- protein binding of famotidine in plasma is only about 16%, and is independent of concentration in the usual therapeutic range;

- plasma and renal clearance are quite variable in healthy people, ranging from 424 mL/minute and 316 mL/minute, respectively, in healthy young persons to 240 mL/minute and 190 mL/minute, respectively in healthy elderly persons;

- after oral administration of PEPCID tablets, peak plasma levels average 71 ng/mL for 20-mg tablets, and 132 ng/mL for 40-mg tablets. The time to peak (Tmax) averaged 2.2 hours at both doses;

- famotidine, unlike cimetidine, did not affect the PK profiles of ——— ——— diazepam, theophylline, ——————— and phenytoin in man and animals. It did not potentiate the anticoagulant effects of warfarin in humans and rats, nor prolong hexabarbital-induced sleeping time in rats;

- famotidine and ranitidine in vitro showed low affinity, cimetidine high affinity, for hepatic microsomal cytochrome P450 enzyme systems.

A comprehensive review of famotidine PKs was published in 1991 (Echizen and Ishizaki). The bioavailability of lower-dose tablets of 10-mg, film-coated tablets (FCT) was studied in Merck Research Laboratory (MRL) Studies 026 (Volume 8, pages 858-60), and was found to be 0.49 (90% confidence interval 0.42 – 0.57), compared to intravenous famotidine 10 mg, by KC Lasseter in December 1990. Other published reports described the effects of antacids on the absorption of famotidine, consistently finding that antacids somewhat reduced the absorption of famotidine, as reflected by lower maximum plasma concentration (Cmax) and area under the plasma concentration curve over time (AUC). For 40 mg famotidine tablets, concurrent administration of Mylanta II suspension (10 mL, 50.8 mEq ANC) reduced the Cmax by 25% and the AUC by 20% (Lin, et al., 1987). Another study showed that absorption of all of the four approved H2-blockers was reduced by 30 mL of double-strength Mylanta suspension (152 mEq), famotidine Cmax by 25% and AUC by 19%, with effect on the time to peak (Tmax) or half-time of elimination (Sullivan, et al., 1994). A lack of significant effect by Mylanta 25 and 50 mEq on famotidine-induced (doses of 10 and 20 mg) elevation of intragastric pH, and Cmax and AUC not much reduced (<17%), were reported in abstract by Schwartz et al. (1994).

**B. Bioequivalence of famotidine tablets and the combination tablets**

Two studies were done to investigate the bioequivalence of the previously approved 10-mg famotidine coated tablet (FCT) and the new famotidine antacid-combination tablet (FACT), Study 095 after a meal, and Study 101 after fasting. Absolute bioavailability of the FACT versus intravenous famotidine 10 mg was compared in Study 096, and the pharmacodynamic effects of the FACT compared to antacid alone and FCT and placebo on intragastric pH was in Study 098.

**1. Study 095** was carried out in June 1996 by Dr. J. Kisicki in Lincoln NE, upon 24 healthy volunteers, 11 men and 13 women, ranging in age from 19 to 44 (median 26) years. Each participant took in random sequence either the marketed FCT or the new FACT

immediately **after eating a standard breakfast** of orange juice, 1% milk, egg O'muffin, and hash-browned potatoes, and then returned a week later for the other preparation. Participants were not allowed coffee or tea, alcohol, or smoking for 24 hours before and after the study day, but they were given a light meal 4 hours after taking the study medication, and were allowed to eat normally thereafter. Blood samples were collected at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 12, 14, and 24 hours. *(Volume 7, pages 1-225.)*

Plasma levels of famotidine were almost identical, for arithmetic and geometric means of the group, and for each individual participant. This resulted in PK data indicating close bioequivalence of the two preparations *(Table 6, sponsor's report)*:

| | Tmax | Cmax | $AUC_{0-\infty}$ |
|---|---|---|---|
| | *hr* | *ng/mL* | *ng-hr/mL* |
| FACT | 2.90 | 37.13 | 252.10 |
| FCT | 2.86 | 38.57 | 243.77 |

The ratios of the geometric mean values for the new FACT, compared to the approved FCT product, were 0.96 (90% confidence interval, 0.91 to 1.02) for Cmax, and 1.03 (90% confidence interval, 0.99 to 1.09) for $AUC_{0-\infty}$. These ratios were very well within the limits of 0.80 to 1.25 set for establishing bioequivalence for both the rate and extent of famotidine absorption.

*Comment: Since physicians usually instruct patients to take antacids after meals, this study provides data that support the practice of medicine and indicate that the bioavailability of famotidine is fully as good using the new FACT preparation as for the approved FCT product. The arithmetic means are even closer than the geometric means: 37.8±6.6 ng/mL for FACT and 38.7±8.3 ng/mL for FCT; 257.8±51.3 ng-hr/mL for FACT and 244.5±52.6 ng-hr/mL for FCT. The results show near-identity of the two preparations, within limits of measurement error and individual variations.*

*It was reported by Schwartz and colleagues (abstract, 1994) that taking famotidine 10 mg tablets with 1 or 2 chewable tablets of Mylanta II (25 or 50 mEq ANC) after a standard meal had little effect on plasma famotidine AUC or Cmax , compared with famotidine tablets alone or taking the famotidine tablets with placebo. Intragastric pH values measured over 12 hours increased as expected after eating, and the famotidine prolonged the pH rises, by the addition of antacid had no significant effect on the pharmacodynamics of the famotidine .*

**2.** **Study 101** was carried out in October 1996 by Dr. A. Laurent in Austin TX, upon 24 healthy volunteers, 14 men and 10 women, ranging in age from 18 to 39 (median 25.5) years. Each participant took in random sequence either the marketed FCT or the new FACT with 120 mL of water, after **fasting** overnight, and then returned a week later for the other preparation. Participants were not allowed coffee or tea, alcohol, or smoking for 24 hours before and after the study day, but they were given a light meal 4 hours after taking the study medication, and were allowed to eat normally thereafter. Blood samples were collected at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 12, 14, and 24 hours. (Volume 7, pages 599-845.)

Plasma levels of famotidine showed more rapid and extensive absorption after FCT than FACT, for arithmetic and geometric means of the group, and for each individual participant. This resulted in PK data indicating considerably less bioequivalence of the two preparations when taken in the fasting state than after a breakfast meal, but with ratios still within the established range of 0.80 to 1.25 for bioequivalence (Table 5, sponsor's report):

| | Tmax | Cmax | $AUC_{0-\infty}$ |
|---|---|---|---|
| | *hr* | *ng/mL* | *ng-hr/mL* |
| FACT | 2.36 | 49.80 | 277.82 |
| FCT | 1.84 | 53.79 | 296.69 |

The ratios of the geometric mean values for the new FACT, compared to the approved FCT product, were 0.93 (90% confidence interval, 0.84 to 1.02) for Cmax, and 0.94 (90% confidence interval, 0.86 to 1.01) for $AUC_{0-\infty}$. These ratios were still within the limits of 0.80 to 1.25 set for establishing bioequivalence for both the rate and extent of famotidine absorption. It was also noted that there was an effect of whether FCT was taken first or second in this study, the differences being much greater when FCT was taken first. When FACT was taken first, the FCT absorption was actually a little less rapid and extensive.

| | | FACT | FCT | FACT/FCT | 90% C.I. | p,treatment | p,period |
|---|---|---|---|---|---|---|---|
| Cmax | Period 1 | *47.05* | *59.68* | *0.79* | | | |
| *ng/mL* | Period 2 | *52.71* | *48.48* | *1.09* | | | |
| | Combined | 49.80 | 53.79 | 0.93 | 0.84-1.02 | 0.18 | 0.41 |
| $AUC_{0-\infty}$ | Period 1 | *269.49* | *322.34* | *0.84* | | | |
| *ng-hr/mL* | Period 2 | *286.42* | *273.09* | *1.05* | | | |
| | Combined | 277.82 | 296.69 | 0.94 | 0.86-1.01 | 0.18 | 0.28 |

*Comment: Although the period differences were not statistically significant, the apparent effects are intriguing. The medications were administered 5 to 7 days apart, and it is difficult to imagine a carryover effect of a medication as short-lived as an antacid, or even famotidine, to have such a remarkable effect a week later. If the study had not been designed to have a random sequence of administration of the two products, the FACT preparation might have failed bioequivalence by criteria of 0.80-1.25 ratio of Cmax.*

**Plasma Famotidine After FACT/FCT, Fasting, Study 101**

**Plasma Famotidine After FACT/FCT, After Breakfast, Study 095**

*The graphically displayed absorption curves for plasma famotidine after taking FCT or FACT in the fed and fasting states allows a visual comparison:*

*It is evident that taking either preparation after a breakfast meal slows and reduces the absorption of the famotidine, and also removes any difference in the uptake of drug. In the fasted state, the FCT is absorbed somewhat faster on average. None of these differences would be expected to have any clinical effects, and probably little or no pharmacodynamic effect on reduction of gastric acidity. (Data for mean plasma famotidine at each time point were taken from sponsor's reports in Volume 7, Tables 4 & 5, pages 8 & 9 of Study Report 095, and from Tables 4 & 5, pages 7 & 8 of Study Report 101.)*

*A slight increase in famotidine absorption was reported (Lin, et al., 1987) as a short report, based on a 12% increase in urinary excretion of unchanged drug after 40 mg oral tablets of famotidine, despite almost no change in Cmax or AUC, when given after standard breakfast. This putative increase in famotidine absorption when FACT or FCT were taken after food was not reflected in these studies, at least not by AUC measurements, although no urinary recoveries were done.*

**C. Bioavailability of the new FACT product**

**1. Study 096** was carried out by Dr. T. Bjornsson in Philadelphia in July 1996 to determine the bioavailability of the FACT product (formulation C-675-8C, the same as to be marketed), compared to intravenous (I.V.) famotidine 10 mg. Participants were 13 healthy adults, 9 men and 4 women of median age 26 years (range 22 to 42) who were scheduled to be studied on two days a week apart, to receive in random order either one FACT or an I.V. bolus of famotidine 10 mg (of the approved prescription product PEPCID® Injection 10 mg/mL). Subject 007, a 40-year-old white male, withdrew after the FACT administration and did not receive the I.V. dose; he was replaced by Subject 107, a 24-year-old white male who completed both studies. There were therefore 12 participants, 8 men and 4 women, who had paired data sets. Participants arrived at the study center in the morning, after an overnight fast, received the study medication and were observed for 24 hours in the center. Blood samples were collected at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, and 24 hours on each study day, and also at 10, 20 and 45 minutes after I.V. dosing.

Comparison of the geometric means of the $AUC_{0-\infty}$ values for the two formulations resulted in an absolute bioavailability of 0.53 (90% C.I., 0.48-0.60). The half-time for plasma famotidine, determined from the I.V. doses, was 3.1 ± 0.6 hr. It was also found that the FACT dissolution rate was 98% in 15 minutes, then 101, 102, 102% at 30, 45, and 60 minutes, respectively.

*Comment: The new FACT product was somewhat more bioavailable than the 20 or 40 mg marketed prescription PEPCID® tablets, described in the labeling as 40-45% bioavailable. The rapid dissolution rate of the FACT formulation, plus the administration as a chewable tablets to be broken up by chewing and moistened by saliva, then washed down with water, may account for the observed greater bioavailability of the FACT product.*

*It is of some interest that the extent of absorption of famotidine (by AUC data) from FACT given to fasting study participants in Study 096 was considerably less than observed in Study 101. This was also true for mean Cmax values. As observed, the famotidine absorption from FACT in the bioavailability Study 096 was closer to that seen in the fed subjects of bioequivalence Study 095:*

| | Cmax | Tmax | $AUC_{0-\infty}$ |
|---|---|---|---|
| | ng/mL | hr | ng-hr/mL |
| Study 095: after meal vs FCT | 37.13 | 2.90 | 252.10 |
| Study 101: fasting vs FCT | 49.80 | 2.36 | 277.82 |
| Study 096: oral FCT vs I.V. famotidine 10 mg | 38.72 | 2.50 | 233.35 |

**D. Pharmacodynamics**

**1. Study 098** was a four-period, open-label, crossover comparison of the pharmacodynamic effect on esophageal and intragastric pH of the four preparations that were to be used in the clinical studies. It was carried out in [redacted] from August 1996 through March 1997 on 27 participants with histories of food-induced heartburn of at least 2 months duration and at least 3 episodes per week. Participants consented to have four sequential transnasal catheterizations at intervals of 3 to 14 days, each lasting about 15 hours.

The rationale for the study design was to prove primarily that the FACT product would be better than FCT in raising esophageal pH during the first hour after dosing, and better than antacid in keeping the intragastric pH higher between 5 and 9 hours after dosing. Secondarily, it was hoped that FACT would be comparable to antacid in raising esophageal pH during the first hour after dosing, and comparable to FCT in keeping the intragastric pH higher between 5 and 9 hours after dosing. It was also planned to compare times of gastric pH >3, esophageal pH <4, number and duration of esophageal reflux episodes.

The protocol prohibited participants from using alcohol for at least 24 hours before reporting, to eat a light lunch before noon and only clear liquids thereafter until reporting to the study site. Participants reported to the study center at about 4 p.m., had the catheters placed with the esophageal probe at 5 cm above the esophagogastric junction and the gastric probe in the stomach at 5 p.m. A 1-hour baseline pH recording was done, capturing pH data every 4 seconds in a solid-sate recorder [redacted] after which they ate a standard meal of hamburger, french-fried potatoes, and an 8-ounce chocolate milkshake, the food in quantity sufficient to cause them to feel full. The meal was to be consumed over 30 minutes, after which pH was monitored for another hour. Participants who did not reach pH of <2.5 on two successive readings 5 minutes apart within that hour at the first visit were excluded from the study. Those who qualified were then given, an hour after completing the meal, a sequence of study medications over the four visits, at each of which the same meal was administered and the pH data collected. Four sequences were designated, and participants were randomly assigned to a sequence: 1) F-C-P-A; 2) C-A-F-P; 3) A-P-C-F; 4) P-F-A-C (where C = FACT, F = FCT, A = antacid, and P = placebo).

Not all of the 27 participants were able to complete this demanding series of four transnasal, overnight catheterizations of their stomachs, but 23 did so and provided comparative data for all four study medications. Participant AN 0007 did not qualify at the first study, and AN 0010 quit during the first study because of mild vomiting after taking FCT, and later flatulence. Participant AN 0022 did not wish to continue after the second treatment and was replaced by AN 0122, who completed three studies but then withdrew because of pregnancy (later delivered a healthy son). A total of 61 participants were solicited or screened to obtain the final 23 who completed the four studies, but 34 were not randomized *(9 did not return the telephone calls, 4 were not interested when details were described, 7 refused overnight stays, 3 would not be catheterized, 5 did not show up for screening, 3 did not meet inclusion criteria when screened, and 3 could not tolerate insertion of the pH probes [Volume 7, page 598] ).*

The study medication was taken one hour after participants completed eating the provocative fatty-chocolate meals, and at each visit consisted of one chewable tablet to be thoroughly chewed and the fragments swallowed, and one tablet simply to be swallowed afterward, washed down by 60 mL of water. The chewable tablets could be FACT (formulation C-675-8C), an antacid tablet of the same composition but with 10 mg of microcrystalline cellulose substituted for the famotidine (formulation C-659-1A), the famotidine without antacid (FCT), or the double placebo chewable tablet with neither antacid (no acid-neutralizing capacity) or famotidine in it, the difference being made up by extra microcrystalline cellulose and sugar. The tablets for swallowing could be either the marketed famotidine 10-mg OTC tablets or a placebo in which 5 mg each of microcrystalline cellulose and pregelatinized starch were substituted for the famotidine. For regimen C, participants chewed one FACT and swallowed a placebo FCT; for regimen F, they chewed a double placebo tablet and swallowed one FCT. For regimen A, they chewed an antacid tablet without famotidine and swallowed a placebo FCT; and for regimen P, they chewed a double placebo tablet and swallowed a placebo FCT.

Comparing esophageal pH geometric means (GM) for AUC over the first 60 minutes after dosing with medication, it was found that the $AUC_{0-60}$ under the esophageal pH curve showed that the FACT and chewable antacid tablets led to very similar results, not statistically different. Both were better than either placebo or famotidine alone, which were very similar to each other.

| | $AUC_{0-60}$ | ln | GM |
|---|---|---|---|
| | GMs of 23 | mean | standard error |
| FACT | 5.99 | 1.79 | 0.019 |
| FCT | 5.19 | 1.65 | 0.019 |
| Antacid | 6.00 | 1.79 | 0.019 |
| Placebo | 5.11 | 1.63 | 0.019 |

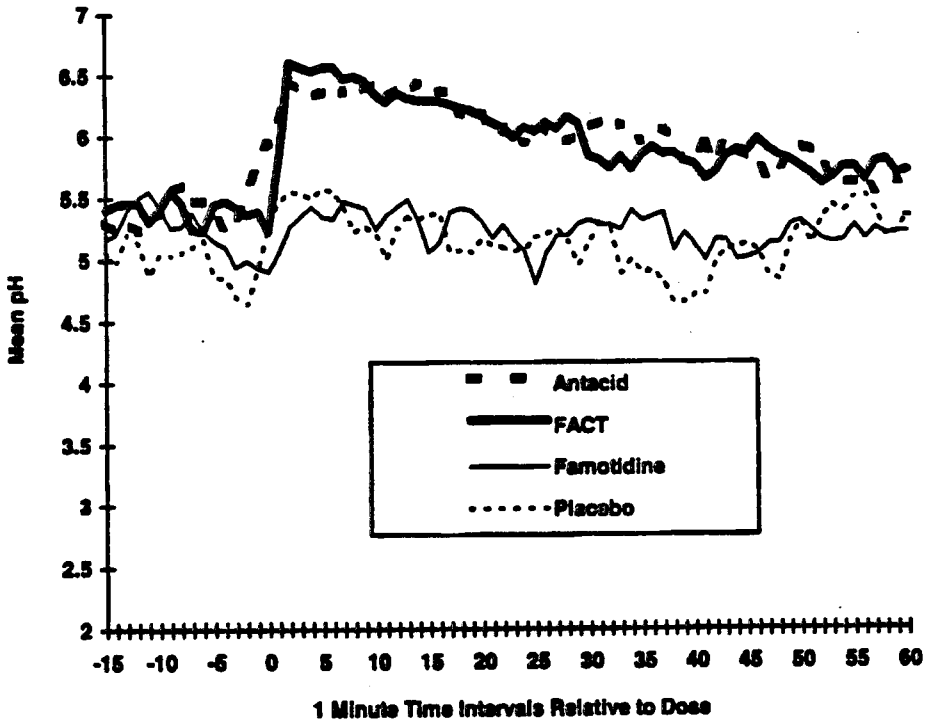
Another measure of pharmacodynamic effect considered secondarily was episodes of reflux of acidic gastric fluid into the esophagus.

NUMBER AND DURATION OF ESOPHAGEAL REFLUX EPISODES

| | episodes of esophageal reflux | |
|---|---|---|
| | *number ± S.E. (of 23)* | *duration ± S.E., minutes* |
| FACT | 1.96 ± 0.53 | 0.25 ± 0.12 |
| FCT | 4.76 ± 0.53 | 0.95 ± 0.12 |
| Antacid | 2.57 ± 0.53 | 0.30 ± 0.12 |
| Placebo | 5.39 ± 0.53 | 0.94 ± 0.12 |

The esophageal pH curves over the first hour were not statistically different (p = 0.931) for FACT and antacid, nor for FCT and placebo (p = 0.554), but both FACT and antacid were better very significantly (p <0.001) than either FCT or placebo. *(Volume 7, pages 447 and 449)*:

Figure 7 Esophageal pH Means at 1-Minute Time Intervals Relative to Dose: 0 to 60 Minutes Postdose (n=23) (Protocol 098)

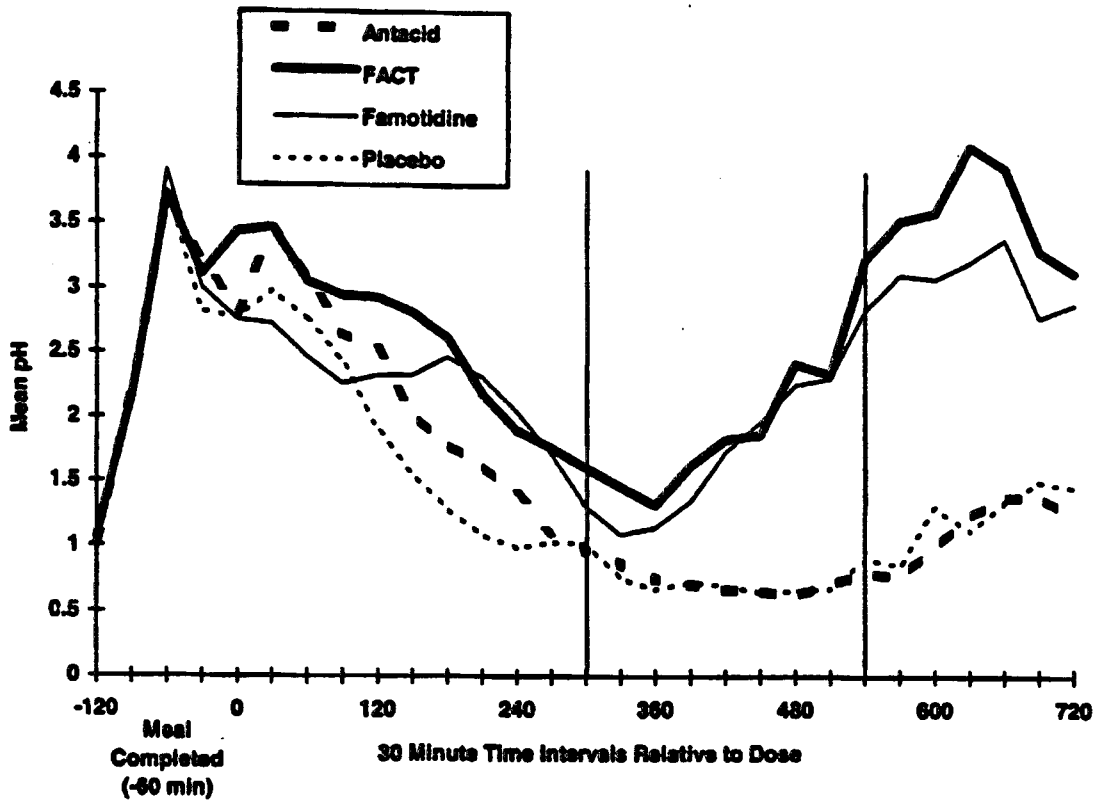



An episode of acidic reflux was counted as a drop from pH 5 or more to 4 or below; the number (± standard error, S.E.) of such episodes in the hour, and the mean duration (± standard error, S.E.) of each in minutes were compared. These results, again, showed FACT and antacid to be very similar, not statistically significantly different (p = 0.420 for number, 0.735 for duration), FCT and placebo also to be almost the same (p = 0.408 for number, 0.948 for duration). Both FACT and antacid were significantly better than either FCT or placebo with respect to both number and duration of esophageal reflux episodes, as defined by esophageal pH decreases (p <0.001 for all except antacid vs FCT, which was <0.005).

For the time esophageal pH was less than 4 out of the first 60 minutes after dosing, once more FACT (0.50 minutes) and antacid (0.83 minutes) were much better than either FCT (7.30 minutes) or placebo (8.21 minutes), all very significant ($p < 0.001$). The FACT and antacid were not statistically significantly different from each other ($p = 0.531$), nor were FCT and placebo from each other ($p = 0.593$).

The other principal comparison was between the four study preparations for raising the $AUC_{5-9}$ for intragastric pH over the period from 5 to 9 hours after dosing, as a measure of duration of the effect on suppressing gastric acidity. *(Volume 7, pages 451)*:

Figure 8 Gastric pH Means at 30-Minute Time Intervals Relative to Dose (n=23) (Protocol 098)




*Comment: It was seen that the intragastric pH rose in all participants after ingestion of the meal, from about 1 before eating to about 3.75 afterward. An hour after eating, when medications were given, the geometric mean pH had fallen to about 2.8 (except 3.4 before participants got FACT).*

Analysis of the $AUC_{5-9}$ of intragastric pH between 5 and 9 hours after dosing showed geometric mean (GM) values for the famotidine-containing preparations, FACT and FCT, to be significantly ($p < 0.001$) higher than for antacid or placebo:

| | $AUC_{5-9}$ | ln | GM |
|---|---|---|---|
| | GMs of 23 | Mean | standard error |
| FACT | 1.68 | 0.52 | 0.089 |
| FCT | 1.52 | 0.42 | 0.089 |
| Antacid | 0.69 | -0.38 | 0.089 |
| Placebo | 0.70 | -0.36 | 0.089 |

The FACT product was at least as good as FCT, if not slightly better, but the difference was not statistically significant ($p = 0.442$). The antacid effects had long since disappeared, and the results were not different than placebo ($p = 0.891$).

The time in minutes, out of the 240 minutes between 5 and 9 hours after dosing, also reflected the longer duration of acid suppression by the famotidine-containing products. For the time esophageal pH was 3 or more out of the 240 minutes from 5 to 9 hours after dosing FACT (41.3 minutes) and FCT (27.5 minutes) were very much better than either antacid (0.05 minutes) or placebo (0.26 minutes), all very significant ($p < 0.001$). The FACT and FCT were not statistically significantly different from each other ($p = 0.208$), nor were antacid and placebo from each other ($p = 0.769$).

*Comment: The protocol of Study 098 allowed the use of "rescue" MYLANTA® tablets if needed for symptoms occurring after 2 hours later than study medication was taken. However, neither the occurrence nor severity of heartburn or other symptoms, nor the use of rescue antacids were recorded on the case report forms and no analyses were done to correlate those observations with the pH recordings.*

It was concluded by the sponsor (Volume 7, page 465) that the antacid-containing products (FACT and antacid without famotidine) were about equally effective in raising esophageal pH during the first hour after dosing. It was also concluded that the famotidine-containing products (FACT and FCT) were about equally effective in keeping intragastric pH higher for longer times, in the range of sleeping time overnight. It was also evident that FACT, the only product that contained both famotidine and antacid, was better than FCT for keeping esophageal pH elevated for the first hour and better than antacid for keeping intragastric pH elevated at 5-9 hours after dosing.

*Comment: The choice of the period of 5 to 9 hours after dosing may have been arbitrary, and the graphic display suggests that the results would be even more impressive if taken from 6 to 10 or 11 hours after dosing. The postprandial decline of pH was slowed but not prevented by addition of famotidine, but it is notable that the mean decline after famotidine-containing products never reached below pH 1, in this study.*

# IV. Clinical Studies

Six clinical studies involving 4944 participants were carried out in support of the efficacy of the combination FACT product. These included two preliminary studies: 1) an antacid dose-ranging study to compare 21 and 42 mEq of acid neutralizing capacity in 474 participants (Study 078), and 2) a pilot investigation (Study 104) of onset and duration of evening heartburn relief at home in 329 participants, and a follow-up study of open-label, pattern-of-use observation of 496 participants (Study 111). Three large, factorial studies in 3645 participants provided the principal efficacy data. These included two single-dose studies of daytime, at-home (Study 106; 1266 participants) and evening, in-clinic with provocative meal (Study 109; 1139 participants) assessments of onset and duration of relief of heartburn, and a four-episode, at-home observation (Study 110; 1240 participants) of the same endpoints.

All of the six clinical studies, as well as the pharmacodynamic Study 098 described above, were done with the same four study preparations:

1) the proposed new chewable FACT product containing 10 mg famotidine and an antacid mixture of 800 mg of $CaCO_3$ and 165 mg of $Mg(OH)_2$ , 21 mEq of ANC (formulation C-675-8C, the same as to be marketed if approved);
2) approved FCT for simple swallowing, currently on the OTC market, containing 10 mg famotidine but no antacid (formulation C-681-1F; 0208FCT047D003); or its matching placebo with no famotidine (P0208FCT047D004).
3) a chewable antacid tablet containing the same ingredients as the FACT but without any famotidine (C-659-1A); and
4) placebo tablets resembling the chewable product but without either famotidine or antacid and placebo FCT with no famotidine (C-657-1B).

A given dose of study medication involved taking two tablets, one to chew thoroughly and one just to swallow. Participants were instructed first to chew the chewable tablet from Bottle A, swallow the fragments, and then to swallow the tablet from Bottle B with 2 ounces of water. Bottle A could contain one of three types of chewable tablets: FACT, antacid without famotidine, or double-placebo containing neither famotidine nor antacid. Bottle B could contain tablets, for simple swallowing with water, of either the marketed FCT product or a matching placebo containing no famotidine.

## A. Preliminary clinical studies

**1. Study 078**, a clinical antacid dose-ranging trial, was done in October-November 1995 by . to determine if 21 mEq of ANC was sufficient, or if twice that was needed. This was needed to establish the composition of the FACT preparation, specifically whether two tablets each with 5 mg of famotidine and 21 mEq of ANC should be in the product to be marketed, or whether one tablet containing 10 mg of famotidine and 21 mEq ANC would be enough. The weight and size of a single tablet containing 42 mEq of ANC (1600 mg $CaCO_3$ and 370 mg $Mg(OH)_2$, plus famotidine and excipients), was considered unacceptably large.

The study *(Volume 11, page 1107 to Volume 12, page 1498)* compared antacid ANC doses of 21 and 42 mEq, with famotidine 10 mg alone, or placebo, in 474 adult participants. To be qualified to enroll, they had to have had at least two months' history of meal-induced heartburn with at least 3 episodes per week and some episodes of nocturnal heartburn, but were otherwise generally healthy. Participants were able to identify specific foods or beverages that induced heartburn symptoms, and used antacids for relief. Three centers participated, each screening over 200 participants to find and study approximately 160 who qualified. Participants reported to each clinic about 5 p.m., after which they consumed a standard provocative meal of Wendy's® chili and onion-cheese seasoning mix and iced tea at 6 p.m. After beginning the meal, participants rated the severity of their heartburn symptoms (0 = none, 1 = mild, 2 = moderate, or 3 = severe) every 10 minutes. If symptoms reached moderate severity, they took one dose of study medication then recorded symptom severity every 10 minutes for 2 hours, then they provided a retrospective global assessment on their Diary Card #1. Participants were released from the study centers at about 9:30 p.m., then took home an overnight Diary Card #2, a snack consisting of a brownie and 8 ounces of Hawaiian Punch to take at bedtime, and a supply of MYLANTA™ Double Strength chewable antacid tablets (each containing 700 mg $CaCO_3$ and 300 mg $Mg(OH)_2$, 24.3 mEq). They were retire by 11 p.m., after eating the snack at 10:30, and were instructed to record the number of nocturnal awakenings because of heartburn, use of antacid tablets, heartburn on waking in the morning, and a global assessment. They were not to eat or drink anything else until after Diary Card #2 was completed, and to return to the clinic within 3 days to turn in the cards and report adverse effects. Some of the participants who participated did not develop at least moderate heartburn after the provocative meal, and they received no study medication (Lanza, 26; Melisch, 81; and Miller, 36; total 149). Another 6 participants were excluded by Melisch because they had some heartburn before the meal and were not given the chili/iced tea. Thus, of 623 participants who were given the meal, 474 were treated with study medication.

| | *recruited* | *given meal* | *studied* | *antacid 21* | *antacid 42* | *famotidine* | *placebo* |
|---|---|---|---|---|---|---|---|
| Lanza | *189* | *189* | 163 | 41 | 40 | 41 | 41 |
| Melisch | *252* | *246* | 159 | 40 | 40 | 39 | 40 |
| Miller | *188* | *188* | 152 | 38 | 38 | 38 | 38 |
| total | *629* | *623* | **474** | **119** | **118** | **118** | **119** |

The participants studied included 138 men and 336 women aged 16 to 70 (median 38) years, mostly Caucasian (63.7%) but with substantial numbers of Blacks (29.5%) and Hispanics (6.8%). Heartburn symptoms in response to the provocative spicy meal were of moderate severity in 95.1%, severe in 4.4%, and mild in 0.4% (2 participants in the placebo group who were treated in violation of the protocol). All 474 participants completed the study. Results were *(Volume 11:1114)*:

| | antacid 21 | antacid 42 | famotidine | placebo |
|---|---|---|---|---|
| | 119 | 118 | 118 | 119 |
| ***Onset of relief:*** | | | | |
| **≥1 grade less within 30 minutes** | **60%[a]** | **60%[a]** | **52%[c]** | **40%** |
| Adequate relief at 30 minutes | 53%[c] | 52% | 42% | 42% |
| Good or better at 2 hours later | 50% | 53% | 45% | 50% |
| ***Duration of effect:*** | | | | |
| **no awakening with heartburn** | 35% | 31%[d] | 42%[b] | 29% |
| no problem falling asleep | 33%[d] | 37%[b] | 43%[a] | 25% |
| use of rescue antacid | 55%[d] | 50% | 44%[b] | 58% |

*Note: ; [a] p <0.01 vs. placebo; [b] p <0.05 vs. placebo; [c] 0.05<p <0.10 vs. placebo; [d] p <0.10 vs. famotidine.*

The results were taken by the sponsor to conclude that 21 mEq of antacid ANC produced similar (p = 0.941) prompt (within 30 minutes) reduction of heartburn severity as did 42 mEq. The doubling of antacid dose did not produce more prompt benefit. Famotidine 10 mg did not produce significantly (p = 0.075) more relief than placebo within 30 minutes, but was significantly more effective than placebo in helping participants fall asleep and not awaken with heartburn. The larger dose of antacid was less effective in preventing awakening than famotidine, but not significantly so (p = 0.075), and there was no difference between the two antacid doses (p = 0.512).

*Comment: It would not have been expected that antacids, in any dose, would have long-lasting effects such as overnight, and this was supported by these findings. The lack of any significant difference between the two antacid doses within the first two hours supported the selection of the 21 mEq dose to combine with famotidine 10 mg in the FACT product resulting from this study. It was also important to note that famotidine alone was only slightly but not significantly better than placebo in providing early relief of heartburn symptoms.*

*Participants seemed less able to distinguish differences between the four preparations when asked to give retrospective global assessments either at 2 hours after dosing or the next morning. The more immediate symptoms and problems such as relief of the severity of heartburn (mostly from moderate to mild or none), and whether or not they could get to sleep and stay asleep, appeared to distinguish better the effects of the several preparations.*

*It should be noted that substantial numbers of participants improved on placebo, indicating that the heartburn symptoms were often self-limiting and frequently resolved spontaneously. Only by comparing results in this manner could treatment effects truly be assessed.*

**2. Study 104** was a pilot investigation of relief of heartburn induced by a self-selected provocative meal at home by participants with histories of such symptoms. The study was carried out at four clinical practice sites [redacted] in November and December 1996. They recruited adults with histories of food or beverage-induced heartburn at least three times per week over at least two months, some episodes of nocturnal heartburn, and knowledge of what specify dietary items tended to cause symptoms for which they took antacids for relief. Participants otherwise were to have no major medical problems, not to be taking any acid-suppressing drugs or others that might interfere.

Participants reported to the clinics for screening, instructions, study medication (a chewable tablet in Bottle A, and a tablet to swallow in Bottle B), a timer, 2-ounce cup for rinse water, and a diary card. At home they were to eat a meal of their choice that they knew from experience was likely to cause heartburn on a day when no heartburn symptoms sufficient to cause them to take antacid had yet occurred. They were to eat the self-defined provocative meal between 6 and 8 p.m., take no more than two standard alcoholic drinks (12 ounces of beer, 5 ounces of wine, or 1.5 ounces of spirits). If heartburn symptoms developed within 2 hours after finishing the meal, they were to begin observing their severity and when they reached the point when they would usually take antacids, they were to chew tablet A and swallow tablet B with 2 ounces of water. They then began recording severity every 10 minutes for an hour, then at 90 and 120 minutes. (They were not to take study medication later than 2 hours after finishing the meal.) They were to eat or drink nothing else until the following morning, go to bed approximately 4 hours after finishing the meal. In the morning they were to record how many times and when they had been awakened by heartburn, if and how many of their own antacid tablets they had taken, and how in general they felt the study medication had worked: 0 = not at all, 1 = poor, 2 = fair, 3 = good, 4 = excellent *(Patient Self Rating Record, Volume 12, page 1747, is reproduced below).*

The four investigators randomized 329 participants ranging in age from 18 to 75 years, but 6 of them neither developed heartburn nor took study medications. The 6 were excluded from the modified intent-to-treat analyses of the remaining 323 participants (143 men, 180 women; 257 Caucasians, 46 Blacks, 17 Hispanics, 3 Asians).

| Investigator | FACT | FCT | antacid | placebo | Total |
|---|---|---|---|---|---|
| Free | 10 | 10 | 11 | 8 | 39 |
| Daniels | 25 | 25 | 23 | 24 | 97 |
| Epstein | 22 | 22 | 21 | 22 | 87 |
| Gutman | 25 | 25 | 25 | 25 | 100 |
| total | 82 | 82 | 80 | 79 | 323 |

The antacids most commonly used during the study were calcium carbonate (78 participants, 24%), dihydroxyaluminum sodium carbonate (39, 12%), aluminum & magnesium hydroxides with simethicone (18, 6%), aluminum & magnesium hydroxides (17, 5%). Of the 323 participants, 11 did not provide any data, but 312 definitely took study medication, and 306 completed the study. Treatment failure was determined if "rescue" antacid medication was taken. There were none who took such antacids within 30 minutes after dosing with study medication, but substantial numbers of participants who did so later:

| | FACT | FCT | antacid | placebo | total |
|---|---|---|---|---|---|
| | 81 | 79 | 77 | 75 | 312 |
| Within 30' | 0 | 0 | 0 | 0 | 0 |
| Before bed | 7 (8.6%) | 10 (12.7%) | 7 (9.1%) | 10 (13.3%) | 34 (10.9%) |
| During night | 5 (6.2%) | 5 (6.3%) | 12 (15.6%) | 5 (6.7%) | 27 (8.7%) |
| Both | 1 (1.2%) | 2 (2.5%) | 2 (2.6%) | 4 (5.3%) | 9 (2.9%) |
| total | 13 (16.0%) | 17 (21.5%) | 21 (27.3%) | 19 (25.3%) | 70 (22.4%) |

FACT (p = 0.014) and antacid (p = 0.015), but not FCT (p = 0.456), were significantly better than placebo in providing "adequate relief" of heartburn at 30 minutes after dosing with study medication.

| treatment | N | adequate relief at 30 minutes, %, 95% C.I. |
|---|---|---|
| FACT | 81 | 31 (38%; 25-49%) |
| FCT | 79 | 20 (25%; 16-35%) |
| Antacid | 77 | 29 (38%; 27-48%) |
| Placebo | 74 | 15 (20%; 11-29%) |

However, the pre-study estimation had been made that antacid or FACT would relieve heartburn within 30 minutes in 50 to 80% of participants. Although they did so more often than FCT or placebo, the results were less dramatic than had been predicted by the *sponsor (Volume 12, pages 1535-6 and 1558)*. It was noted that FACT and antacid treatment led to slightly shorter times to adequate relief of heartburn, and to slightly more participants who reported at least reduction in severity of the symptoms, but the differences from FCT and placebo were not statistically significant *(Volume 12, pages 1539-41 and 1544-6)*.

Although FACT and FCT led to slightly fewer participants awakened by heartburn, the results were not significantly better than after antacids or placebo; most (about 70%) of the participants slept through the night. Participants who needed and took rescue antacids during the night provided another measure of clinical benefit, and third measure was the participants' retrospective morning recollection of how well the medication worked during the night. Results are summarized below:

| | | not awakened at night | night rescue antacids | overall good night |
|---|---|---|---|---|
| | | *participants - %, 95% C.I.* | *participants - %, 95% C.I.* | *participants - %, 95% C.I.* |
| FACT | 81 | 60 – 74%, 65-84% | 6 – 7%, 3-15% | 45 – 56%, 45-66% |
| FCT | 79 | 56 – 71%, 61-81% | 7 – 9%, 4-17% | 33 – 42%, 31-53% |
| Antacid | 77 | 53 – 69%, 58-79% | 14 – 18%, 10-27% | 42 – 55%, 43-66% |
| Placebo | 75 | 50 – 67%, 56-77% | 9 – 12%, 6-22% | 27 – 36%, 25-47% |
| *total* | *312* | *291 – 70%* | *36 – 12%* | *147 – 47%* |

Comparisons of treatment, by chi-square test, showed only one statistically significant difference between treatments in the proportions of participants with these responses, namely the superiority of FACT over antacid (p = 0.046) in rescue antacid taken. Although FCT was also better than antacid in this respect, the result was not statistically significant (p = 0.093) in this pilot study. In this study, neither FACT nor FCT were significantly better than placebo, however, in reducing the proportions of participants taking nocturnal antacids. The awakenings during the night were almost the same regardless of treatment after the previous evening after the meal, and the morning overall, global assessments also showed only that FACT and antacid were better than placebo (p = 0.013 and 0.019, respectively); the other comparisons showed no significant differences.

The sponsor in the protocol *(Volume 12, page 1695)* estimated that about 80 participants per study arm would be sufficient to show significant differences on adequate heartburn relief at 30

minutes after dosing, and no awakenings with heartburn during the night. These estimates were based on a previous study (Protocol 078, the dose-ranging study summarized above) of famotidine 10 mg alone, antacid 21 mEq of ANC, and placebo given after a similar provocative evening meal. In that study, adequate heartburn relief at 30 minutes after dosing was a secondary outcome measure that showed this in 50/118 (42.4%) participants after famotidine, 63/119 (52.9%) after antacid 21 mEq, and 50/199 (42.0%) after placebo. . Also from that study, no awakenings with heartburn were reported as a primary outcome measure by 50/118 (42.4%) after famotidine, 42/119 (35.3%) after antacid 21 mEq, and 35/119 (29.4%) after placebo. From those results, the sponsor estimated that between 50 and 80% of FACT or antacid-treated participants, but only 30-60% of FCT or placebo-treated participants would show the prompt effect. Between 40 and 70% of FACT or FCT were expected to show the nocturnal effect, versus only 20-50% after antacid or placebo.

In discussion of the results of the pilot study 104, the sponsor states that the approximately 75 participants per study arm were *not expected* to show significant differences between treatment groups *(Volume 12, page 1559)*. It was discussed that the large numbers of participants awakening with heartburn, and the small proportions of them who used rescue antacids, were not expected, and alternative study designs were considered.

*Comment: This pilot study revealed that the immediate effects of treatment on what they judged to be adequate relief of symptoms seemed to be a more powerful measure of clinical benefit than time to relief or reduction in grade of severity of heartburn. For the longer duration of effects, the need to use antacids during the night was more powerful in revealing differences than just waking at night or retrospective global assessments in the morning. The very considerable placebo effects on all the measures showed that spontaneous recovery, wishful thinking, and the hope of benefit could not be ignored in trying to determine if treatment truly provided additional clinical benefit. The differences between treatments were not so large that studies with relatively small numbers of participants could be contemplated for the definitive studies. The pilot study did show what should be looked for, and provided some estimates of what study sizes might be needed. It is interesting that the predictions of what proportions of participants would respond promptly to treatment (adequate relief of heartburn at 30 minutes) were correct, but the differences between the FACT/antacid and the FCT/placebo were much less than the 20% differences between the predicted ranges of results. For the effects on awakening with heartburn sufficient to require rescue antacids, the results in this pilot study that smaller-than-predicted proportions of participants actually took antacids, 7 and 9% after FACT and FCT (instead of predicted 58% after FCT), and only 18% and 12% after antacids and placebo (instead of predicted 65% and 71%). It was speculated that enrollment of participants with histories of frequent nocturnal heartburn, or having them eat a bedtime snack, might enhance the sensitivity of the design to detect treatment differences. It was also apparent that quite large numbers of participants would have to be studied if statistically significant differences in treatment were to be shown, even though the preliminary results were in the predicted directions.*

**B. Principal efficacy studies**

**1. Study 106** was designed to investigate single-dose, at-home-daytime onset and duration of relief of spontaneously occurring heartburn during waking and active hours. Five investigators screened 1500 and randomized 1266 participants with histories of at least three episodes per week of heartburn for at least two months and experience with what specific foods or drinks caused symptoms and use of antacids to relieve them. The studies were carried out in March to June 1997 by Drs. M. Epstein (Annapolis MD), D. Gutman (Bethpage NY), E. Harris (Whittier CA), S. Plevin (Palm Harbor FL), and J. Kisicki (Lincoln NE). Participants were screened in offices of the physicians, and 234 were excluded from randomization because they did not meet inclusion/exclusion criteria (76), had disqualifying medical histories (73), did not use or get relief from antacids (30), were taking prohibited other medications (25), lived too far away (13), did not have spontaneous or daytime heartburn (7), were from the same family as other participants (2), or for miscellaneous other reasons (8).

Eligible participants were randomized to receive a chewable tablet and another tablet to be swallowed with 60 mL of water, upon development before 3 p.m. of mild, moderate, or severe heartburn. The medication could be FACT (formulation C-675-8C), placebo antacid with FCT, antacid 21 mEq ANC with placebo famotidine, or double placebo. Participants were instructed to record the time and severity of the heartburn, notify their study center that they were taking medication, and to record on their diary cards every 15 minutes for 2 hours, and at 3 and 4 hours, the severity of heartburn symptoms (none, mild, moderate, severe) and whether adequate relief had been obtained. At 4 hours after taking the study medication, if their heartburn was no worse than mild, participants were to eat one of two possible provocative meals, either 1) pizza or 2) lasagna, depending on which their experience indicated caused them to have heartburn symptoms. All of the participants were also to drink 12 ounces of cola and a chocolate brownie; all of the food and drink were to be eaten within 30 minutes, and symptoms were to be recorded every 30 minutes for 4 more hours. Rescue treatment with two MYLANTA™ Double Strength antacid tablets (48 mEq ANC) was allowed 2 hours or more after the study medication, if participants had heartburn of severity they would ordinarily treat with an antacid.

The five investigators randomized 1266 participants ranging in age from 18 to 88 (median 38), 487 men and 779 women. Of those randomized, 26 never developed heartburn and never took any study medication and 3 others withdrew before taking medication, so no data were obtained for 29 participants, leaving 1237 whose data could have been analyzed. No data were entered on diary cards by 9 of them, 2 did not turn in diary cards, and 1 admitted falsifying her entries. This left only 1225 participants for whom efficacy data (all-participants-treated set) could be assessed (308 on FACT, 306 on FCT, 304 on antacid, and 307 on placebo). Another 2 participants turned in no pre-treatment information, and so could not be assessed for time to adequate relief or time to reduction in severity of heartburn by at least one grade. Other participants (98) had some missing data for the onset period from 0 to 4 hours after study medication was taken, and 290 participants did not report complete data for the 4 hours after the meal, which 115 of them did not eat. The safety analyses were carried out on 1237 (the "safety" set), assuming they had taken study medication, even though no results were recorded. About 50% of the participants chose pizza, 40% lasagna, and 10% neither (most, 112/127, because they were designated as failing treatment before the meal).

| *Investigator* | *participants* | *FACT* | *FCT* | *antacid* | *placebo* |
|---|---|---|---|---|---|
| Epstein | 419 | 105 | 104 | 105 | 105 |
| Gutman | 202 | 51 | 50 | 49 | 52 |
| Harris | 203 | 51 | 51 | 50 | 51 |
| Plevin | 205 | 51 | 52 | 51 | 51 |
| Kisicki | 208 | 51 | 54 | 51 | 52 |
| *Total* | *1237* | *309* | *311* | *306* | *311* |

The efficacy results were based on varying numbers of participants for whom data were reported by the participants and available for analyses. The primary outcome measures were 1) proportions of participants reporting adequate relief of symptoms at 30 minutes after dosing for the onset assessment, and 2) peak heartburn severity after the meal, 4 to 8 hours after the dose of study medication. Treatment failure, defined as heartburn before the meal, need for rescue antacid before the meal, or need for antacid after the meal, occurred as follows:

| | *FACT (306)* | *FCT (308)* | *antacid (304)* | *placebo (307)* | total (1225) |
|---|---|---|---|---|---|
| Pre-meal heartburn | 8 (2.6%) | 10 (3.2%) | 11 (3.6%) | 14 (4.6%) | 43 (3.5%) |
| Pre-meal rescue antacid | 7 (2.3%) | 4 (1.3%) | 10 (3.3%) | 4 (1.3%) | 25 (2.0%) |
| Post-meal rescue antacid | 10 (3.3%) | 19 (6.2%) | 14 (4.6%) | 18 (5.9%) | 61 (5.0%) |
| Total treatment failures | 41 (13.4%) | 49 (15.9%) | 55 (18.1%) | 48 (15.6%) | 193 (15.8%) |

*Comment: There were no statistically significant differences between treatment groups with respect to total number of participants who had one or another type of treatment failure, nor for any of the subtypes of defined treatment failure. The FACT treatment was slightly better than any of the others, but even with these substantial numbers of participants, the results were not statistically significant.*

The primary outcome measure of promptness of onset efficacy was predefined as proportions of participants reporting adequate relief at 30 minutes after dosing. For the 1209 participants for whom data were available for this analysis, no treatment group showed a significant advantage. Antacid and FACT were slightly better, but was only when results were considered at 45 and 60 minutes after dosing that the new FACT preparation was significantly better (more prompt) than FCT. Because of missing data reported by the participants, the denominators are not constant. For various times after dosing, at 15-minute intervals, the proportions of participants reporting adequate relief of heartburn were:

ADEQUATE HEARTBURN RELIEF AFTER STUDY MEDICATION

| minutes after dose | FACT | FCT | antacid | placebo |
|---|---|---|---|---|
| 15 | 43/303 (14.2%) | 40/305 (13.1%) | 50/300 (16.7%) | 35/302 (11.6%) |
| *30* | *64/299 (21.4%)* | *60/305 (19.7%)* | *70/301 (23.3%)* | *56/304 (18.4%)* |
| 45 | 122/302 (40.4%) | 93/306 (30.4%) | 112/300 (37.3%) | 98/304 (32.2%) |
| 60 | 161/299 (53.8%) | 137/304 (45.1%) | 145/296 (49.0%) | 148/304 (48.7%) |

*Comment: The placebo response is substantial, even numerically better than FCT at 45 and 60 minutes (but not significantly so). This simply means that symptoms of this type are self-limited, and often subside on their own, without treatment, at least in many people. The FACT preparation is not quite as good as antacid at 15 and 30 minutes (but not significantly less so), and is slightly better than antacid at 45 and 60 minutes (but not significantly so). The greatest difference, which reaches statistical significance, is between the FACT and FCT at 45 minutes (10%, p = 0.010) and 60 minutes (8.7%, p = 0.032), even with about 300 participants per group. As a product designed to be more rapid in effect than famotidine alone, this study does not support such a claim for FACT, but it was not significantly inferior to antacid (-2.5%, p N.S.)*

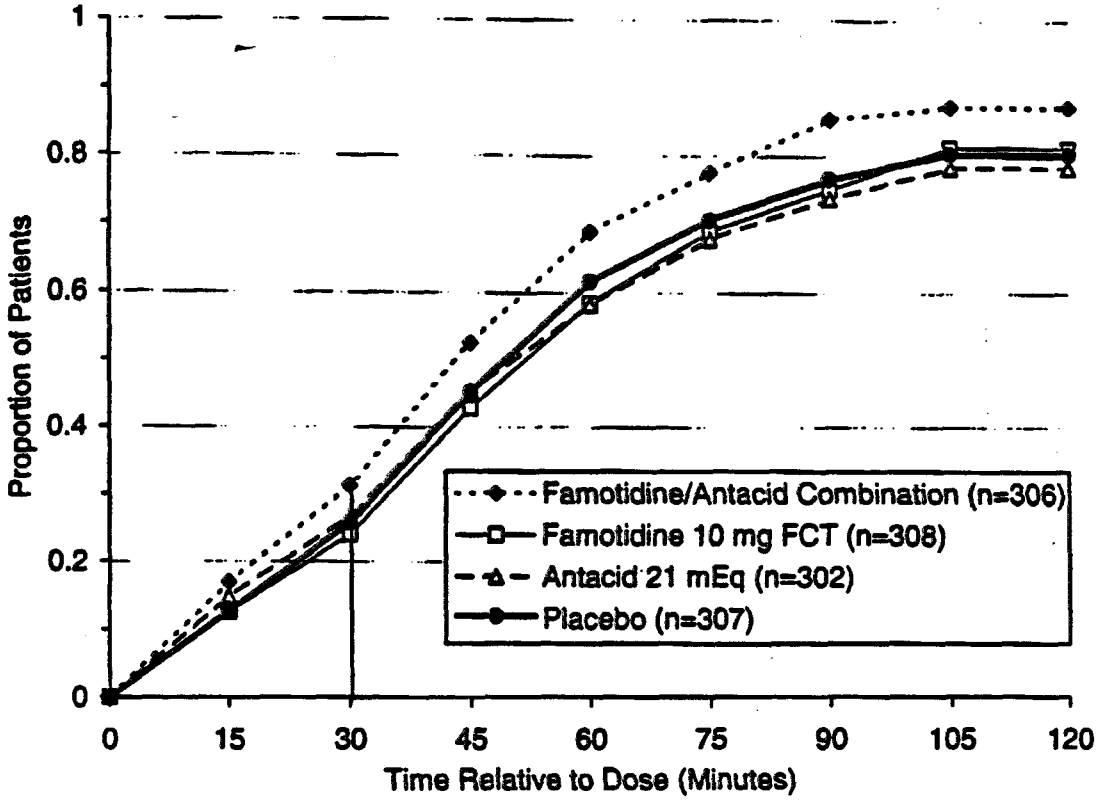
Secondary measures of efficacy, time to adequate relief and mean heartburn severity for 4 hours after dosing, showed no significant differences between treatment groups. However, time to **reduction of at least one grade in heartburn severity**, and proportions of participants reporting as least one grade reduction in heartburn severity at 30, 45 and 60 minutes, did show statistically significant advantages of FACT over the other preparations:

PARTICIPANTS REPORTING REDUCTION IN HEARTBURN SEVERITY OF AT LEAST ONE GRADE

| minutes after dose | FACT | FCT | antacid | placebo |
|---|---|---|---|---|
| 15 | 52/305 (17.1%) | 41/305 (13.4%) | 49/299 (16.4%) | 41/304 (13.5%) |
| ***30*** | ***96/303 (31.7%)*** | ***75/305 (24.6%)*** | ***82/300 (27.3%)*** | ***82/306 (26.8%)*** |
| 45 | 161/304 (53.0%) | 131/306 (42.8%) | 138/299 (46.2%) | 140/307 (45.6%) |
| 60 | 203/301 (67.4%) | 180/305 (59.0%) | 173/297 (58.2%) | 185/306 (60.5%) |

The FACT preparation was significantly better than FCT at 30 (p = 0.042) and 45 (p = 0.010) minutes after dosing, and at 60 minutes after dosing than FCT (p = 0.025) and antacid (p = 0.018) but not than placebo. There were no other statistically significant differences.

Time to Achieve ≥1 Grade Reduction in Heartburn Severity†
All-Patients-Treated Approach (N=1223)



*Comment : The FACT preparation was at least slightly better than all of the other treatments, but not statistically significantly so except as mentioned, in producing these relatively prompt effects. The requirement that the FACT be significantly faster than FCT and about equivalent to the antacid appeared to be met, although it required a quite large study to show it. It was also seen that FACT was significantly better than any of the other three preparations i.. time to produce a reduction of at least one grade in heartburn severity, as may be seen from the graphic presentation (Volume 13, page 1927).*

Analyses of the hazard ratios of the time to reach at least one grade reduction in heartburn severity were significant for FACT vs all of the other three preparations: FCT 1.24, p = 0.015; antacid 1.23, p = 0.020; and placebo 1.21, p = 0.031 *(Volume 13, pages 1925-6).*

For the primary efficacy assessment of treatment **duration** of effect, the peak heartburn severity in the period 4 to 8 hours after dosing had been chosen, and showed the following results:

PEAK HEARTBURN SEVERITY 4 TO 8 HOURS AFTER DOSING IN 1218 PARTICIPANTS

| | FACT | FCT | antacid | placebo |
|---|---|---|---|---|
| | n = 305 | n = 305 | n = 303 | n = 305 |
| Severe | 46 (15.1%) | 52 (17.0%) | 63 (20.8%) | 54 (16.7% |
| Moderate | 46 (15.1%) | 45 (14.8%) | 41 (13.5%) | 54 (16.7% |
| Mild | 99 (32.5%) | 114 (37.4%) | 115 (38.0%) | 111 (36.4%) |
| None | 114 (37.4%) | 94 (30.8%) | 84 (27.7%) | 86 (28.2%) |

Results showed FACT significantly better than antacid (p = 0.020) or placebo (p = 0.027) but not than FCT (p = 0.145). The other comparisons were not statistically significantly different from each other.

In the global rating done 8 hours after dosing, FACT and FCT were significantly better than antacid and better but not significantly so than placebo. There were no statistically significant differences in need for use of rescue antacid in the period 4 to 8 hours after dosing.

When both onset and duration of benefit in the same participant were compared, proportions of participants "successfully treated" were described. Success was defined as adequate relief within 60 minutes after dosing, OR reduction in heartburn by at least one grade within 60 minutes AND no heartburn between 4 and 8 hours after dosing AND no use of rescue medication at any time. The results were very similar for the two choices, and most impressive for the prompt effect at 30, 45, and 60 minutes after dosing for reduction in heartburn severity by at least one grade *(Volume 13, page 1951)*:

**Proportion of Patients "Successfully Treated" for Onset and Duration Where Onset is Defined as ≥1 Grade Reduction at 15, 30, 45, or 60 Minutes Postdose All-Patients-Treated Approach**

| "Onset" = ≥1 Grade Reduction at | FACT | | Famotidine 10-mg FCT | | Antacid 21 mEq | | Placebo | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| 15 min | 30/305 | (9.8) | 18/305 | (5.9) | 20/299 | (6.7) | 13/304 | (4.3) |
| 30 min | 55/303 | (18.2) | 32/305 | (10.5) | 33/300 | (11.0) | 28/306 | (9.2) |
| 45 min | 85/304 | (28.0) | 54/306 | (17.6) | 51/299 | (17.1) | 51/307 | (16.6) |
| 60 min | 96/301 | (31.9) | 63/305 | (20.7) | 62/297 | (20.9) | 67/306 | (21.9) |

| "Onset" = ≥1 Grade Reduction at | Treatment Comparison | Model-Adjusted Odds-Ratio (95% CI) | Chi-Square | p-Value |
|---|---|---|---|---|
| 15 min | FACT vs. FAM 10-mg FCT | 1.78 (0.97, 3.30) | 3.43 | 0.064 |
| | FACT vs. AA 21 mEq | 1.54 (0.85, 2.80) | 2.03 | 0.155 |
| | FACT vs. placebo | 2.46 (1.25, 4.85) | 6.82 | 0.009 |
| | FAM 10-mg FCT vs. placebo | 1.38 (0.66, 2.88) | 0.74 | 0.391 |
| | AA 21 mEq vs. placebo | 1.60 (0.78, 3.29) | 1.62 | 0.203 |
| | FAM 10-mg FCT vs. AA 21 mEq | 0.86 (0.45, 1.68) | 0.19 | 0.666 |
| 30 min | FACT vs. FAM 10-mg FCT | 1.96 (1.22, 3.15) | 7.65 | 0.006 |
| | FACT vs. AA 21 mEq | 1.84 (1.15, 2.95) | 6.41 | 0.011 |
| | FACT vs. placebo | 2.25 (1.38, 3.69) | 10.44 | 0.001 |
| | FAM 10-mg FCT vs. placebo | 1.15 (0.67, 1.98) | 0.26 | 0.608 |
| | AA 21 mEq vs. placebo | 1.23 (0.72, 2.10) | 0.55 | 0.458 |
| | FAM 10-mg FCT vs. AA 21 mEq | 0.94 (0.56, 1.58) | 0.05 | 0.816 |
| 45 min | FACT vs. FAM 10-mg FCT | 1.87 (1.26, 2.77) | 9.61 | 0.002 |
| | FACT vs. AA 21 mEq | 1.93 (1.29, 2.88) | 10.41 | 0.001 |
| | FACT vs. placebo | 1.99 (1.34, 2.97) | 11.41 | 0.001 |
| | FAM 10-mg FCT vs. placebo | 1.07 (0.70, 1.64) | 0.09 | 0.768 |
| | AA 21 mEq vs. placebo | 1.03 (0.67, 1.59) | 0.02 | 0.892 |
| | FAM 10-mg FCT vs. AA 21 mEq | 1.03 (0.67, 1.59) | 0.02 | 0.875 |
| 60 min | FACT vs. FAM 10-mg FCT | 1.86 (1.28, 2.70) | 10.55 | 0.001 |
| | FACT vs. AA 21 mEq | 1.82 (1.25, 2.65) | 9.76 | 0.002 |
| | FACT vs. placebo | 1.71 (1.18, 2.47) | 8.02 | 0.005 |
| | FAM 10-mg FCT vs. placebo | 0.92 (0.62, 1.36) | 0.19 | 0.666 |
| | AA 21 mEq vs. placebo | 0.94 (0.63, 1.39) | 0.11 | 0.744 |
| | FAM 10-mg FCT vs. AA 21 mEq | 0.98 (0.66, 1.46) | 0.01 | 0.919 |

FACT = Famotidine/antacid combination; FAM = Famotidine; AA = Antacid.

*Comment: This analysis represents the severest test of the medications, in which both prompt and sustained efficacy are required in the individual participant. It also represents the analysis that most impressively demonstrates the differences between the preparations. The new FACT was significantly better than antacid, FCT, or placebo at 30, 45, and 60 minutes of prompt effect, and better than placebo at 15 minutes. The other preparations all failed in one way or another.*

As mentioned by the sponsor in the discussion (pages 1960-2, Volume 13), the requirement that participants perceive "adequate relief" rather than just a reduction of one grade or more in severity of heartburn, was an even more stringent criterion. When participants also had no heartburn 4-8 hours after dosing nor needed rescue antacids, the strictest comparison resulted. In these comparisons, FACT was significantly better at 45 and 60 minutes for prompt adequate relief, better but not significantly so at 30 and 15 minutes, than any of the other three treatments in this study.

There were no safety problems in this study, no serious adverse effects and no discontinuations from study because of adverse events, and participants receiving FACT did not have significantly more of any adverse effect than those on placebo or either of the already marketed OTC products, FCT and antacid.

Proportion of Patients "Successfully Treated" for Onset and Duration
Where Onset is Defined as Adequate Relief at 15, 30, 45, or 60 Minutes Postdose
All-Patients-Treated Approach

| "Onset" = Adequate Relief at | FACT | | Famotidine 10-mg FCT | | Antacid 21 mEq | | Placebo | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| 15 min | 22/303 | (7.3) | 13/305 | (4.3) | 16/300 | (5.3) | 13/302 | (4.3) |
| 30 min | 35/299 | (11.7) | 20/305 | (6.6) | 28/301 | (9.3) | 23/304 | (7.6) |
| 45 min | 67/302 | (22.2) | 37/306 | (12.1) | 46/300 | (15.3) | 45/304 | (14.8) |
| 60 min | 82/299 | (27.4) | 48/304 | (15.8) | 56/296 | (18.9) | 64/304 | (21.1) |

Data Source: [4.9]

| "Onset" = Adequate Relief at | Treatment Comparison | Model-Adjusted Odds-Ratio (95% CI) | Chi-Square | p-Value |
|---|---|---|---|---|
| 15 min | FACT vs. FAM 10-mg FCT | 1.78 (0.88, 3.62) | 2.56 | 0.110 |
| | FACT vs. AA 21 mEq | 1.40 (0.72, 2.73) | 0.97 | 0.325 |
| | FACT vs. placebo | 1.74 (0.85, 3.53) | 2.33 | 0.127 |
| | FAM 10-mg FCT vs. placebo | 0.97 (0.44, 2.14) | 0.00 | 0.947 |
| | AA 21 mEq vs. placebo | 1.24 (0.58, 2.64) | 0.32 | 0.574 |
| | FAM 10-mg FCT vs. AA 21 mEq | 0.78 (0.37, 1.67) | 0.40 | 0.527 |
| 30 min | FACT vs. FAM 10-mg FCT | 1.91 (1.07, 3.40) | 4.80 | 0.028 |
| | FACT vs. AA 21 mEq | 1.30 (0.77, 2.20) | 0.94 | 0.333 |
| | FACT vs. placebo | 1.62 (0.93, 2.82) | 2.86 | 0.091 |
| | FAM 10-mg FCT vs. placebo | 0.85 (0.45, 1.58) | 0.27 | 0.601 |
| | AA 21 mEq vs. placebo | 1.24 (0.70, 2.22) | 0.55 | 0.460 |
| | FAM 10-mg FCT vs. AA 21 mEq | 0.68 (0.37, 1.24) | 1.58 | 0.209 |
| 45 min | FACT vs. FAM 10-mg FCT | 2.11 (1.36, 3.29) | 10.92 | 0.001 |
| | FACT vs. AA 21 mEq | 1.58 (1.04, 2.41) | 4.59 | 0.032 |
| | FACT vs. placebo | 1.64 (1.08, 2.51) | 5.32 | 0.021 |
| | FAM 10-mg FCT vs. placebo | 0.78 (0.49, 1.25) | 1.08 | 0.299 |
| | AA 21 mEq vs. placebo | 1.04 (0.66, 1.63) | 0.03 | 0.870 |
| | FAM 10-mg FCT vs. AA 21 mEq | 0.75 (0.47, 1.20) | 1.44 | 0.231 |
| 60 min | FACT vs. FAM 10-mg FCT | 2.08 (1.38, 3.11) | 12.52 | <0.001 |
| | FACT vs. AA 21 mEq | 1.64 (1.11, 2.43) | 6.21 | 0.013 |
| | FACT vs. placebo | 1.43 (0.98, 2.09) | 3.36 | 0.067 |
| | FAM 10-mg FCT vs. placebo | 0.69 (0.45, 1.04) | 3.09 | 0.079 |
| | AA 21 mEq vs. placebo | 0.87 (0.58, 1.30) | 0.47 | 0.492 |
| | FAM 10-mg FCT vs. AA 21 mEq | 0.79 (0.52, 1.22) | 1.14 | 0.287 |

FACT = Famotidine/antacid combination; FAM = Famotidine; AA = Antacid.

## 2. Study 109: single-dose, in-clinic-evening response to provocative meal

**Study 109** was carried out from 29 April to 14 July 1997 by ten investigators who randomized 1139 participants to the same four study medications as had been used in the previous studies: FACT (chewable antacid 21 mEq ANC and famotidine 10 mg tablet), FCT (famotidine 10 mg tablet for swallowing, placebo chewable antacid), antacid (chewable 21 mEq ANC, no famotidine) and double placebo (chewable placebo antacid, swallowable placebo famotidine). The participants, again, were adults of 18 and over who had histories of at least at least two months of at least three episodes per week of heartburn after specific foods or beverages that at times interfered with sleep and required them to take antacids for relief. Participants were to be otherwise free of serious illnesses, not using acid-suppressing medications. The study was conducted by Drs. M. Gunsberger (Levittown NY), J. Keppler (Valley Stream NY), R. Kurker (South Windsor CT), M. Gilio (Woodbridge CT), E. Catala (Woodbridge CT), D. Williams (Dayton Beach FL), J Colton (St. Petersburg FL), F. Olash (Prospect KY), Saul Jeck (Philadelphia PA), and T. O'Barr (Marietta GA), [Vol. 14, pp 2753-4].

The study design called for participants to restrict alcohol to no more than 2 drinks/day for 48 hours and none for 12 hours before coming for study, to avoid foods known to provoke symptoms for 24 hours and to fast for 5 hours before coming. They were then to report to the offices or clinics at 6 p.m., consume a provocative meal of Wendy's® chili plus onion-cheese seasoning mix and chilled but not iced tea at 7 p.m., finishing what each felt to be a normal amount by 7:30, and record heartburn severity at 10-minute intervals from the time of starting the meal on Diary Card #1. If and only if they experienced heartburn of at least moderate severity, using the same scale used in the previous studies (0 = none, 1 = mild, 2 = moderate, 3 = severe), they were then to chew one tablet and swallow another with 60 mL of water and then continue to record heartburn severity every 10 minutes until 10 p.m. If unbearably severe heartburn occurred after 9:00 p.m., participants were allowed to take MYLANTA® Double Strength tablets for relief (and treatment failure be declared).

Participants were then released to go home, with Diary Card #2 and a supply of rescue antacids to use if needed. At home they were to record the number of times they awoke from sleep with heartburn symptoms and the use of antacids for relief. As well as a global morning assessment of how well the medication worked. It was estimated that 1300 participants would have to be given the provocative meal in order to obtain at least 1100 who could be randomized and evaluated. The study size was based on assuming that the hazard ratio of obtaining prompt relief of heartburn by FACT would be 1.39 compared to FCT, as derived from the results of Study 078 *(Volume 14, pages 2642-3)*. The primary outcome measures were to be: 1) significantly shorter time to adequate symptom relief by FACT than by FCT, and 2) significantly fewer participants awaking with heartburn symptoms after FACT then after antacid. Secondary endpoints were to be that FACT and antacid would be better than placebo or FCT for prompt relief, while FACT and FCT would be better than placebo or antacid for duration of effect and fewer awakenings with heartburn during the night.

A total of 1525 participants were screened, 386 of whom were not randomized to study medication, 196 before the test meal, and 190 during or after the meal but before dosing because

they did not develop at least moderately intense heartburn. Of 1139 randomized, 1136 completed the study.

| | FACT | FCT | antacid | placebo | total |
|---|---|---|---|---|---|
| Gunsberger | 53 | 53 | 54 | 54 | 214 |
| Keppler | 28 | 29 | 28 | 29 | 114 |
| Kurker | 41 | 41 | 41 | 40 | 163 |
| Gilio | 14 | 14 | 14 | 14 | 56 |
| Catala | 22 | 22 | 22 | 23 | 89 |
| Williams | 31 | 31 | 31 | 32 | 125 |
| Colton | 19 | 21 | 21 | 20 | 81 |
| Olash | 30 | 30 | 29 | 30 | 119 |
| Jeck | 26 | 25 | 25 | 25 | 101 |
| O'Barr | 19 | 19 | 19 | 20 | 77 |
| total | 283 | 285 | 284 | 287 | 1139 |

The participants ranged in age from 18 to 83 (median 39), 667 women (58.6%), 991 Caucasian (87.0%), 112 Black (9.8%), 35 Hispanic (3.1%), 1 Indian (0.1%). There were no significant differences between the randomized groups in age, gender, race, heartburn severity or frequency. Most (1095, 96.1%) of the participants had moderate heartburn severity after the provocative meal at the time of dosing.

By study design, participants could take study medication at any time from 10 to 90 minutes after the meal, recorded post-dose severity and relief of heartburn until 3 hours after the meal, so post-dosing assessments could range from 90 to 170 minutes. Most (936/1139, 82%) of randomized participants provided at least 2 hours of post-dose data, so time to adequate relief and time to at least one grade reduction in heartburn severity were calculated using relief up to 2 hours post-dose, and participants not achieving the specific event were right-censored at the earlier of their last observation or 2 hours post-dose. One participant on placebo (AN0351/109-003) withdrew from the study after baseline; another (AN1082/109-013) developed nausea 45 minutes after taking FACT, and a third (AN0989/ 109-012) after FACT developed unbearable heartburn and took rescue MYLANTA. Data were therefore incomplete on these three participants.

"Treatment failure" was declared if participants felt that they had to take rescue antacids, which occurred in 513 participants, 4 at clinic, 392 at home before bedtime, and 117 during the night.

TREATMENT FAILURE – NEED TO TAKE RESCUE ANTACID

| *Rescue antacid taken* | FACT | FCT | antacid | placebo | total |
|---|---|---|---|---|---|
| | *n = 282* | *n = 285* | *n = 284* | *n = 286* | *n = 1137* |
| At clinic | 2 (0.7%) | 0 (0.0%) | 1 (0.35%) | 1 (0.35%) | *4 (0.35%)* |
| At home before bed | 81 (28.7%) | 99 (34.7%) | 98 (34.5%) | 114 (39.9%) | *392 (34.5%)* |
| During night | 51 (18.1%) | 58 (20.4%) | 70 (24.6%) | 77 (26.9%) | *256 (22.5%)* |
| Before bed & at night | 21 (7.4%) | 27 (9.5%) | 41 (14.4%) | 49 (17.1%) | *138 (12.1%)* |
| total* | 112 (39.7%) | 130 (45.6%) | 128 (45.1%) | 143 (50.0%) | *513 (45.1%)* |

** Some participants were in more than one category.*

*Comment: Although there appeared to be somewhat fewer treatment failures in the participants treated with FACT, the only statistically significant comparison was between FACT and placebo for total treatment failure (10.3%, p = 0.014, by chi squared test).*

For assessing the *prompt* effect of treatment, the primary outcome measure was time to adequate relief of heartburn, as defined by the participants. Additional secondary assessments were made of the proportions of participants reporting adequate relief or reduction in heartburn severity at 30 or at 60 minutes, time to reach reduction of at least one grade in heartburn severity, mean heartburn severity over the first 2 hours after dosing. Analyses of all participants treated included the 1139 who were randomized and received study medication, but additional analyses were also done of the 1126 who followed the protocol as written, excluding the 13 participants or investigators who deviated from the protocol in one way or another. These deviations *(Volume 13, page 2437)* included entering the study twice (2), taking prohibited medication (3), heartburn before the meal (3), dosed twice by error (2), no heartburn within 90 minutes after the meal (3).

For assessing the primary outcome measure, the only significant difference between treatments was the FACT was significantly faster-acting than FCT (p = 0.034) by chi squared test *(Volume 13, page 2440)*:

All-Patients-Treated Approach
Time to Adequate Relief (N=1138)

| Treatment Group | n | Median (min) (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) |
| FAM 10-mg FCT | 285 | 70.0 (60, 80) | 30, >120 | 95 (33.3) | 0 (0.0) |
| Antacid 21 mEq | 284 | 60.0 (40,70) | 30, >120 | 83 (29.2) | 1 (<1) |
| Placebo | 286 | 70.0 (60, 80) | 30, >120 | 94 (32.9) | 1 (<1) |

FACT = Famotidine/antacid combination; FAM = Famotidine.
† Patients were censored at 2 hours postdose if they failed to achieve adequate relief or if use of rescue medication preceded the time to event.

Data Source: [4.9]

| Treatment Comparison | Hazard Ratio (95% CI) | Chi-Square | p-Value |
|---|---|---|---|
| FACT vs. FAM 10-mg FCT [P] | 1.24 (1.02, 1.51) | 4.48 | 0.034 |
| FACT vs. AA 21 mEq | 1.08 (0.89, 1.31) | 0.61 | 0.437 |
| FACT vs. placebo | 1.18 (0.97, 1.44) | 2.68 | 0.102 |
| FAM 10-mg FCT vs. placebo | 0.95 (0.78, 1.17) | 0.22 | 0.638 |
| AA 21 mEq vs. placebo | 1.09 (0.90, 1.33) | 0.74 | 0.389 |
| FAM 10-mg FCT vs. AA 21 mEq | 0.87 (0.72, 1.07) | 1.79 | 0.181 |

FACT = Famotidine/antacid combination; FAM = Famotidine; AA = Antacid.
[P]: FACT vs. FAM 10-mg FCT is the primary treatment comparison.