famotidine 20 mg.

### **1.3.2 Treatment of Heartburn**

The sponsor's analyses presented in current statistical report were post-hoc re-analyses. These analysis results of the efficacy data were based on retrospectively defined endpoints and analyses. The analyses was performed using GEE (Generalized Estimating Equations) method adjusted for study site, average heartburn severity during baseline week, number of heartburn episodes during double-blind phase.

For both studies, the patients in both the famotidine 20-mg and 10-mg groups had a significantly greater probability of achieving complete relief within 1 hour of dosing than the patients in the placebo group

For proportion of heartburn episodes completely relieved within 3 hours of dosing, the lower bound of 95% confidence interval of odds-ratio between famotidine 20 mg and placebo and between famotidine 10 mg and placebo was 1.0456 and 1.0618 for Studies 017 and 019, respectively. These lower bounds slightly greater than 1.0 suggests the benefit of either famotidine 10 or famotidine 20 mg over placebo is moderate. It re-confirmed the finding stated “very small numerical advantages in favor of famotidine regarding the proportion of patient-episodes completely relieved within three hours of treatment medication. The treatment differences range from 3% to 4% for protocol #019” in Statistical Review and Evaluation (Addendum) dated May 13, 1994.

It was also found that the reported effectiveness results for study 019 in the current statistical report regarding protocol and post-hoc defined primary endpoint proportion of patient-episodes completely relieved is method dependent and reanalysis driven.

## **2. STATISTICAL REVIEW AND EVALUATION**

### **2.1 Background:**

Pepcid AC (famotidine 10 mg), an OTC H<sub>2</sub>RA, was approved on April 28, 1995 for both the prevention and treatment of heartburn.

In memorandum of meeting minutes dated December 16, 1998, it stated that for the severe heartburn population, famotidine 20 mg must be statistically superior to both famotidine 10 mg and placebo while famotidine 10 mg must be at least numerically better than placebo.

In memorandum of meeting minutes dated August 7, 2002, it stated that FDA agreed that a third study with similar study design that replicated the results of Study 117 is sufficient to support an NDA filing for famotidine 20 mg OTC for intermittent dosing to prevent frequent and sometime severe heartburn. The proposed target population for the 20 mg product should be separate and distinct from that for the 10 mg product.

In the current NDA, the sponsor seeks approval of a 20-mg nonprescription famotidine for prevention and treatment of heartburn. The proposed product (famotidine 20 mg) is intended to be an extra strength product intended for the severe heartburn sufferers who do not obtain adequate relief from the 10 mg product.

Data from original NDA treatment study (017 and 019) would be used to support a treatment indication for a 20-mg dose. These two studies were included in the original NDA submission. Statistical Review and Evaluation for this original NDA was performed and documented December 16, 1993 and May 13, 1994. The sponsor has submitted the results of supplemental analyses to support a treatment claim for nonprescription famotidine 20mg.

The sponsor has submitted four new studies (114, 117, 128 and 137) for prevention of heartburn. These new studies include:

Study 114: to compare famotidine 20 mg, famotidine 10 mg, and placebo in preventing heartburn symptoms when administered ten minutes prior to a provocative meal.

Study 117: to compare famotidine 20 mg, famotidine 10 mg, and placebo in preventing heartburn symptoms when administered 10 minutes prior to a provocative meal.

Study 128: to compare famotidine 20 mg, famotidine 10 mg, and placebo in preventing heartburn symptoms when administered prior to a provocative meal.

Study 137: to compare the efficacy of famotidine 20 mg and placebo in preventing heartburn and acid reflux when administered immediately prior to a provocative meal.

Studies 114, 117, 128, and 137 were double-blind, randomized, placebo-controlled, parallel-group multicenter studies.

Study 137 was considered as not a pivotal trial. This study will not statistically reviewed.

## **2.2 Prevention of Heartburn**

### **2.2.1 Study Design**

Studies 114, 117, and 128 were conducted to investigate the efficacy of famotidine 20 mg in preventing heartburn when administered 10 minutes prior to provocative meal. These were randomized, single-dose, double-blind, parallel studies comparing famotidine 20 mg, famotidine 10 mg, and placebo. Study 114 was conducted in patients with moderate to severe heartburn by history. In addition, patients had to develop severe heartburn after ingestion an in-clinic provocative meal to qualify for randomization to the double-blind, in-clinic treatment session. Study 117 was conducted in patients with frequently severe heartburn by history. In contrast to Study 114, patients in Study 117 completed a 1-week at-home baseline period to verify heartburn frequency/severity and qualify for randomization to an in-clinic treatment session. Study 128 was replicate of Study 117.

In addition, a multidose pilot efficacy study (Study 137) was conducted to compare the efficacy of famotidine 20 mg and placebo in preventing heartburn and acid reflux symptoms when administered immediately prior to a provocative meal. An at-home meal model was used in which patients self-selected meals known by them to produce heartburn and acid reflux symptoms. Patients had the opportunity to use 4 doses over a 2-week period.

### **2.2.2 Protocol 114**

#### **2.2.2.1 Study Design**

This study was a multi-center (10 sites), randomized, double-blind, placebo-controlled study to evaluate the efficacy of famotidine 20 mg and famotidine 10 mg in preventing heartburn symptoms when administered ten minutes prior to provocative meal.

The major objective of this study was to assess the ability of famotidine 20 mg and famotidine 10 mg to prevent heartburn in patients treated 10 minutes prior to an evening provocative meal.

To be qualified to participate in the screen session, patients should have a history of food-induced heartburn, of at least 2 months' duration with at least three episodes per week. Patients should consider their symptoms to be of at least moderate to severe intensity. Patients should be able to identify specific foods and beverages that produced symptoms and should use antacids and/or OTC H<sub>2</sub>-receptor antagonists for effective relief of their symptoms. Qualified patients underwent a placebo-treated screening provocative meal consisting of chili and cola to ascertain whether the meal produced a grade 3 (severe) heartburn rating. Eligible patients were randomized into a 4-hour treatment session. Heartburn evaluation performed at 30-minute intervals for 3 hours after the start of a provocative meal. A snack consisting of chocolate brownie and fruit punch, and a diary card and instruction gave to each patient before leave the clinic. Patients recorded any heartburn symptoms that they had experience during the night using three-point scale (1=mild, 2=moderate, and 3= severe). On the morning after the treatment session the patient was asked to rate the overall effect using five point scale (4=excellent, 3=very good, 2=good, 1=fair, and 0=poor). Patients return their diary to the clinic within 72 hours after the treatment meal. Patients with unbearably severe symptoms might take rescue medication, but they were asked to take the rescue until at least 3 hours after the provocative meal. The rescue medication consisted of MYLANTA Double-Strength antacid tablets. Study duration was approximately 8 weeks.

Efficacy measurements were heartburn severity evaluation at 30-minute intervals; heartburn symptoms experienced during the overnight evaluation period; global evaluation of efficacy at the end of the overnight evaluation period.

The primary endpoint was the peak heartburn severity during the 3 hours following the start of the provocative meal.

The secondary endpoints were the proportion of patient with no heartburn during the 3 hours following the start of the meal, mean heartburn severity during the 3 hours following the start of the meal, global assessment of efficacy at the end of the treatment period, and the proportion of patients who did not awaken with heartburn.

Both an all-patients-treated and a per-protocol approach were used for analysis of efficacy. In the all-patients-treated approach, all patients who were randomized and received study medication were included. In the per-protocol approach, serious protocol violators were excluded.

Patient who took rescue at any time following the start of the meal was considered a "treatment failure" for all points subsequent to the use of rescue or to the time of the meal. Prior to analysis, all patients who were considered treatment failure were assigned severity scores of "Severe" for these time points and a global assessment score of Poor (0). Patients

who took rescue medication prior to going to bed were counted as if they had awakened with heartburn.

Peak heartburn severity in the 3 hours following the start of the provocative meal and global assessment of efficacy measured at the end of the treatment period was analyzed using logistic regression models for ordered categorical data. The proportion of patients who reported no heartburn symptoms during the 3 hours following the start of the meal was analyzed using a logistic regression model for binary data. Mean heartburn severity during the 3 hours following the start of the meal was analyzed using an ANOV model. All models contained factors for treatment group and investigator site.

Because only one treatment comparison was performed for the primary hypothesis, no correction for multiple comparisons was necessary.

It was assumed that between 65% and 71% of the patients given famotidine 20 mg reported none or mild peak heartburn and between 51% and 54% of the patients given famotidine 10 mg reported none or mild peak heartburn. With 260 patients per treatment group, the power to detect difference between famotidine 20 mg and famotidine 10 mg and placebo as follows ( $\alpha=0.05$ , two tailed):

Response to Famotidine 20 mg	Response to Famotidine 10 mg	
71%	54%	51%
68%	98% ( $\Delta=17$ )	99% ( $\Delta=20$ )
65%	91% ( $\Delta=14$ )	98% ( $\Delta=17$ )
	73% ( $\Delta=11$ )	90% ( $\Delta=14$ )
Response to Placebo	Response to Famotidine 10 mg	
38%	54%	51%
	96% ( $\Delta=16$ )	85% ( $\Delta=13$ )
Response=none/mild peak heartburn during the 3½ hours following start of treatment meal.		

#### 2.2.2.2 Sponsor's Analysis

Of a total of 1739 patients screened, 1539 patients participated in the placebo screening phase. Of these 1539 patients, a total of 794 patients were randomized into treatment phase (261 in famotidine 20 mg, 271 in famotidine 10 mg, 262 in placebo). Of 794 patients, 793 completed the study.

298 patients (84 in famotidine 20 mg, 97 in famotidine 10 mg, and 117 in placebo) were considered "treatment failure" and were assigned the worst scores. 11 patients (2 in famotidine 20 mg, 3 in famotidine 10 mg, and 6 in placebo) who used rescue during the 3-hour postmeal period was assigned a score of severe for all heartburn severity evaluation after the use of rescue. With the exception of 1 patients (famotidine 10 mg) who discontinued early, the remaining 297 patients who took rescue at any time after treatment

were assigned a global assessment score of poor and were counted as if they had awakened with heartburn.

### 2.2.2.3 Treatment Group Comparability

A summary of the number of patients by baseline characteristics by treatment group is given in Attached Table 1.

As seen from Attached Table 1, the treatment groups appeared similar with regard to all baseline characteristics with one exception. More placebo patients (84%) than famotidine 20-mg patients (76%) or famotidine 10-mg patients (74%) reported that they frequently experienced more than 1 episode of heartburn in a day.

### 2.2.2.4 Sponsor's Analysis of Primary Efficacy Variable

The primary efficacy parameter was the peak heartburn severity during the 3 hours following the start of the provocative meal. Peak heartburn severity in the 3 hours following the start of the provocative meal was analyzed using logistic regression models for ordered categorical data. The results for the analysis of primary efficacy parameter are given below.

Peak Heartburn Severity During the 3 Hours Postmeal  
All-Patients-Treated Approach (N=794)

	Famotidine 20 mg (n=261)	Famotidine 10 mg (n=271)	Placebo (n=262)
	n (cum %)	n (cum %)	n (cum %)
None	28 (10.7)	21 (7.7)	11 (4.2)
Mild	67 (36.4)	57 (28.8)	47 (22.1)
Moderate	71 (63.6)	81 (58.7)	89 (56.1)
Severe	95 (100.0)	112 (100.0)	115 (100.0)

Data Source: [4.9]

Treatment Comparison	Model-Adjusted Odds-Ratio (95% CI)	Chi-Square	p-Value
Famotidine 20 mg vs. Famotidine 10 mg [P]	1.34 (0.98, 1.84)	3.42	0.064
Famotidine 20 mg vs. Placebo	1.73 (1.26, 2.39)	11.38	<0.001
Famotidine 10 mg vs. Placebo	1.29 (0.94, 1.77)	2.47	0.116

[P] = Primary treatment comparison.

Data Source: [4.9]

As seen from the table above, the difference between famotidine 20 mg and famotidine 10 mg was marginally significant. The difference between famotidine 20 and placebo was statistically significant. The famotidine 10 mg versus placebo difference was not statistically significant.

### 2.2.2.5 Sponsor's Analysis of Secondary Efficacy Variable

The secondary endpoints were the proportion of patient with no heartburn during the 3 hours following the start of the meal, mean heartburn severity during the 3 hours following the start of the meal, global assessment of efficacy at the end of the treatment period, and the proportion of patients who did not awaken with heartburn.

#### 2.2.2.5.1 Proportion of Patients Reporting No Heartburn During the 3 Hours Following the Start of the Meal

The results for the analysis of the proportion of patients reporting no heartburn during the 3-hour postmeal period are given below.

#### Proportion of Patients Reporting No Heartburn Symptoms During the 3 Hours Postmeal All-Patients-Treated Approach

Treatment Group	No Heartburn	vs. placebo p-value	vs. famotidine 10 mg p-value
Famotidine 20 mg	28/261 (11%)	0.004	0.241
Famotidine 10 mg	21/271 (8%)	0.070	
Placebo	11/262 (4%)		

Copied from Table 13

As seen from the table above, the difference between famotidine 10 mg and famotidine 20 mg was not statistically significant. Both famotidine groups had a greater percentage of patients with no heartburn compared to the placebo. The famotidine 20 mg versus placebo difference was statistically significant.

#### 2.2.2.5.2 Mean Heartburn Severity During the 3 Hours Following the Start of the Meal

The results for the analysis of mean heartburn severity during the 3-hour postmeal period are given below.

#### Mean Heartburn Severity During the 3 Hours Postmeal All-Patients-Treated Approach

Treatment Group	Mean (SE)	vs. placebo p-value	vs. famotidine 10 mg p-value
Famotidine 20 mg	1.20 (0.051)	<0.001	0.106
Famotidine 10 mg	1.32 (0.050)	0.044	
Placebo	1.46 (0.051)		

Copied from Table 14

As seen from the table above, the difference between famotidine 10 mg and famotidine 20 mg was not statistically significant. Patients receiving famotidine 20 mg experienced significantly less severe mean symptoms as compared to those receiving placebo.

### 2.2.2.5.3 Global Assessment of Efficacy Measured at the End of the Treatment Period

Global assessment of efficacy measured at the end of the treatment period was analyzed using logistic regression models. The results for the analysis of the global assessment of treatment efficacy measured the next morning at the end of the treatment period are given below.

Global Assessment of Efficacy  
All-Patients-Treated Approach (N=793)

	Famotidine 20 mg (n=261)	Famotidine 10 mg (n=270)	Placebo (n=262)
	n (cum %)	n (cum %)	n (cum %)
Excellent	37 (14.2)	28 (10.4)	16 (6.1)
Very Good	65 (39.1)	59 (32.2)	47 (24.0)
Good	44 (55.9)	40 (47.0)	40 (39.3)
Fair	21 (64.0)	34 (59.6)	33 (51.9)
Poor	94 (100.0)	109 (100.0)	126 (100.0)

Data Source: [4.9]

Treatment Comparison	Model-Adjusted Odds-Ratio (95% CI)	Chi-Square	p-Value
Proportion of Patients Reporting Good, Very Good, or Excellent			
Famotidine 20 mg vs. Famotidine 10 mg	1.44 (1.02, 2.04)	4.32	0.038
Famotidine 20 mg vs. Placebo	2.02 (1.42, 2.87)	15.15	<0.001
Famotidine 10 mg vs. Placebo	1.40 (0.99, 1.98)	3.52	0.061
All Categories			
Famotidine 20 mg vs. Famotidine 10 mg	1.33 (0.97, 1.80)	3.22	0.073
Famotidine 20 mg vs. Placebo	1.94 (1.41, 2.66)	16.90	<0.001
Famotidine 10 mg vs. Placebo	1.46 (1.07, 2.00)	5.65	0.017

Data Source: [4.9]

As seen from the table above, for the analyses across all categories of global assessment, the famotidine 20-mg vs. placebo comparison was statistically significant, but the famotidine 20-mg vs. famotidine 10-mg comparison was only marginally significant. The famotidine 10-mg vs. placebo comparison was statistically significant.

#### 2.2.2.5.4 Proportion of Patients Reporting No Awakening with Heartburn

The results for the analysis of the proportion of patients reporting no awakening with heartburn are given below.

#### Proportion of Patients Reporting No Awakenings with Heartburn All-Patients-Treated Approach

Treatment Group	No Heartburn	vs. placebo p-value	vs. famotidine 10 mg p-value
Famotidine 20 mg	156/261 (60%)	<0.001	0.505
Famotidine 10 mg	153/269 (57%)	0.001	
Placebo	113/262 (43%)		

Copied from Table 16

As seen from the table above, the famotidine 20-mg and famotidine 10-mg groups were similar with respect to this endpoint. Significantly greater proportions of patients in the famotidine 20-mg and 10-mg groups reported no awakenings with heartburn compared to the placebo group.

#### 2.2.2.6 Reviewer's Evaluation

##### 2.2.2.6.1 Reviewer's Comments on Sponsor's Analysis of Primary Efficacy Variable

###### 2.2.2.6.1.1 Comments on Statistical Method for Ordered Categorical Data

The sponsor performed ordered logistic regression method using the proportional odds model. The ordered logistic regression for ordered categorical data is a model approach. The model approach is commonly used for explorative analyses.

This reviewer performed an alternative analysis of peak heartburn severity during the 3 hours postmeal using Mantel-Haenszel method. Since the response levels for degree of peak heartburn severity during 3 hours postmeal might not be equally spaced, the modified ridit scores were used. The results of analyses are given below.

Study	Comparison	Sponsor's p-value	Reviewer's p-value
114	Famotidine 20 mg vs. Famotidine 10 mg	0.064	0.0836
	Famotidine 20 mg vs. Placebo	<0.001	0.0021
	Famotidine 10 mg vs. Placebo	0.116	0.1852

Compiled by the reviewer.

As seen from the table above, the p-values obtained by the sponsor using ordered logistic regression were similar to those obtained by this reviewer in terms of statistical significance.

### 2.2.2.6.1.2 Proportion of Patients Reporting None or Mild in the Peak Heartburn Severity

In the sponsor's proposed labeling for famotidine 20 mg, the sponsor combined "none" and "mild" in peak heartburn severity during the 3-hour post meal as the efficacy endpoint. This reviewer analyzed this efficacy endpoint: proportion of patients reporting none or mild in peak heartburn severity during the 3-hour post meal. The results are listed below.

#### Proportion of Patients Reporting None or Mild in the Peak Heartburn Severity During the 3 Hours Postmeal All-Patients-Treated Approach

Treatment Group	None or Mild in Peak Heartburn Severity	Vs. placebo p-value	vs. famotidine 10 mg p-value
Famotidine 20 mg	95/261 (36%)	0.0004	0.0646
Famotidine 10 mg	78/271 (29%)	0.0911	
Placebo	58/262 (22%)		

Complied by this reviewer.

p-values were obtained using Fisher's exact method.

As seen from the table above, the difference between famotidine 20 mg and famotidine 10 mg was marginally significant. The difference between famotidine 20 and placebo was statistically significant. The comparison of famotidine 10 mg versus placebo was not statistically significant.

### 2.2.2.6.1.3 Subgroup Analysis

This reviewer performed subgroup analyses of proportion of patients reporting none or mild in the peak heartburn severity during the 3 hours postmeal by race, gender and age. The results of subgroup analyses are given below.

#### Subgroup Analysis

Subgroup	famotidine 20 mg	famotidine 10 mg	Placebo
<b>Race</b>			
Caucasian	81/184 (44.0%)	64/187 (34.2%)	45/183 (24.6%)
Black	11/58 (19.0%)	8/62 (12.9%)	8/60 (13.3%)
Hispanic	3/17 (17.7%)	5/20 (25.0%)	5/18 (27.8%)
<b>Gender</b>			
Female	58/174 (33.3%)	48/184 (26.1%)	38/178 (21.4%)
Male	37/87 (42.5%)	30/87 (34.5%)	20/84 (23.8%)
<b>Age</b>			
≥65	3/13 (23.1%)	4/12 (33.3%)	1/11 (9.1%)
<65	92/248 (37.1%)	74/259 (28.6%)	57/251 (22.7%)

**P-value (Fisher's Exact Test)**

Subgroup	famotidine 20 mg vs. famotidine 10 mg	famotidine 20 mg vs. placebo	famotidine 10 mg vs. placebo
<b>Race</b>			
Caucasian	0.0562	0.0001	0.0523
Black	0.4553	0.4593	1.0000
Hispanic	0.7013	0.6906	1.0000
Breslow-Day Test	0.5585	0.1718	0.6141
<b>Gender</b>			
Female	0.1644	0.0122	0.3238
Male	0.3500	0.0101	0.1340
Breslow-Day Test	0.9845	0.5447	0.5398
<b>Age</b>			
≥65	0.6728	0.5963	0.3168
<65	0.0468	0.0006	0.1557
Breslow-Day Test	0.3223	0.7476	0.2726

Compiled by this reviewer.

Breslow-Day test is for testing homogeneity of odds ratio.

As seen from the table above, the comparison between famotidine 20 mg and placebo was statistically significant for Caucasian, females and males and aged <65. There was slight race by treatment effect for comparison between famotidine 20 mg and placebo (Breslow-Day  $p < 0.20$ ).

### 2.2.3 Protocol 117

#### 2.2.3.1 Study Design

This study was a multi-center (13 sites), randomized, double-blind, placebo-controlled study to evaluate the efficacy of famotidine 20 mg and famotidine 10 mg in preventing heartburn symptoms when administered ten minutes prior to provocative meal.

The design of this study was similar to that of protocol 114.

This study differed from the protocol 114 in the screening criteria used to select the population. Protocol 114 used a placebo-controlled, provocative meal to screen patients where only those patients experiencing severe symptoms during the 3-hour postmeal period were eligible for randomization. This study would screen patients using an observational baseline run-in week. Patients who treated at least 3 episodes during the run-in week with a least 1 of the episodes being severe would be eligible for randomization. This screening criterion would result in less severe patients than in protocol 114.

Secondary efficacy parameters included the proportion of patients who took rescue medication anytime during the study.

Patients would be randomized 2:2:1 to 1 of 3 treatment groups (famotidine 20 mg; famotidine 10 mg; placebo).

With 500 patients per active treatment groups, the power was at least 89% to detect a difference of 10% between famotidine 20 mg and famotidine 10 mg ( $\alpha=0.05$ , two tailed).

With 500 patients per active treatment groups and 250 patients in the placebo group, the power was at least 73% to detect a difference of 10% between active treatment and placebo ( $\alpha=0.05$ , two tailed).

### **2.2.3.2 Sponsor's Analysis**

Of a total of 1799 patients screened, 1229 patients were randomized into treatment phase (489 in famotidine 20 mg, 491 in famotidine 10 mg, 249 in placebo).

Two patients (1 in famotidine 10 mg and 1 in famotidine 20 mg) had heartburn at the time of dosing and were discontinued prior to meal. These two patients were excluded from the efficacy analyses but were included in the safety analyses.

328 patients (111 in famotidine 20 mg, 124 in famotidine 10 mg, and 93 in placebo) were considered "treatment failure" and were assigned the worst scores. One patient (famotidine 10 mg) who used rescue during the 3-hour postmeal period was assigned a score of Severe for all heartburn severity evaluation after the use of rescue. The remaining 327 patients who took rescue at any time after treatment were assigned a global assessment score of Poor and were counted as if they had awakened with heartburn.

### **2.2.3.3 Treatment Group Comparability**

A summary of the number of patients by baseline characteristics by treatment group is given in Attached Table 2.

As seen from Attached Table 2, the treatment groups appeared similar with regard to all baseline characteristics.

### **2.2.3.4 Sponsor's Analysis of Primary Efficacy Variable**

The primary efficacy parameter was the peak heartburn severity during the 3 hours following the start of the provocative meal. The results for the analysis of primary efficacy parameter are given below.

**Peak Heartburn Severity During the 3 Hours Postmeal  
All-Patients-Treated Approach (N=1227)**

	Famotidine 20 mg (n=488)		Famotidine 10 mg (n=490)		Placebo (n=249)	
	n	(cum %)	n	(cum %)	n	(cum %)
None	185	(37.9)	147	(30.0)	47	(18.9)
Mild	156	(69.9)	153	(61.2)	77	(49.8)
Moderate	93	(88.9)	126	(86.9)	77	(80.7)
Severe	54	(100.0)	64	(100.0)	48	(100.0)

Data Source: [4.9]

Treatment Comparison	Model-Adjusted Odds-Ratio (95% CI)	Chi-Square	p-Value
Famotidine 20 mg versus famotidine 10 mg [P]	1.44 (1.14, 1.81)	9.57	0.002
Famotidine 20 mg versus placebo	2.47 (1.86, 3.27)	39.55	<0.001
Famotidine 10 mg versus placebo	1.71 (1.30, 2.26)	14.45	<0.001

[P] = Primary treatment comparison.

Data Source: [4.9]

As seen from the table above, patients in the famotidine 20-mg group had significantly less severe peak heartburn symptoms than those in both the famotidine 10-mg and placebo group. The patients in the famotidine 10-mg group had significantly less severe peak heartburn symptoms than those in the placebo group.

### 2.2.3.5 Sponsor's Analysis of Secondary Efficacy Variable

The secondary endpoints were the proportion of patient with no heartburn during the 3 hours following the start of the meal, mean heartburn severity during the 3 hours following the start of the meal, global assessment of efficacy at the end of the treatment period, and the proportion of patients who did not awaken with heartburn.

#### 2.2.3.5.1 Proportion of Patients Reporting No Heartburn During the 3 Hours Following the Start of the Meal

The results for the analysis of the proportion of patients reporting no heartburn during the 3-hour postmeal period are given below.

**Proportion of Patients Reporting No Heartburn Symptoms  
During the 3 Hours Postmeal  
All-Patients-Treated Approach**

Treatment Group	No Heartburn	vs. placebo p-value	vs. famotidine 10 mg p-value
Famotidine 20 mg	185/488 (38%)	< 0.001	0.006
Famotidine 10 mg	147/490 (30%)	0.001	
Placebo	47/249 (19%)		

Copied from Table 15

As seen from the table above, there was a significantly greater percentage of patients with no heartburn in the famotidine 20-mg group than in both the famotidine 10-mg and the placebo groups. The famotidine 10-mg group had a significantly greater percentage of patients with no heartburn than placebo group.

**2.2.3.5.2 Mean Heartburn Severity During the 3 Hours Following the Start of the Meal**

The results for the analysis of mean heartburn severity during the 3-hour postmeal period are given below.

**Mean Heartburn Severity During the 3 Hours Postmeal  
All-Patients-Treated Approach (N=1227)**

Treatment Group	N	Mean (SE)	vs. placebo p-value	vs. famotidine 10 mg p-value
Famotidine 20 mg	488	0.53 (0.030)	<0.001	0.006
Famotidine 10 mg	490	0.65 (0.030)	0.007	
Placebo	249	0.78 (0.042)		

Copied from Table 16

As seen from the table above, the patients receiving famotidine 20 mg experienced significantly less severe mean heartburn symptoms as compared to patients receiving famotidine 10 mg and patients receiving placebo. Patients receiving famotidine 10 mg experienced significantly less severe mean heartburn symptoms as compared to patients receiving placebo.

**2.2.3.5.3 Global Assessment of Efficacy Measured at the End of the Treatment Period**

The results for the analysis of the global assessment of treatment efficacy measured the next morning at the end of the treatment period are given below.

Global Assessment of Efficacy  
All-Patients-Treated Approach (N=1223)

	Famotidine 20 mg (n=488)	Famotidine 10 mg (n=487)	Placebo (n=248)
	n (cum %)	n (cum %)	n (cum %)
Excellent	147 (30.1)	115 (23.6)	36 (14.5)
Very Good	126 (55.9)	125 (49.3)	54 (36.3)
Good	62 (68.6)	76 (64.9)	30 (48.4)
Fair	28 (74.4)	31 (71.3)	22 (57.3)
Poor	125 (100.0)	140 (100.0)	106 (100.0)

Data Source: [4.9]

Treatment Comparison	Model-Adjusted Odds-Ratio (95% CI)	Chi-Square	p-Value
Proportion of Patients Reporting Good, Very Good, or Excellent			
Famotidine 20 mg versus famotidine 10 mg	1.20 (0.91, 1.58)	1.70	0.192
Famotidine 20 mg versus placebo	2.45 (1.78, 3.38)	29.74	<0.001
Famotidine 10 mg versus placebo	2.04 (1.49, 2.81)	19.31	<0.001
All Categories			
Famotidine 20 mg versus famotidine 10 mg	1.30 (1.04, 1.63)	5.13	0.024
Famotidine 20 mg versus placebo	2.40 (1.81, 3.18)	37.34	<0.001
Famotidine 10 mg versus placebo	1.85 (1.40, 2.44)	18.55	<0.001

Data Source: [4.9]

As seen from the table above, based on the analysis across all categories of global assessment, famotidine 20-mg patients reported significantly more favorable global assessments compared to both famotidine 10-mg and placebo patients. Patients who received famotidine 10 mg reported significantly more favorable global assessments than patients who received placebo.

#### 2.2.3.5.4 Proportion of Patients Reporting No Awakening with Heartburn

The results for the analysis of the proportion of patients reporting no awakening with heartburn are given below.

**Proportion of Patients Reporting No Awakenings with Heartburn  
All-Patients-Treated Approach (N=1221)**

Treatment Group	No Heartburn	vs. placebo p-value	vs. famotidine 10 mg p-value
Famotidine 20 mg	339/485 (70%)	<0.001	0.641
Famotidine 10 mg	336/489 (69%)	<0.001	
Placebo	132/247 (53%)		

Copied from Table 18

As seen from the table above, the famotidine 20-mg and famotidine 10-mg groups were similar with respect to this endpoint. Significantly greater proportions of patients in the famotidine 20-mg and 10-mg groups reported no awakenings with heartburn compared to the placebo group.

#### 2.2.3.5.5 Proportion of Patients Using Rescue Medication During the Study

The results for the analysis of the proportion of patients using rescue medication are given below.

#### Proportion of Patients Using Rescue Medication During the Study All-Patients-Treated Approach (N=1227)

Treatment Group	Any Rescue	vs. placebo p-value	vs. famotidine 10 mg p-value
Famotidine 20 mg	111/488 (23%)	<0.001	0.323
Famotidine 10 mg	124/490 (25%)	<0.001	
Placebo	93/249 (37%)		

Copied from Table 18

As seen from the table above, the famotidine 20-mg and famotidine 10-mg groups were similar with respect to this endpoint. A significantly greater proportion of patients in the placebo group used rescue medication compared to patients in the famotidine 20-mg and famotidine 10-mg groups.

#### 2.2.3.6 Reviewer's Evaluation

##### 2.2.3.6.1 Reviewer's Comments on Sponsor's Analysis of Primary Efficacy Variable

###### 2.2.3.6.1.1 Comments on Statistical Method for Ordered Categorical Data

The sponsor performed ordered logistic regression method using the proportional odds model. The ordered logistic regression for ordered categorical data is a model approach. The model approach is commonly used for explorative analyses.

This reviewer performed an alternative analysis of peak heartburn severity during the 3 hours postmeal using Mantel-Haenszel method. Since the response levels for degree of peak heartburn severity during 3 hours postmeal might not be equally spaced, the modified ridit scores were used. The results of analyses are given below.

Study	Comparison	Sponsor's p-value	Reviewer's p-value
117	Famotidine 20 mg vs. Famotidine 10 mg	0.002	0.0029
	Famotidine 20 mg vs. Placebo	<0.001	<0.0001
	Famotidine 10 mg vs. Placebo	<0.001	0.0003

Compiled by this reviewer.

As seen from the table above, the p-values obtained by sponsor using ordered logistic regression were similar to those obtained by this reviewer in terms of statistical significance.

### 2.2.3.6.1.2 Proportion of Patients Reporting None or Mild in the Peak Heartburn Severity

In the sponsor's proposed labeling for famotidine 20 mg, the sponsor combined "none" and "mild" in peak heartburn severity during the 3-hour post meal as the efficacy endpoint. This reviewer analyzed this efficacy endpoint: proportion of patients reporting none or mild in peak heartburn severity during the 3-hour post meal. The results are listed below.

#### Proportion of Patients Reporting None or Mild in the Peak Heartburn Severity During the 3 Hours Postmeal All-Patients-Treated Approach

Treatment Group	None or Mild in Peak Heartburn Severity	vs. placebo p-value	vs. famotidine 10 mg p-value
Famotidine 20 mg	341/488 (70%)	<0.0001	0.0047
Famotidine 10 mg	300/490 (61%)	0.0036	
Placebo	124/249 (50%)		

Complied by this reviewer.

p-values were obtained using Fisher's exact method.

As seen from the table above, patients in the famotidine 20-mg group had significantly less severe peak heartburn symptoms than those in both the famotidine 10-mg and placebo group. The patients in the famotidine 10-mg group had significantly less severe peak heartburn symptoms than those in the placebo group.

### 2.2.3.6.1.3 Subgroup Analysis

This reviewer performed subgroup analyses of proportion of patients reporting none or mild in the peak heartburn severity during the 3 hours postmeal by race, gender and age. The results of subgroup analyses are given below.

#### Subgroup Analysis

Subgroup	famotidine 20 mg	famotidine 10 mg	Placebo
<b>Race</b>			
Caucasian	271/372 (72.9%)	235/366 (64.2%)	95/191 (50.0%)
Black	37/76 (48.7%)	35/80 (43.8%)	18/38 (47.4%)
Hispanic	33/39 (84.6%)	29/43 (67.4%)	10/17 (58.8%)
<b>Gender</b>			
Female	197/298 (66.1%)	165/291 (56.7%)	67/144 (46.5%)
Male	144/190 (75.8%)	135/199 (67.8%)	57/105 (54.3%)
<b>Age</b>			
≥65	30/38 (79.0%)	20/32 (62.5%)	7/12 (58.3%)
<65	311/450 (69.1%)	280/458 (61.1%)	117/237 (49.4%)

**P-value (Fisher's Exact Test)**

Subgroup	famotidine 20 mg vs. famotidine 10 mg	famotidine 20 mg vs. placebo	famotidine 10 mg vs. placebo
<b>Race</b>			
Caucasian	0.0139	<0.0001	0.0011
Black	0.6301	1.0000	0.8432
Hispanic	0.0790	0.0464	0.5596
Breslow-Day Test	0.4712	0.1025	0.2287
<b>Gender</b>			
Female	0.0222	0.0001	0.0524
Male	0.0915	0.0002	0.0243
Breslow-Day Test	0.9898	0.6248	0.6060
<b>Age</b>			
≥65	0.1847	0.25557	1.0000
<65	0.0123	<0.0001	0.0036
Breslow-Day Test	0.4098	0.8315	0.6676

Compiled by this reviewer.

Breslow-Day test is for testing homogeneity of odds ratio.

As seen from the table above, the comparison between famotidine 20 mg and placebo was statistically significant for Caucasian, females and males and aged <65. The comparison between famotidine 10 mg and placebo was statistically significant for Caucasian, female and aged <65. There was no treatment effect for Black for both comparisons between famotidine 20 mg and placebo and between famotidine 10 mg and placebo (Breslow-Day  $p < 0.20$  for famotidine 20 mg vs. placebo).

## 2.2.4 Protocol 128

### 2.2.4.1 Study Design

This study was a multi-center (15 sites), randomized, double-blind, placebo-controlled study to evaluate the efficacy of famotidine 20 mg and famotidine 10 mg in preventing heartburn symptoms when administered ten minutes prior to provocative meal.

This design of this study was similar to that of protocol 117.

Secondary efficacy parameters included the proportion of patients who took rescue medication during the 3 hours following the start of the meal. The proportion of patients who did not awaken with heartburn was not included as secondary efficacy parameter.

With 500 patients per active treatment groups, the power was at least 89% to detect a difference of 10% between famotidine 20 mg and famotidine 10 mg ( $\alpha = 0.05$ , two tailed).

With 500 patients per active treatment groups and 250 patients in the placebo group, the power was at least 73% to detect a difference of 10% between active treatment and placebo ( $\alpha=0.05$ , two tailed).

#### 2.2.4.2 Sponsor's Analysis

Of a total of 1923 patients screened, 1334 patients were randomized into treatment phase (532 in famotidine 20 mg, 537 in famotidine 10 mg, 265 in placebo).

Of 1334 patients randomized, 1330 completed the study (529 in famotidine 20 mg, 536 in famotidine 10 mg, 265 in placebo). Two patients (1 in famotidine 20 mg and 1 in placebo) were excluded from the all-patients-treated efficacy analysis but were included in the safety analysis.

#### 2.2.4.3 Treatment Group Comparability

A summary of the number of patients by baseline characteristics by treatment group is given in Attached Table 3.

As seen from Attached Table 3, the treatment groups appeared similar with regard to all baseline characteristics.

#### 2.2.4.4 Sponsor's Analysis of Primary Efficacy Variable

The primary efficacy parameter was the peak heartburn severity during the 3 hours following the start of the provocative meal. The results for the analysis of primary efficacy parameter are given below.

Peak Heartburn Severity During the 3 Hours Postmeal  
All-Patients-Treated Approach (N=1332)

	Famotidine 20 mg (n=531)	Famotidine 10 mg (n=537)	Placebo (n=264)
	n (cum %)	n (cum %)	n (cum %)
None	219 (41.2)	190 (35.4)	71 (26.9)
Mild	165 (72.3)	178 (68.5)	90 (61.0)
Moderate	98 (90.8)	112 (89.4)	65 (85.6)
Severe	49 (100.0)	57 (100.0)	38 (100.0)

Treatment Comparison	Model-Adjusted Odds-Ratio (95% CI)	Chi-Square	p-Value
Famotidine 20 mg versus famotidine 10 mg [P]	1.23 (0.99, 1.53)	3.38	0.066
Famotidine 20 mg versus placebo	1.79 (1.37, 2.35)	17.97	<0.001
Famotidine 10 mg versus placebo	1.46 (1.12, 1.91)	7.61	0.006

[P] = Primary treatment comparison.

Data Source: [4.9]

As seen from the table above, the difference between famotidine 20 mg and famotidine 10 mg was marginally significant. The patients in both the famotidine 20- and 10-mg groups has significantly less severe peak heartburn symptom than those in the placebo group.

#### 2.2.4.5 Sponsor's Analysis of Secondary Efficacy Variable

The secondary endpoints were the proportion of patient with no heartburn during the 3 hours following the start of the meal, mean heartburn severity during the 3 hours following the start of the meal, global assessment of efficacy at the end of the treatment period, and the proportion of patients who did not awaken with heartburn.

##### 2.2.4.5.1 Proportion of Patients Reporting No Heartburn During the 3 Hours Following the Start of the Meal

The results for the analysis of the proportion of patients reporting no heartburn during the 3-hour postmeal period are given below.

#### Proportion of Patients Reporting No Heartburn Symptoms During the 3 Hours Postmeal All-Patients-Treated Approach (N=1332)

Treatment Group	No Heartburn	vs. placebo p-value	vs. famotidine 10 mg p-value
Famotidine 20 mg	219/531 (41%)	< 0.001	0.047
Famotidine 10 mg	190/537 (35%)	0.017	
Placebo	71/264 (27%)		

Copied from Table 13

As seen from the table above, there was a significantly greater percentage of patients with no heartburn in the famotidine 20-mg group than in both the famotidine 10-mg and the placebo groups. The famotidine 10-mg group had a significantly greater percentage of patients with no heartburn than placebo group.

##### 2.2.4.5.2 Mean Heartburn Severity During the 3 Hours Following the Start of the Meal

The results for the analysis of mean heartburn severity during the 3-hour postmeal period are given below.

#### Mean Heartburn Severity During the 3 Hours Postmeal All-Patients-Treated Approach (N=1332)

Treatment Group	N	Mean (SE)	vs. placebo p-value	vs. famotidine 10 mg p-value
Famotidine 20 mg	531	0.49 (0.028)	0.003	0.509
Famotidine 10 mg	537	0.52 (0.028)	0.016	
Placebo	264	0.63 (0.039)		

Copied from Table 16

As seen from the table above, there was no statistically significant difference between famotidine 10 mg and famotidine 20 mg group. Patients receiving either famotidine 20 mg or famotidine 10 mg experienced significantly less severe mean heartburn symptoms as compared to patients receiving placebo.

#### 2.2.4.5.3 Global Assessment of Efficacy Measured at the End of the Treatment Period

The results for the analysis of the global assessment of treatment efficacy measured the next morning at the end of the treatment period are given below.

Global Assessment of Efficacy  
All-Patients-Treated Approach (N=1330)

	Famotidine 20 mg (n=530)		Famotidine 10 mg (n=536)		Placebo (n=264)	
	n	(cum %)	n	(cum %)	n	(cum %)
Excellent	176	(33.2)	181	(33.8)	57	(21.6)
Very Good	160	(63.4)	142	(60.3)	66	(46.6)
Good	96	(81.5)	101	(79.1)	57	(68.2)
Fair	73	(95.3)	68	(91.8)	52	(87.9)
Poor	25	(100.0)	44	(100.0)	32	(100.0)

Treatment Comparison	Model-Adjusted Odds-Ratio (95% CI)	Chi-Square	p-Value
Proportion of Patients Reporting Good, Very Good, or Excellent			
Famotidine 20 mg versus famotidine 10 mg	1.17 (0.86, 1.58)	0.97	0.324
Famotidine 20 mg versus placebo	2.07 (1.47, 2.91)	17.24	<0.001
Famotidine 10 mg versus placebo	1.77 (1.27, 2.48)	11.17	<0.001
All Categories			
Famotidine 20 mg versus famotidine 10 mg	1.08 (0.87, 1.35)	0.52	0.471
Famotidine 20 mg versus placebo	1.96 (1.50, 2.55)	24.48	<0.001
Famotidine 10 mg versus placebo	1.81 (1.39, 2.35)	19.17	<0.001

Data Source: [4.9]

As seen from the table above, the difference between famotidine 20 mg and famotidine 10 mg was not statistically significant. Both famotidine 20 mg and famotidine 10 mg patients reported significantly more favorable global assessment compared to placebo patients.

#### 2.2.4.6 Reviewer's Evaluation

##### 2.2.4.6.1 Reviewer's Comments on Sponsor's Analysis of Primary Efficacy Variable

###### 2.2.4.6.1.1 Comments on Statistical Method for Ordered Categorical Data

The sponsor performed ordered logistic regression method using the proportional odds model. The ordered logistic regression for ordered categorical data is a model approach. The model approach is commonly used for explorative analyses.

This reviewer performed an alternative analysis of peak heartburn severity during the 3 hours postmeal using Mantel-Haenszel method. Since the response levels for degree of

peak heartburn severity during 3 hours postmeal might are not be equally space, the modified ridit scores were used. The results of analyses are given below.

Study	Comparison	Sponsor's p-value	Reviewer's p-value
	Famotidine 20 mg vs. Famotidine 10 mg	0.066	0.0529
	Famotidine 20 mg vs. Placebo	<0.001	<0.0001
	Famotidine 10 mg vs. Placebo	0.006	0.0077

Complied by this reviewer.

As seen from the table above, the p-values obtained by sponsor using ordered logistic regression were similar to those obtained by this reviewer in term of significance.

#### **2.2.4.6.1.2 Proportion of Patients Reporting None or Mild in the Peak Heartburn Severity**

In the sponsor's proposed labeling for famotidine 20 mg, the sponsor combined "none" and "mild" in peak heartburn severity during the 3-hour post meal as the efficacy endpoint. This reviewer analyzed this efficacy endpoint: proportion of patients reporting none or mild in peak heartburn severity during the 3-hour post meal. The results are listed below.

#### **Proportion of Patients Reporting None or Mild in the Peak Heartburn Severity During the 3 Hours Postmeal All-Patients-Treated Approach**

Treatment Group	None or Mild in Peak Heartburn Severity	vs. placebo p-value	vs. famotidine 10 mg p-value
Famotidine 20 mg	384/531 (72%)	0.0015	0.1805
Famotidine 10 mg	368/537 (69%)	0.0390	
Placebo	161/264 (61%)		

Complied by this reviewer.

p-values were obtained using Fisher's exact method.

As seen from the table above, the difference between famotidine 20 mg and famotidine 10 mg was not statistically significant. The patients in famotidine 20 have significantly less severe peak heartburn symptom than those in the placebo group.

#### **2.2.4.6.1.3 Subgroup Analysis**

This reviewer performed subgroup analyses of proportion of patients reporting none or mild in the peak heartburn severity during the 3 hours postmeal by race, gender and age. The results of subgroup analyses are given below.

### Subgroup Analysis

Subgroup	famotidine 20 mg	famotidine 10 mg	Placebo
<b>Race</b>			
Caucasian	322/422 (76.3%)	315/442 (71.3%)	116/198 (58.6%)
Black	53/98 (54.1%)	42/82 (51.2%)	38/55 (69.1%)
Hispanic	7/8 (87.5%)	8/9 (88.9%)	6/9 (66.7%)
<b>Gender</b>			
Female	231/344 (67.2%)	229/348 (65.8%)	95/164 (57.9%)
Male	153/187 (81.8%)	139/189 (73.5%)	66/100 (66.0%)
<b>Age</b>			
≥65	28/40 (70.0%)	29/39 (74.4%)	5/13 (38.5%)
<65	356/491 (72.5%)	339/498 (68.1%)	156/251 (62.2%)

### P-value (Fisher's Exact Test)

Subgroup	famotidine 20 mg vs. famotidine 10 mg	famotidine 20 mg vs. placebo	famotidine 10 mg vs. placebo
<b>Race</b>			
Caucasian	0.1044	<0.0001	0.0019
Black	0.7649	0.0865	0.0515
Hispanic	1.0000	0.5765	0.5765
Breslow-Day Test	0.8845	0.0009	0.0032
<b>Gender</b>			
Female	0.7475	0.0479	0.0950
Male	0.0633	0.0035	0.2200
Breslow-Day Test	0.1576	0.1954	0.9414
<b>Age</b>			
≥65	0.8027	0.0541	0.0402
<65	0.1439	0.0044	0.1203
Breslow-Day Test	0.4094	0.2144	0.0616

Compiled by this reviewer.

Breslow-Day test is for testing homogeneity of odds ratio.

As seen from the table above, the comparison between famotidine 20 mg and placebo was statistically significant for Caucasian, females and males, and aged ≥65 and aged <65. But, race by treatment effect was statistically significant for comparisons between famotidine 20 mg and placebo and between famotidine 10 mg and placebo (Breslow-Day  $p < 0.20$ ). There was no treatment effect for Black; the placebo rate was higher than either famotidine 10 mg or famotidine 20 mg.

### 2.2.5 Overall Summary

All three studies (114, 117 and 128) showed that famotidine 20 mg was superior to placebo in terms of peak heartburn severity during the 3 hours postmeal. Furthermore, study 117

showed that famotidine 20 mg was statistically significant less severe peak heartburn symptoms than famotidine 10 mg. Study 128 also showed that famotidine 20 mg was marginally significant better than famotidine 10 mg.

Based on this reviewer's subgroup analysis for race, it was found that the statistically significant race by treatment interaction effect was observed in all three studies (114, 117 and 128) (Breslow-Day p-value <0.20). In particular, study 128 revealed that there was no treatment effect for Black; the placebo rate was higher than either famotidine 10 mg or famotidine 20 mg.

## **2.3 Treatment of Heartburn**

### **2.3.1 Study Design for Protocols 017 and 019**

Study 017 was a two phase placebo-control, double-blind, multi-center, dose ranging, parallel design comparing the efficacy and tolerability of antacid, famotidine 5 mg, 10 mg, and 20 mg versus placebo in the treatment of symptoms of upper gastrointestinal (UGI) discomfort.

Study 019 was a two phase placebo-control, double-blind, multi-center, dose ranging, parallel design comparing the efficacy and tolerability of antacid, famotidine 10 mg, and 20 mg versus placebo in the treatment of symptoms of upper gastrointestinal (UGI) discomfort.

After initial screening by history, physical exam and laboratory test, patients entered a one-week single-blind (baseline) screening phase, followed by a 4-week randomization double-blind treatment phase. The single-blind phase was designed to familiarize patients with diary cards, medications and to assure that patients had heartburn relieved by self-medication with antacid three or more times per week.

Only patients who experienced, in the single-blind screening phase, at least three episodes of heartburn that were improved within an hour by self medication with single-blind antacid and had satisfactorily completed their diary cards were allowed to enter into the randomization double-blind treatment phase. Thus, only antacid responders were randomized into the double-blind treatment phase of the study.

Patients who qualified for the treatment phase were randomized into one of five treatment groups: placebo, famotidine 5 mg, famotidine 10 mg, famotidine 20 mg, and antacid (Study 017) or into four treatment groups: placebo, famotidine 10 mg, famotidine 20 mg, and antacid (Study 019).

Patients evaluations included diary assessments (by patient-episode) for UGI discomfort symptoms on a 4-point scale (mild, moderate, severe, very severe), patient global evaluations (by patient-episode) on a 5-point scale (excellent, good, fair, poor, none) prior to rescue medication, global evaluations at the end of the 4-week double-blind treatment phase, clinical lab tests and physical examinations.

Efficacy variable was patient's response to treatment at hourly intervals for a total of 3 hours in Study 017 and for a total of 5 hours in Study 019 using a 4-point scale: completely relieved, better, unchanged, and worse.

The primary efficacy endpoints were:

1. Global Evaluation: Patients globally assessed their response to treatment by answering the question "how did heartburn respond to test medication?" at the end of the 4-week double-blind treatment phase on a 5-point scale: excellent, good, fair, poor, and none.
2. The Number of Heartburn Episodes: Patients were allowed to self medicate for heartburn up to twice daily. The number of heartburn episodes recorded and/or treated was analyzed to determine if active treatment reduced the total number of heartburn episodes during the 4-week double-blind treatment phase.
3. Proportion of Heartburn Episodes Completely Relieved: An episode was described as "completely relieved" if it was relieved within one hour of the first test medication or the patient indicated in the diary card that a successful relief occurred after one hour and no backup medication was used.
4. Proportion of Heartburn Episodes Requiring Rescue (Backup) Medication: Patients were instructed to take backup medication (an open-label antacid) if heartburn persisted one hour after a single dose of the test medication.
5. Proportion of Heartburn Episodes Requiring Re-medication: If heartburn persisted 3 hours after a dose of test medication, patients were permitted to take an additional dose of test medication.
6. Time to Relief of First Episode: For this primary endpoint, "relief" was defined as a successfully treated episode, i.e., a response of "completely relieved" at one or two doses without the use of backup medication.

### **2.3.2 Sponsor's Analysis of Primary Efficacy Variable in Original DNA**

The Statistical Review and Evaluation for sponsor's analysis of primary efficacy variable in original DNA was documented in December 16, 1993.

In the statistical review, it was stated that "there are problems with the sponsor's methods of analysis for the efficacy data of the proportion of episodes and time to relief of first episode endpoints. There is also a potentially confounding problem with the global data analysis."

Furthermore, it was commented for proportion of heartburn episodes completely relieved that "These proportions were analyzed in a way as if the episodes were randomized and not the patients. An appropriate analysis would be one that is based on the randomization patients and not the patient-episodes. This is because within patient episodes for the same

patients are expected to be correlated. Any statistical analysis which ignores this correlation structure would not be correct; it will artificially increase the power of the test.”

### **2.3.3. Sponsor’s Supplemental Analyses**

The sponsor performed some supplemental analyses to support a treatment claim for nonprescription famotidine 20 mg. Some of these analyses had previously been performed by the sponsor using different statistical software and had been submitted during FDA review of the original NDA.

#### **2.3.3.1 Key Efficacy Results Presented in the Original NDA**

The patients in both studies provided data on self-treatment of about 23,000 heartburn episode. Following dosing, each heartburn episode was evaluated hourly for a total of 3 hours for Study 017 and for a total of 5 hours for Study 019, using a 4-point scale: completely relieved, better, unchanged, and worse. The proportion of episodes completely relieved during the entire evaluation period was analyzed using a logistic regression model. The analysis did not take into account the actual time of complete relief for each episode, and did not account for the fact that individual patients treated multiple heartburn episodes.

The results for Study 017, based on the proportion of each patient’s episodes that were completely relieved during the 3-hour evaluation period, demonstrated a significant advantage of famotidine 10 mg and 20 mg compared to placebo. The results for Study 019, based on a 5-hour evaluation period, did not show a significant difference between placebo and famotidine (as seen from Table in Section 2).

The difference in results between Studies 017 and 019 could be attributed to the difference in the length of the evaluation period. In Study 019, relief measurements were extended to include Hours 4 and 5 after each dose of test medication in an attempt to obtain preliminary information on recurrence of heartburn.

Although the proportion of episodes relieved increased over time as would be expected, the differences were smaller with respect to placebo at later time points due to increasing relief in the placebo group. This increase in relief with placebo treatment is consistent with the clinical observation that intermittent heartburn episodes are self limited (i.e., given sufficient time, episodes resolved spontaneously).

So, based on the analyses and endpoints presented in the original NDA, it was concluded for both studies that there was no consistent evidence of a dose response for famotidine.

#### **2.3.3.2 Key Efficacy Results Presented During FDA Reviewing of the Original NDA**

The data from Study 017 and Study 019 were analyzed comparably by examining the proportion of episodes relieved at 3 hours and at 1, 2, and 3 hours. These analyses demonstrated statistically significant advantages versus placebo favoring famotidine in

both Study 017 and Study 019 (see Attachment 4). Therefore, where heartburn relief was measured similarly, the results were comparable.

Additional statistical analyses were completed as requested by the FDA during the FDA 1994 review of the NDA to support approval of the treatment claim for PEPCID™ AC FCT (see Attachment 5). The statistical method used (generalized estimating equations) was not commonly used at the time the NDA was submitted, but is now more widely accepted. These analyses used the maximum amount of information available in the data, and thus increased the precision of measurement. This was achieved by employing a definition of success that takes time to complete relief into account explicitly, and by accounting for the fact that individual patients treated multiple heartburn episodes. The results of these post-hoc analyses further strengthen the favorable results seen in the analyses described above.

The above analyses led to the 1995 approval of the treatment of heartburn indication for nonprescription famotidine 10 mg. One consideration for recommending 10 mg for the over-the-counter (OTC) famotidine dose was that Studies 017 and 019 document that 10 mg effectively treats heartburn over a 3-hour evaluation period, and that famotidine 20 mg did not seem to offer a consistent benefit over the 10-mg dose. A second consideration was that the studies submitted to support a prevention of heartburn indication also did not show a consistent benefit of famotidine 20 mg over the 10-mg dose. Finally, the recommended dose of 10 mg is lower than the lowest prescription dose (20 mg), and represented a more conservative approach when considering initial OTC status for this class of antisecretory agents.

### **2.3.3.3 Rationale for Efficacy Analyses Presented in Current Statistical Report**

Studies 017 and 019 as presented in the original NDA focused on differences for famotidine 10 mg versus placebo and famotidine 20 mg versus placebo. Both studies show statistically significant differences for 10 mg and 20 mg versus placebo. These studies were not designed or powered to address a comparison among the various famotidine doses.

#### **2.3.3.3.1 Proportion of Heartburn Episodes Completely Relieved Within 1 Hour of Dosing**

The results for the analysis of complete relief within 1 hour of dosing are given below. Only the famotidine 20-mg, famotidine 10-mg, and placebo treatment comparisons are presented.

Complete Relief Within 1 Hour of Dosing—  
Efficacy Population (Protocol 017, N=552)

Treatment Group	N	Total Heartburn Episodes	Model-Adjusted Probability of Complete Relief Within 1 Hour
Famotidine 20 mg	113	2664	0.379
Famotidine 10 mg	109	2642	0.344
Famotidine 5 mg	110	2612	0.307
Antacid	112	2559	0.296
Placebo	108	2534	0.235

N = Number of patients.

Data Source: [4.3.3]

Treatment Comparison	Model-Adjusted Odds-Ratio (95% CI)	Chi-Square	p-Value
Famotidine 20 mg versus placebo	1.98 (1.38, 2.86)	13.49	<0.001
Famotidine 10 mg versus placebo	1.70 (1.18, 2.45)	8.28	0.004
Famotidine 20 mg versus famotidine 10 mg	1.17 (0.82, 1.67)	0.71	0.400

Data Source: [4.3.3]

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Complete Relief Within 1 Hour of Dosing—  
Efficacy Population (Protocol 019, N=500)

Treatment Group	N	Total Heartburn Episodes	Model-Adjusted Probability of Complete Relief Within 1 Hour
Famotidine 20 mg	129	2512	0.362
Famotidine 10 mg	122	2364	0.325
Antacid	121	2456	0.301
Placebo	128	2619	0.217
N = Number of patients.			

Data Source: [4.6.3]

Treatment Comparison	Model-Adjusted Odds-Ratio (95% CI)	Chi-Square	p-Value
Famotidine 20 mg versus placebo	2.05 (1.48, 2.85)	18.36	<0.001
Famotidine 10 mg versus placebo	1.73 (1.26, 2.38)	11.58	<0.001
Famotidine 20 mg versus famotidine 10 mg	1.18 (0.85, 1.65)	0.97	0.325

Data Source: [4.6.3]

As seen from tables above, for both studies, the patients in both the famotidine 20-mg and 10-mg groups had a significantly greater probability of achieving complete relief within 1 hour of dosing than the patients in the placebo group.

For both Studies 017 and 019, the patients in the famotidine 20-mg group had a numerically greater probability of complete relief within 1 hour (0.379 and 0.362, respectively) than the patients in the famotidine 10-mg group (0.344 and 0.325, respectively). These probabilities represent the proportion of episodes, adjusted for the model, that are completely relieved within 1 hour.

The odds-ratios for Study 017 indicate that famotidine 20-mg patients were 1.17 and 1.98 times more likely to report complete relief within 1 hour of dosing than famotidine 10-mg and placebo patients, respectively. For Protocol 019, the odds-ratios indicate that famotidine 20-mg patients were 1.18 and 2.05 times more likely to report complete relief within 1 hour of dosing than famotidine 10-mg and placebo patients, respectively.

This efficacy results demonstrate evidence of a numerical trend for 20 mg versus 10 mg at the early time points, e.g., 1 hour.

### 2.3.3.3.2 Proportion of Heartburn Episodes Completely Relieved Within 3 Hour of Dosing

Per this reviewer's request, the sponsor provided the results for the analysis of complete relief within 3-hour of dosing. The results are given below. Only the famotidine 20-mg, famotidine 10-mg, and placebo treatment comparisons are presented.

Complete Relief Within 3 Hours of Dosing

Protocol 017, N=552

Treatment Group	N	Total Heartburn Episodes	Model-Adjusted Probability of Complete Relief Within 3 Hours
Famotidine 20 mg	113	2664	0.604
Famotidine 10 mg	109	2642	0.584
Famotidine 5 mg	110	2612	0.521
Antacid	112	2559	0.535
Placebo	108	2534	0.409

N = Number of patients.

Treatment Comparison	Model-Adjusted Odds-Ratio (95% CI)	Chi-Square	p-Value
Famotidine 20 mg vs. placebo	2.21 (1.59, 3.07)	22.17	<b>&lt;0.001</b>
Famotidine 10 mg vs. placebo	2.03 (1.48, 2.77)	19.63	<b>&lt;0.001</b>
Famotidine 20 mg vs. famotidine 10 mg	1.09 (0.77, 1.53)	0.24	0.625

Statistically significant differences ( $p \leq 0.050$ ) are indicated in **bold**.

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**Protocol 019, N=498**

Treatment Group	N	Total Heartburn Episodes	Model-Adjusted Probability of Complete Relief Within 3 Hours
Famotidine 20 mg	129	2512	0.592
Famotidine 10 mg	122	2364	0.594
Antacid	121	2456	0.589
Placebo	128	2619	0.502

N = Number of patients.

Treatment Comparison	Model-Adjusted Odds-Ratio (95% CI)	Chi-Square	p-Value
Famotidine 20 mg vs. placebo	1.44 (1.06, 1.94)	5.61	<b>0.018</b>
Famotidine 10 mg vs. placebo	1.45 (1.07, 1.96)	5.74	<b>0.017</b>
Famotidine 20 mg vs. famotidine 10 mg	0.99 (0.73, 1.36)	0.00	0.965

Statistically significant differences ( $p \leq 0.050$ ) are indicated in **bold**.

As seen from tables above, for both Study 017 and 019, the patients in both the famotidine 20-mg and 10-mg groups had a significantly greater probability of achieving complete relief within 3 hours of dosing than the patients in the placebo group.

For Study 017 the patients in the famotidine 20-mg group had a slightly numerically greater probability of complete relief within 3 hours (0.604) than the patients in the famotidine 10-mg group (0.584). For Study 019 the patients in the famotidine 20-mg group had about the same probability of complete relief within 3 hours (0.592) with the patients in the famotidine 10-mg group (0.594). These probabilities represent the proportion of episodes, adjusted for the model, that are completely relieved within 3 hours.

The odds-ratios for Study 017 indicate that famotidine 20-mg patients were 1.09 and 2.21 times more likely to report complete relief within 3 hour of dosing than famotidine 10-mg and placebo patients, respectively. For Protocol 019, the odds- ratios indicate that famotidine 20-mg patients were 0.99 and 1.44 times more likely to report complete relief within 3 hour of dosing than famotidine 10-mg and placebo patients, respectively.

These efficacy results demonstrate evidence of a slightly numerical trend for 20 mg versus 10 mg at the time point of 3 hour for Study 017. But, no numerical trend in favor of 20 mg vs. 10 mg was observed in the Study 019.

### **2.3.4 Reviewer's Evaluation**

#### **2.3.4.1 Reviewer's Comments on Sponsor's Analyses for Origin NDA**

The Statistical Review and Evaluation dated December 16, 1993 stated in the overall conclusion, the global efficacy data of the two trials (protocol #017 and #019) indicated effectiveness of famotidine 10 mg and 20 mg for OTC use. However, the data should be reanalyzed adjusting for total antacid usage to resolve the confounding issues of concomitant antacid usage. There was a lack of consistency of results in these two trials for other endpoints:

1. For the first episode endpoint, famotidine 20 mg was shown effective only in study protocol #019 while famotidine 10 mg indicated borderline effectiveness only in study protocol #017.
2. For the proportion of episodes, the effectiveness of famotidine was shown from study protocol #017 only. Study protocol #019 did not support the effectiveness either famotidine 10 mg or 20 mg.

#### **2.3.4.2 Reviewer's Comments on Sponsor's Supplemental Analyses**

The sponsor's analyses were post-hoc re-analyses. Some new analysis results of the efficacy data were based on retrospectively defined endpoints and analyses.

The results these analyses were reviewed and documented in Statistical Review and Evaluation dated July 5, 1994, July 15, 1994 and November 29, 1994.

The overall conclusions from these above listed statistical reviews were:

From the statistical review dated July 5, 1994,

- 1) The efficacy data from protocol #017 suggest effectiveness of famotidine 10 mg and 20 mg with respect to the proportion of episode completely relieved and requiring backup medication. But this effectiveness is not replicated in protocol #019.
- 2) The efficacy data from protocol #019 suggest efficacy of famotidine 20 mg with respect to global evaluations. Again, this effectiveness is not replicated in protocol #017.
- 3) There is a lack of consistency of results in these two studies across endpoints, Of the three (hard) primary endpoints, time-to-relief of first episodes, proportion of episodes completely relieved and global, none was shown effective in both studies.
- 4) The global and significance pattern adjustment procedures that are being suggested by the sponsor for the adjustment of multiplicity are inappropriate in the current setting.

From the statistical reviews dated July 15, 1994 and November 29, 1994,

The efficacy data in study #19 do not provide adequate support for famotidine effectiveness for the treatment of intermittent heartburn for the following reasons:

- a. the reported effectiveness results for study #19 regarding the protocol and post-hoc defined primary endpoint proportion of patient-episodes completely relieved is method dependent and reanalysis driven;
- b. the efficacy results for study #019 regard the protocol defined primary endpoint time-to-relief of first episode don not replicated the effectiveness results seen in study #17;
- c. neither study efficacy data show convincing evidence of famotidine effectiveness regarding the protocol defined primary endpoint patient global evaluations.

From the reviewer's recommendation is that the sponsor should conduct another study to provide adequate support for the effectiveness results seen in study #17 regarding the two major primary endpoints: time-to-relief of first patient-episode and the proportion of patient-episodes completely relieved.

### **2.3.4.3 Reviewer's Comments on Efficacy Analyses Presented in Current Statistical Report**

The sponsor's analyses presented in current statistical report were post-hoc re-analyses. These analysis results of the efficacy data were based on retrospectively defined endpoints and analyses. The analyses was performed using GEE (Generalized Estimating Equations) method adjusted for study site, average heartburn severity during baseline week, number of heartburn episodes during double-blind phase.

#### **2.3.4.3.1 Proportion of Heartburn Episodes Completely Relieved Within 1 Hour of Dosing**

This reviewer ran SAS programs provided by the sponsor to reproduce the sponsor's results. The results for Study 017 were reproduced. The results for Study 019 were similar to those reported by the application.

Score statistics for Type 3 GEE Analysis for Studies 017 and 019 are given below.

Score Statistics For Type 3 GEE Analysis (Study 017)

Source	DF	Chi-Square	Pr > ChiSq
STUDY	28	58.30	0.0007
BLAVESEV	1	50.09	<.0001
TRTDEPS	1	4.93	0.0264
TRT	4	14.88	0.0049

Score Statistics for Type 3 GEE Analysis (Study 019)

Source	DF	Chi-Square	Pr > ChiSq
STUDY	22	51.67	0.0003
BLAVESEV	1	21.19	<.0001
TRTDEPS	1	0.32	0.5702
TRT	3	20.92	0.0001

As seen from the table above, study site, baseline heartburn severity, treatment effects were statistically significant.

### 2.3.4.3.2 Proportion of Heartburn Episodes Completely Relieved Within 3 Hour of Dosing

This reviewer ran SAS programs provided by the sponsor to reproduce the sponsor's results. The results for Study 017 were reproduced. The results for Study 019 gave similar results with slightly large p-values (0.0245 vs. 0.018 for the comparison between famotidine 20 mg and placebo; 0.0186 vs. 0.017 for the comparison between famotidine 10 mg and placebo). The lower bound of 95% confidence interval of odds-ratio between famotidine 20 mg and placebo and between famotidine 10 mg and placebo was 1.0456 and 1.0618 for studies 017 and 019, respectively. These lower bounds slightly greater than 1.0 suggest the benefit of either famotidine 10 or famotidine 20 mg over placebo is moderate. It re-confirmed the finding stated "very small numerical advantages in favor of famotidine regarding the proportion of patient-episodes completed relieved within three hours of treatment medication. The treatment differences range from 3% to 4% for protocol #019" in Statistical Review and Evaluation (Addendum) dated May 13, 1994.

Score statistics for Type 3 GEE Analysis for Studies 017 and 019 are given below

Score Statistics For Type 3 GEE Analysis (Study 017)

Source	DF	Chi-Square	Pr > ChiSq
STUDY	28	32.16	0.2681
BLAVESEV	1	37.39	<.0001
TRTDEPS	1	0.21	0.6501
TRT	4	26.14	<.0001

Score Statistics For Type 3 GEE Analysis (Study 019)

Source	DF	Chi-Square	Pr > ChiSq
STUDY	22	29.49	0.1315
TRTDEPS	1	5.24	0.0220
BLAVESEV	1	21.67	<.0001
TRT	3	8.24	0.0413

As seen from the table above, baseline heartburn severity effect was statistically significant. Treatment effect was highly statistically significant for Study 017 but treatment effect was just statistically significant for Study 019. However, if study site was not included in the model, p-value for treatment effect would 0.0537 as seen table below.

Score Statistics For Type 3 GEE Analysis (Study0 19)

Source	DF	Chi-Square	Pr > ChiSq
TRTDEPS	1	4.32	0.0377
BLAVESEV	1	24.69	<.0001
TRT	3	7.65	0.0537

P-values for comparisons between famotidine 20 and placebo and between famotidine 10 mg and placebo would be 0.0314 and 0.0277, respectively. Assuming the primary analyses were comparisons between famotidine 10 mg vs. placebo and between famotidine 20 mg vs. placebo, both famotidine 10 mg and famotidine 20 mg are statistically significant from placebo by Hochberg's method for multiple comparison, However, both famotidine 10 mg and famotidine 20 mg are not statistically significant from placebo by either Bonferroni or Holm methods for adjusting for multiple comparisons.

So, the reported effectiveness results for study #19 in the current statistical report regarding protocol and post-hoc defined primary endpoint proportion of patient-episodes completely relieved is method dependent and reanalysis driven.

### 2.3.5 Reviewer's Overall Summary and Recommendation

In General, the sponsor's analyses were post-hoc re-analyses. Some new analysis results of the efficacy data were based on retrospectively defined endpoints and analyses. These analyses were based on the efficacy data that was used to approve famotidine 10 mg in 1994.

The efficacy data in Study 019 do not provide adequate support for famotidine effectiveness for the treatment of intermittent heartburn. The reported effectiveness results for study #19 regarding the protocol and post-hoc defined primary endpoint proportion of patient-episodes completely relieved is method dependent and reanalysis driven.

From the reviewer's recommendation is that the sponsor should conduct a new study for famotidine 20 mg to provide adequate support for the effectiveness results seen in study #17 regarding the primary endpoint: proportion of patient-episodes completely relieved.

## 3. Overall Summary and Recommendation

### 3.1 Prevention of Heartburn

All three studies (114, 117 and 128) showed that famotidine 20 mg was superior to placebo in terms of peak heartburn severity during the 3 hours postmeal. Furthermore, study 117

showed that famotidine 20 mg was statistically significant less severe peak heartburn symptoms than famotidine 10 mg. Study 128 also showed that famotidine 20 mg was marginally significant better than famotidine 10 mg.

Based on this reviewer's subgroup analysis for race, it was found that the statistically significant race by treatment interaction effect was observed in all three studies (114, 117 and 128) (Breslow-Day p-value <0.20). In particular, study 128 revealed that there was no treatment effect for Black; the placebo rate was higher than either famotidine 10 mg or famotidine 20 mg.

### **3.1.1 Reviewer's Comments on Sponsor's Proposed Labeling**

The sponsor's proposed graphs for prevention are reasonable. There are from combining "none" and "mild" in peak heartburn severity during the 3-hour post meal from studies 117 and 128. Both studies were 10 minutes prior to provocative meal. The title should be included "10 minutes." word similar to the original label for 10 mg. The sponsor's rationale to remove "15 to 60 minutes before" from the 10 mg labeling was based on the results from Study 137. But, study 137 was a pilot study and was not a confirmatory study. The study population was meal and was not patient. The graphs were not from study 137 but were from studies 117 and 128.

### **3.2 Treatment of Heartburn**

In General, the sponsor's analyses were post-hoc re-analyses. Some new analysis results of the efficacy data were based on retrospectively defined endpoints and analyses. These analyses were based on the efficacy data that was used to approve famotidine 10 mg in 1994.

The efficacy data in Study 019 do not provide adequate support for famotidine effectiveness for the treatment of intermittent heartburn. The reported effectiveness results for study #19 regarding the protocol and post-hoc defined primary endpoint proportion of patient-episodes completely relieved is method dependent and reanalysis driven.

From the reviewer's recommendation is that the sponsor should conduct a new study for famotidine 20 mg to provide adequate support for the effectiveness results seen in study 017 regarding the primary endpoint: proportion of patient-episodes completely relieved.

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Table 1 Baseline Patient Characteristic by Treatment Group --- Protocol 114  
All-Patients-Treated

Characteristic	Famotidine 20 mg (N=261)	Famotidine 10 mg (N=271)	Placebo (N=262)	Among Groups p-value
Gender				0.9394
Male	87 (33.3%)	87 (32.1%)	84 (32.5%)	
Female	174 (66.7%)	184 (67.9%)	178 (67.5%)	
Race				0.9510
Caucasian	184 (70.5%)	187 (69.0%)	183 (69.8%)	
Black	58 (22.2%)	62 (22.9%)	60 (22.9%)	
Hispanic	17 (6.5%)	20 (7.4%)	18 (6.9%)	
Native American	1 (0.4%)	2 (0.7%)	1 (0.4%)	
Asian	1 (0.4%)	0 (0%)	0 (0%)	
Age (yr)				0.4852
Mean (SD)	40.5 (12.2)	39.8 (12.1)	41.0 (12.2)	
Height (inches)				0.8686
Mean (SD)	66.5 (4.1)	66.4 (3.7%)	66.3 (3.9)	
Weight (lbs)				0.8378
Mean (SD)	182.9 (45.5)	180.6 (46.8)	182.1 (41.7%)	
Screening Meal Severity Compared to Typical Symptoms				0.4847
Much Milder	2 (0.8%)	1 (0.4%)	1 (0.4%)	
Milder	9 (3.4%)	12 (4.4%)	5 (1.9%)	
About the same	157 (60.2%)	150 (55.4%)	165 (63.0%)	
Worse	77 (29.5%)	95 (35.1%)	74 (28.2%)	
Much Worse	16 (6.1%)	13 (4.8%)	17 (6.5%)	
Duration of Heartburn				0.6227
<2 Months	0 (0%)	0 (0%)	0 (0%)	
2 to 6 Months	2 (0.8%)	2 (0.7%)	3 (1.1%)	
6 to 12 Months	6 (2.3%)	8 (3.0%)	12 (4.6%)	
>12 Months	253 (96.9%)	261 (96.3%)	247 (94.3%)	
No. of Days Since Last Episode				
Mean (SD)	1.3 (1.0)	1.3 (0.9)	1.3 (0.9)	
Typical Heartburn Severity				0.8051
Moderate	14 (5.4%)	13 (4.8%)	8 (3.1%)	
Moderate severe	124 (47.5%)	136 (50.2%)	126 (48.1%)	
Severe	109 (41.8%)	104 (38.4%)	110 (42.0%)	
Very severe	14 (5.4%)	18 (6.6%)	18 (6.9%)	
Heartburn Episodes Per Week				
Mean (SD)	5.1 (2.2)	5.3 (2.4)	5.1 (2.2)	
Frequently More Than 1 Episode/Day?				0.0163
No	63 (24.1%)	69 (25.5%)	42 (16.0%)	
Yes	198 (75.9%)	200 (73.8%)	220 (84.0%)	

Nocturnal Heartburn?				0.9363
No	81 (31.0%)	85 (31.4%)	85 (32.4%)	
Yes	180 (69.0%)	186 (68.6%)	177 (67.6%)	

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Table 2 Baseline Patient Characteristic by Treatment Group --- Protocol 117  
All-Patients-Treated

Characteristic	Famotidine 20 mg (N=489)	Famotidine 10 mg (N=491)	Placebo (N=249)	Among Groups p-value
Gender				0.6731
Male	190 (38.9%)	199 (40.5%)	105 (42.2%)	
Female	299 (61.1%)	292 (59.5%)	144 (57.8%)	
Race				0.2405
Caucasian	373 (76.3%)	366 (74.5%)	191 (76.7%)	
Black	76 (15.5%)	81 (16.5%)	38 (15.3%)	
Hispanic	39 (8.0%)	43 (8.8%)	17 (6.8%)	
Native American	0 (0%)	1 (0.2%)	0 (0%)	
Asian	1 (0.2%)	0 (0%)	3 (1.2%)	
Age (yr)				0.5990
Mean (SD)	42.3 (13.3)	41.6 (12.9)	42.3 (12.5)	
Height (inches)				0.6704
Mean (SD)	66.9 (4.0)	66.8 (4.1%)	67.2 (3.7)	
Weight (lbs)				0.4237
Mean (SD)	180.8 (41.3)	183.0 (41.1)	180.9 (42.1%)	
Duration of Heartburn				0.8321
<2 Months	0 (0%)	0 (0%)	0 (0%)	
2 to 6 Months	7 (1.4%)	10 (2.0%)	6 (2.4%)	
6 to 12 Months	19 (3.9%)	21 (4.3%)	8 (3.2%)	
>12 Months	463 (94.7%)	460 (93.7%)	235 (94.4%)	
No. of Days Since Last Episode				
Mean (SD)	1.6 (1.1)	1.5 (1.1)	1.4 (0.9)	
Typical Heartburn Severity				0.4144
Mild	2 (0.4)	0 (0%)	0 (0%)	
Moderate	48 (9.8%)	48 (9.8%)	21 (8.4%)	
Moderate severe	258 (52.8%)	269 (54.8%)	133 (53.4%)	
Severe	170 (34.8%)	153 (31.2%)	88 (35.4%)	
Very severe	11 (2.2%)	21 (4.3%)	7 (2.8%)	
Heartburn Episodes Per Week				
Mean (SD)	4.9 (2.4)	4.7 (2.0)	5.1 (3.3)	
Frequently More Than 1 Episode/Day?				0.9484
No	179 (36.6%)	176 (35.8%)	92 (36.9%)	
Yes	310 (75.7%)	315 (64.2%)	157 (63.1%)	
Nocturnal Heartburn?				0.5114
No	175 (35.8%)	159 (32.4%)	88 (35.3%)	
Yes	314 (64.2%)	331 (67.4%)	161 (64.7%)	

Table 3 Baseline Patient Characteristic by Treatment Group --- Protocol 128  
All-Patients-Treated

Characteristic	Famotidine 20 mg (N=532)	Famotidine 10 mg (N=537)	Placebo (N=265)	Among Groups p-value
<b>Gender</b>				0.6705
Male	187 (35.2%)	189 (35.2%)	101 (38.1%)	
Female	345 (64.8%)	348 (64.8%)	164 (61.9%)	
<b>Race</b>				0.2120
Caucasian	422 (79.3%)	442 (82.3%)	199 (75.1%)	
Black	99 (18.6%)	82 (15.3%)	55 (20.8%)	
Hispanic	8 (1.5%)	9 (1.7%)	9 (3.4%)	
Native American	0 (0%)	1 (0.2%)	1 (0.4%)	
Asian	2 (0.4%)	3 (0.6%)	0 (0.0%)	
Other	1 (0.2%)	0 (0.0%)	1 (0.4%)	
<b>Age (yr)</b>				0.4223
Mean (SD)	43.4 (13.5)	42.5 (13.4)	42.2 (12.4)	
<b>Height (inches)</b>				0.8160
Mean (SD)	67.0 (3.9)	66.8 (3.6%)	67.0 (4.2)	
<b>Weight (lbs)</b>				0.8656
Mean (SD)	185.6 (44.0)	185.9 (44.8)	187.4 (45.6%)	
<b>Duration of Heartburn</b>				0.3764
<2 Months	0 (0%)	0 (0%)	0 (0%)	
2 to 6 Months	13 (2.4%)	9 (1.7%)	2 (0.8%)	
6 to 12 Months	13 (2.4%)	11 (2.0%)	9 (3.4%)	
>12 Months	506 (95.1%)	517 (96.3%)	254 (95.8%)	
<b>No. of Days Since Last Episode</b>				
Mean (SD)	1.4 (1.2)	1.3 (1.0)	1.3 (1.1)	
<b>Typical Heartburn Severity</b>				0.5723
Very Mild	0 (0%)	0 (0%)	0 (0%)	
Mild	0 (0%)	1 (0.2%)	0 (0%)	
Moderate	29 (5.5%)	33 (6.1%)	17 (6.4%)	
Moderate severe	357 (67.1%)	336 (62.6%)	164 (61.9%)	
Severe	126 (23.7%)	143 (26.6%)	77 (29.1%)	
Very severe	20 (3.8%)	24 (4.5%)	7 (2.6%)	
<b>Heartburn Episodes Per Week</b>				
Mean (SD)	5.5 (3.8)	5.0 (3.2)	5.4 (5.0)	
<b>Frequently More Than 1 Episode/Day?</b>				0.7809
No	206 (38.7%)	216 (40.2%)	109 (41.1%)	
Yes	326 (61.3%)	321 (59.8%)	156 (58.9%)	
<b>Nocturnal Heartburn?</b>				0.9286
No	244 (45.9%)	240 (44.7%)	120 (45.3%)	
Yes	288 (54.1%)	297 (55.3%)	145 (54.7%)	

Asian included American Indian, Asian, Asian/Pacific Islander, and Korean. Other included Mixed and Bi-racial.

Attachment 4

**TABLE 1**

**MK-208 -- Protocol Nos. 017 and 019 -- Intermittent Heartburn Studies  
Proportion of Episodes Completely Relieved in 3 Hours  
Without Use of Additional Double-Blind Medication or Backup Antacid**

**"ALL-PATIENTS-TREATED" ANALYSIS****Protocol 017 (N=553\*)**

	<u>Placebo</u> (n=109)	<u>Antacid</u> (n=112)	<u>FAM 5 mg</u> (n=110)	<u>FAM 10 mg</u> (n=109)	<u>FAM 20 mg</u> (n=113)
Median Proportion:	0.41	0.61	0.57	0.69	0.69
<u>Category</u>	<u>Placebo</u> N (Cum %)	<u>Antacid</u> N (Cum %)	<u>FAM 5 mg</u> N (Cum %)	<u>FAM 10 mg</u> N (Cum %)	<u>FAM 20 mg</u> N (Cum %)
All Relieved	9 ( 8%)	6 ( 5%)	8 ( 7%)	10 ( 9%)	18 ( 16%)
2/3 to All	19 ( 26%)	34 ( 36%)	30 ( 35%)	47 ( 52%)	40 ( 51%)
1/3 to 2/3	41 ( 63%)	45 ( 76%)	42 ( 73%)	26 ( 76%)	28 ( 76%)
0 to 1/3	29 ( 90%)	22 ( 96%)	19 ( 90%)	19 ( 94%)	20 ( 94%)
None Relieved	11 (100%)	5 (100%)	11 (100%)	7 (100%)	7 (100%)
<u>Treatment Effect</u>	<u>Odds-Ratio</u>	<u>95% C.I.</u>	<u>Chi-Square</u>	<u>p-Value</u>	
Placebo vs. Antacid	1.59	0.98, 2.58	3.59	0.0580	
Placebo vs. 5 mg	1.49	0.92, 2.43	2.64	0.1045	
Placebo vs. 10 mg	2.39	1.46, 3.89	12.12	0.0005	
Placebo vs. 20 mg	2.75	1.69, 4.48	16.48	0.0001	
Antacid vs. 5 mg	0.94	0.58, 1.51	0.07	0.7921	
Antacid vs. 10 mg	1.50	0.92, 2.42	2.69	0.1012	
Antacid vs. 20 mg	1.72	1.07, 2.78	4.97	0.0257	
5 mg vs. 10 mg	1.60	0.98, 2.59	3.58	0.0585	
5 mg vs. 20 mg	1.84	1.14, 2.98	6.16	0.0131	
10 mg vs. 20 mg	1.15	0.71, 1.87	0.33	0.5633	

\* Only 552 of the 553 patients could be included in the analysis of the categorized proportions due to a missing value for the covariate for average daily severity of baseline episodes.

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**TABLE 2**

**MK-208 -- Protocol Nos. 017 and 019 -- Intermittent Heartburn Studies  
Proportion of Episodes Completely Relieved in 3 Hours  
Without Use of Additional Double-Blind Medication or Backup Antacid**

**"ALL-PATIENTS-TREATED" ANALYSIS****Protocol 019 (N=500)**

	<u>Placebo</u> (n=128)	<u>Antacid</u> (n=121)	<u>FAM 10 mg</u> (n=122)	<u>FAM 20 mg</u> (n=129)
Median Proportion:	0.53	0.65	0.67	0.67
<u>Category</u>	<u>Placebo</u> N (Cum %)	<u>Antacid</u> N (Cum %)	<u>FAM 10 mg</u> N (Cum %)	<u>FAM 20 mg</u> N (Cum %)
All Relieved	11 ( 9%)	15 ( 12%)	18 ( 15%)	18 ( 14%)
2/3 to All	30 ( 32%)	42 ( 47%)	42 ( 49%)	42 ( 47%)
1/3 to 2/3	54 ( 74%)	40 ( 80%)	32 ( 75%)	38 ( 76%)
0 to 1/3	27 ( 95%)	21 ( 98%)	23 ( 94%)	26 ( 96%)
None Relieved	6 (100%)	3 (100%)	7 (100%)	5 (100%)
<u>Treatment Effect</u>	<u>Odds-Ratio</u>	<u>95% C.I.</u>	<u>Chi-Square</u>	<u>p-Value</u>
Placebo vs. Antacid	1.69	1.07, 2.66	5.11	0.0238
Placebo vs. 10 mg	1.70	1.08, 2.68	5.27	0.0216
Placebo vs. 20 mg	1.52	0.98, 2.38	3.44	0.0637
Antacid vs. 10 mg	0.90	0.57, 1.42	0.20	0.6544
Antacid vs. 20 mg	1.01	0.64, 1.59	0.00	0.9782
10 mg vs. 20 mg	0.90	0.57, 1.41	0.23	0.6330

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Attachment 5:

**TABLE 1**  
**Analyses of Proportion of Episodes Completely Relieved**  
**Within 1, 2, or 3 Hours**  
**(Famotidine 10 mg Compared to Placebo)**

Protocol 017		Protocol 019	
Odds Ratio	P-Value	Odds Ratio	P-Value
1.94	<0.001	1.48	0.005

**TABLE 3**  
**Median Percentage of Patients' Episodes Relieved Within**  
**1, 2 or 3 Hours by Treatment and Protocol**  
**(All-Patients-Treated)**

	Median Percent of Episodes Relieved Within		
	1 Hour	2 Hours	3 Hours
Protocol 017			
Placebo	16.7%	32.4%	41.1%
Famotidine 10 mg	38.5%	56.8%	69.2%
Protocol 019			
Placebo	16.0%	41.7%	53.3%
Famotidine 10 mg	32.6%	57.1%	66.7%

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