Table 3.3 (Reviewer's): Proportion of Patients with Heartburn Relief at 30-Minute

Onset of Action Parameters	FACT (n=283)	Famot (n=285)	Antacid (n=284)	Plac (n=287)	p-value	p-value	p-value	p-value	p-value
					FACT Vs Famot	Famot Vs Plac	FACT Vs Plac	FACT Vs Antacid	Antacid Vs Plac
Number (%) of Patents with Adequate Relief at	105 (37.10)	81 (28.42)	101 (35.56)	90 (31.36)	.032	.466	.158	.727	.289

This reviewer's analysis results are similar to the sponsor's Cox regression primary analysis results described above. That is, the proportion of patients reporting adequate relief at 30-minute post-dose was significantly greater for FACT than Famotidine. However, there are no significant differences between the FACT treated group and placebo treated group. In addition, the proportion of patients reporting adequate relief at 30 minutes was numerically greater for Placebo (31.36%) than for Famotidine (28.42%), although this difference was not statistically significant.

This reviewer used PROC LIFETEST of SAS to obtain the 25th, 50th (median) and 75th percentiles are presented for each treatment group (based on Kaplan-Meier estimates). The results are in agreement with the results reported by the sponsor. The results are shown in Table 3.4.

Table 3.4 (reviewer's / sponsor's) Median Time to Adequate Relief (n=1137)

Treatment Group	n	Median (Minutes) (95% CI)	25th, 75th Percentiles	Number (%) of Patients Censored +	
				No Relief	Rescue Use
FACT	283	50.0 (40,60)	20, >120	74 (26.1)	1 (<1)
Famotidine	285	70.0 (60,80)	30, >120	95,(33.3)	0 (0.0)
Antacid	284	60.0 (40,70)	30, >120	83 (29.2)	(<1)
Placebo	286	70.0 (60,80)	30, >120	94 (32.9)	1 (<1)

Note: +: Patients were censored at 2 hours post-dose if they failed to achieve adequate relief or if use of rescue medication preceded the time to event.

The median time to adequate relief was 20 minutes shorter with FACT (50 minutes) than with Famotidine (70 minutes) or placebo (70 minutes). Time to adequate relief with Antacid also tended to be shorter than with placebo.

Duration of Adequate Relief:

The null hypothesis for the "duration" of adequate relief is that the distributions of peak heartburn responses during the four hours (4-8 hours post-dose) following the test meal are equal for the FACT and the Antacid treatment groups.

According to the protocol, the sponsor performed an analysis of ordered categorical data (e.g. peak heartburn severity: 0: none; 1; mild; 2: moderate and 4: severe) using logistic regression models (treatment groups and centers in the model) for ordinal data. The time range was used as 15-minute after post-dose, 2 hours post-dose (114 minutes to 150 minutes post-dose), 3 hours post-dose (151 minutes to 210 minutes post-dose) and at end of the 8 hours post-dose.

The primary duration endpoint was the proportion of patients reporting no awakenings with heartburn. The planned approach for analysis of this parameter was to treat those patients who took rescue at anytime following treatment as "treatment failure" and to impute that they awakened with heartburn. The sponsor conducted logistic regression models for binary data with treatments and sites in the model. In the following we provide the model adjusted odds-ratio based on the logistic regression model with treatment groups and centers.

Table 3.5 (Sponsor's Table From Page C-37, Volume 2)

Treatment Comparison	Treatment Difference Model Based	Model-Adjusted Odds-ratios	(95% CI)	p-value
FACT Vs. Famotidine	.270	1.31	(.93, 1.83)	.123
FACT Vs. Antacid	.322	1.38	(.98, 1.93)	.065
FACT Vs. Placebo	.542	1.72	(1.23, 2.42)	.002
Antacid Vs Placebo	.223	1.25	(.89, 1.75)	.194
Famotidine Vs Placebo	.277	1.32	(.94, 1.85)	.108

The results indicate:

1) A FACT advantage over placebo

2) No FACT significant advantage over Antacid alone

3) No Famotidine advantage over placebo

The results for the analysis of the primary endpoint (duration) using the per protocol population were similar to those using the all patients-treated with one exception: the

difference between FACT and Antacid was 8.5 percentage points (56.3% versus 47.8%) and was statistically significant (p-value=.045).

This reviewer performed an analysis on the proportion of patients reporting no awakenings with heartburn (accounting for rescue Antacid usage) are given in Table 3.5.

Table 3.6 (Reviewer's): Number of No Awakenings in Different Treatment Groups

Onset of Action Parameter	FACT (n=282)	Famotidine (n=285)	Antacid (n=284)	Placebo (n=286)	p-value	p-value	p-value
					FACT Vs Famotidine	FACT Vs Antacid	FACT Vs Placebo
Number (%) of patients with no Awakenings	158 (56.02)	141 (49.47)	137 (48.23)	123 (43.00)	.130	.065	.0025

The results are similar to sponsor's primary analysis results described above.

Patients Requiring Rescue Medication:

The following table summarizes the proportion of patients who required rescue medication 4 to 8 hours of post-dose.

Table 3.7 (reviewer's): Proportion of Patients Requiring Rescue Medication 4 to 8 Hours Post-dose (n=1136)

	FACT (n=281)	Famotidine (n=285)	Antacid (n=284)	Placebo (n=286)	p-value (FACT Vs Famotidine)	p-value (FACT Vs Antacid)	p-value (FACT Vs Placebo)
	n %	n %	n %	n %			
Rescue 4 to 8 hours	51 18.2	58 20.4	77 24.7	77 26.9	.524	.012	.016

This reviewer performed the Fisher's exact test on the proportion of patients who required rescue medications during 4 to 8 hours post-dose. However, there were no significant treatment differences for the proportion of patients who required rescue medication between the FACT treated group and Famotidine treatment group. There were significantly lower number of patients who required rescue medication in FACT than both Antacid and placebo treated groups.

Subgroup Analyses:

Gender:

The sponsor reported that there was no evidence of treatment-by-gender interaction for the primary endpoints indicating that the treatment effects were consistent for both males and

females.

This reviewer's gender analysis tables for onset and duration parameters are given in the appendix (onset:Table A.9 ; duration: Table A.12); the results are consistent with those by the sponsor.

Age:
The sponsor reported that there was no evidence of a treatment by age interaction when patients were classified as age less than or equal to median or greater than median age (see Table A.8 for median ages in different treatment groups), indicating that the treatment effects were consistent across the age group. There were not enough patients aged 65 or older in each efficacy study for analysis of that demographic subgroup.

This reviewer's age group (<65 and >=65) analysis tables for onset and duration parameters are given in the appendix (onset: Table A.10 ; duration: Table A.13).

Race:
There was no evidence of treatment-by-race interaction (Caucasian or non-Caucasian) suggesting that FACT should be equally effective in all races.

This reviewer's racial (Caucasian and non-Caucasian) analysis tables for onset and duration parameters are given in the appendix (onset: Table A.11 ; duration: Table A.14)

3.3 Summary of Safety Analysis Results

In the following table we summarize adverse experiences.

Table 3.8 (Reviewer's): Adverse Experiences Summary

Clinical Adverse Experiences(AEs)	FACT (n=283)	Famotidine (n=285)	Antacid (n=284)	Placebo (n= 286)	p-value	p-value	p-value
					FACT Vs Famotidine	FACT Vs Antacid	FACT Vs Placebo
Number (%) of Patients	n (%)	n (%)	n (%)	n (%)			
With 1 or More AEs	16 (5.7)	6 (2.1)	15 (5.3)	12 (4.3)	.031	.856	.444
With drug Related AEs	13 (4.6)	6 (2.1)	11 (3.9)	5 (1.7)	.108	.679	.058
With Serious AEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.0	1.0	1.0
Discontinued due to AEs	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1.0	1.0	1.0

It is seen from the above table that the FACT treated patients experienced significantly more (3.6%) adverse events than the Famotidine treated patients. FACT treated group experienced similar drug related and serious adverse experiences to Famotidine, Antacid and placebo

treated patients.

3.4 Conclusions:

The efficacy data in this study suggest the following:

1) FACT has no significant advantage over placebo regarding onset of adequate relief
2) Famotidine alone has no significant advantage over placebo regarding onset of adequate relief; in fact, Famotidine alone performed numerically worse than placebo.
3) FACT has a significant advantage over Famotidine alone regarding onset of adequate relief
4) FACT has a significant advantage over placebo regarding duration of adequate relief.
5) FACT has no significant advantage over Antacid alone regarding duration of adequate relief
6) Antacid has no significant advantage over placebo regarding duration of adequate relief.

4. Multiple-Episode Study (Protocol 110)

4.1 Description

The Multiple-Episode study was a two-phased study. In the first phase, patients were enrolled into a single blind Antacid run-in-week. They rated their heartburn relief for 2 hours after each dose up to 30 doses of medication (24meq ANC). Patients who met the following criteria during the Antacid run-in phase were then randomized to the double blind phase (second phase):

a) medicated with single-blind drug on at least 3 days;
b) needed to medicate twice within a 24-hour period at least once during the week; and
c) had adequate relief within 1 hour in the majority of episodes.

Qualified patients were allowed to use the double-blind medication to treat four episodes of spontaneously occurring heartburn within a 2-week period. They rated their relief (adequate: yes or no) every 15 minutes for the first hour then hourly through 8 hours post-dose. Patients could eat or sleep after the first hour post-dose, but they were asked to record those events on their diary. The analysis considered patients to have adequate relief at those time points when they were sleeping. Patients could take up to two doses of study medication in a 24-hour period, but not less than 8 hours apart. Open-label Antacid (24 meq ANC) was provided for use as rescue during the 1 to 8 hour post-dose periods. A global rating (excellent, good, fair, poor, ineffective) was recorded at the final visit.

Table 4.1 Patients Dispositions

Population	FACT	Famotidine	Antacid	Placebo	Total
Entered	308	313	310	309	1240
Patients Treated	307	311	309	307	1234
All Patients Treated	305	311	308	307	1232

A total of 2144 patients were enrolled in the run-in period; 1240 of those patients were subsequently randomized to double-blind medication. Of the 1240 patients randomized, 6 patients did not medicate and were not included in the safety or efficacy analyses. The remaining 1234 patients comprised the safety population and included 1232 patients who took at least one dose of study medication and 2 patients who were lost to follow-up. The patients lost to follow-up were included in the safety analyses assuming they had dosed and reported no adverse experiences. The all-patients- treated population comprised of 1232 patients who dosed. One patient in the FACT group treated only one episode and was excluded from GEE analyses. Thirty-one patients (6 in FACT group, 8 in Famotidine group, 8 in Antacid group, and 9 in placebo group) were classified as serious protocol violators and excluded from per-protocol analyses.

Demographic characteristics are summarized in Table A.15 in the Appendix. Study patients were predominantly female (66.9%). The treatment groups did not differ significantly in gender distribution. No notable differences in other baseline characteristics (e.g. age, race, and baseline heartburn and average number of episodes per week) were observed across treatment group.

Duration of Treatment:

One-week single blind Antacid baseline, 2week double-blind therapy- four doses, taken as required.

Primary Objective:

To compare the efficacy of FACT, Famotidine, Antacid, and placebo among patients with frequent heartburn.

Patient Selection:

Inclusion Criteria:
Male and female patients who are at least 18 years of age with a history of food-induced heartburn of at least two months duration with at least three episodes per week. Patients must have used Antacids or OTC acid reducers for effective relief of their symptoms.

Exclusion Criteria:
Patients were excluded from participation in the study if they meet the criteria in protocol 106.

Primary Endpoints:

Efficacy:

There are two primary endpoints in this protocol:

Onset of Adequate Relief:

(1) Number of episodes with adequate relief first occurring at each of the following six time points: 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours and >2 hours.

Adequate relief was assessed by patients answering the following question at 15-minute intervals for 1 hour post-dose, at 2 hours post-dose and at 2 to 8 hours post-dose:

"Do you have adequate relief of your heartburn symptoms at this time?"

1=Yes; 2=No; and =Sleeping.

The sleeping response was not an option until 2 hours post-dose.
Note that sleeping option is considered as no heartburn.

Patients rated heartburn severity immediately before taking study drug during both baseline run-in and double blind periods, patients used the following 3-point scale to assess duration of adequate relief:

Grade	Severity
.=	Missing
1=	Mild
2=	Moderate
3=	Severe

(2) Duration of adequate relief: The primary endpoint for duration of adequate relief during the 8-hour post-dose observation period across each patient's four episodes of heartburn.

Secondary Endpoints:

(1) Global evaluation of treatment after 8 hours of dosing.

Safety:

(1) Proportion of patients with one or more clinical adverse experiences.

(2) Proportion of patients who experienced a serious clinical adverse event.

The investigator evaluated all adverse experiences as to:

Maximum Intensity:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort enough to cause interference with usual activity)
- Severe (incapacitating with inability to work or do usual activity)

Seriousness:

- Results in death;
- Is immediately life threatening
- Results in permanent or substantial disability
- Results in or prolongs an existing inpatient hospitalization
- Is a congenital anomaly
- Is a cancer
- Is the result of accidental overdose.

Screening, Randomization, and Sample Size Determination:

Although the actual analysis of the time to adequate relief and duration of adequate relief endpoints made use of the ordered categorical nature of the data, the sample size calculations were based on a binary cut off of the data (probability of adequate relief at 30 minutes and duration of adequate relief greater or equal to 6 hours).

With 300 patients per treatment group, 600 patients and 2400 episodes would be involved in the comparison of any two treatments. Assuming a type I error rate of .05 (two-tailed) and an intra-class correlation among episodes within a patient of .8, these sample sizes provided greater than 96% power to detect a difference of .13 in the probability of adequate relief at 30 minutes (.38 for FACT versus .25 for Famotidine) and greater than 98% power to detect a difference of .15 in the probability of duration of adequate relief greater or equal to 6 hours (.65 for FACT versus .50 for Antacid).

4.2 Sponsor's and Reviewer's Statistical Analyses/Reviewer's Comments

Onset of Adequate Relief:

The primary alternative hypothesis regarding onset of treatment effect is that FACT has a faster time to adequate relief than Famotidine. The data used to address this question were the number of episodes each patient recorded with adequate relief first occurring at each time point

within 2 hours post-dose (six time points: 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, and greater than two hours). The sponsor used generalized estimating equations (GEE) for ordered categorical outcomes. This method accounts for the intra-patient correlation resulting from analyzing multiple episodes per patient. The final model used in making comparisons among the treatment groups included factors for treatment group, investigator site, and a covariate for average baseline severity.

The results of the analysis are displayed in Table 4.2.

Table 4.2 (reviewer's and sponsor's): Model Adjusted Estimates (difference) and Odd Ratios for Onset Data (n=1231)

Treatment Comparison	Estimate (difference)	Model- Adjusted Odds-ratio	(95% CI)	p-value (odds-ratio)
FACT vs. Famotidine	.293	1.34	(1.07,1.69)	0.011
FACT vs. Antacid	.247	1.28	(1.01, 1.63)	0.042
FACT vs. Placebo	.477	1.61	(1.29, 2.01)	<0.001
Famotidine vs. Placebo	.182	1.20	(0.97, 1.49)	0.096
Antacid vs. Placebo	.231	1.26	(1.00, 1.58)	0.050
Famotidine vs.Antacid	-.051	.95	(0.75, 1.21)	0.702

The results of this study indicate that FACT is significantly different from both Famotidine and Placebo.

1) The odds ratios (see Table 4.2) indicates that heartburn episodes treated with FACT were 1.34 times more likely to achieve adequate relief at an earlier time point than episodes treated with Famotidine ; this difference was statistically significant. Compared to Famotidine, the proportion of episodes relieved with FACT within 30 minutes was 7.5 percentage points greater.

2) The odds-ratio indicate that FACT and Antacid were both significantly better than placebo with regard to onset of adequate relief, while Famotidine tended to be better than placebo within the first 2 hours post-dose. The treatment effect was consistent across episodes one to four.

In the following we describe the distribution of adequate relief.

Table 4.3: Onset Data: Number (cumulative %) of Episodes (n=1231) Adequately Relieved

Relief at:	FACT n=305 Total Eps *=1205		Famotidine n=311 Total Eps=1229		Antacid n=308 Total Eps=1212		Placebo n=307 Total Eps=1217	
	n	cum % **	n	cum % **	n	cum %**	n	cum % **
15 minutes	322	27.0	249	20.3	301	25.1	191	15.7
30 minutes	222	45.3	215	37.8	190	40.9	210	33.0
45 minutes	234	64.6	257	58.6	200	57.4	262	54.4
60 minutes	172	78.8	190	73.9	159	70.5	203	71.2
120 minutes	77	85.3	94	81.5	102	78.8	77	77.5
>120 minutes	178	100.0	224	100.0	260	100.0	274	100.0

*** Eps=episodes; ** Cumulative percentages are based on the number of episodes within each patient**

The distribution of episodes adequately relieved with FACT is shifted towards the earlier time points relative to the other treatment groups.

For ease of comparison, this reviewer performed Fisher's exact test for onset of adequate relief at 30 minutes. The results summarized in the following table indicate no FACT advantage.

Table 4.4 (Reviewer's): Number of Episodes Adequately Relieved at 30-Minute

Adequately Relieved	FACT (Total # of Episodes relieved =1205)	(Total # of Episodes relieved 1229)	Antacid (Total # of Episodes relieve= 1212)	Plac (Total # of Episodes relieved =1217)	p-value FACT Vs Famot	p-value Vs Plac	p-value FACT Vs Plac	p-value FACT Vs Antacid	p-value Antacid Vs Plac
Number (%)	222 (18.42)	215 (17.49)	190 (15.68)	210 (17.26)	.562	.915	.458	.074	.299

Note: :Famotidine; Plac: Placebo

Duration of Adequate Relief:

The primary hypothesis regarding duration of treatment effect is that FACT produces a longer duration of adequate relief than Antacid. The data used to address this hypothesis were the number of episodes with adequate relief that were sustained through each of the following time points: greater or equal to 7 hours, 6 hours, five hours, four hours, less than 4 hours and "no onset of adequate relief." The sponsor used generalized estimating equations (GEE) for ordered categorical outcomes. This method accounts for the intra-patient correlation resulting

from analyzing multiple episodes per patient. The final model used in making comparisons among the treatment groups included factors for treatment group, investigator site, and a covariate for average baseline severity. The results of the analysis are displayed in Table 4.5.

Table 4.5(reviewer's and sponsors): Model Adjusted Estimates (difference) and Odds - Ratios (n=1231)

Treatment Comparisons	Estimate (difference)	Model Adjusted Odds-Ratio	(95% CI)	p-value (odds-ratio)
FACT vs. Famotidine	.104	1.11	(.89, 1.39)	.366
FACT vs. Antacid	.398	1.49	(1.19, 1.87)	.001
FACT vs. Placebo	.464	1.59	(1.28, 1.97)	<.001
Famotidine vs. Placebo	.357	1.43	(1.15, 1.77)	.001
Antacid vs. Placebo	.058	1.06	(.86, 1.32)	.579
Famotidine vs. Antacid	.293	1.34	(1.07, 1.68)	.010

The odds-ratio indicates that heartburn episodes treated with FACT were 1.49 times more likely to maintain adequate relief at a later time point than episodes treated with Antacid. The proportion of episodes relieved for at least seven hours was 9 percentage points greater with FACT than Antacid. The results for the per-protocol analyses are consistent with the all-patients treated approach.

The distribution of episodes (patient-based) are reported in the following table.

Table 4.6: Number (cumulative %) of Episodes Adequately Relieved (n=1231)

Adequate Relief	FACT (n=305) Total Episodes=1205		Famotidine (n=311) Total Episodes=1229		Antacid Total Episode=1212		Placebo (n=307) Total Episode=1217	
	n	Cum %*	n	Cum %	n	Cum %	n	Cum %
Greater than 7 hours	845	70.4	842	68.3	741	61.3	718	59.0
6 hours	20	72.0	19	69.8	14	62.4	22	60.8
5 hours	28	74.3	29	72.2	30	64.9	43	64.3
4 hours	26	76.5	31	74.7	41	68.2	48	68.2
<4 hours	152	80.0	142	86.2	180	83.2	182	83.2
No onset	134	100	166	100.0	206	100.0	204	100.0

Note: Cumulative percentages are based on the number episodes within each patient

The distribution of episodes (patient based) for FACT is shifted towards the later time points

relative to Antacid and placebo.

For ease of comparison, this reviewer performed Fisher's exact test based on number of episodes relieved first 4 hours. The results are summarized in the following table indicate no FACT advantage of the duration of relief.

Table 4.7 (Reviewer's): Number of Episodes Adequately Relieved at Less than 4 Hours

Adequately relieved during less than 4 hours	FACT (Total # of Episodes relieved =1205)	Famot (Total # of Episodes relieved = 1229)	Antacid (Total # of Episodes relieve= 1212)	Plac (Total # of Episodes relieved =1217)	p-value	p-value	p-value	p-value	p-value
					FACT Vs Famot	Famot Vs Plac	FACT Vs Plac	FACT Vs Antacid	Antacid Vs Plac
Number (%)	152 (12.61)	142 (11.78)	180 (14.85)	182 (14.95)	.575	.032	.099	.111	.955

Note: Famotidine; Plac: Placebo

Rescue Medication Use:

The results for the analysis of proportion of episodes requiring rescue medication during the 8 hours post doses are given Table 4.6.

Table 4.6 (sponsor's): Number (Cumulative %) of Episodes Requiring Rescue Medication (extracted from sponsor's table C-10, Volume 2)

Use of Rescue Medication	FACT n=305 Total Episodes=1205		Famotidine n=311 Total Episodes=1229		Antacid n=308 Total Episodes=1212		Placebo n=307 Total Episodes=1217	
	n	cumulative %	n	cumulative %	n	cumulative %	n	cumulative %
< = 1 hour	35	2.9	46	3.9	47	4.0	45	3.8
< =2 hours	70	8.6	90	11.4	101	12.2	107	12.5
< = 4 hours	98	16.7	108	20.2	141	23.8	135	23.6
< =6 hours	55	21.2	73	26.1	69	29.6	102	31.9
< = 8 hours	47	25.1	31	28.6	34	32.4	51	36.1
No rescue	900	100.0	881	100.0	819	100.0	777	100.0

It is seen that the patients in the FACT group had a lower percentage of episodes that required the use of rescue medicine than patients in any other group.

Subgroup Analyses:

Gender:
The sponsor reported that there was no evidence of treatment-by-gender interaction for the primary endpoints indicating that the treatment effects were consistent for both males and females.

The sponsor's gender analysis tables for onset and duration of relief parameters are given in the appendix (onset:Table A.16 ; duration: Table A.19)

Age:
The sponsor reported that there was no evidence of a treatment by age interaction when patients were classified as age less than or equal to median or greater than median age (see Table A.15 for median ages in different treatment groups) indicating that the treatment effects were consistent across the age group. There were not enough patients aged 65 or older in this study to analysis of that demographic subgroup.

The sponsor's age group (<65 and >=65) analysis tables for onset and duration parameters are given in the appendix (onset: Table A.17 ; duration: Table A.20)

Race:
The sponsor reported that there was a significant treatment-by-race (Caucasian or non-Caucasian) interaction for the primary endpoint, duration of adequate relief parameter. The treatment differences that were observed in the overall population were not consistently observed in the black, Hispanic, and other subgroups. This is most likely due to the small sample sizes.

The sponsor's racial (Caucasian and non-Caucasian) origin analysis tables for onset and duration parameters are given in the appendix (onset: Table A.18 ; duration: Tables A.21)

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4.3 Summary of Safety Analyses

In the following we summarize adverse experiences.

Table 4.7: Safety Events (Reviewer's)

Clinical Adverse Experiences(AEs)	FACT (n=307)	Famotidine (n=311)	Antacid (n=309)	Placebo (n=307)	p-value		
					FACT Vs Famotidine	FACT Vs Antacid	FACT Vs Placebo
Number (%) of patients	n (%)	n (%)	n (%)	n (%)			
With 1 or more AEs	24 (7.8)	23 (7.4)	26 (8.4)	20 (6.5)	.880	.883	.639
With drug related AEs	11 (3.6)	7 (2.3)	6 (1.9)	7 (2.3)	.349	.230	.474
With serious AEs	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1.0	1.0	1.0
Discontinued due to AEs	0 (0.0)	0 (0.3)	1 (0.3)	0 (0.0)	1.0	1.0	1.0

It is seen from the above table that The FACT treated patients are as safe as Famotidine, Antacid and placebo treated patients.

4.3 Conclusions:

The efficacy data in this study indicate

1) FACT has a faster onset of symptom relief than Famotidine alone.

2) FACT has a longer duration of effect than Antacid alone.

3) FACT is as safe as Famotidine, Antacid or placebo.

4) However, this reviewer's (Fisher's exact) analysis results for patient-episodes adequately relieved in 30 minutes (for onset) and in less than four hours (for duration) showed no significant

   (i) FACT advantage over placebo for both onset (Table 4.4) and duration (Table 4.7)
   (ii) FACT advantage over Famotidine alone for onset (Table 4.4) or Antacid alone for duration (Table 4.7).

5. OVERALL REVIEWER'S SUMMARY/CONCLUSIONS:

The efficacy results of the three protocols are summarized in the following table.

Table 5.1: Efficacy Summaries in Terms of P-values of the Primary Analysis results Across the Three Studies

Study Protocol #	106 (Daytime Heartburn Study)	109 (Evening Heartburn Study)	110 (Multiple Episodes)
Onset of Relief	Onset of Relief	Onset of Relief	Onset of Relief
FACT Vs Placebo	.091 (logistic) .417 (Fisher's)	.109 (Cox regression) .158 (Fisher's*)	.011 (GEE OC) .458 (Fisher's at 30-mins)
FACT Vs Famotidine	.621 (logistic) .688 (Fisher's)	.034 (Cox regression) .032 (Fisher's*)	.011 (GEE OC) .562 (Fisher's at 30-mins)
Famotidine Vs Placebo	.539 (logistic) .757 (Fisher's)	.660(Cox regression)** .466 (Fisher's*)	.096 (GEE OC) .915 (Fisher's at 30-mins)
FACT Vs Antacid	.325 (logistic) .558(Fisher's)	.437 (Cox regression) .727 (Fisher's*)	.042 (GEE OC) .074 (Fisher's at 30-mins)
Antacid Vs Placebo	.071 (logistic) .231 (Fisher's)	.389 (logistic) .158 (Fisher's*)	.050 (GEE OC) .299 (Fisher's at 30-mins)
Duration	Duration	Duration	Duration
FACT Vs Placebo	.027 (logistic)	.002 (logistic)	< .001 (GEE OC) .099 (Fisher's < 4 hrs)
FACT Vs Antacid	.020 (logistic)	.065 (logistic)	.001 (GEE OC) .111 (Fisher's < 4 hrs)
Antacid Vs Placebo	.897 (logistic)	.194 (logistic)	.579 (GEE OC) .955 (Fisher's < 4 hrs)
Famotidine Vs Placebo	.450 (logistic)	.108 (logistic)	
FACT Vs Famotidine	.145 (logistic)	.123 (logistic)	.001 (GEE OC) .032 (Fisher's < 4 hrs) .366 (GEE OC) .575 (Fisher's < 4 hrs)

Note: GEE OC: Generalized estimating equations for time ordered categorical data

* As in the primary endpoint of protocol 106 (30 minute time point)

** Famotidine numerically worse than placebo

Conclusions:

Onset of Relief:

(1) Sponsor's analysis results across the studies indicate the following:

i) For both studies 106 and 109 (where logistic regression was the primary analysis method), the combination therapy was not significantly different from placebo.

ii) For study 110 where GEE is the primary analysis, FACT is significantly (by sponsor's analysis results) better than placebo. However, there is no significant difference between the combination and placebo and between the combination and Famotidine alone at the 30-minute post-dose time point (by this reviewer's analysis results, Table 4.4).

iii) Thus although FACT appears to be significantly better than Famotidine alone in both study 109 (Evening Heartburn Study) and 110 (patient episodes) by sponsor's analysis results, this reviewer's analysis results only replicated the sponsor's study 109 findings. This reviewer's analysis results at the 30-minute (primary time point for study 106 and 109) did support the sponsor's findings. Furthermore, study 106 (Daytime Heartburn Study) did not show any FACT advantage.

iv) In all three studies, Famotidine has no advantage over placebo. Also, except for study 110, Antacid has no advantage over placebo.

Duration of Adequate Relief:

(2) Sponsor's analysis results across the three studies indicate the following:

i) For all three studies, the combination therapy was significantly better than placebo.

ii) The combination therapy was significantly better than Antacid alone in study 106 (Daytime Heartburn Study) and in study 110 (patient episodes) but not in study 109 (Evening Heartburn Study).

iii) However, this reviewer's analysis results based on patient-episodes relieved in less than four hours (study 110) showed no significant difference between FACT and Antacid, FACT and placebo, Antacid and placebo, and FACT and Famotidine.

iv) Antacid alone has no advantage over placebo in all three studies, and except for study 110 (patient episodes), Famotidine alone has no advantage over placebo.

Safety:

According to this reviewer's assessment, FACT is generally well tolerated when used to treat episodic heartburn.

Pediatric:

Because the minimum age requirement for all three studies is 18 years, the implications of these findings on patients who are less than 18 years are unclear.

Overall Conclusion

a) For the ***onset of adequate relief***, sponsor's analysis results based on patient-episodes (study 110) produced the strongest efficacy evidence in favor of the combination whilst the analysis results based on Daytime Heartburn (study 106) produced the weakest efficacy evidence against the combination.

b) For the ***duration of adequate relief***, sponsor's analysis results based on patient-episodes (study 110) produced the strongest efficacy evidence in favor of the combination whilst the analysis based on Evening Heartburn (study 109) produced the weakest efficacy evidence against the combination.

c) Thus the results across the three studies appear to be analysis method dependent, lead to inconsistent conclusions, and to suggest a problem with the study designs as *evidenced by the lack of a significant advantage over placebo by either the combination therapy or the individual components in most cases*.

In a combination therapy, the validity of the study design, internal consistency of the results, and the contributions of the individual components of the combination therapy must be demonstrated. Validity and internal consistency is demonstrated by showing that both the individual components and the combination therapy are significantly better than placebo. The contributions of the individual components are demonstrated by showing that the combination therapy is better than Famotidine alone (for onset of adequate relief) and better than Antacid alone (for duration of adequate relief) as per this trial. This has not been adequately demonstrated in this trial. Thus, this reviewer's recommendation is for non-approval.

/S/

M. Mushfiqur Rashid, Ph.D.
Mathematical Statistician

Concur: /S/ 1/8/99
Dr. Sankoh
Dr. Welch

cc: Archival NDA # 20958
HFD - 180
HFD - 180/ Dr. Talarico
HFD - 180/ Mr. Folkendt
HFD - 180/ Dr. Senior
HFD - 715/ Dr. Nevius
HFD - 715/ Dr. Welch
HFD - 715/ Dr. Sankoh
HFD - 715/ Dr. Rashid
HFD - 715/ File Copy
Rashid/x73121/MMR/

Table A.1 (reviewer's): Baseline Characteristics: Protocol 106

	FACT (n=309)	Famotidine (n=311)	Antacid (n=306)	Placebo (n=311)	Total (n=1237)
Age (year)					
Mean	39.7	40.4	39.1	39.8	39.8
<65	273	295	290	298	1156
>65	16	16	16	13	61
Median	37.0	39.0	37.0	38.0	38
Gender					
Male	130(42.1%)	113(36.3%)	113(36.9%)	120(38.6%)	476(38.5%)
Female	179(57.9%)	198(63.7%)	193(63.1%)	191(61.4%)	761(61.5%)
Racial Origin					
Caucasian	233(75.4%)	245(78.8%)	226(73.9%)	252(81.0%)	956(77.3%)
Black	44(14.2%)	32(12.2%)	52 (17.0%)	35(11.3%)	169(13.7%)
Hispanic	31(10.0%)	28(9.0%)	26(8.5%)	22 (7.1%)	107(8.6%)
American Indian	0(0.0%)	0(0.0%)	1(0.3%)	1(0.3%)	2(0.2%)
Puerto Rican	1(.3%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.1%)
Asian	0(0.0%)	0(0.0%)	1(0.3%)	0(0.0%)	1(0.1%)
Persian	0(0.0%)	0(0.0%)	0(0.0%)	1(0.3%)	1(0.1%)

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Table A.2(reviewer's): Heartburn Relief at 30-Minute Post-Dose in Protocol 106 (Onset)

Sex	Relief	FACT	Famotidine	Antacid	Placebo
Female	No(%)	143(81%)	163(83%)	148(77%)	157(83%)
	Yes(%)	33(19%)	34(17%)	44(23%)	32(17%)
Male	No(%)	99(76%)	85(77%)	86(77%)	94(80%)
	Yes(%)	31(24%)	26(23%)	26(23%)	24(20%)

Table A.3 (reviewer's): Peak Heartburn 4-8 Hours Post-Dose in Protocol 106 (duration)

Sex	Peak-Heartburn	FACT	Famotidine	Antacid	Placebo
Female	None	56(32%)	58(29%)	54(28%)	48(25%)
	Mild	61(35%)	75(38%)	73(38%)	69(37%)
	Moderate	27(15%)	25(13%)	30(16%)	31(16%)
	Severe	32(18%)	39(%20)	35(18%)	41(22%)
Male	None	58(45%)	36(32%)	30(27%)	38(32%)
	Mild	38(29%)	39(35%)	42(37%)	42(36%)
	Moderate	19(15%)	20(18%)	11(10%)	23(19%)
	Severe	15(11%)	16(15%)	29(26%)	15(13%)

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Table A.4(reviewer's): Heartburn Relief at 30-Minute Post-Dose in Protocol 106 (onset)

Age group	Relief	FACT	Famotidine	Antacid	Placebo
Age <65	No(%)	230(79%)	236(81%)	225(78%)	242(82%)
	Yes(%)	60(21%)	56(19%)	63(22%)	52(18%)
Age>= 65	No(%)	12(75%)	12 (75%)	9(56%)	9(69%)
	Yes(%)	4(25%)	4 (25%)	7(44%)	4(31%)

Table A.5 (reviewer's): Peak Heartburn 4-8 Hours Post-Dose in Protocol 106 (duration)

Age Group	Peak-Heartburn	FACT	Famotidine	Antacid	Placebo
Age<65	None	107(37%)	88(30%)	81(28%)	84(29%)
	Mild	93(32%)	109(37 %)	108(38 %)	106(36%)
	Moderate	45(15%)	43(15 %)	38(13 %)	53(18%)
	Severe	45(16%)	52(18 %)	61(21%)	51(17.35 %)
Age >=65	None	7(44%)	6(38%)	3(19%)	2(16%)
	Mild	6(38%)	5(31%)	7(44%)	5(38%)
	Moderate	1(6%)	2(13%)	3(19%)	1(8 %)
	Severe	2(13%)	3(19%)	3(19%)	5(38%)

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Table A.6 (reviewer's): Heartburn Relief at 30-Minute Post-Dose in Protocol 106 (onset)

Race	Relief	FACT	Famotidine	Antacid	Placebo
Caucasian	No(%)	180(78%)	195(80%)	178(79%)	207(83%)
	Yes(%)	50 (22%)	48(20%)	47(21%)	41(17%)
Non-Caucasian	No(%)	62(82%)	53 (82%)	56(71%)	44 (75%)
	Yes(%)	14 (18%)	12 (18%)	23(29%)	15(25%)

Table A.7 (reviewer's): Peak Heartburn 4-8 Hours Post-Dose in Protocol 106 (duration)

Race	Peak-Heartburn	FACT	Famotidine	Antacid	Placebo
Caucasian	None	95(41%)	79(33%)	67(30 %)	71(29 %)
	Mild	75(33%)	91(37%)	84(37%)	93(38%)
	Moderate	33(14%)	38 (16%)	30(13%)	38(15%)
	Severe	27(12%)	35(14%)	44(20%)	46(19%)
Non-Caucasian	None	19(25%)	15(23%)	17(22%)	15(25%)
	Mild	24(32%)	23(35%)	31(39%)	18(31%)
	Moderate	13(17%)	7(11%)	11(14%)	16(27%)
	Severe	20(26%)	20(31%)	20(25%)	10(17%)

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Table A.8 (reviewer's): Baseline Characteristics: Protocol 109

	FACT (n=283)	Famotidine (n=285)	Antacid (n=284)	Placebo (n=287)	Total (n=1139)
Age (year)					
Mean	40.1	38.5	39.4	39.1	39.3
<65	268	274	277	273	1092
>65	15	11	7	14	47
Median	39.0	37.0	39.0	38.0	39
Gender					
Male	117(41.3%)	125(43.9%)	116(40.8%)	114(39.7%)	472(41.4%)
Female	166 (58.7%)	160 (56.1%)	168 (59.2%)	173(60.73%)	667 (58.6%)
Racial Origin					
Caucasian	249(88.0%)	243 (85.3%)	249(87.7%)	250 (87.1%)	991 (87.0%)
Black	23 (8.1%)	34(11.9%)	26 (9.2%)	29 (10.1%)	112 (9.8%)
Hispanic	10 (3.5%)	8(2.8%)	9 (3.2%)	8 (2.8%)	35 (3.1%)
Indian	1 (<1%)	0(0.0%)	0(0.0%)	0(0.0%)	1(<1%)

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Table A.9 (reviewer's):Model Adjusted Estimates(difference)and Risk (Hazard) Ratios Based on Time to Adequate Symptom Relief by Sex (Onset: Protocol - 109)

Treatment Comparison	Estimates (Model based)	Risk Ratio (Hazard Ratio)	Chi-square (Wald)	P-value
Male				
FACT Vs Famotidine	-.00098	.990 (1.01)	.0004	.9496
FACT Vs Placebo	-.02688	.973 (1.027)	.23812	.6256
Famotidine Vs Placebo	-.010394	.990 (1.01)	.0162	.8977
Female				
FACT Vs Famotidine	-.331261	.718 (1.392)	6.14934	.0131
FACT Vs Placebo	-.06460	.937 (1.067)	2.2507	.1336
Famotidine Vs Placebo	.05344	1.055 (.9478)	.63203	.4266

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Table A.10 (reviewer's): Model Adjusted Estimates (difference) and Risk (Hazard) Ratios Based on Time to Adequate Symptom Relief by Age Group (Onset: Protocol - 109)

Treatment Comparison	Estimates (Model based)	Risk Ratio (Hazard Ratio)	Chi-square (Wald)	P-value
Age<65				
FACT Vs Famotidine	-.180418	.835 (1.197)	3.09928	.835
FACT Vs Placebo	-.049212	.952 (1.0504)	2.04406	.1528
Famotidine Vs Placebo	-.014	1.015 (.985)	.07821	..7797
Age>=65				
FACT Vs Famotidine	-.719438	.487 (2.0533)	1.22134	.487
FACT Vs Placebo	-.131803	.877 (1.140)	.70505	.4011
Famotidine Vs Placebo	-.2330	.712 (1.404)	.4020	.5261

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Table A.11(reviewer's): Model Adjusted Estimates(difference)and Risk (Hazard) Ratios Based on Time to Adequate Symptom Relief by Race (Onset: Protocol - 109)

Treatment Comparison	Estimates (Model Based)	Risk Ratio (Hazard Ratio)	Chi-square (Wald)	P-value
Caucasian				
FACT Vs Famotidine	-.160098	.852 (1.173)	2.19274	.1387
FACT Vs Placebo	-.068512	.934 (1.0706)	3.560	.0592
Famotidine Vs Placebo	-.022421	.978 (1.0224)	.16383	.6857
Non-Caucasian				
FACT Vs Famotidine	-.5594	.572 (1.74825)	3.60939	.0575
FACT Vs Placebo	.096644	1.101 (.99)	1.118	.2917
Famotidine Vs Placebo	.3544	1.425 (.701)	5.691	.0171

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Table A.12 (reviewer's): Number (Proportion) of Patients Reporting No Awakenings with Heartburn by Sex (Duration: Protocol - 109)

Treatment Comparison		Number (%)	P-value (Fisher's Exact)		
			FACT Vs Antacid	FACT Vs Placebo	Antacid Vs Placebo
Male	**n**				
FACT	117	71 (60.68)	.355	.291	.047
Antacid	116	63 (54.31)			
Placebo	113	53 (46.90)			
Female	**n**				
FACT	165	87 (52.73)	.125	.029	.513
Antacid	168	74 (44.05)			
Placebo	173	70 (40.46)			

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Table A.13 (reviewer's): Number (Proportion) of Patients Reporting No Awakenings with Heartburn by Sex (Duration: Protocol - 109)

Treatment Comparison		Number (%)	P-value (Fisher's exact)		
			FACT Vs Antacid	FACT Vs Placebo	Antacid Vs Placebo
AGE <65	**n**				
FACT	267	149 (55.81)	.072	.0045	.304
Antacid	277	133 (48.01)			
Placebo	272	118 (43.38)			
Age >=65	**n**				
FACT	15	9 (60.0)	1.00	.272	.397
Antacid	7	4 (57.14)			
Placebo	14	5 (35.71)			

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Table A.14 (reviewer's): Number (Proportion) of Patients Reporting No Awakenings with Heartburn by Race (Duration: Protocol - 109)

Treatment Comparison		Number (%)	P-value (Fisher's exact)		
			FACT Vs Antacid	FACT Vs Placebo	Antacid Vs Placebo
Caucasian	**n**				
FACT	248	133 (53.63)	.128	.0053	.240
Antacid	249	116 (46.58)			
Placebo	249	102 (40.96)			
Non-Caucasian	**n**				
FACT	34	25 (73.52)	.309	.213	.815
Antacid	35	20 (60.0)			
Placebo	37	21 (56.75)			

APPEARS THIS WAY ON ORIGINAL

Table A.15 (reviewer's): Baseline Characteristics: Protocol 110

	FACT (n=307)	Famotidine (n=311)	Antacid (n=309)	Placebo (n=307)	Total (n=1234)
Age (year)					
Mean	43.0	44.7	42.4	42.3	43.1
<65	283	287	295	289	1154
>65	24	24	14	18	80
Median	41.0	44.0	40.5	41.0	42.0
Gender					
Male	109(35.5%)	94(30.2%)	98(31.7%)	108(35.2%)	409(33.1%)
Female	198(64.5%)	217(68.8%)	211(68.3%)	199(64.8%)	825(66.9%)
Racial Origin					
Caucasian	259(84.4%)	265(85.2%)	266(86.1%)	265(86.3%)	1055(85.5%)
Black	25 (8.1%)	28 (9.0%)	26(8.4%)	23(7.5%)	102 (8.3%)
Hispanic	20(6.5%)	14 (4.5)	15(4.9%)	17(5.5%)	66(5.3%)
American Indian	0(0.0%)	2(0.6%)	1(%0.3%)	1(0.3%)	4(0.3%)
Asian	0(0.0)	0(0.0%)	1(0.3%)	1(0.3%)	2(0.2%)
Cuban	2(0.7%)	0(0.0%)	0(0.0%)	0(0.0%)	2(0.2%)
Indian	0(0.0%)	1(0.3%)	0(0.0%)	0(0.0%)	1(0.1%)
Oriental	1(0.3%)	1(0.3%)	0(0.0%)	0(0.0%)	2(0.2%)

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Table A.16 (sponsor's): Number (Cumulative %) of Episodes Adequately Relieved By Sex (Onset: Protocol - 110)

Treatment Group	Gender	n	Total Episodes	"Patient Based " Cumulative Percentages Adequate Relief					
				15 Mins	30 mins	45 mins	60 mins	120 mins	>120 mins
FACT	Male	109	432	36.7	55.8	71.3	81.2	86.0	100.0
	Female	196	773	21.6	39.5	60.9	77.5	84.9	100.0
Famotidine	Male	94	372	23.6	42.6	62.6	77.2	84.9	100.0
	Female	217	857	18.9	35.7	56.9	72.5	80.0	100.0
Placebo	Male	108	429	20.1	35.3	56.8	73.1	77.1	100.0
	Female	199	788	13.2	31.7	53.1	70.1	77.7	100.0

Table A.17 (sponsor's): Number (Cumulative %) of Episodes Adequately Relieved By Age Group(Onset: Protocol - 110)

Treatment Group	Age Group	n	Total Episodes	"Patient Based " Cumulative Percentages Adequate Relief					
				15 Mins	30 mins	45 mins	60 mins	120 mins	>120 mins
FACT	<65	284	1121	27.0	45.0	65.1	79.2	85.5	100.0
	>=65	21	84	27.4	48.8	58.3	73.8	82.1	100.0
Famotidine	<65	294	1164	20.6	38.6	59.4	74.4	81.7	100.0
	>=65	17	65	14.7	23.5	45.6	64.7	77.0	100.0
Placebo	<65	293	1161	16.0	33.4	54.9	71.4	77.7	100.0
	>=65	14	56	8.0	23.2	44.6	66.1	73.2	100.0

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Table A.18 (sponsor's): Number (Cumulative %) of Episodes Adequately Relieved By Race(Onset: Protocol - 110)

Treatment Group	Race	n	Total Episodes	"Patient Based " Cumulative Percentages Adequate Relief					
				15 Mins	30 mins	45 mins	60 mins	120 mins	>120 mins
FACT	Caucasian	258	1024	27.1	45.4	64.1	78.6	85.6	100.0
	Non-Caucasian	47	181	26.2	44.5	67.6	79.6	83.7	100.0
Famotidine	Caucasian	265	1048	21.7	39.3	58.6	72.9	80.9	100.0
	Non-Caucasian	46	181	12.5	28.8	59.1	79.7	84.6	100.0
Placebo	Caucasian	265	1049	15.8	33.2	55.0	71.8	78.1	100.0
	Non-Caucasian	42	168	14.9	31.5	50.6	67.3	73.2	100.0

Table A.19 (sponsor's): Number (Cumulative %) of Episodes Adequately Relieved By Sex (Duration: Protocol - 110)

Treatment Group	Gender	n	Total Episodes	"Patient Based " Cumulative Percentages Adequate Relief					
				>=7 hours	6 hrs	5 hrs	4 hrs	<4 hrs	No Onset
FACT	Male	109	432	70.4	72.0	73.4	75.5	89.7	100.0
	Female	196	773	70.3	72.0	74.8	77.0	88.6	100.0
Antacid	Male	98	385	57.7	59.3	61.4	65.0	85.2	100.0
	Female	210	827	62.9	63.9	66.5	69.8	82.3	100.0
Placebo	Male	108	429	54.2	56.9	60.4	62.9	82.6	100.0
	Female	199	788	61.6	62.9	66.4	71.1	83.5	100.0

Table A.20 (sponsor's): Number (Cumulative %) of Episodes Adequately Relieved By Age Group(Duration: Protocol - 110)

Treatment Group	Age Group	n	Total Episodes	"Patient Based " Cumulative Percentages					
				Adequate Relief					
				>=7 hrs	6 hrs	5 hrs	4 hrs	<4 hrs	No Onset
FACT	<65	284	1121	70.2	71.8	73.7	76.0	88.9	100.0
	>=65	21	84	72.6	75.0	82.1	83.3	89.3	100.0
Antacid	<65	294	1160	60.8	61.9	64.5	67.7	82.9	100.0
	>=65	17	52	73.1	75.0	75.0	80.8	90.4	100.0
Placebo	<65	293	1161	59.3	61.2	64.9	69.0	83.6	100.0
	>=65	14	56	51.8	51.8	51.8	51.8	75.0	100.0

Table A.21 (sponsor's): Number (Cumulative %) of Episodes Adequately Relieved By Race (Duration: Protocol - 110)

Treatment Group	Race	n	Total Episodes	"Patient Based " Cumulative Percentages					
				Adequate Relief					
				>=7 hrs	6 hrs	5 hrs	4 hrs	<4 hrs	No Onset
FACT	Caucasian	258	1024	72.5	73.8	76.0	78.1	89.3	100.0
	Non-Caucasian	47	181	58.5	62.2	64.9	67.7	86.9	100.0
Famotidine	Caucasian	266	1045	60.5	61.5	63.8	67.1	82.0	100.0
	Non-Caucasian	42	167	66.1	68.7	72.2	75.2	90.5	100.0
Placebo	Caucasian	265	1049	58.5	60.4	63.9	67.5	83.5	100.0
	Non-Caucasian	42	168	61.9	63.1	66.7	72.6	81.5	100.0

Statistical Review and Evaluation

NDA 20-958

Drug Name: Famotidine/Antacids Combination Chewable Tablets
Applicant: Merck Research Laboratories
Indication: Short-term Treatment of Heartburn, Acid Indigestion
Document Reviewed: Open-label Use Study Report (from Vol.1.15)
Statistical Reviewer: Qian Li, Sc.D.
Date of Review: November 11, 1998

I. Introduction

Famotidine/Antacid combination tablet is an OTC product for the treatment of intermittent heartburn. The purpose of this review is to evaluate the result reported by the sponsor from an open-label study on the patterns of use of Famotidine/Antacid combination tablets in patients who use antacid or OTC acid reducer.

The study was a multicenter, open-label, 2-week home-use study to evaluate the patterns of use of famotidine/antacid combination tablets. Diary cards were used for patients to record the actual usage of the study medicine, while safety information was reported through a toll-free pager.

496 patients were enrolled into the study. 370 of the 496 patients completed the study and returned diaries. 125 discontinued study, of which, 88 were lost to follow-up and 29 did not medicate themselves. It is worth to note that there was no information about the 88 lost to follow-up patients regarding their usage patterns and safety profiles.

II. Comment on Study Design

According to the study protocol, "only patients who indicate taking at least one dose of study medication throughout the study period, as recorded on product use diary, will be included in the analysis of patterns of use. In addition, only patients who take study medication will be included in the analysis of safety."

Based on the criteria of patient classification above, only patients who returned medication diaries could be considered for the analysis of pattern use. However, the definition of safety population for safety analysis was ambiguous. It may or may not include the patients who did not return the diaries (i.e., the 88 patients who were lost to follow-up), depending on the assumptions made on those patients who did not return their diaries. The definitions of patient classification have two problems. First, excluding patients who did not return medication diary, such as lost to follow-up patients, could have resulted in biased analysis since it is possible that the lost to follow-up patients

could have higher non-compliance rate compared to the patients who have responded. Second, in the definition of safety population, it did not specify what was the basis for determining who took study medicine or not. Therefore, the safety population could be different depending on the assumption whether the patients, who did not return medication diaries, had taken study medication or not. And such an assumption should be established up front in study design stage.

III. Analyses done by sponsor:

Based on the definition for patterns of use analysis, the sponsor included 373 patients in patterns of use analysis out of 496 enrolled patients. Note only 3 patients from discontinued category were included in this analysis. 91 patients who did not return diaries were excluded (88 were lost to follow-up). The result of the patterns of use analysis done by sponsor showed a 76.1% compliance rate. The 95% confidence interval (CI) based on sponsor's analysis but calculated by the reviewer is (71.8%, 80.4%). The lower limit of the 95% CI barely exceeds the expected 70% minimum compliance rate indicated in the study protocol.

It can be seen that in this analysis it was implicitly implied that those patients who were lost to follow-up either did not take study medication or took the study medication and had the same compliance rate as the response group. It is difficult to judge the validity of the assumptions, however, conservative assumptions can be made by assuming higher non-compliance rates among the patients who did not return the diaries. To contrast with the sponsor's analysis of patterns of use, a couple of analyses by this reviewer are presented in next section.

Different from usage pattern analysis, the sponsor made explicit assumptions on the lost to follow-up patients in safety analysis. On page 3626 of the study report, section 2.b on Accounting for Patients in the Analysis, it indicated that "...The remaining 88 patients of the 465 were lost to follow-up and are included in the safety analyses as if they took test medication and did not report any adverse experiences." In this statement, two assumptions are made: (1) it was assumed that the 88 lost to follow-up patients did take study medicine; (2) it was also assumed that the 88 patients did not experience any adverse events. The combination of the two assumptions can be considered as an extreme: the result of such a analysis yielded the lowest possible AE rates.

IV. Reviewer's analysis:

Since 18% (91/496) patients did not return their medication diaries and only about 75% patients were included in sponsor's patterns of use analysis, the sponsor's result would change if different usage patterns were assumed among those who did not return medication diaries. Two analyses are performed by this reviewer to illustrate the range of possible study results. These analyses assume higher non-compliance rates in patients who did not return diaries. The assumptions made are as follows:

Assuming all the 91 patients who did not return diaries did take study medicine;

- (1) Assuming 50% compliance rate in the 91 patients, the overall compliance rate becomes 71.1% with 95% CI (67.1%-75.1%).
- (2) Assuming 0% compliance rate in the 91 patients, the overall compliance rate becomes 61.2% with 95% CI (56.8%-65.6%).

The lower limits of the 95% CI in both analyses fall below the expected 70% compliance rate.

V. Other Issue:

Based on the definition of noncompliance, only those who took more than one pill at one dose or more than two pills per day are defined as noncompliance. This definition does not capture, if any, those who took more than two pills within a 24 hours interval which covered two days, but no more than two pills within each day.

Other than the primary analysis in patterns of use analysis, the sponsor also provided many analyses including subgroup and dosage analyses. Those analyses, nevertheless, suffer the same problem as discussed above. Since those analyses will not be the focus from the medical reviewer's stand point, no further discussion is given.

VI. Conclusion:

The analyses performed by the sponsor are weak because there is insufficient discussion on handling patients who did not return diaries. The assumptions made in safety analysis were too extreme. As shown above, the target of a minimum of 70% compliance rate may or may not have achieved in this study depending on how one chooses to account for the 91 patients (18% of enrollment), who did not return their medication diaries, in the analysis.

/S/

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