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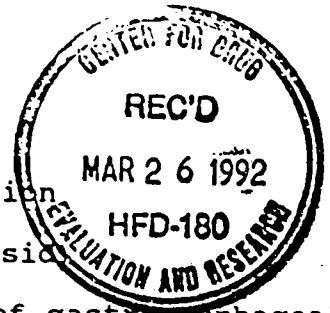
STATISTICAL REVIEW AND EVALUATION



NDA #: 20-210/Drug Class 1S

Applicant: Janssen Research Foundation

Drug: Cisapride (Trade Name: Propulsid)

Indication: Treatment of symptoms of gastroesophageal reflux disease (GERD)

Volumes Reviewed: 1.1, 1.88 - 1.92, 1.94 - 1.98, 1.100 - 1.104
August 29, 1991

This review addresses the efficacy of cisapride from the two U. S. studies # 1201 and # 1203, and efficacy data from the Multicenter study # 121-5.

The issues in this review have been discussed with the medical officer Dr. Andre DuBois, M.D.

I U.S. STUDY #1201 (Protocol 51, 619/1201)

1.1 STUDY DESIGN

This was a randomized, multicenter, double-blind, placebo controlled trial with two doses (10 mg and 20 mg) of cisapride in the treatment of symptoms of gastroesophageal reflux disease (GERD). The patients were treated with cisapride 10 mg or 20 mg or placebo as two tablets QID, given 30 minutes before each meal and at bedtime for a period of twelve weeks. A total of 14 centers participated. The protocol called for 15 to 20 patients per center for an estimated 180 patient population. There was no indication that any stratification was used in this trial.

Patients qualified for this trial if they

-- were ambulatory

-- were diagnosed and confirmed to have gastroesophageal reflux disease by endoscopy

-- had a grade 1 or higher macroscopic finding

-- had a positive Bernstein test

-- exhibited moderate to severe day and night heartburn

during the screening visit

-- had symptoms for at least 3 months

-- free of active ulcer disease, anatomic obstruction, infections or inflammations of the small and large intestines.

Patients did not qualified if they had any of the following conditions:

-- infectious esophagitis, esophagitis caused by exogenous acidic or alkaline substances, Barrett's esophagus

-- grade 0 esophagitis or peptic stenosis

-- had prior gastric surgery other than appendectomy or cholecystectomy

-- had significant cardiovascular, renal or hepatic impairment or were on renal analysis

-- pregnant females

-- had a history of seizure, worked during the night, were known to use street drugs or required daily use of non-steroidal anti-inflammatory drugs.

Qualifying patients, after a two week compliance and eligibility phase (see **Table 1a**), were randomized in a double-blind fashion into placebo or cisapride 10 mg or cisapride 20 mg group. The randomization was done by assigning the patients a 4-digit computed generate random number.

Patients were allowed to take Maalox (antacid) on a prn basis, each patient maintained a daily diary which included antacid usage.

Table 1a shows the schedule of evaluations for each patient. Patients evaluations included symptom assessments, diary, overall assessments, global assessments, endoscopies, biopsies, Bernstein test, lower esophageal sphincter pressure (LESP) measurements, clinical labs, physical exam and EKG. These evaluations were done at baseline, week 4, week 8 and at week 12. This table also contains the summary of patient dispositions and demographics.

Primary Efficacy Endpoints

The primary efficacy parameters listed in the protocol are:

a) daytime and nighttime heartburn assessments

b) the number of daytime and nighttime maalox tablets consumed

c) global assessments.

Symptom related efficacy endpoints were assessed by both patient and investigator. For patient's assessment, the patient recorded in a daily diary the intensity of each symptom (heartburn daytime, heartburn nighttime, regurgitation daytime and regurgitation nighttime) on a 100 mm visual analog scale of 0 to 100 where 0 was "none" and 100 was the "worst ever had". The patient also recorded Maalox tablets taken on the same daily diary. For investigator assessment, at each visit, the investigator asked the patient to rate the overall intensity of the aforementioned symptoms since the last visit on a numerical scale of 0 ("none") to 10 ("worst ever had").

Sample Size Estimation

A sample size of 180 randomized patients with 60 evaluables in each treatment group was planned. With 60 patients per treatment group, 80% power was postulated to detect a difference of two units on the investigator's assessment for nighttime heartburn.

1.2.0 SPONSOR'S ANALYSIS METHODS & RESULTS

1.2.1 Analysis Methods and Group Comparability

The efficacy analyses were performed

1) by the intent-to-treat (ITT) principle,

2) for the evaluable subset

3) for the subgroup of patients formed by the baseline endoscopic grade (subgroups formed were: grade 1 only, grade 2 to 4, and grade 4 only).

The sponsor reported 2-sided p-values for treatment comparisons (between cisapride doses and placebo) as <u>significant</u> if 2-sided $p<.05$ and <u>marginally significant</u> if 2-sided p was between .05 and .10.

A total of 182 patients were randomized; 60 in the placebo, 63 in the 10 mg and 59 in the 20 mg cisapride group. The ITT analysis excluded 6 patients (3 placebo, 3 cisapride), because these patients did not have any efficacy data. The middle part of Table 1a summarizes patient dispositions and patient dropouts by reasons.

The three treatment groups were comparable with respect to demographic characteristics (see bottom part of Table 1a). The mean age of patients was 44.4 years. Sixty-four percent of these were

males, 93.5% white, 5.5% black and 1% Hispanic. The mean GERD symptom duration was 8.4 years.

1.2.2 Sponsor's Heartburn Results/ITT & Efficacy Subset

Tables 2a summarizes the patient's and investigator's mean daytime and nighttime heartburn intensity assessments significant findings by the sponsor's ITT principle and for the evaluable subset.

For daytime and nighttime, significant and marginally significant results in favor of cisapride were as follows:

Daytime Heartburn Results				
ITT	2-sided p* (significant, marginally significant): wk4	wk8	wk12	endpoint**
10 mg vs pl:				
patient	.024	-	.063	-
invest.	-	-	.057	-
20 mg vs pl:				
patient	-	-	-	-
invest.	-	-	-	-
Efficacy				
10 mg vs pl:				
patient	.027	-	.057	.089
invest.	-	-	.055	.071
20 mg vs pl:				
patient	-	-	-	-
invest.	-	-	-	-

"*" p-values<.10 (adjusted for baseline and investigator) in favor of drug.
"**" patient's final assessments during double-blind treatment.
"-" p-value not even marginally significant (not reported)

Nighttime Heartburn Results				
ITT	2-sided p* (significant, marginally significant)			
	wk4	wk8	wk12	endpoint**
10 mg vs pl:				
patient	.044	-	-	-
invest.	.040	.062	.010	.006
20 mg vs pl:				
patient	-	-	-	-
invest.	-	-	-	-
Efficacy				
10 mg vs pl:				
patient	.044	-	.057	.089
invest.	.070	.062	.012	.005
20 mg vs pl:				
patient	-	-	-	-
invest.	-	-	-	-

"*" p-values<.10 (adjusted for baseline and investigator) in favor of drug.
"**" patient's final assessments during double-blind treatment.
"-" p-value not even marginally significant (not reported)

1.2.3 Sponsor's Subgroup Analyses For Heartburn

The sponsor's results for the subgroup analyses (by baseline endoscopic grade) for daytime and nighttime heartburn are summarized in **Tables 3a and 4a.**

For daytime and nighttime heartburn, significant and marginally significant results in favor of cisapride were:

Daytime Heartburn Results				
	2-sided p* (significant, marginally significant)			
Subgroup	wk4	wk8	wk12	endpoint**
Grade 1				
10 mg vs pl:				
patient	-	.050	.0[illegible]	-
invest.	-	-	.030	-
20 mg vs pl:				
patient	-	-	-	-
invest.	-	-	-	-
Grade 2 to 4				
10 mg vs pl:				
patient	.090	-	-	-
invest.	-	-	-	.049
20 mg vs pl:				
patient	-	-	-	-
invest.	-	-	-	-
Grade 4				
10 mg vs pl:				
patient	-	.058	.054	.055
invest.	-	-	-	-
20 mg vs pl:				
patient	-	.006	.030	.065
invest.	-	-	-	-

"*" p-values<.10 (adjusted for baseline and investigator) in favor of drug.
"**" patient's final assessments during double-blind treatment.
"-" p-value not even marginally significant (not reported)

Nighttime Heartburn Results				
	2-sided p* (significant, marginally significant)			
	wk4	wk8	wk12	endpoint**
Grade 1				
10 mg vs pl:				
patient	-	-	.081	-
invest.	-	-	.035	-
20 mg vs pl:				
patient	-	-	-	-
invest.	-	-	-	-
Grade 2 to 4				
10 mg vs pl:				
patient	-	-	-	-
invest.	-	-	.078	.006
20 mg vs pl:				
patient	-	-	-	-
invest.	-	-	-	-
Grade 4				
10 mg vs pl:				
patient	.051	.002	.002	.001
invest.	-	-	.017	.027
20 mg vs pl:				
patient	-	.002	.004	.003
invest.	-	-	.068	-

"*" p-values<.10 (adjusted for baseline and investigator) in favor of drug.
"**" patient's final assessments during double-blind treatment.
"-" p-value not even marginally significant (not reported)

1.2.4 Sponsor's ITT & Subgroup Analyses for Maalox intake

The sponsor's mean (daily) Maalox intake results were as follows. Significant or marginally 2-sided p-values were claimed at week 4 for the ITT and the efficacy subset, and at week 4 and week 8 for the subgroup analyses.

Mean Maalox Intake and 2-sided p

ITT daytime	N*	wk4	wk8	wk12	endpoint	p(#)
placebo	54	1.5	1.5	1.3	1.7	
10 mg	55	1.5	1.5	1.3	1.3	-
20 mg	51	2.3	1.9	1.8	2.2	-
Nighttime						
Placebo	54	1.2	1.3	1.1	1.4	
10 mg	55	1.3	1.4	1.1	1.1	.025(4)
20 mg	51	1.5	1.4	1.4	1.6	.048(4)
Subgroup:						
Grade 1						
daytime						
placebo	26	1.3	1.5	1.2	1.7	
10 mg	15	1.1	0.7	0.8	0.8	-
20 mg	17	1.7	1.7	1.7	1.7	.067(8)
Nighttime						
Placebo	25	1.2	1.3	1.0	1.5	
10 mg	15	0.8	0.5	0.6	0.6	-
20 mg	17	0.7	0.8	0.9	0.9	-
Grade 2 to 4						
daytime						
placebo	28	1.7	1.5	1.5	1.6	
10 mg	40	1.7	1.7	1.5	1.5	.077(4)
20 mg	33	2.7	2.0	1.8	2.5	
Nighttime						
Placebo	28	1.2	1.4	1.2	1.3	
10 mg	40	1.5	1.7	1.2	1.3	.042(4)
20 mg	33	1.9	1.7	1.6	1.9	-
Grade 4						
daytime						
placebo	2	1.2	1.6	1.6	1.6	
10 mg	9	3.1	3.5	2.5	2.6	-
20 mg	10	2.8	2.2	1.9	2.5	.024(8)
Nighttime						
Placebo	2	1.8	2.4	2.5	2.5	
10 mg	9	2.4	2.6	1.6	2.0	
20 mg	10	2.1	1.8	1.2	2.0	.060(8) .060(12) .088(end)

"N*" average # of patients across different visits.
"p(#)" is 2-sided p-value placebo versus cisapride at week # ()
"-" p-value not even marginally significant

The mean Maalox results for the efficacy subset were similar to those of the ITT principle.

1.2.5 Sponsor's Global Evaluations Results/ITT & Efficacy Subset

Below is a summary of the significant and marginally significant results for the global evaluations. For the magnitude of the effects, see **Tables 5a and 6a.**

Global Assessments: 2-side p-values Results (Cisapride vs placebo)		
ITT	10 mg	20 mg
Invest.	-	-
Patient	.061	-
Evaluable		
Invest.	.081	-
Patient	.036	-

"-" p-value not even marginally significant

1.3 REVIEWER'S EVALUATIONS & COMMENTS/ STUDY #1201

Heartburn Results for 10 mg

The results summarized in section 1.2.2 (based on ITT and efficacy methods) suggest that the 10 mg dose was effective in the treatment of heartburn symptoms of GERD.

The ITT and efficacy subset results at week 12 were significant in favor of the 10 mg dose for the nighttime symptoms. The ITT and efficacy subset results at week 12 were only borderline significant in favor of the 10 mg dose for the daytime symptoms. However, a repeated measures analysis of variance showed a significant p=.038 in favor of the 10 mg dose daytime symptoms for patient's assessments.

2-sided p, placebo vs 10 mg (Repeated Measures Analyses)				
	Inv (day)	Pat (day)	Inv (night)	Pat (night)
2-sided p	-	.039	.019	-

For details regarding the repeated measures analysis, see **Table S1/1201.**

Heartburn Results for 20 mg

Surprisingly, for this study, both the efficacy and ITT analyses do not support the effectiveness of the 20 mg dose in reducing the symptoms of heartburn. None of the comparisons (see the summary of results in section 1.2.2, page 4), either by the ITT principle or for the efficacy subset, were even marginally significant; all p-values were greater than .10. Also, the subgroup of patients with endoscopic grades of 2 to 4 did not produce any significant or marginally significant results in favor of the 20 mg dose (see section 1.2.3, page 5, and the middle part of Tables 3a and 4a).

However, for the subgroup of patients with endoscopic grade of 4, there are analyses results in favor of the 20 mg dose (see section 1.2.3 and bottom portion of Tables 3a and 4a). However, in this analysis for grade 4 patients, there were only 2 patients in the placebo group and 9 - 12 patients in the 20 mg group. The fact that this analysis is a subgroup analysis and there are only 2 patients in the placebo group, do not statistically establish the effectiveness of the 20 mg dose for this trial.

Antacid Usage

Based on mean Maalox intake data (see table on page 6), the sponsor's claimed significant reduction in antacid usage in the cisapride than in comparison to that for placebo:

> "the cisapride 10 mg group had significantly (p=.02) larger reduction than placebo at week 4, ... In addition, the 10 mg group had a significantly larger reduction than the cisapride 20 mg group at endpoint (p=.04), ...". [page 020-00151 of the NDA]

However, the review of the cumulative antacid usage data did not support this hypothesis of less antacid usage in the cisapride groups (see the table below). However, this reviewer's analyses on adjusting for the effect of antacid usage did not alter the efficacy results for heartburn symptoms.

End of Double-Blind (Week 12)

Cumulative	Placebo	10 mg	20 mg	Total
Usage>201	38(34%)	42(37%)	33(29%)	113(100%)
200<Usage<481	15(35%)	13(30%)	15(35%)	43(100%)
Usage>480	5(24%)	7(33%)	9(43%)	21(100%)
Total	58(33%)	62(35%)	57(32%)	177

Mantel-Haenszel chisquare=1.496, 2-sided p=.473.

Global Evaluations

The results in section 1.2.5 (for the ITT and efficacy) analyses support the hypothesis that the 10 mg dose is effective in this trial; for patient's assessments p=.036 in favor of the drug for the evaluable subset analysis and p=.061 for the ITT principle.

There were no significant or marginally significant results for the 20 mg dose.

II U.S. STUDY #1203 (Protocol 51, 619/1203)

2.1 Study Design

This was a randomized, multicenter, double-blind, placebo controlled trial of two doses (10 mg and 20 mg) of cisapride in the treatment of symptoms of gastroesophageal reflux disease (GERD). The patients were treated with cisapride 10 mg or 20 mg or placebo as two tablets QID, given 30 minutes before each meal and at bedtime for a period of twelve weeks. Protocol called for 12 centers with 12 to 18 patients per center for an estimated total of 180 patient population. There was no indication that any stratification was used.

Inclusion/Exclusion Criteria

Same as for U. S. 1201 (already discussed).

Table 1b shows the schedule of evaluations for each patients. Patients evaluations included symptom assessments, diary, overall assessments, global assessments, endoscopies, clinical labs, physical exam and EKG. These evaluations were done at baseline, week 4, week 8 and at week 12. This table also contains the summary of patient dispositions and demographics.

Primary Efficacy Parameters

Same as for U. S. study 1201 (already discussed).

Sample Size Estimation

A sample size of 180 randomized patients with 60 evaluables in each treatment group was planned. With 60 patients per treatment group, 80% power was postulated to detect a difference of two units on the investigator's assessment for nighttime heartburn.

2.2.0 Sponsor's Analysis Methods & Results

2.2.1 Analyses Methods and Group Comparability

The efficacy analyses were performed

1) by the intent-to-treat (ITT) principle,

2) for the evaluable subset

3) for the subgroup of patients formed by the baseline endoscopic grade (subgroups were: grade 1 only, grade 2 to 4, and grade 4 only).

The sponsor reported 2-sided p-values for treatment comparisons (between cisapride doses and placebo) as significant if 2-sided $p<.05$ and marginally significant if 2-sided p was between .05 and .10.

A total of 177 patients were randomized; 60 in the placebo, 56 in the 10 mg cisapride and 61 in the 20 mg cisapride treatment groups. The ITT analyses excluded 6 patients (one placebo, 5 cisapride), because of lack of any efficacy data for these patients. The middle part of **Table 1b** provides a summary of patient dispositions and patient dropouts by reasons.

The three treatment groups were comparable with respect to demographic characteristics (see bottom part of **Table 1b**). The mean age of patients was 44.7 years. Fifty-five percent of the patients were males, 88% white and 9.7% black. About three percent were Hispanic. The mean GERD symptom duration was 8.1 years.

2.2.2 Sponsor's Heartburn Results/ITT & Efficacy Subset

Table 2b summarizes the patient's and investigator's mean daytime and heartburn intensity assessments findings by the sponsor's ITT principle and for the evaluable subset.

For daytime and nighttime, significant and marginally significant results in favor of cisapride were as follows:

Daytime Heartburn Results

	2-sided p* (significant, marginally significant) wk4	wk8	wk12	endpoint**
ITT				
10 mg vs pl:				
patient	.079	-	-	-
invest	.010	-	-	-
20 mg vs pl:				
patient	.022	.017	.008	.033
invest	.002	.011	.011	.028
Efficacy				
10 mg vs pl:				
patient	.087	-	-	-
invest	.026	-	-	-
20 mg vs pl:				
patient	.026	.016	.006	.038
invest	.001	.014	.008	.018

Nighttime Heartburn Results

	2-sided p* (significant, marginally significant) wk4	wk8	wk12	endpoint**
ITT				
10 mg vs pl:				
patient	.008	-	.086	-
invest	-	-	-	-
20 mg vs pl:				
patient	.034	.020	.003	.029
invest	-	-	.009	-
Efficacy				
10 mg vs pl:				
patient	.013	-	.082	-
invest	-	-	-	-
20 mg vs pl:				
patient	.031	.017	.002	.028
invest	-	-	.015	-

"*"p-values<.10 (adjusted for baseline and investigator) in favor of drug.
"**" patient's final assessments during double-blind treatment.
"-" p-value not even marginally significant (not reported).

2.2.3 Sponsor's Subgroup Analyses For Heartburn

The sponsor's results for the subgroup analyses (by baseline endoscopic grade) for daytime and nighttime heartburn are summarized in **Tables 3b and 4b).**

For daytime and nighttime heartburn, significant and marginally significant results were:

Daytime Heartburn Results

	2-sided p (significant, marginally significant)			
Subgroup	wk4	wk8	wk12	endpoint
Grade 1				
10 mg vs pl:				
patient	-	-	-	-
invest	-	-	-	-
20 mg vs pl:				
patient	-	-	-	-
invest	-	-	-	-
Grade 2 to 4				
10 mg vs pl:				
patient	.044	-	.024	.081
invest	.019	-	-	-
20 mg vs pl:				
patient	.038	.025	.003	.023
invest	.025	.011	.003	.060
Grade 4				
10 mg vs pl:				
patient	-	-	-	-
invest	-	-	-	-
20 mg vs pl:				
patient	-	-	-	-
invest	-	-	-	-

"*" p-values<.10 (adjusted for baseline and investigator) in favor of drug.
"**" patient's final assessments during double-blind treatment.
"-" p-value not even marginally significant not reported

Nighttime Heartburn Results				
	2-sided p (significant, marginally significant)			
	wk4	wk8	wk12	endpoint
Grade 1				
10 mg vs pl:				
patient	-	-	-	-
invest	-	-	-	-
20 mg vs pl:				
patient	-	-	-	-
invest	-	-	-	-
Grade 2 to 4				
10 mg vs pl:				
patient	.006	-	.010	.067
invest	-	-	-	-
20 mg vs pl:				
patient	.064	.065	.004	.044
invest	-	-	.004	.084
Grade 4				
10 mg vs pl:				
patient	-	-	-	-
invest	-	-	-	-
20 mg vs pl:				
patient	-	.094	-	-
invest	-	-	-	-

"*" p-values<.10 (adjusted for baseline and investigator) in favor of drug.
"**" patient's final assessments during double-blind treatment.
"-" p-value not even marginally significant not reported

2.2.4 Sponsor's ITT & Subgroup Analyses for Maalox intake

For thee mean (daily) Maalox intake, the sponsor claimed significant results in favor of the drug as follows:

1) Less antacid usage for both the 10 and 20 mg dose for nighttime heartburn at week 4 and 12,

2) Less antacid usage for the 20 mg dose for daytime heartburn.

Mean Maalox Intake and 2-sided p

ITT daytime	N*	wk4	wk8	wk12	endpoint	p(#)
placebo	56	2.0	1.7	1.9	1.8	
10 mg	50	1.6	1.5	1.5	1.5	
20 mg	53	1.3	1.3	1.0	1.0	.022(4)
						.040(12)
						.056(end)
Nighttime						
Placebo	56	1.3	1.1	1.3	1.2	
10 mg	50	0.9	0.9	0.7	0.8	<.045(4,12,end
20 mg	53	1.3	1.1	1.2	1.2	.034(4)
						.071(12)
Subgroup:						
Grade 1						
daytime	N*	wk4	wk8	wk12	endpoint	p(#)
placebo	28	1.3	1.1	1.1	1.1	
10 mg	17	0.6	0.7	0.6	0.6	-
20 mg	13	0.8	0.5	0.4	0.5	-
Nighttime						
Placebo	28	1.1	1.1	1.0	1.0	
10 mg	17	0.8	0.9	0.8	0.8	-
20 mg	17	1.2	1.1	1.3	1.3	-
Grade 2 to 4						
daytime	N*	wk4	wk8	wk12	endpoint	
placebo	29	2.7	2.4	2.6	2.4	
10 mg	33	2.2	1.9	2.0	2.0	-
20 mg	41	1.5	1.5	1.2	1.2	.017(4)
						.031(12)
Nighttime						
Placebo	29	1.4	1.1	1.5	1.4	
10 mg	33	1.0	0.8	0.6	0.7	.044(4,12
20 mg	41	1.3	1.2	1.1	1.2	.063(12)
Grade 4						
daytime	N*	wk4	wk8	wk12	endpoint	
placebo	5	1.5	1.0	0.9	1.0	
10 mg	6	1.5	1.5	2.3	1.9	-
20 mg	7	2.2	1.6	1.5	1.5	-
Nighttime						
Placebo	5	2.2	1.4	1.4	1.4	
10 mg	6	2.7	2.7	3.5	2.9	-
20 mg	7	3.7	3.0	3.0	3.0	-
						.060(12)
						.088(end)

"N*" average # of patients across time points.
"p(#)" is 2-sided p-value placebo versus cisapride at week # ()

The mean Maalox results for the efficacy subset were similar.

2.2.5 Sponsor's Global Evaluations Results/ITT & Efficacy Subset

Below is a summary of the significant and marginally significant results for the global evaluations. For the magnitude of the effect, see **Tables 5b and 6b.**

Global Assessments 2-side p-values Results		
ITT	10 mg	20 mg
Investigator	-	.006
Patient	-	.009
Evaluable		
Investigator	-	.003
Patient	-	.006

"-" p-value not even marginally significant

2.3 REVIEWER'S EVALUATIONS & COMMENTS/ STUDY #1203)

Heartburn Results for 20 mg

The results summarized in sections 1.2.2 (based on ITT and efficacy methods) suggest that the 20 mg dose was effective in this trial in the treatment of GERD related symptoms of heartburn.

The repeated measures analysis (**Table S1/1203**) also support the effectiveness of the 20 mg dose for this trial.

1. According to the repeated measures analyses the 20 mg dose was superior to placebo for daytime and nighttime symptoms of heartburn.

2-sided p, placebo vs 20 mg (Repeated Measures Analyses)				
	Inv (day)	Pat (day)	Inv (night)	Pat (night)
2-sided p	.002	.007	.014	.003

Heartburn Results for 10 mg

For the relief of daytime symptoms, the 10 mg dose did not give any evidence of effectiveness either by the patient's or by the investigator's evaluations. The p-values for the ITT, efficacy and for the global analyses were not statistically significant in favor of the 10 mg dose. For the daytime symptoms, only the subgroup of patients with endoscopic grade 2 to 4 for the patient evaluations showed some activity in favor of the 10 mg dose.

Daytime/Patient & Investigator

Sponsor's 2-sided p, placebo vs 10 mg			
	ITT Principle		
	wk4	wk8	wk12
Patient	.079	-	-
Investi.	.010	-	-
	Efficacy Analyses		
Patient	.087	-	-
Investi.	.026	-	-

For the relief of nighttime symptoms, there are some activities in favor of the 10 mg dose by the patient's evaluations but not according to the investigator's evaluations. For patient's evaluations, both the ITT and efficacy subset analyses gave consistently borderline significant results. The subgroup analysis (patients with endoscopic grade 2 to 4) gave significant p-values (p=.010 for patient's evaluations).

Nighttime/Patient & Investigator

Sponsor's 2-sided p, placebo vs 10 mg			
	ITT Principle		
	wk4	wk8	wk12
Patient	.008	-	.086
Investi.	-	-	-
	Efficacy Analyses		
Patient	.013	-	.082
Investi.	-	-	-

Thus, although the efficacy data showed some results in favor of the 10 mg dose, in this reviewer's assessment, this statistical evidence is not consistent (patient versus investigator) and substantial to convincingly conclude that the 10 mg dose was effective in this study.

Results for Antacid Usage

Based on mean Maalox intake data (see table on page 6), the sponsor's claimed significant (nighttime) reduction in antacid usage in the cisapride than in the placebo group:

> "the cisapride 10 mg group had significantly (p=.03) larger reduction than placebo at week 4 and the cisapride 20 mg group had significantly larger reduction than placebo at week 4 (p=.01), week 12 (p=.04), ...". [page 020-00163 of this NDA].

However, the review of the cumulative antacid usage data supports this hypothesis of less antacid usage only for the 20 mg when compared to placebo (2-sided p = .036). However, this reviewer's analyses adjusting for the effect of antacid usage did not alter the results for the heartburn symptoms

End of Double-Blind (Week 12)

Cumulative	Placebo	10 mg	20 mg	Row Total
Usage>201	36(32%)	38(34%)	39(35%)	113(100%)
200<Usage<481	11(28%)	11(28%)	17(44%)	39(100%)
Usage>480	10(56%)	6(33%)	2(11%)	18(100%)
Total	57(34%)	55(32%)	58(34%)	170

Mantel-Haenszel chisquare=6.690, p=.035

End of Double-Blind:placebo vs 10 mg (Week 12)

Cumulative	Placebo	10 mg	
Usage>201	36(49%)	38(51%)	74
200<Usage<481	11(50%)	11(50%)	22
Usage>480	10(63%)	6(38%)	16
Total	57(51%)	55(49%)	112

Mantel-Haenszel chisquare=1.010, p=.604

End of Double-Blind:placebo vs 20 mg (Week 12)

Cumulative	Placebo	20 mg	
Usage>201	36(45%)	39(52)	75
200<Usage<481	11(39%)	17(61%)	28
Usage>480	10(83%)	2(17%)	12
Total	57(50%)	55(50%)	115

Mantel-Haenszel chisquare=6.672, p=.036

Global Evaluations

The results in section 2.2.5 (for the ITT and efficacy) analyses support the hypothesis that the 20 mg dose was effective in this trial, but that the 10 mg dose was not effective.

The 10 mg dose was also shown to be effective in this trial for the efficacy subset, but not by the ITT principle (see table in section 2.25).

III MULTICENTER STUDY #121-5, 851-2 (Protocol 51, 619/121-5, 851)

3.1 Study Design

This was a randomized, multicenter, double-blind, placebo controlled trial of cisapride (10 mg dose) in the treatment of symptoms of gastroesophageal reflux disease (GERD). The patients were treated with cisapride 10 mg or placebo as one tablet QID, given 30 minutes before each meal and at bedtime for a period of eight weeks. A total of 7 centers participated. The protocol called for an estimated 100 patient population.

Inclusion/Exclusion Criteria

See U. S. studies (already discussed).

Qualifying patients, after a two week compliance and eligibility phase (see **Table 1c**), were randomized in a double-blind fashion into placebo or cisapride 10 mg group. The randomization was done by assigning the patients a 4-digit computer generated random number.

Patients were allowed to take Maalox (antacid) on a prn basis, each patient maintained a daily diary which included antacid usage.

Table 1c shows the schedule of evaluations for each patent. Patients evaluations included symptom assessments, diary, overall

assessments, global assessments, endoscopies, biopsies, Bernstein test, manometry, -pH probe, lower esophageal sphincter pressure (LESP) measurements, clinical labs, physical exam and ECG. These evaluations were done at baseline, week 4, week 8 and at week 10 as shown in the table. This table also contains the summary of patient dispositions and demographics.

Primary Efficacy Parameters

Same as U. S. studies (already discussed).

Sample Size Estimation

A sample size of 100 randomized patients with 60 evaluables in each treatment group was planned. With 60 patients per treatment group, 80% power was postulated to detect a difference of two units on the investigator's assessment for nighttime heartburn.

3.2.0 SPONSOR'S ANALYSIS METHODS & RESULTS

3.2.1 Analysis Methods and Group Comparability

The efficacy analyses were performed

1) by the intent-to-treat (ITT) principle,

2) for the subgroup of patients formed by pre-treatment patient characteristics (the groups formed were patients with LESP(<=18) at baseline, patients without esophageal ulcer at baseline and severe heartburn at pre-treatment:>30 on 0-100 analogue).

The sponsor reported 2-sided p-values for the treatment effect significant if 2-sided $p<.05$ and marginally significant if 2-sided p is between .05 and .10.

A total of 147 patients were randomized; 71 in the placebo and 76 in the cisapride treatment group. The ITT analyses excluded 2 patients (both in the placebo group), because these patients did not have any efficacy data. The middle portion of **Table 1c** summarizes patient disposition and patient dropouts by reasons.

The two treatment groups were comparable with respect to demographic characteristics (see bottom part of **Table 1c**). The mean age of patients was 47.4 years. Seventy-six percent of these were males, 93% white, .5% black, .07% Orientals and .07 American Indian. The mean GERD symptom duration was 9 years.

3.2.2 Sponsor's Heartburn Results/ITT

Table 2c summarizes the patient's and investigator's mean daytime and nighttime intensity assessments findings by sponsor's ITT

analyses.

For daytime and nighttime, significant and marginally significant results in favor of cisapride were as follows:

Heartburn Results/ITT

	2-sided p* (significant, marginally significant)				
	wk2	wk4	wk6	wk8	endpoint**
Daytime					
10 mg vs pl:					
patient	-	-	-	-	-
invest.	-	-	-	-	-
Nighttime					
10 mg vs pl:					
patient	.02	.02	<.01	<.01	<.01
invest.	-	-	.03	.05	-

"*" based on type III SSS (adjusted for baseline and investigator) for ranked data
"**"last available double-blind visit.
"-" p-value not even marginally significant (not reported)

3.2.3 Sponsor's Subgroup Analyses For Heartburn

The sponsor's results for the subgroup analyses for daytime and nighttime heartburn are summarized in Tables 3c to 5c).

For daytime and nighttime heartburn, significant and marginally significant results as noted in these tables were as follows:

Heartburn Results

2-sided p (significant, marginally significant)

Subgroup	wk2	wk4	wk6	wk8	endpoint
Moderate HB					
Daytime					
patient	-	-	-	-	-
invest	-	-	.06	-	-
Nighttime					
patient	.06	.09	.01	.02	.05
invest	-	-	-	.08	-
Without Ulcer					
Daytime					
patient	-	-	-	-	-
invest	-	-	-	-	-
Nighttime					
patient	-	-	.01	.05	.07
invest	-	-	-	-	-
LESP<=18					
Daytime					
patient	-	-	-	-	-
invest	-	-	.02	.08	-
Nighttime					
patient	.04	-	<.01	<.01	<.01
invest	-	-	.01	.05	-

"*" based on type III SSS (adjusted for baseline and investigator) for ranked data
"**"last available double-blind visit.
"-" p-value not even marginally significant (not reported)
"HB"=heartburn

3.2.4 Sponsor's ITT & Subgroup Analyses for Maalox intake

The sponsor's mean (daily) Maalox intake results were as follows.

Mean Maalox Intake and 2-sided Wilcoxon Sign rank p

ITT HB	N*	wk2	wk4	wk6	wk8	endpoint	p(#)
placebo	67	3.5	3.5	3.8	3.7	3.6	
10 mg	72	3.4	3.5	3.4	3.3	3.1	-
Moderate HB							
	N*	wk2	wk4	wk6	wk8	endpoint	p(#)
placebo	40	3.8	4.3	4.5	4.4	4.3	
10 mg	48	4.3	4.1	4.2	4.0	3.8	-
Without Ulcer							
placebo	47	3.4	3.2	3.5	3.3	3.2	
10 mg	45	4.2	4.1	4.1	4.0	3.7	-
LESP<=18							
placebo	46	4.0	4.3	4.4	4.6	4.5	
10 mg	49	2.9	2.8	2.5	2.4	2.4	<.07 (all)

"N*" average # of patients across time points.
"p(#)" is 2-sided p-value placebo versus cisapride at week # ()
"all" = at all visits.

3.2.5 Sponsor's Global Evaluations Results/ITT & Subgroup

Below is a summary of the significant and marginally significant results for the global evaluations. For the magnitude of the effect, see Table 6c.

Global Assessments 2-side p* Results

	Pat	Inv.
ITT	-	.02
Moderate HB	-	.02
Without Ulcer	.08	.01
LESP<=18	-	<.01

"*": based on Mantel-Haenszel test controlling for investigator.

3.3 REVIEWER'S EVALUATIONS & COMMENTS/ STUDY 121-5

Heartburn Results for 10 mg

For the daytime symptoms relief, the 10 mg dose was clearly not effective in this trial. There were no significant daytime findings in favor of the cisapride 10 mg either by the ITT or by the subgroup analyses (see summary of results in section 3.2.2).

For the nighttime relief of symptoms, however, the efficacy data suggest that cisapride 10 mg was effective both by patient's and investigator's assessments.

Nighttime/Patient & Investigator: ITT

Sponsor's 2-sided p, placebo vs 10 mg					
	wk2	wk4	wk6	wk8	
Patient	.02	.02	.01	.01	ITT
Investi.	-	-	.03	.05	
Patient	.06	.09	.01	.02	Subgroup Moderate to Severe
Investi.	-	-	-	.08	

Also, the sponsor's rank data analyses (**Table S1/121-5**) support the nighttime effectiveness of cisapride 10 mg but not the daytime effectiveness of cisapride 10 mg in reducing the heartburn symptoms.

2-sided p, placebo vs 10 mg (rank data analyses)			
Pat(day)	Inv(day)	Pat(night)	Inv(night)
-	-	.001	.049

Results for Antacid Usage

The ITT analyses results summarized in section 3.2.4 showed no significant differences in the mean Maalox intake between placebo and cisapride 10 mg.

Results for Global Evaluations

For the nighttime relief of heartburn symptoms, the results in section 3.2.5 (for the ITT) analyses indicate that cisapride 10 mg is effective in this trial by investigator's assessments but not by patient's evaluations.

There were no significant daytime results.

III Summary of Week 12 Heartburn Results Across Studies

The following tables summarize the heartburn results for the 10 mg dose at week 12 (end of treatment) across the three studies. The purpose of the summary is to assess the inter-studies consistency of the effect of the 10 mg dose.

Nighttime Heartburn/ Patient's Evaluations

Week 12 2-sided p, Placebo versus 10 mg			
	Study #1201	Study #1203	Study #121-5
ITT	-	.086	<.01*
EFF	.057	.082	not done
Comment-	Some support	Weak support	Strong support

Nighttime Heartburn/ Investigator's Evaluations

Week 12 2-sided p, Placebo versus 10 mg			
	Study #1201	Study #1203	Study #121-5
ITT	.010	-	.05*
EFF	.012	-	not done
Comment-	Strong support	No support	Strong support

Daytime Heartburn/ Patient's Evaluations

Week 12 2-sided p, Placebo versus 10 mg			
	Study #1201	Study #1203	Study #121-5
ITT	.063	-	-
EFF	.057	-	not done
Comment-	Weak support	No support	No support

Daytime Heartburn/ Investigator's Evaluations

Week 12 2-sided p, Placebo versus 10 mg			
	Study #1201	Study #1203	Study #121-5
ITT	.057	-	-
EFF	.055	-	not done
Comment	Weak support	No support	No support

Global Evaluations 2-sided p, Placebo versus 10 mg					
	Study #1201		Study #1203		Study #121-5
	ITT	EFF	ITT	EFF	ITT
Pat	.061	.036	-	-	-
Inv	-	.081	-	-	.02
Comment	Some support		No support		Some support

IV. COMMENTS & CONCLUSIONS (Which May Be Conveyed To The Sponsor)

Results for 10 mg

1. In study #1201, the heartburn symptoms data supported the effectiveness of the 10 mg dose in comparison to placebo. The data indicated that, for this dose, the results were convincing for the nighttime symptoms relief ($p<.013$ for investigator's assessments and $p=.057$ for patient's efficacy evaluations' at week 12), and less convincing for the daytime symptoms relief ($p>058$ for both patient's and investigator's week 12 assessments).

2. In study #1203, for daytime heartburn, there was no statistical evidence to support the hypothesis that the 10 mg dose was effective. For the nighttime symptoms, the results showed some activity in favor of the 10 mg dose. But the statistical evidence was not substantial ($p>.085$ for week 12 patient's evaluations).

3. For study #121-5, there were no statistically significant daytime findings in favor of the 10 mg dose ($p>.10$ week 12). But the 10 mg dose was effective for the relief of nighttime symptoms ($p<.051$ week 12).

Results for 20 mg

1. The effectiveness data of study #1201 did not support the

claim that the 20 mg dose was effective in this trial.

2. In study #1203, which is similarly designed as study #1201, the 20 mg dose was effective. The repeated measures analysis also supported the effectiveness of the 20 mg dose ($p<.028$).

OVERALL CONCLUSION

The 20 mg dose was effective in reducing both daytime and nighttime symptoms of GERD in study #1203. But this result for the 20 mg dose was not replicated in the second study # 1201.

The 10 mg dose was effective in reducing the nighttime symptoms of heartburn in study # 1201 and in study # 121-5. The efficacy data in study # 1203 showed some activity in favor of the 10 mg dose for the nighttime symptoms ($p>.081$ for week 12 patient's assessments), but the statistical evidence was not substantial to claim that the 10 mg dose was effective in this study for nighttime symptoms. The 10 mg dose did not show any convincing statistical evidence in this study for the relief of daytime symptoms of heartburn.

A J Sankoh

A. J. Sankoh, Ph. D.

Mathematical Statistician

Concur: Found Ateeq for Huque

Dr. Huque

Dr. Dubey 3-23-92

cc: Orig. NDA 20-210
HFD - 180
HFD - 180/Dr. Fredd
HFD - 180/Dr. DuBois
HFD - 180/Mr. Hassell
HFD - 713/Dr. Dubey [File: DRU 1.3.2 NDA]
HFD - 713/Dr. Huque
HFD - 713/Dr. Sankoh
Chron.
Sankoh/x4710/AJS/03-23-92

Table 1a
Visits Schedule, Patient Dispositions & Demographics

Schedule of Evaluations					
	Visit 1 (Wk-2)	Visit2 (Wk 0)	Visit3 (Wk4)	Visit4 (Wk8)	Visit5 (Wk12)
Assessments	Selection	Baseline Phase	Double-Blind Treatment Phase		
Symptoms (Inv)	X	X	X	X	X
Diary (Pat)		X	X	X	X
Overall Assess		X	X	X	X
Global Assess					X
Endoscopy	In 7 days				X
Endo. Biopsy	In 7 days				5 days
Bernstein test	In 7 days				5 days
LESP	In 7 days				X
Laboratory determinations	X	X	X	X	X
Physical	X				X
EKG	X				

Note: In 7 days/5 days means within 7 days/within 5 days.

	PLACEBO	CISAPRIDE 10MG	CISAPRIDE 20MG	TOTAL*
ENTERED(ALL CENTERS)	60	63	59	182
CAMARA/01	3	4	4	11
SCHUBERT/02	2	2	1	5
BEHAR/03	4	4	5	13
ROBINSON/04	6	4	4	14
CASTELL/05	6	6	7	19
SHOCKETT/06	4	5	4	13
DINICCO/07	8	10	9	28
BERENSON/08	8	8	9	25
TRAUBE/09	2	1	2	5
SHAKER/10	4	5	5	14
MCCALLUM/11	4	4	3	11
MCQUAID/12	2	2	1	5
LANZA/13	6	6	4	16
BENJAMIN/14	1	2	1	4
PREMATURELY DISCONTINUED	16	14	15	45
REASON FOR DISCONTINUATION				
INTERCURRENT ILLNESS	0	0	1	1
UNCOOPERATIVE	3	2	1	6
ADVERSE EXPERIENCE	2	1	4	7
INELIGIBLE	1	3	1	5
INADEQUATE RESPONSE	8	1	5	11
LOST TO FOLLOW UP	1	3	0	4
CHOSE TO DISCONTINUE	2	0	0	2
OTHER REASON	2	4	3	9

PARAMETER*	TREATMENT GROUP PLACEBO	CISAPRIDE 10 MG	CISAPRIDE 20 MG	TOTAL	P-VALUE *
SEX					
MALE	41	44	33	118	0.178 **
FEMALE	19	19	26	64	
RACE					
WHITE	57	56	56	169	0.625 **
BLACK	3	5	2	10	
HISPANIC		2	1	3	
AGE(YEARS)					
N	60	63	59	182	0.859 ***
MEAN	44.4	47.3	47.5	44.4	
STD.DEV.	13.6	13.0	14.7	13.6	
MEDIAN	42.5	39.0	46.0	42.0	
MINIMUM	21.0	21.0	22.0	21.0	
MAXIMUM	73.0	69.0	75.0	75.0	
GERD SYMPTOM DURATION(YEAR)					
N	60	63	59	182	0.946 ***
MEAN	8.5	8.7	8.8	8.4	
STD.DEV.	7.4	7.4	8.9	7.9	
MEDIAN	6.0	6.0	5.0	6.0	
MINIMUM	0.3	0.7	0.3	0.3	
MAXIMUM	30.0	28.0	40.0	40.0	

* BETWEEN-TREATMENT COMPARISONS
** GENERALIZED COCHRAN-MANTEL-HAENSZEL TEST, CONTROLLING FOR INVESTIGATOR
*** ANOVA MODEL INCLUDING TREATMENT, INVESTIGATOR, AND TREATMENT X INVESTIGATOR INTERACTION EFFECTS. (P-VALUE BASED ON TYPE III SS.)

Table 2a/ITT & Efficacy Subset
Heartburn Intensity Evaluation Results

Patient

POPULATION: INTENT-TO-TREAT
ASSESSMENT: INTENSITY SCALE 0=NONE, ... 100=WORST, LOWER SCORE IS BETTER
SOURCE: PATIENT'S DIARY DATA: AVERAGE OVER DAYS WITHIN MONTHLY PERIOD

PARAMETER	PLACEBO N	PLACEBO LSM*	PLACEBO DIFF. FROM BASELINE	PLACEBO P-VAL*	CISAPRIDE 10MG N	CISAPRIDE 10MG LSM*	CISAPRIDE 10MG DIFF. FROM BASELINE	CISAPRIDE 10MG P-VAL*	CISAPRIDE 20MG N	CISAPRIDE 20MG LSM*	CISAPRIDE 20MG DIFF. FROM BASELINE	CISAPRIDE 20MG P-VAL*	P-VALUES (1) TRT	P-VALUES (1) TRT-INV	PAIRWISE COMPARISON (2) P. VS 10	PAIRWISE COMPARISON (2) P. VS 20	PAIRWISE COMPARISON (2) 10 VS 20
HEARTBURN INT. - DAY																	
BASELINE	87	48.8			61	49.4			56	50.4			0.879	0.396	0.812	0.613	0.781
D/B WEEK 4	87	35.6	-10.6	<0.001	60	30.1	-19.1	<0.001	56	38.8	-10.8	<0.001	0.036	0.641	0.074AA	0.963	0.029AA
D/B WEEK 8	85	30.3	-18.2	<0.001	52	23.8	-25.8	<0.001	47	34.1	-15.4	<0.001	0.073	0.403	0.178	0.407	0.025AA
D/B WEEK 12	47	27.0	-22.8	<0.001	48	18.8	-31.0	<0.001	44	28.3	-21.2	<0.001	0.001	0.171	0.063A	0.779	0.048AA
ENDPOINT	87	28.8	-20.5	<0.001	61	22.5	-26.9	<0.001	56	32.2	-17.2	<0.001	0.077	0.137	0.139	0.453	0.077AA
OVERALL	87	32.4	-17.0	<0.001	61	26.7	-22.7	<0.001	56	35.2	-14.3	<0.001	0.090	0.399	0.145	0.485	0.033AA
HEARTBURN INT. - NIGHT																	
BASELINE	87	47.5			61	42.0			56	51.4			0.110	0.519	0.314	0.394	0.038AA
D/B WEEK 4	87	35.8	-10.2	<0.001	60	27.9	-18.0	<0.001	56	32.6	-13.3	<0.001	0.127	0.871	0.044AA	0.436	0.220
D/B WEEK 8	85	28.2	-18.8	<0.001	52	22.9	-24.2	<0.001	47	31.1	-16.1	<0.001	0.211	0.508	0.234	0.542	0.089A
D/B WEEK 12	47	24.0	-22.4	<0.001	48	18.7	-27.6	<0.001	44	25.7	-20.7	<0.001	0.816	0.282	0.249	0.717	0.158
ENDPOINT	87	26.4	-18.7	<0.001	61	21.8	-24.3	<0.001	56	29.0	-17.1	<0.001	0.256	0.313	0.290	0.556	0.105
OVERALL	87	28.4	-16.7	<0.001	61	24.9	-21.2	<0.001	56	31.0	-15.1	<0.001	0.289	0.853	0.256	0.691	0.132
SOURCE: INVESTIGATOR'S CLINIC EVALUATION																	
HEARTBURN INT. - DAY																	
BASELINE	86	5.8			60	6.2			57	5.7			0.371	0.628	0.416	0.567	0.163
D/B WEEK 4	86	4.7	-1.2	<0.001	60	4.1	-1.8	<0.001	57	4.8	-1.1	0.002	0.109	0.937	0.178	0.624	0.044AA
D/B WEEK 8	83	3.8	-2.1	<0.001	52	3.8	-2.4	<0.001	47	4.4	-1.5	<0.001	0.194	0.333	0.467	0.261*	0.072A
D/B WEEK 12	46	3.9	-2.0	<0.001	48	3.9	-3.0	<0.001	44	4.0	-1.9	<0.001	0.085	0.595	0.057A	0.882	0.057A
ENDPOINT	86	4.0	-1.9	<0.001	60	3.3	-2.7	<0.001	57	4.5	-1.4	<0.001	0.026	0.153	0.100	0.300	0.009AA
OVERALL	86	4.2	-1.8	<0.001	60	3.7	-2.3	<0.001	57	4.7	-1.3	<0.001	0.034	0.453	0.100	0.188	0.009AA
HEARTBURN INT. - NIGHT																	
BASELINE	87	5.8			60	6.3			57	6.4			0.352	0.708	0.255	0.180	0.818
D/B WEEK 4	87	4.7	-1.4	<0.001	60	3.8	-2.4	<0.001	57	4.7	-1.6	<0.001	0.069	0.334	0.040AA	0.906	0.054A
D/B WEEK 8	84	4.1	-2.0	<0.001	52	3.0	-3.1	<0.001	47	4.6	-2.1	<0.001	0.116	0.766	0.047A	0.946	0.087A
D/B WEEK 12	47	3.7	-2.4	<0.001	49	2.3	-3.8	<0.001	44	3.3	-2.8	<0.001	0.029	0.504	0.010AA	0.479	0.085A
ENDPOINT	87	4.1	-2.0	<0.001	60	2.7	-3.4	<0.001	57	4.1	-2.1	<0.001	0.007	0.079	0.006AA	0.947	0.007AA
OVERALL	87	4.3	-1.9	<0.001	60	3.2	-2.9	<0.001	57	4.4	-1.7	<0.001	0.016	0.220	0.020AA	0.773	0.009AA

POPULATION: EVALUABLE DATA ONLY
ASSESSMENT: INTENSITY SCALE 0=NONE, ... 100=WORST, LOWER SCORE IS BETTER
SOURCE: PATIENT'S DIARY DATA: AVERAGE OVER DAYS WITHIN MONTHLY PERIOD

PARAMETER	PLACEBO N	PLACEBO LSM*	PLACEBO DIFF. FROM BASELINE	PLACEBO P-VAL*	CISAPRIDE 10MG N	CISAPRIDE 10MG LSM*	CISAPRIDE 10MG DIFF. FROM BASELINE	CISAPRIDE 10MG P-VAL*	CISAPRIDE 20MG N	CISAPRIDE 20MG LSM*	CISAPRIDE 20MG DIFF. FROM BASELINE	CISAPRIDE 20MG P-VAL*	P-VALUES (1) TRT	P-VALUES (1) TRT-INV	PAIRWISE COMPARISON (2) P. VS 10	PAIRWISE COMPARISON (2) P. VS 20	PAIRWISE COMPARISON (2) 10 VS 20
HEARTBURN INT. - DAY																	
BASELINE	83	48.8			58	52.0			55	50.9			0.803	0.404	0.508	0.732	0.750
D/B WEEK 4	83	35.3	-10.9	<0.001	57	30.3	-19.9	<0.001	55	38.8	-11.8	<0.001	0.048	0.718	0.027AA	0.867	0.040AA
D/B WEEK 8	81	31.8	-18.7	<0.001	51	24.1	-26.3	<0.001	46	33.8	-16.7	<0.001	0.107	0.788	0.009A	0.683	0.050A
D/B WEEK 12	44	28.0	-22.1	<0.001	47	18.8	-31.3	<0.001	44	28.8	-21.5	<0.001	0.091	0.187	0.057A	0.909	0.058A
ENDPOINT	83	30.4	-20.0	<0.001	58	22.5	-27.8	<0.001	55	32.0	-18.3	<0.001	0.091	0.153	0.089A	0.727	0.041AA
OVERALL	83	33.6	-18.8	<0.001	58	26.7	-23.6	<0.001	55	35.1	-15.2	<0.001	0.107	0.414	0.107	0.707	0.046AA
HEARTBURN INT. - NIGHT																	
BASELINE	83	49.3			58	44.6			55	51.6			0.318	0.743	0.309	0.640	0.138
D/B WEEK 4	83	36.9	-9.8	<0.001	57	28.6	-18.3	<0.001	55	33.1	-13.7	<0.001	0.130	0.870	0.044AA	0.760	0.268
D/B WEEK 8	81	29.4	-18.4	<0.001	51	23.4	-24.4	<0.001	46	30.9	-16.9	<0.001	0.367	0.488	0.700	0.751	0.128
D/B WEEK 12	44	24.8	-22.1	<0.001	47	18.6	-28.3	<0.001	44	26.0	-20.8	<0.001	0.289	0.280	0.202	0.805	0.151
ENDPOINT	83	27.8	-18.5	<0.001	58	21.8	-26.2	<0.001	55	29.1	-18.0	<0.001	0.242	0.303	0.216	0.749	0.122
OVERALL	83	30.7	-16.4	<0.001	58	26.2	-21.8	<0.001	55	31.3	-15.7	<0.001	0.291	0.709	0.201	0.872	0.152
SOURCE: INVESTIGATOR'S CLINIC EVALUATION																	
HEARTBURN INT. - DAY																	
BASELINE	82	6.0			57	6.2			56	5.7			0.437	0.648	0.633	0.434	0.703
D/B WEEK 4	82	4.7	-1.3	<0.001	57	4.2	-1.8	<0.001	56	4.9	-1.1	0.002	0.184	0.960	0.198	0.630	0.075A
D/B WEEK 8	80	4.0	-2.1	<0.001	51	3.8	-2.4	<0.001	48	4.4	-1.6	<0.001	0.304	0.337	0.455	0.403	0.124
D/B WEEK 12	43	4.0	-1.9	<0.001	48	3.0	-3.0	<0.001	44	4.0	-2.0	<0.001	0.103	0.568	0.055A	0.951	0.030A
ENDPOINT	82	4.2	-1.8	<0.001	57	3.3	-2.7	<0.001	56	4.5	-1.5	<0.001	0.035	0.144	0.031A	0.687	0.012AA
OVERALL	82	4.3	-1.7	<0.001	57	3.7	-2.3	<0.001	56	4.7	-1.3	<0.001	0.060	0.487	0.201	0.278	0.018AA
HEARTBURN INT. - NIGHT																	
BASELINE	83	6.0			57	6.4			56	6.4			0.863	0.917	0.365	0.378	0.918
D/B WEEK 4	83	4.8	-1.4	<0.001	57	3.8	-2.3	<0.001	56	4.7	-1.5	<0.001	0.136	0.448	0.070A	0.841	0.102
D/B WEEK 8	80	4.2	-2.0	<0.001	51	3.1	-3.1	<0.001	46	4.0	-2.2	<0.001	0.140	0.805	0.062A	0.768	0.135
D/B WEEK 12	44	3.8	-2.3	<0.001	48	2.4	-3.7	<0.001	44	3.3	-2.8	<0.001	0.039	0.480	0.012AA	0.384	0.131
ENDPOINT	83	4.2	-2.0	<0.001	57	2.7	-3.5	<0.001	56	4.1	-2.2	<0.001	0.009	0.078	0.005AA	0.761	0.012AA
OVERALL	83	4.4	-1.9	<0.001	57	3.3	-3.0	<0.001	56	4.4	-1.8	<0.001	0.026	0.314	0.023AA	0.917	0.016AA

* LSM: LEAST SQUARES MEAN.
* P-VALUE FROM ONE-SAMPLE TWO-SIDED T-TEST.
(1) P-VALUES FROM ANCOVA MODEL WITH TREATMENT(TRT), INVESTIGATOR, TREATMENT X INVESTIGATOR INTERACTION, AND BASELINE VALUE(EXCEPT AT BASELINE).
(2) P-VALUES FROM FISHER'S LSD TWO-SIDED TEST FROM THE SAME ANCOVA MODEL.
"P": TWO-SIDED P-VALUE <=0.10 WITH PLACEBO HAVING LOWER (BETTER) SCORES; "AA": P-VALUE <=0.05.
"A": TWO-SIDED P-VALUE <=0.10 WITH CISAPRIDE 10MG HAVING LOWER (BETTER) SCORES; "BB": P-VALUE <=0.05.
"B": TWO-SIDED P-VALUE <=0.10 WITH CISAPRIDE 20MG HAVING LOWER (BETTER) SCORES;

Table 3a/Subgroup
Patient's Heartburn Intensity Assessments Results

..A : SUMMARY OF PATIENT'S DIARY SYMPTOM INTENSITY ASSESSMENTS - PATIENTS WITH PRE-TREATMENT ENDOS. GRADE OF 1

POPULATION: INTENT-TO-TREAT
ASSESSMENT: INTENSITY SCALE 0=NONE, ... 100=WORST, LOWER SCORE IS BETTER
SOURCE: PATIENT'S DIARY DATA: AVERAGE OVER DAYS WITHIN MONTHLY PERIOD

	----- PLACEBO -----			- CISAPRIDE 10MG --			- CISAPRIDE 20MG --					
		DIFF. FROM BASELINE			DIFF. FROM BASELINE			DIFF. FROM BASELINE		P-VALUES (1)	PAIRWISE COMPARISON (2)	
PARAMETER	N LSM*	LSM*	P-VAL*	N LSM*	LSM*	P-VAL*	N LSM*	LSM*	P-VAL*	TREATMENT	P. VS 10	P. VS 20 10 VS 20
HEARTBURN INT. - DAY												
BASELINE	27 45.4			19 39.2			20 46.9			0.274	0.187	0.745 0.134
D/B WEEK 4	27 34.6	-8.8	0.004	19 29.4	-14.7	0.076	20 39.0	-4.6	0.243	0.347	0.385	0.452 0.148
D/B WEEK 8	26 24.6	-18.2	<0.001	12 11.5	-31.3	<0.001	18 35.0	-7.8	0.243	0.034	0.101	0.150 0.010AA
D/B WEEK 12	23 22.3	-20.5	0.001	11 6.8	-36.0	<0.001	14 23.6	-19.2	0.005	0.112	0.050A	0.862 0.069A
ENDPOINT	27 25.3	-16.3	0.001	19 18.1	-25.4	0.002	20 28.9	-14.6	0.007	0.370	0.317	0.591 0.167
OVERALL	27 28.1	-15.4	<0.001	19 23.2	-20.4	0.006	20 35.0	-8.5	0.073	0.249	0.447	0.276 0.101
HEARTBURN INT. - NIGHT												
BASELINE	27 42.5			19 29.5			20 43.8			0.037	0.023AA	0.824 0.027AA
D/B WEEK 4	27 31.0	-8.8	0.007	19 27.9	-11.8	0.078	20 31.8	-7.9	0.032	0.840	0.634	0.884 0.574
D/B WEEK 8	26 23.7	-16.4	0.001	12 13.1	-27.0	0.002	16 30.9	-9.3	0.114	0.190	0.247	0.361 0.070A
D/B WEEK 12	23 21.1	-17.7	0.005	11 6.1	-32.6	<0.001	14 21.6	-17.2	0.003	0.175	0.081A	0.945 0.108
ENDPOINT	27 23.7	-16.0	0.005	19 20.1	-19.6	0.024	20 25.0	-14.8	0.007	0.837	0.643	0.861 0.565
OVERALL	27 25.5	-14.3	0.002	19 23.4	-16.4	0.042	20 29.5	-10.2	0.013	0.703	0.768	0.535 0.473

..AB : SUMMARY OF PATIENT'S DIARY SYMPTOM INTENSITY ASSESSMENTS - PATIENTS WITH PRE-TREATMENT ENDOS. GRADE OF 2,3, OR 4

POPULATION: INTENT-TO-TREAT
ASSESSMENT: INTENSITY SCALE 0=NONE, ... 100=WORST, LOWER SCORE IS BETTER
SOURCE: PATIENT'S DIARY DATA: AVERAGE OVER DAYS WITHIN MONTHLY PERIOD

	----- PLACEBO -----			- CISAPRIDE 10MG --			- CISAPRIDE 20MG --					
		DIFF. FROM BASELINE			DIFF. FROM BASELINE			DIFF. FROM BASELINE		P-VALUES (1)	PAIRWISE COMPARISON (2)	
PARAMETER	N LSM*	LSM*	P-VAL*	N LSM*	LSM*	P-VAL*	N LSM*	LSM*	P-VAL*	TREATMENT	P. VS 10	P. VS 20 10 VS 20
HEARTBURN INT. - DAY												
BASELINE	30 54.0			42 64.0			36 55.8			0.906	0.988	0.720 0.687
D/B WEEK 4	30 41.1	-11.6	<0.001	41 33.0	-19.7	<0.001	36 38.5	-14.2	<0.001	0.207	0.090A	0.595 0.718
D/B WEEK 8	29 36.3	-16.8	<0.001	40 31.1	-22..	<0.001	31 32.3	-20.8	<0.001	0.592	0.319	0.468 0.810
D/B WEEK 12	24 28.2	-23.9	<0.001	37 23.0	-30.1	<0.001	30 27.4	-25.7	<0.001	0.536	0.296	0.777 0.424
ENDPOINT	30 34.6	-18.4	<0.001	42 25.8	-27.1	<0.001	36 34.1	-18.9	<0.001	0.190	0.121	0.922 0.121
OVERALL	30 37.0	-15.9	<0.001	42 30.1	-22.8	<0.001	36 35.5	-17.5	<0.001	0.315	0.180	0.750 0.251
HEARTBURN INT. - NIGHT												
BASELINE	30 51.3			42 49.3			36 56.9			0.404	0.744	0.371 0.190
D/B WEEK 4	30 37.2	-12.4	<0.001	41 30.6	-19.1	<0.001	36 34.7	-14.9	<0.001	0.373	0.171	0.611 0.369
D/B WEEK 8	29 32.8	-18.0	<0.001	40 28.3	-21.6	<0.001	31 30.3	-20.7	<0.001	0.792	0.505	0.639 0.862
D/B WEEK 12	24 24.7	-25.7	<0.001	37 23.1	-27.3	<0.001	30 25.6	-24.8	<0.001	0.893	0.779	0.878 0.641
ENDPOINT	30 30.1	-19.9	<0.001	42 24.8	-25.1	<0.001	36 31.9	-18.1	<0.001	0.381	0.241	0.757 0.184
OVERALL	30 32.8	-17.2	<0.001	42 28.0	-22.0	<0.001	36 32.8	-17.2	<0.001	0.505	0.336	0.990 0.308

..AC : SUMMARY OF PATIENT'S DIARY SYMPTOM INTENSITY ASSESSMENTS - PATIENTS WITH PRE-TREATMENT ENDOS. GRADE OF 4

POPULATION: INTENT-TO-TREAT
ASSESSMENT: INTENSITY SCALE 0=NONE, ... 100=WORST, LOWER SCORE IS BETTER
SOURCE: PATIENT'S DIARY DATA: AVERAGE OVER DAYS WITHIN MONTHLY PERIOD

	----- PLACEBO -----			- CISAPRIDE 10MG --			- CISAPRIDE 20MG --					
		DIFF. FROM BASELINE			DIFF. FROM BASELINE			DIFF. FROM BASELINE		P-VALUES (1)	PAIRWISE COMPARISON (2)	
PARAMETER	N LSM*	LSM*	P-VAL*	N LSM*	LSM*	P-VAL*	N LSM*	LSM*	P-VAL*	TREATMENT	P. VS 10	P. VS 20 10 VS 20
HEARTBURN INT. - DAY												
BASELINE	2 51.2			10 58.0			11 52.1			0.812	0.677	0.957 0.563
D/B WEEK 4	2 53.2	1.9	0.567	10 38.4	-12.9	0.072	11 41.1	-10.2	0.003	0.278	0.118	0.193 0.640
D/B WEEK 8	2 59.3	7.8	0.307	9 40.5	-11.0	0.018	10 28.2	-23.2	0.001	0.016	0.058A	0.00688 0.0688
D/B WEEK 12	2 46.8	-2.8	0.144	8 20.0	-29.7	0.002	9 15.4	-34.7	0.003	0.001	0.054A	0.03088 0.596
ENDPOINT	2 47.8	11.7	0.144	10 33.8	-17.5	0.009	11 35.0	-16.3	0.008	0.131	0.055A	0.0658 0.897
OVERALL	2 58.5	7.2	0.728	10 36.6	-14.7	0.007	11 35.8	-15.5	0.001	0.058	0.028AA	0.07488 0.888
HEARTBURN INT. - NIGHT												
BASELINE	2 84.0			10 59.4			11 56.5			0.219	0.174	0.0978 0.759
D/B WEEK 4	2 86.5	3.1	0.310	10 33.2	-20.2	<0.001	11 39.9	-13.8	0.019	0.122	0.051A	0.158 0.307
D/B WEEK 8	2 72.5	18.0	0.673	9 35.4	-19.1	<0.001	10 36.3	-18.1	0.007	0.006	0.002AA	0.00288 0.858
D/B WEEK 12	2 60.3	8.8	0.602	8 17.6	-33.8	0.001	9 20.3	-31.2	0.026	0.007	0.002AA	0.00488 0.659
ENDPOINT	2 78.1	24.7	0.602	10 32.0	-21.4	0.001	11 38.2	-15.2	0.035	0.003	<0.001AA	<0.00188 0.310
OVERALL	2 68.3	14.9	0.518	10 32.2	-21.2	<0.001	11 37.6	-15.8	0.012	0.002	<0.001AA	0.00388 0.246

* LSM: LEAST SQUARES MEAN.
* P-VALUE FROM ONE-SAMPLE TWO-SIDED T-TEST.
(1) P-VALUES FROM ANCOVA MODEL WITH TREATMENT(TRT), INVESTIGATOR, AND BASELINE VALUE (EXCEPT AT BASELINE).
(2) P-VALUES FROM FISHER'S LSD TWO-SIDED TEST FROM THE SAME ANCOVA MODEL.
"P": TWO-SIDED P-VALUE <=0.10 WITH PLACEBO HAVING LOWER (BETTER) SCORES; "PP": P-VALUE <=0.05.
"A": TWO-SIDED P-VALUE <=0.10 WITH CISAPRIDE 10MG HAVING LOWER (BETTER) SCORES; "AA": P-VALUE <=0.05.
"B": TWO-SIDED P-VALUE <=0.10 WITH CISAPRIDE 20MG HAVING LOWER (BETTER) SCORES; "BB": P-VALUE <=0.05.

Table 4a/Subgroup
Investigator's Heartburn Intensity Assessments Results

. . . SUMMARY OF INVESTIGATOR'S SYMPTOM INTENSITY ASSESSMENTS - PATIENTS WITH PRE-TREATMENT ENDOS. GRADE OF 1

POPULATION: INTENT-TO-TREAT
ASSESSMENT: INTENSITY SCALE 0=NONE, ... 10=WORST, LOWER SCORE IS BETTER
SOURCE: INVESTIGATOR'S CLINIC EVALUATION

PARAMETER	PLACEBO N	PLACEBO LSM*	PLACEBO DIFF. FROM BASELINE LSM*	PLACEBO DIFF. FROM BASELINE P-VAL*	CISAPRIDE 10MG N	CISAPRIDE 10MG LSM*	CISAPRIDE 10MG DIFF. FROM BASELINE LSM*	CISAPRIDE 10MG DIFF. FROM BASELINE P-VAL*	CISAPRIDE 20MG N	CISAPRIDE 20MG LSM*	CISAPRIDE 20MG DIFF. FROM BASELINE LSM*	CISAPRIDE 20MG DIFF. FROM BASELINE P-VAL*	P-VALUES (1) TREATMENT	PAIRWISE COMPARISON (2) P. VS 10	P. VS 20	10 VS 20
HEARTBURN INT. - DAY																
BASELINE	28	6.0			18	5.7			20	5.8			0.761	0.600	0.494	0.899
D/B WEEK 4	26	4.7	-1.0	0.006	18	4.0	-1.7	0.003	20	5.2	-0.5	0.415	0.735	0.312	0.393	0.090A
D/B WEEK 8	25	3.7	-1.9	<0.001	12	2.8	-3.8	0.015	16	4.3	-1.5	0.123	0.336	0.356	0.448	0.147
D/B WEEK 12	22	3.8	-1.6	0.006	11	1.7	-3.8	<0.001	14	3.6	-1.9	0.079	0.086	0.030AA	0.747	0.088A
ENDPOINT	28	4.1	-1.6	0.003	18	2.9	-3.8	<0.001	20	4.6	-1.1	0.131	0.713	0.187	0.608	0.091A
OVERALL	26	4.1	-1.5	<0.001	18	3.3	-2.4	<0.001	20	4.9	-0.8	0.266	0.142	0.278	0.278	0.049AA
HEARTBURN INT. - NIGHT																
BASELINE	27	5.5			18	5.8			20	5.6			0.870	0.684	0.884	0.807
D/B WEEK 4	27	4.8	-0.8	0.063	18	3.5	-2.1	0.016	20	4.5	-1.0	0.066	0.341	0.169	0.834	0.737
D/B WEEK 8	26	4.0	-1.5	0.009	12	2.4	-3.0	0.027	16	3.4	-2.0	0.078	0.382	0.168	0.598	0.418
D/B WEEK 12	23	3.5	-1.7	0.027	11	1.2	-4.1	<0.001	14	2.6	-2.6	0.014	0.107	0.035AA	0.361	0.741
ENDPOINT	27	4.1	-1.5	0.015	18	2.5	-3.0	0.003	20	3.9	-1.7	0.031	0.281	0.127	0.838	0.219
OVERALL	27	4.2	-1.4	0.007	18	2.9	-2.6	0.007	20	4.2	-1.3	0.040	0.272	0.144	0.967	0.165

. . . SUMMARY OF INVESTIGATOR'S SYMPTOM INTENSITY ASSESSMENTS - PATIENTS WITH PRE-TREATMENT ENDOS. GRADE OF 2,3, OR 4

POPULATION: INTENT-TO-TREAT
ASSESSMENT: INTENSITY SCALE 0=NONE, ... 10=WORST, LOWER SCORE IS BETTER
SOURCE: INVESTIGATOR'S CLINIC EVALUATION

PARAMETER	PLACEBO N	PLACEBO LSM*	PLACEBO DIFF. FROM BASELINE LSM*	PLACEBO DIFF. FROM BASELINE P-VAL*	CISAPRIDE 10MG N	CISAPRIDE 10MG LSM*	CISAPRIDE 10MG DIFF. FROM BASELINE LSM*	CISAPRIDE 10MG DIFF. FROM BASELINE P-VAL*	CISAPRIDE 20MG N	CISAPRIDE 20MG LSM*	CISAPRIDE 20MG DIFF. FROM BASELINE LSM*	CISAPRIDE 20MG DIFF. FROM BASELINE P-VAL*	P-VALUES (1) TREATMENT	PAIRWISE COMPARISON (2) P. VS 10	P. VS 20	10 VS 20
HEARTBURN INT. - DAY																
BASELINE	30	6.1			42	6.6			37	6.0			0.259	0.758	0.737	0.118
D/B WEEK 4	30	4.7	-1.4	0.003	42	4.2	-1.9	<0.001	37	4.7	-1.5	<0.001	0.453	0.265	0.898	0.300
D/B WEEK 8	28	4.5	-1.6	<0.001	40	3.9	-2.2	<0.001	31	4.5	-1.7	0.001	0.485	0.390	0.978	0.328
D/B WEEK 12	24	3.8	-2.3	<0.001	36	3.2	-3.0	<0.001	30	3.8	-2.3	<0.001	0.395	0.384	0.987	0.237
ENDPOINT	30	4.5	-1.6	<0.001	42	3.4	-2.7	<0.001	37	4.4	-1.7	<0.001	0.078	0.049AA	0.867	0.056A
OVERALL	30	4.5	-1.6	<0.001	42	3.8	-2.3	<0.001	37	4.5	-1.6	<0.001	0.171	0.122	0.983	0.097A
HEARTBURN INT. - NIGHT																
BASELINE	30	6.2			42	6.8			37	6.9			0.418	0.304	0.707	0.1.
D/B WEEK 4	30	4.6	-1.9	<0.001	42	4.2	-2.3	<0.001	37	4.6	-1.9	<0.001	0.871	0.430	0.988	0.389
D/B WEEK 8	28	4.2	-2.2	<0.001	40	3.6	-2.8	<0.001	31	4.3	-2.2	<0.001	0.485	0.336	0.941	0.267
D/B WEEK 12	24	3.7	-2.8	<0.001	36	2.6	-3.9	<0.001	30	3.3	-3.2	<0.001	0.183	0.078A	0.548	0.222
ENDPOINT	30	4.6	-1.9	<0.001	42	2.9	-3.6	<0.001	37	4.0	-2.5	<0.001	0.016	0.006AA	0.349	0.048AA
OVERALL	30	4.4	-2.1	<0.001	42	3.5	-3.0	<0.001	37	4.4	-2.1	<0.001	0.139	0.089A	0.487	0.095A

. . . SUMMARY OF INVESTIGATOR'S SYMPTOM INTENSITY ASSESSMENTS - PATIENTS WITH PRE-TREATMENT ENDOS. GRADE OF 4

POPULATION: INTENT-TO-TREAT
ASSESSMENT: INTENSITY SCALE 0=NONE, ... 10=WORST, LOWER SCORE IS BETTER
SOURCE: INVESTIGATOR'S CLINIC EVALUATION

PARAMETER	PLACEBO N	PLACEBO LSM*	PLACEBO DIFF. FROM BASELINE LSM*	PLACEBO DIFF. FROM BASELINE P-VAL*	CISAPRIDE 10MG N	CISAPRIDE 10MG LSM*	CISAPRIDE 10MG DIFF. FROM BASELINE LSM*	CISAPRIDE 10MG DIFF. FROM BASELINE P-VAL*	CISAPRIDE 20MG N	CISAPRIDE 20MG LSM*	CISAPRIDE 20MG DIFF. FROM BASELINE LSM*	CISAPRIDE 20MG DIFF. FROM BASELINE P-VAL*	P-VALUES (1) TREATMENT	PAIRWISE COMPARISON (2) P. VS 10	P. VS 20	10 VS 20
HEARTBURN INT. - DAY																
BASELINE	2	6.8			10	7.7			12	5.5			0.042	0.512	0.338	0.01388
D/B WEEK 4	2	5.2	-1.0	0.500	10	4.9	-1.3	0.008	12	4.2	-1.9	0.050	0.714	0.848	0.502	0.497
D/B WEEK 8	2	5.5	-0.8	0.500	8	5.0	-1.3	0.111	10	4.8	-1.5	0.022	0.860	0.711	0.593	0.819
D/B WEEK 12	2	4.9	-1.7	-	8	3.0	-3.1	<0.001	9	3.7	-2.4	0.031	0.496	0.252	0.487	0.577
ENDPOINT	2	6.0	-0.2	-	10	4.1	-2.1	0.001	12	4.8	-1.4	0.020	0.444	0.220	0.448	0.521
OVERALL	2	5.6	-0.7	-	10	4.5	-1.6	<0.001	12	4.6	-1.8	0.010	0.689	0.399	0.479	0.966
HEARTBURN INT. - NIGHT																
BASELINE	2	6.0			10	8.7			12	6.6			0.118	0.875	0.174	0.0578
D/B WEEK 4	2	6.4	-1.0	0.344	10	4.9	-2.7	0.007	12	6.4	-1.9	0.011	0.609	0.549	0.995	0.376
D/B WEEK 8	2	6.2	-0.9	0.385	8	5.3	-1.9	0.013	10	5.3	-2.0	0.030	0.385	0.142	0.239	0.976
D/B WEEK 12	2	6.0	-1.1	0.344	8	2.6	-4.4	0.001	9	3.3	-3.8	0.010	0.051	0.017AA	0.068B	0.526
ENDPOINT	2	6.7	-0.6	0.344	10	3.3	-4.0	<0.001	12	5.2	-2.1	0.008	0.036	0.077AA	0.327	0.059A
OVERALL	2	6.4	-0.8	0.330	10	4.0	-3.2	0.001	12	5.3	-2.0	0.006	0.165	0.103	0.460	0.191

* LSM: LEAST SQUARES MEAN.
* P-VALUE FROM ONE-SAMPLE TWO-SIDED T-TEST.
(1) P-VALUES FROM ANCOVA MODEL WITH TREATMENT(TRT), INVESTIGATOR, AND BASELINE VALUE (EXCEPT AT BASELINE).
(2) P-VALUES FROM FISHER'S LSD TWO-SIDED TEST FROM THE SAME ANCOVA MODEL.
"P": TWO-SIDED P-VALUE <=0.10 WITH PLACEBO HAVING LOWER (BETTER) SCORES; "PP": P-VALUE <=0.05.
"A": TWO-SIDED P-VALUE <=0.10 WITH CISAPRIDE 10MG HAVING LOWER (BETTER) SCORES; "AA": P-VALUE <=0.05.
"B": TWO-SIDED P-VALUE <=0.10 WITH CISAPRIDE 20MG HAVING LOWER (BETTER) SCORES; "BB": P-VALUE <=0.05.

Table 5a/Global Evaluations

POPULATION: INTENT-TO-TREAT
ASSESSMENT: 1=MARKED IMP., 2=MODERATE IMP., 3=MINIMAL IMP., 4=UNCHANGED, 5=DETERIORATED; LOWER SCORE IS BETTER

EVALUATION	PLACEBO N	PLACEBO %	CISAPRIDE 10MG N	CISAPRIDE 10MG %	CISAPRIDE 20MG N	CISAPRIDE 20MG %	OVERALL P-VALUE(1)	PAIRWISE TEST(1) P. VS 10	P. VS 20	10 VS 20
INVESTIGATOR'S GLOBAL ASSESS.										
MARKED IMPROVEMENT	15	26.8	18	32.8	13	23.2				
MODERATE IMPROVEMENT	14	25.0	17	29.3	20	36.7				
MINIMAL IMPROVEMENT	12	21.4	10	25.9	10	17.9				
UNCHANGED	11	19.6	5	8.6	9	16.1				
DETERIORATED	4	7.1	2	3.4	4	7.1				
NOT ASSESSED(2)	3	-	6	-	3	-				
TOTAL	56	100	58	100	56	100	0.285	0.154	0.974	0.155
PATIENT'S GLOBAL ASSESS.										
MARKED IMPROVEMENT	14	25.9	19	33.9	11	20.0				
MODERATE IMPROVEMENT	14	25.9	20	35.7	25	45.5				
MINIMAL IMPROVEMENT	13	24.1	11	19.6	4	7.3				
UNCHANGED	8	14.8	4	7.1	11	20.0				
DETERIORATED	5	9.3	2	3.6	4	7.3				
NOT ASSESSED(2)	4	-	6	-	3	-				
TOTAL	54	100	56	100	55	100	0.116	0.061 A	0.901	0.067 A

POPULATION: EVALUABLE DATA ONLY
ASSESSMENT: 1=MARKED IMP., 2=MODERATE IMP., 3=MINIMAL IMP., 4=UNCHANGED, 5=DETERIORATED; LOWER SCORE IS BETTER

EVALUATION	PLACEBO N	PLACEBO %	CISAPRIDE 10MG N	CISAPRIDE 10MG %	CISAPRIDE 20MG N	CISAPRIDE 20MG %	OVERALL P-VALUE(1)	PAIRWISE TEST(1) P. VS 10	P. VS 20	10 VS 20
INVESTIGATOR'S GLOBAL ASSESS.										
MARKED IMPROVEMENT	14	26.9	18	32.1	13	23.6				
MODERATE IMPROVEMENT	12	23.1	17	30.4	20	36.4				
MINIMAL IMPROVEMENT	11	21.2	15	26.8	9	16.4				
UNCHANGED	11	21.2	4	7.1	9	16.4				
DETERIORATED	4	7.7	2	3.6	4	7.3				
NOT ASSESSED(2)	2	-	4	-	3	-				
TOTAL	52	100	56	100	55	100	0.249	0.081 A	0.803	0.209
PATIENT'S GLOBAL ASSESS.										
MARKED IMPROVEMENT	13	26.0	18	33.3	11	20.4				
MODERATE IMPROVEMENT	12	24.0	20	37.0	25	46.3				
MINIMAL IMPROVEMENT	13	26.0	11	20.4	3	5.6				
UNCHANGED	7	14.0	3	5.6	11	20.4				
DETERIORATED	5	10.0	2	3.7	4	7.4				
NOT ASSESSED(2)	3	-	6	-	3	-				
TOTAL	50	100	54	100	54	100	0.112	0.036 AA	0.878	0.094 A

(1) GENERALIZED COCHRAN-MANTEL-HAENSZEL TEST CONTROLLING FOR INVESTIGATOR. (RESPONSE SCORES USED IN THE TEST.)
(2) 'NOT ASSESSED' EVALUATION PATIENTS NOT INCLUDED IN THE ANALYSIS, TOTALS OR THE PERCENTAGES.

"P": TWO-SIDED P-VALUE <=0.10 WITH PLACEBO HAVING LOWER (BETTER) SCORES; "PP": P-VALUE <=0.05.
"A": TWO-SIDED P-VALUE <=0.10 WITH CISAPRIDE 10MG HAVING LOWER (BETTER) SCORES; "AA": P-VALUE <=0.05.
"B": TWO-SIDED P-VALUE <=0.10 WITH CISAPRIDE 20MG HAVING LOWER (BETTER) SCORES; "BB": P-VALUE <=0.05.

Table 6a/Global Evaluations: Subgroup

Grade -1

POPULATION: INTENT-TO-TREAT
ASSESSMENT: 1=MARKED IMP., 2=MODERATE IMP., 3=MINIMAL IMP., 4=UNCHANGED, 5=DETERIORATED; LOWER SCORE IS BETTER

EVALUATION	--- PLACEBO --- N	%	CISAPRIDE 10MG N	%	CISAPRIDE 20MG N	%	OVERALL P-VALUE(1)	---- PAIRWISE TEST(1) ---- P. VS 10	P. VS 20	10 VS 20
INVESTIGATOR'S GLOBAL ASSESS.										
MARKED IMPROVEMENT	7	26.9	7	41.2	5	26.3				
MODERATE IMPROVEMENT	6	23.1	3	17.6	6	31.6				
MINIMAL IMPROVEMENT	8	30.8	3	17.6	3	15.8				
UNCHANGED	3	11.5	2	11.8	3	15.8				
DETERIORATED	2	7.7	2	11.8	2	10.5				
NOT ASSESSED(2)	1	-	3	-	3	-				
TOTAL	26	100	17	100	19	100	0.457	0.339	0.348	0.366
PATIENT'S GLOBAL ASSESS.										
MARKED IMPROVEMENT	7	28.0	7	43.8	5	26.3				
MODERATE IMPROVEMENT	7	28.0	4	25.0	7	36.8				
MINIMAL IMPROVEMENT	8	32.0	2	12.5	2	10.5				
UNCHANGED	1	4.0	2	12.5	3	15.8				
DETERIORATED	2	8.0	1	6.3	2	10.5				
NOT ASSESSED(2)	2	-	3	-	3	-				
TOTAL	25	100	16	100	19	100	0.228	0.339	0.193	0.157

Grade 2 to 4

INVESTIGATOR'S GLOBAL ASSESS.										
MARKED IMPROVEMENT	8	26.7	12	29.3	8	21.6				
MODERATE IMPROVEMENT	8	26.7	14	34.1	14	37.8				
MINIMAL IMPROVEMENT	4	13.3	12	29.3	7	18.9				
UNCHANGED	8	26.7	3	7.3	6	16.2				
DETERIORATED	2	6.7	0	0.0	2	5.4				
NOT ASSESSED(2)	2	-	2	-	0	0.0				
TOTAL	30	100	41	100	37	100	0.288	0.222	0.575	0.274
PATIENT'S GLOBAL ASSESS.										
MARKED IMPROVEMENT	7	24.1	12	30.0	6	16.7				
MODERATE IMPROVEMENT	7	24.1	16	40.0	18	50.0				
MINIMAL IMPROVEMENT	5	17.2	9	22.5	2	5.6				
UNCHANGED	7	24.1	2	5.0	8	22.2				
DETERIORATED	3	10.3	1	2.5	2	5.6				
NOT ASSESSED(2)	2	-	3	-	0	0.0				
TOTAL	29	100	40	100	36	100	0.087	0.064 A	0.368	0.163

Grade 4

INVESTIGATOR'S GLOBAL ASSESS.										
MARKED IMPROVEMENT	0	0.0	0	0.0	2	16.7				
MODERATE IMPROVEMENT	0	0.0	7	70.0	7	58.3				
MINIMAL IMPROVEMENT	1	50.0	3	30.0	0	0.0				
UNCHANGED	1	50.0	0	0.0	3	25.0				
DETERIORATED	0	0.0	0	0.0	0	0.0				
NOT ASSESSED(2)	0	0.0	0	0.0	0	0.0				
TOTAL	2	100	10	100	12	100	0.145	0.157	0.102	0.717
PATIENT'S GLOBAL ASSESS.										
MARKED IMPROVEMENT	0	0.0	1	11.1	2	18.2				
MODERATE IMPROVEMENT	0	0.0	6	66.7	6	54.5				
MINIMAL IMPROVEMENT	1	50.0	2	22.2	0	0.0				
UNCHANGED	1	50.0	0	0.0	3	27.3				
DETERIORATED	0	0.0	0	0.0	0	0.0				
NOT ASSESSED(2)	0	0.0	1	-	0	0.0				
TOTAL	2	100	9	100	11	100	0.107	0.114	0.102	0.978

(1) GENERALIZED COCHRAN-MANTEL-HAENSZEL TEST CONTROLLING FOR INVESTIGATOR. (RESPONSE SCORES USED IN THE TEST.)
(2) "NOT ASSESSED" EVALUATION PATIENTS NOT INCLUDED IN THE ANALYSIS. TOTALS OR THE PERCENTAGES.

"P": TWO-SIDED P-VALUE <=0.10 WITH PLACEBO HAVING LOWER (BETTER) SCORES; "PP": P-VALUE <=0.05.
"A": TWO-SIDED P-VALUE <=0.10 WITH CISAPRIDE 10MG HAVING LOWER (BETTER) SCORES; "AA": P-VALUE <=0.05.
"B": TWO-SIDED P-VALUE <=0.10 WITH CISAPRIDE 20MG HAVING LOWER (BETTER) SCORES; "BB": P-VALUE <=0.05.

Table 81/1201
Repeated Measures Analysis Results For
Heartburn Intensity (Sponsor's Analysis)

Analysis/	Change From Baseline LSMEAN			2-sided p (Placebo vs)			
#1	Placebo	10 mg	20 mg	10	20	overall	10 +20
Day							
Investig	-1.9	-2.5	-1.6	-	-	.135	.568
Patient	-18.5	-27.0	-16.5	.04	.64	.035	.373
Night							
Investig	-2.1	-3.2	-2.3	.02	.65	.049	.108
Patient	-18.6	-24.3	-17.2	-	-	.224	.552
#2							
Day							
Investig	-1.8	-2.3	-1.2	.20	.18	.030	.958
Patient	-16.8	-22.9	-14.1	.12	.50	.070	.616
Night							
Investig	-1.8	-2.9	-1.7	.02	.82	.014	.214
Patient	-16.3	-21.3	-15.1	-	-	.255	.580

Note: Pairwise comparison p-values are given only when the overall p-value is at least statitically significant at the 10% level.

Analysis#1=Analysis for patient with complete data adjusted for investigator.

Analysis#2=Last observation carried forward analysis adjusted for investigator.

Table 1b
Visits Schedule, Patient Dispositions & Demographics

Schedule of Evaluations					
	Visit 1 (Week -2)	Visit 2 (Week 0)	Visit 3 (Week 4)	Visit 4 (Week 8)	Visit 5 (Week 12)
Assessments	Selection	End of s/b placebo phase	Double-blind treatment phase		
Symptoms (Inv.)	X	X	X	X	X
Diary (Pat.)		X	X	X	X
Overall Assess.		X	X	X	X
Global Assess.					X
Endoscopy	within 7 days				X
Laboratory determinations	X	X	X	X	X
Physical exam	X				X
EKG	X				X

SUMMARY OF DISPOSITION OF PATIENTS

	PLACEBO	CISAPRIDE 10MG	CISAPRIDE 20MG	TOTAL
ENTERED(ALL CENTERS)	60	56	61	177
EHTAN/02	5	5	6	16
FANUOUI/03	7	7	7	21
LIEBLMANN/04	6	5	4	15
MIYUMPA/05	2	1	3	6
PHUIII/06	5	6	6	17
MILLOW/07	6	6	6	18
MICHTIN/08	4	5	5	14
FIICH/09	7	6	6	19
SIGMUND/10	7	6	7	20
MCLAULUGHLIN/11	2	2	2	6
SMITH/12	7	6	7	20
GULUMENG/13	2	1	2	5
PREMATUREL Y DISCONTINUED	8	10	12	30
REASON FOR DISCONTINUATION				
ADVERSE EXPERIENCE	0	4	3	7
INELIGIBLE	2	1	4	7
INADEQUATE RESPONSE	1	2	1	4
LOST TO FOLLOW UP	2	2	3	7
CHOSE TO DISCONTINUE	1	1	0	2
OTHER REASON	0	0	1	1

SUMMARY OF DEMOGRAPHIC AND BACKGROUND DATA FOR INTENT-TO-TREAT

INVESTIGATOR: ALL INVESTIGATORS

PARAMETER	TREATMENT GROUP PLACEBO	CISAPRIDE 10 MG	CISAPRIDE 20 MG	TOTAL	P-VALUE *
SEX					
MALE	34	30	34	98	0.813 **
FEMALE	26	26	27	79	
RACE					
WHITE	49	49	55	153	0.717 **
BLACK	6	5	4	15	
HISPANIC	3	2	2	7	
AGE(YEARS)					
N	60	56	61	177	
MEAN	45.4	48.1	48.6	47.4	0.539 ***
STD.DEV.	13.3	13.8	12.8	13.2	
MEDIAN	44.0	51.0	47.0	46.0	
MINIMUM	25.0	18.0	21.0	18.0	
MAXIMUM	77.0	76.0	70.0	77.0	
GERD SYMPTOM DURATION(YEAR)					
N	60	56	61	177	
MEAN	9.4	6.6	8.2	8.1	0.179 ***
STD.DEV.	8.7	6.0	10.8	8.6	
MEDIAN	5.0	5.5	5.0	5.0	
MINIMUM	0.3	0.3	0.3	0.3	
MAXIMUM	40.0	20.0	80.0	80.0	

* BETWEEN-TREATMENT COMPARISONS
** GENERALIZED COCHRAN-MANTEL-HAENSZEL TEST, CONTROLLING FOR INVESTIGATOR
*** ANOVA MODEL INCLUDING TREATMENT, INVESTIGATOR, AND TREATMENT X INVESTIGATOR INTERACTION EFFECTS (P-VALUE BASED ON TYPE III SS.)

Table 2b/ITT & Efficacy Subset
Heartburn Intensity Evaluation Results

Patient

SYMPTOM INTENSITY ASSESSMENTS - ALL PATIENTS

POPULATION: INTENT-TO-TREAT
ASSESSMENT: INTENSITY SCALE 0=NONE, ... 100=WORST, LOWER SCORE IS BETTER
SOURCE: PATIENT'S DIARY DATA; AVERAGE OVER DAYS WITHIN MONTHLY PERIOD

PARAMETER	PLACEBO N	PLACEBO LSM*	PLACEBO DIFF. FROM BASELINE LSM*	PLACEBO DIFF. FROM BASELINE P-VAL*	CISAPRIDE 10MG N	CISAPRIDE 10MG LSM*	CISAPRIDE 10MG DIFF. FROM BASELINE LSM*	CISAPRIDE 10MG DIFF. FROM BASELINE P-VAL*	CISAPRIDE 20MG N	CISAPRIDE 20MG LSM*	CISAPRIDE 20MG DIFF. FROM BASELINE LSM*	CISAPRIDE 20MG DIFF. FROM BASELINE P-VAL*	P-VALUES (1) TRT	P-VALUES (1) TRT-INV	PAIRWISE COMPARISON (2) P. VS 10	PAIRWISE COMPARISON (2) P. VS 20	PAIRWISE COMPARISON (2) 10 VS 20
HEARTBURN INT. - DAY																	
BASELINE	58	44.8			52	42.4			58	44.4			0.750	0.477	0.467	0.871	0.567
D/B WEEK 4	58	35.1	-9.1	<0.001	52	28.7	-14.4	<0.001	58	28.4	-15.8	<0.001	0.054	0.015	0.079A	0.037BB	0.659
D/B WEEK 8	55	28.0	-16.8	<0.001	48	23.0	-21.9	<0.001	50	19.4	-25.5	<0.001	0.056	0.260	0.189	0.01788	0.342
D/B WEEK 12	54	27.0	-17.6	<0.001	46	21.1	-23.5	<0.001	47	16.7	-27.8	<0.001	0.028	0.578	0.159	0.00888	0.308
ENDPOINT	58	27.3	-16.8	<0.001	52	23.6	-20.6	<0.001	58	19.5	-24.7	<0.001	0.103	0.138	0.333	0.03388	0.362
OVERALL	58	30.3	-13.8	<0.001	52	26.3	-17.8	<0.001	58	23.3	-20.8	<0.001	0.088	0.047	0.230	0.02888	0.364
HEARTBURN INT. - NIGHT																	
BASELINE	59	40.9			52	39.8			58	43.9			0.534	0.834	0.771	0.417	0.287
D/B WEEK 4	59	34.6	-7.3	<0.001	52	25.7	-16.2	<0.001	58	27.8	-14.1	<0.001	0.019	0.069	0.008AA	0.03488	0.539
D/B WEEK 8	55	26.8	-15.4	<0.001	48	21.7	-20.5	<0.001	50	18.4	-23.8	<0.001	0.064	0.036	0.180A	0.07088	0.388
D/B WEEK 12	54	26.6	-15.5	<0.001	46	18.8	-22.3	<0.001	47	15.7	-26.4	<0.001	0.010	0.092	0.008AA	0.00288	0.314
ENDPOINT	59	26.7	-15.2	<0.001	52	21.3	-20.8	<0.001	58	18.9	-25.0	<0.001	0.063	0.050	0.147	0.02888	0.518
OVERALL	59	29.8	-12.3	<0.001	52	23.8	-18.4	<0.001	58	22.9	-18.0	<0.001	0.070	0.073	0.067A	0.03688	0.851

SOURCE: Investigator

PARAMETER	PLACEBO N	PLACEBO LSM*	PLACEBO DIFF. FROM BASELINE LSM*	PLACEBO DIFF. FROM BASELINE P-VAL*	CISAPRIDE 10MG N	CISAPRIDE 10MG LSM*	CISAPRIDE 10MG DIFF. FROM BASELINE LSM*	CISAPRIDE 10MG DIFF. FROM BASELINE P-VAL*	CISAPRIDE 20MG N	CISAPRIDE 20MG LSM*	CISAPRIDE 20MG DIFF. FROM BASELINE LSM*	CISAPRIDE 20MG DIFF. FROM BASELINE P-VAL*	P-VALUES (1) TRT	P-VALUES (1) TRT-INV	PAIRWISE COMPARISON (2) P. VS 10	PAIRWISE COMPARISON (2) P. VS 20	PAIRWISE COMPARISON (2) 10 VS 20
HEARTBURN INT. - DAY																	
BASELINE	57	5.9			53	5.7			59	5.6			0.618	0.340	0.453	0.356	0.888
D/B WEEK 4	57	4.9	-0.8	<0.001	53	3.9	-1.8	<0.001	52	3.8	-2.0	<0.001	0.004	0.069	0.010AA	0.00288	0.641
D/B WEEK 8	55	4.0	-1.7	<0.001	48	3.7	-2.0	<0.001	49	2.9	-2.9	<0.001	0.033	0.47U	0.515	0.01188	0.0798
D/B WEEK 12	54	3.6	-2.1	<0.001	46	3.8	-2.2	<0.001	49	2.4	-3.3	<0.001	0.01-	0.520	0.793	0.01188	0.045CB
ENDPOINT	57	3.8	-1.9	<0.001	53	3.5	-2.2	<0.001	59	2.8	-2.9	<0.001	0.01-	0.583	0.564	0.02888	0.114
OVERALL	57	4.3	-1.4	<0.001	53	3.7	-2.0	<0.001	59	3.2	-2.5	<0.001	0.013	0.482	0.111	0.00388	0.701
HEARTBURN INT. - NIGHT																	
BASELINE	57	5.7			53	5.6			59	5.3			0.005	<0.001	0.895	0.070P	0.058A
D/B WEEK 4	57	4.3	-1.6	<0.001	53	4.0	-1.9	<0.001	59	3.8	-2.1	<0.001	0.323	0.007	0.347	0.139	0.812
D/B WEEK 8	55	3.5	-2.4	<0.001	48	3.6	-2.4	<0.001	49	2.9	-3.0	<0.001	0.376	0.406	0.882	0.181	0.747
D/B WEEK 12	54	3.3	-2.5	<0.001	46	3.2	-2.7	<0.001	49	2.1	-3.7	<0.001	0.072	0.163	0.803	0.00988	0.04088
ENDPOINT	57	3.4	-2.5	<0.001	53	3.2	-2.7	<0.001	59	2.8	-3.1	<0.001	0.370	0.383	0.744	0.175	0.319
OVERALL	57	3.8	-2.1	<0.001	53	3.6	-2.3	<0.001	59	3.3	-2.6	<0.001	0.458	0.156	0.573	0.212	0.511

Patient

POPULATION: EVALUABLE DATA ONLY
ASSESSMENT: INTENSITY SCALE 0=NONE, ... 100=WORST, LOWER SCORE IS BETTER
SOURCE: PATIENT'S DIARY DATA; AVERAGE OVER DAYS WITHIN MONTHLY PERIOD

PARAMETER	PLACEBO N	PLACEBO LSM*	PLACEBO DIFF. FROM BASELINE LSM*	PLACEBO DIFF. FROM BASELINE P-VAL*	CISAPRIDE 10MG N	CISAPRIDE 10MG LSM*	CISAPRIDE 10MG DIFF. FROM BASELINE LSM*	CISAPRIDE 10MG DIFF. FROM BASELINE P-VAL*	CISAPRIDE 20MG N	CISAPRIDE 20MG LSM*	CISAPRIDE 20MG DIFF. FROM BASELINE LSM*	CISAPRIDE 20MG DIFF. FROM BASELINE P-VAL*	P-VALUES (1) TRT	P-VALUES (1) TRT-INV	PAIRWISE COMPARISON (2) P. VS 10	PAIRWISE COMPARISON (2) P. VS 20	PAIRWISE COMPARISON (2) 10 VS 20
HEARTBURN INT. - DAY																	
BASELINE	58	45.1			50	43.2			54	46.7			0.847	0.276	0.565	0.823	0.303
D/B WEEK 4	58	36.0	-9.2	<0.001	50	30.6	-14.6	<0.001	54	29.2	-16.0	<0.001	0.063	0.022	0.007A	0.02688	0.668
D/B WEEK 8	55	28.2	-17.0	<0.001	47	23.0	-22.2	<0.001	49	19.2	-26.0	<0.001	0.052	0.280	0.179	0.01688	0.331
D/B WEEK 12	54	27.2	-17.7	<0.001	45	21.3	-23.6	<0.001	46	18.2	-28.7	<0.001	0.022	0.553	0.165	0.00688	0.250
ENDPOINT	58	28.0	-17.2	<0.001	50	24.5	-20.7	<0.001	54	20.0	-25.2	<0.001	0.114	0.190	0.373	0.03888	0.272
OVERALL	58	31.1	-14.1	<0.001	50	27.1	-18.1	<0.001	54	24.1	-21.1	<0.001	0.106	0.067	0.248	0.03588	0.388
HEARTBURN INT. - NIGHT																	
BASELINE	58	41.1			50	39.7			54	45.7			0.275	0.011	0.707	0.228	0.121
D/B WEEK 4	58	33.3	-7.2	<0.001	50	26.7	-15.8	<0.001	54	28.1	-14.4	<0.001	0.024	0.056	0.013AA	0.03188	0.678
D/B WEEK 8	55	26.9	-15.5	<0.001	47	21.4	-21.0	<0.001	49	18.0	-24.4	<0.001	0.052	-0.027	0.152	0.01788	0.388
D/B WEEK 12	54	26.7	-15.6	<0.001	45	19.8	-22.5	<0.001	46	15.3	-27.0	<0.001	0.009	0.076	0.007A	0.00788	0.284
ENDPOINT	58	27.4	-15.1	<0.001	50	22.3	-20.2	<0.001	54	19.3	-23.3	<0.001	0.082	0.044	0.197	0.07888	0.431
OVERALL	58	30.3	-12.3	<0.001	50	24.4	-18.2	<0.001	54	23.3	-18.3	<0.001	0.073	0.016	0.082A	0.03488	0.757

SOURCE: Investigator

PARAMETER	PLACEBO N	PLACEBO LSM*	PLACEBO DIFF. FROM BASELINE LSM*	PLACEBO DIFF. FROM BASELINE P-VAL*	CISAPRIDE 10MG N	CISAPRIDE 10MG LSM*	CISAPRIDE 10MG DIFF. FROM BASELINE LSM*	CISAPRIDE 10MG DIFF. FROM BASELINE P-VAL*	CISAPRIDE 20MG N	CISAPRIDE 20MG LSM*	CISAPRIDE 20MG DIFF. FROM BASELINE LSM*	CISAPRIDE 20MG DIFF. FROM BASELINE P-VAL*	P-VALUES (1) TRT	P-VALUES (1) TRT-INV	PAIRWISE COMPARISON (2) P. VS 10	PAIRWISE COMPARISON (2) P. VS 20	PAIRWISE COMPARISON (2) 10 VS 20
HEARTBURN INT. - DAY																	
BASELINE	57	5.8			51	5.7			55	5.8			0.745	0.200	0.463	0.588	0.835
D/B WEEK 4	57	4.8	-0.8	<0.001	51	4.1	-1.7	<0.001	55	3.7	-2.1	<0.001	0.005	0.152	0.076AA	0.00188	0.379
D/B WEEK 8	55	4.0	-1.7	<0.001	47	3.7	-2.1	<0.001	48	2.8	-2.9	<0.001	0.044	0.723	0.502	0.01488	0.0978
D/B WEEK 12	54	3.6	-2.1	<0.001	45	3.8	-2.2	<0.001	48	2.4	-3.4	<0.001	0.018	0.588	0.916	0.00888	0.03188
ENDPOINT	57	3.8	-1.8	<0.001	51	3.7	-2.1	<0.001	55	2.7	-3.0	<0.001	0.038	0.780	0.761	U.01888	0.04488
OVERALL	57	4.3	-1.5	<0.001	51	3.8	-2.0	<0.001	55	3.2	-2.6	<0.001	0.018	0.781	0.708	0.00388	0.0938
HEARTBURN INT. - NIGHT																	
BASELINE	57	5.7			51	5.6			55	5.3			0.044	<0.001	0.881	U.0668P	0.030AA
D/B WEEK 4	57	4.3	-1.6	<0.001	51	4.1	-1.8	<0.001	55	3.7	-2.1	<0.001	0.323	0.018	0.571	0.134	0.416
D/B WEEK 8	55	3.5	-2.3	<0.001	47	3.4	-2.5	<0.001	48	2.8	-2.9	<0.001	0.438	-0.451	0.784	U.210	0.367
D/B WEEK 12	54	3.3	-2.5	<0.001	45	3.2	-2.7	<0.001	48	2.2	-3.4	<0.001	0.038	0.758	0.775	0.01588	0.0618
ENDPOINT	57	3.4	-2.5	<0.001	51	3.3	-2.5	<0.001	55	2.8	-3.1	<0.001	0.377	0.600	0.907	0.199	U.764
OVERALL	57	3.8	-2.1	<0.001	51	3.8	-2.2	<0.001	55	3.3	-2.6	<0.001	0.477	0.781	0.733	U.334	0.419

* LSM: LEAST SQUARES MEAN.
* P-VALUE FROM ONE-SAMPLE TWO-SIDED T-TEST.
(1) P-VALUES FROM ANCOVA MODEL WITH TREATMENT(TRT), INVESTIGATOR, TREATMENT X INVESTIGATOR INTERACTION, AND BASELINE VALUE(EXCEPT AT BASELINE).
(2) P-VALUES FROM FISHER'S LSD TWO-SIDED TEST FROM THE SAME ANCOVA MODEL.
"P": TWO-SIDED P-VALUE <=0.10 WITH PLACEBO HAVING LOWER (BETTER) SCORES; "PP": P-VALUE <=0.05.
"A": TWO-SIDED P-VALUE <=0.10 WITH CISAPRIDE 10MG HAVING LOWER (BETTER) SCORES; "AA": P-VALUE <=0.05.
"B": TWO-SIDED P-VALUE <=0.10 WITH CISAPRIDE 20MG HAVING LOWER (BETTER) SCORES; "BB": P-VALUE <=0.05.

Table 3b/Subgroup
Patient's Heartburn Intensity Assessments Results
(Grade 1)

POPULATION: INTENT-TO-TREAT
ASSESSMENT: INTENSITY SCALE 0=NONE, ... 100=WORST, LOWER SCORE IS BETTER
SOURCE: PATIENT'S DIARY DATA; AVERAGE OVER DAYS WITHIN MONTHLY PERIOD

PARAMETER	PLACEBO N	PLACEBO LSM*	PLACEBO DIFF. FROM BASELINE	PLACEBO P-VAL*	CISAPRIDE 10MG N	CISAPRIDE 10MG LSM*	CISAPRIDE 10MG DIFF. FROM BASELINE	CISAPRIDE 10MG P-VAL*	CISAPRIDE 20MG N	CISAPRIDE 20MG LSM*	CISAPRIDE 20MG DIFF. FROM BASELINE	CISAPRIDE 20MG P-VAL*	P-VALUES (1) TREATMENT	PAIRWISE COMPARISON (2) P. VS 10	P. VS 20	10 VS 20
HEARTBURN INT. - DAY																
BASELINE	29	42.0			18	44.8			14	45.3			0.746	0.535	0.570	0.840
D/B WEEK 4	29	33.8	-8.7	<0.001	18	36.0	-8.3	0.003	14	31.7	-11.6	0.009	0.580	0.428	0.748	0.329
D/B WEEK 8	26	26.3	-17.7	<0.001	16	27.4	-16.6	0.003	12	24.4	-18.7	0.005	0.938	0.876	0.809	0.725
D/B WEEK 12	26	23.1	-20.6	<0.001	15	24.5	-18.3	0.004	11	15.6	-28.1	0.001	0.567	0.854	0.355	0.323
ENDPOINT	29	23.1	-20.2	<0.001	18	27.2	-16.1	0.025	14	17.0	-26.3	<0.001	0.455	0.581	0.418	0.212
OVERALL	29	27.8	-15.5	<0.001	18	33.3	-11.0	0.035	14	24.9	-18.4	0.002	0.568	0.463	0.865	0.304
HEARTBURN INT. - NIGHT																
BASELINE	29	36.7			18	47.7			14	46.1			0.085	0.042PP	0.111	0.804
D/B WEEK 4	28	33.5	-7.5	0.009	18	33.3	-7.7	0.090	14	29.0	-12.0	0.037	0.772	0.973	0.506	0.543
D/B WEEK 8	26	28.3	-13.4	0.002	16	24.4	-17.3	0.007	12	23.6	-19.0	0.014	0.766	0.818	0.499	0.838
D/B WEEK 12	26	25.1	-16.3	<0.001	15	22.7	-18.7	0.009	11	13.5	-27.9	0.004	0.348	0.726	0.151	0.291
ENDPOINT	29	24.3	-16.8	<0.001	18	23.3	-17.7	0.019	14	15.2	-25.8	0.002	0.443	0.885	0.276	0.300
OVERALL	29	28.8	-12.4	<0.001	18	28.2	-12.8	0.037	14	23.3	-17.7	0.010	0.713	0.943	0.440	0.497

Grade 2 to 4

PARAMETER	PLACEBO N	PLACEBO LSM*	PLACEBO DIFF. FROM BASELINE	PLACEBO P-VAL*	CISAPRIDE 10MG N	CISAPRIDE 10MG LSM*	CISAPRIDE 10MG DIFF. FROM BASELINE	CISAPRIDE 10MG P-VAL*	CISAPRIDE 20MG N	CISAPRIDE 20MG LSM*	CISAPRIDE 20MG DIFF. FROM BASELINE	CISAPRIDE 20MG P-VAL*	P-VALUES (1) TREATMENT	PAIRWISE COMPARISON (2) P. VS 10	P. VS 20	10 VS 20
HEARTBURN INT. - DAY																
BASELINE	30	47.8			34	41.7			44	43.9			0.447	0.217	0.387	0.632
D/B WEEK 4	30	35.2	-9.4	0.009	34	26.9	-17.7	<0.001	44	27.2	-17.5	<0.001	0.088	0.044AA	0.03688	0.943
D/B WEEK 8	29	28.8	-16.8	<0.001	32	23.4	-21.9	<0.001	38	18.8	-26.5	<0.001	0.081	0.240	0.07588	0.267
D/B WEEK 12	28	30.3	-14.7	<0.001	31	19.5	-25.5	<0.001	36	16.5	-28.5	<0.001	0.010	0.074AA	0.00388	0.490
ENDPOINT	30	30.0	-14.6	0.001	34	21.3	-23.3	<0.001	44	18.4	-25.3	<0.001	0.065	0.081A	0.07388	0.665
OVERALL	30	31.5	-13.2	0.001	34	24.1	-20.6	<0.001	44	22.8	-22.0	<0.001	0.084	0.091A	0.03288	0.714
HEARTBURN INT. - NIGHT																
BASELINE	30	45.1			34	36.6			44	42.7			0.271	0.123	0.637	0.278
D/B WEEK 4	30	34.6	-7.8	0.012	34	22.4	-20.8	<0.001	44	27.0	-15.4	<0.001	0.071	0.006AA	0.0648	0.249
D/B WEEK 8	29	26.1	-16.4	<0.001	32	21.5	-21.0	<0.001	38	17.5	-25.0	<0.001	0.179	0.336	0.0658	0.382
D/B WEEK 12	28	28.0	-14.5	<0.001	31	15.8	-26.7	<0.001	36	14.8	-27.7	<0.001	0.008	0.010AA	0.00488	0.827
ENDPOINT	30	27.9	-14.5	<0.001	34	18.7	-23.7	<0.001	44	18.5	-23.9	<0.001	0.091	0.067A	0.04488	0.960
OVERALL	30	29.7	-12.7	<0.001	34	21.1	-21.3	<0.001	44	22.0	-20.4	<0.001	0.103	0.055A	0.10858	0.827

Grade 4

PARAMETER	PLACEBO N	PLACEBO LSM*	PLACEBO DIFF. FROM BASELINE	PLACEBO P-VAL*	CISAPRIDE 10MG N	CISAPRIDE 10MG LSM*	CISAPRIDE 10MG DIFF. FROM BASELINE	CISAPRIDE 10MG P-VAL*	CISAPRIDE 20MG N	CISAPRIDE 20MG LSM*	CISAPRIDE 20MG DIFF. FROM BASELINE	CISAPRIDE 20MG P-VAL*	P-VALUES (1) TREATMENT	PAIRWISE COMPARISON (2) P. VS 10	P. VS 20	10 VS 20
HEARTBURN INT. - DAY																
BASELINE	5	37.3			6	63.7			8	40.8			0.186	0.077P	0.782	0.126
D/B WEEK 4	5	36.1	-8.9	0.366	6	25.3	-19.6	0.005	8	28.7	-16.3	0.056	0.516	0.316	0.374	0.743
D/B WEEK 8	5	33.7	-13.4	0.333	6	26.0	-20.6	0.012	7	19.9	-26.7	0.005	0.679	0.676	0.398	0.737
D/B WEEK 12	4	25.2	-19.7	0.533	5	16.4	-28.5	0.004	6	11.3	-33.7	0.037	0.871	0.616	0.399	0.778
ENDPOINT	5	32.2	-12.7	0.330	6	24.6	-20.3	0.016	8	21.4	-23.6	0.011	0.648	0.618	0.371	0.825
OVERALL	5	33.0	-12.0	0.348	6	24.7	-20.3	0.005	8	23.4	-21.5	0.006	0.551	0.480	0.308	0.913
HEARTBURN INT. - NIGHT																
BASELINE	5	42.4			6	55.2			8	44.4			0.730	0.459	0.896	0.543
D/B WEEK 4	5	36.4	-6.7	0.037	6	28.8	-16.3	0.023	8	24.7	-16.4	0.088	0.334	0.297	0.171	0.814
D/B WEEK 8	5	42.5	-1.9	0.181	6	32.9	-11.5	0.093	7	17.2	-27.2	0.022	0.224	0.478	0.0948	0.324
D/B WEEK 12	4	31.5	-11.5	0.234	5	15.7	-27.3	0.078	6	8.5	-36.7	0.040	0.211	0.347	0.102	0.530
ENDPOINT	5	38.3	-4.8	0.100	6	25.3	-17.8	0.122	8	20.0	-23.1	0.016	0.270	0.302	0.125	0.669
OVERALL	5	37.7	-5.4	0.078	6	28.8	-16.2	0.045	8	20.7	-22.4	0.015	0.148	0.243	0.0608	0.499

* LSM: LEAST SQUARES MEAN.
* P-VALUE FROM ONE-SAMPLE TWO-SIDED T-TEST.
(1) P-VALUES FROM ANCOVA MODEL WITH TREATMENT(TRT), INVESTIGATOR, AND BASELINE VALUE (EXCEPT AT BASELINE).
(2) P-VALUES FROM FISHER'S LSD TWO-SIDED TEST FROM THE SAME ANCOVA MODEL.
"P": TWO-SIDED P-VALUE <=0.10 WITH PLACEBO HAVING LOWER (BETTER) SCORES; "PP": P-VALUE <=0.05.
"A": TWO-SIDED P-VALUE <=0.10 WITH CISAPRIDE 10MG HAVING LOWER (BETTER) SCORES; "AA": P-VALUE <=0.05.
"B": TWO-SIDED P-VALUE <=0.10 WITH CISAPRIDE 20MG HAVING LOWER (BETTER) SCORES; "BB": P-VALUE <=0.05.

Table 4b/Subgroup
Investigator's Heartburn Intensity Assessments Results

PRE-TREATMENT ENDOS. GRADE OF 1

POPULATION: INTENT-TO-TREAT
ASSESSMENT: INTENSITY SCALE 0=NONE, ... 10=WORST, LOWER SCORE IS BETTER
SOURCE: INVESTIGATOR'S CLINIC EVALUATION

	PLACEBO				CISAPRIDE 10MG				CISAPRIDE 20MG				P-VALUES (1)	PAIRWISE COMPARISON (2)		
			DIFF. FROM BASELINE				DIFF. FROM BASELINE				DIFF. FROM BASELINE					
PARAMETER	N	LSM*	LSM*	P-VAL*	N	LSM*	LSM*	P-VAL*	N	LSM*	LSM*	P-VAL*	TREATMENT	P. VS 10	P. VS 20	10 VS 20
HEARTBURN INT. - DAY																
BASELINE	28	5.5			18	5.7			15	5.6			0.909	0.665	0.889	0.803
D/B WEEK 4	28	4.7	-1.1	0.018	18	4.6	-1.2	0.011	15	3.6	-2.0	0.018	0.446	0.893	0.228	0.306
D/B WEEK 8	26	3.9	-1.8	<0.001	16	4.0	-1.6	0.007	11	3.7	-2.0	0.066	0.944	0.901	0.001	0.738
D/B WEEK 12	26	3.6	-2.0	<0.001	15	3.7	-2.0	0.009	11	2.5	-3.2	0.020	0.874	0.974	0.301	0.312
ENDPOINT	28	3.9	-1.9	<0.001	18	3.5	-2.3	0.003	15	2.6	-3.2	0.003	0.349	0.650	0.151	0.333
OVERALL	28	4.3	-1.5	<0.001	18	4.0	-1.8	0.001	15	3.3	-2.5	0.006	0.405	0.669	0.183	0.373
HEARTBURN INT. - NIGHT																
BASELINE	28	5.1			18	6.3			15	6.6			0.040	0.046PP	0.024PP	0.689
D/B WEEK 4	28	4.2	-1.6	0.001	18	4.7	-1.1	0.028	15	4.1	-1.7	0.057	0.898	0.520	0.843	0.434
D/B WEEK 8	26	3.9	-1.8	<0.001	16	3.8	-2.0	0.005	11	3.3	-2.4	0.045	0.854	0.887	0.580	0.681
D/B WEEK 12	26	3.4	-2.4	<0.001	15	3.6	-2.1	0.004	11	1.8	-4.0	0.005	0.203	0.772	0.124	0.0948
ENDPOINT	28	3.5	-2.3	<0.001	18	3.4	-2.3	0.002	15	2.7	-3.1	0.017	0.611	0.987	0.374	0.385
OVERALL	28	3.9	-1.9	<0.001	18	4.0	-1.8	0.003	15	3.5	-2.3	0.038	0.845	0.921	0.643	0.582

PRE-TREATMENT ENDOS. GRADE OF 2, 3, OR 4

HEARTBURN INT. - DAY																
BASELINE	29	6.1			35	5.5			44	5.6			0.332	0.190	0.187	0.946
D/B WEEK 4	29	4.7	-1.1	0.006	35	3.5	-2.2	<0.001	44	3.6	-2.1	<0.001	0.036	0.019AA	0.02588	0.609
D/B WEEK 8	28	3.9	-1.8	<0.001	32	3.6	-2.1	<0.001	38	2.6	-3.1	<0.001	0.024	0.550	0.01188	0.04488
D/B WEEK 12	28	3.7	-2.0	<0.001	31	3.2	-2.6	<0.001	38	2.2	-3.5	<0.001	0.009	0.272	0.00388	0.04888
ENDPOINT	29	3.6	-2.1	<0.001	35	3.2	-2.5	<0.001	44	2.6	-3.1	<0.001	0.153	0.473	0.0608	0.231
OVERALL	29	4.0	-1.7	<0.001	35	3.4	-2.3	<0.001	44	3.1	-2.6	<0.001	0.085	0.171	0.02788	0.407
HEARTBURN INT. - NIGHT																
BASELINE	29	6.3			35	5.8			44	6.3			0.178	0.139	0.936	0.086A
D/B WEEK 4	29	4.2	-1.8	<0.001	35	3.7	-2.2	<0.001	44	3.5	-2.5	<0.001	0.340	0.366	0.143	0.575
D/B WEEK 8	29	3.3	-2.7	<0.001	32	3.6	-2.4	<0.001	38	2.6	-3.3	<0.001	0.178	0.561	0.227	0.0738
D/B WEEK 12	28	3.5	-2.5	<0.001	31	2.8	-3.3	<0.001	38	1.9	-4.0	<0.001	0.015	0.133	0.00488	0.174
ENDPOINT	29	3.3	-2.7	<0.001	35	2.7	-3.2	<0.001	44	2.3	-3.8	<0.001	0.723	0.343	0.0848	0.455
OVERALL	29	3.6	-2.4	<0.001	35	3.3	-2.7	<0.001	44	2.8	-3.0	<0.001	0.385	0.598	0.177	0.419

PRE-TREATMENT ENDOS. GRADE OF 4

HEARTBURN INT. - DAY																
BASELINE	5	5.7			6	7.0			8	4.8			0.047	0.074P	0.319	0.01788
D/B WEEK 4	5	4.5	-1.2	0.208	6	4.0	-1.7	0.023	8	4.1	-1.6	0.370	0.877	0.666	0.726	0.922
D/B WEEK 8	5	4.7	-1.1	0.145	6	3.9	-1.8	0.022	7	4.1	-1.7	0.006	0.704	0.505	0.563	0.896
D/B WEEK 12	4	3.9	-1.9	0.182	5	3.3	-2.5	0.012	7	2.6	-3.2	0.023	0.684	0.718	0.420	0.730
ENDPOINT	5	4.3	-1.4	0.078	6	3.8	-1.9	0.037	8	3.3	-2.3	0.015	0.675	0.690	0.412	0.806
OVERALL	5	4.4	-1.2	0.021	6	3.8	-1.9	0.016	8	3.8	-1.9	0.004	0.379	0.324	0.358	0.981
HEARTBURN INT. - NIGHT																
BASELINE	5	6.5			6	7.1			8	6.4			0.544	0.359	0.907	0.370
D/B WEEK 4	5	4.9	-1.4	0.003	6	5.0	-1.4	0.032	8	4.2	-2.2	0.088	0.736	0.961	0.499	0.529
D/B WEEK 8	5	5.5	-1.0	0.033	6	4.3	-2.2	0.023	7	3.8	-2.7	0.009	0.491	0.476	0.278	0.766
D/B WEEK 12	4	5.3	-1.1	0.161	5	3.5	-2.9	0.007	7	2.7	-3.7	0.007	0.268	0.338	0.198	0.681
ENDPOINT	5	5.1	-1.3	0.065	6	3.6	-2.8	0.028	8	3.4	-3.0	0.002	0.530	0.418	0.311	0.918
OVERALL	5	5.2	-1.2	0.017	6	4.3	-2.1	0.017	8	3.8	-2.6	0.062	0.369	0.429	0.177	0.650

* LSM: LEAST SQUARES MEAN.
* P-VALUE FROM ONE-SAMPLE TWO-SIDED T-TEST.
(1) P-VALUES FROM ANCOVA MODEL WITH TREATMENT(TRT), INVESTIGATOR, AND BASELINE VALUE (EXCEPT AT BASELINE).
(2) P-VALUES FROM FISHER'S LSD TWO-SIDED TEST FROM THE SAME ANCOVA MODEL.
"P": TWO-SIDED P-VALUE <=0.10 WITH PLACEBO HAVING LOWER (BETTER) SCORES; "PP": P-VALUE <=0.05.
"A": TWO-SIDED P-VALUE <=0.10 WITH CISAPRIDE 10MG HAVING LOWER (BETTER) SCORES; "AA": P-VALUE <=0.05.
"B": TWO-SIDED P-VALUE <=0.10 WITH CISAPRIDE 20MG HAVING LOWER (BETTER) SCORES; "BB": P-VALUE <=0.05.

GLOBAL EVALUATION AT THE END OF DOUBLE-BLIND - ALL PATIENTS

POPULATION: INTENT-TO-TREAT
ASSESSMENT: 1=MARKED IMP., 2=MODERATE IMP., 3=MINIMAL IMP., 4=UNCHANGED, 5=DETERIORATED; LOWER SCORE IS BETTER

EVALUATION	PLACEBO N	PLACEBO %	CISAPRIDE 10MG N	CISAPRIDE 10MG %	CISAPRIDE 20MG N	CISAPRIDE 20MG %	OVERALL P-VALUE(1)	PAIRWISE TEST(1) P. VS 10	PAIRWISE TEST(1) P. VS 20	PAIRWISE TEST(1) 10 VS 20
INVESTIGATOR'S GLOBAL ASSESS.										
MARKED IMPROVEMENT	14	24.6	14	26.9	23	40.4				
MODERATE IMPROVEMENT	14	24.6	20	38.5	19	33.3				
MINIMAL IMPROVEMENT	20	35.1	7	13.5	10	17.5				
UNCHANGED	6	10.5	8	15.4	4	7.0				
DETERIORATED	3	5.3	3	5.8	1	1.8				
NOT ASSESSED(2)	3	-	4	-	4	-				
TOTAL	57	100	52	100	57	100	0.021	0.458	0.006 BB	0.059 B
PATIENT'S GLOBAL ASSESS.										
MARKED IMPROVEMENT	15	27.3	17	32.7	25	46.3				
MODERATE IMPROVEMENT	14	25.5	20	38.5	15	27.8				
MINIMAL IMPROVEMENT	15	27.3	6	11.5	10	18.5				
UNCHANGED	9	16.4	5	9.6	3	5.6				
DETERIORATED	2	3.6	4	7.7	1	1.9				
NOT ASSESSED(2)	5	-	4	-	7	-				
TOTAL	55	100	52	100	54	100	0.032	0.268	0.008 BB	0.109

POPULATION: EVALUABLE DATA ONLY
ASSESSMENT: 1=MARKED IMP., 2=MODERATE IMP., 3=MINIMAL IMP., 4=UNCHANGED, 5=DETERIORATED; LOWER SCORE IS BETTER

EVALUATION	PLACEBO N	PLACEBO %	CISAPRIDE 10MG N	CISAPRIDE 10MG %	CISAPRIDE 20MG N	CISAPRIDE 20MG %	OVERALL P-VALUE(1)	PAIRWISE TEST(1) P. VS 10	PAIRWISE TEST(1) P. VS 20	PAIRWISE TEST(1) 10 VS 20
INVESTIGATOR'S GLOBAL ASSESS.										
MARKED IMPROVEMENT	14	24.6	13	26.0	22	41.5				
MODERATE IMPROVEMENT	14	24.6	19	38.0	17	32.1				
MINIMAL IMPROVEMENT	20	35.1	7	14.0	10	18.9				
UNCHANGED	6	10.5	8	16.0	3	5.7				
DETERIORATED	3	5.3	3	6.0	1	1.9				
NOT ASSESSED(2)	2	-	3	-	4	-				
TOTAL	57	100	50	100	53	100	0.010	0.858	0.003 BB	0.030 BB
PATIENT'S GLOBAL ASSESS.										
MARKED IMPROVEMENT	15	27.3	16	32.0	24	48.0				
MODERATE IMPROVEMENT	14	25.5	19	38.0	13	26.0				
MINIMAL IMPROVEMENT	15	27.3	6	12.0	9	18.0				
UNCHANGED	9	16.4	5	10.0	3	6.0				
DETERIORATED	2	3.6	4	8.0	1	2.0				
NOT ASSESSED(2)	4	-	3	-	7	-				
TOTAL	55	100	50	100	50	100	0.023	0.321	0.006 BB	0.083 B

(1) GENERALIZED COCHRAN-MANTEL-HAENSZEL TEST CONTROLLING FOR INVESTIGATOR. (RESPONSE SCORES USED IN THE TEST.)
(2) 'NOT ASSESSED' EVALUATION PATIENTS NOT INCLUDED IN THE ANALYSIS. TOTALS OR THE PERCENTAGES.

"P": TWO-SIDED P-VALUE <=0.10 WITH PLACEBO HAVING LOWER (BETTER) SCORES; "PP": P-VALUE <=0.05.
"A": TWO-SIDED P-VALUE <=0.10 WITH CISAPRIDE 10MG HAVING LOWER (BETTER) SCORES; "AA": P-VALUE <=0.05.
"B": TWO-SIDED P-VALUE <=0.10 WITH CISAPRIDE 20MG HAVING LOWER (BETTER) SCORES; "BB": P-VALUE <=0.05.

Table 6b/Global Evaluations: Subgroup

: GLOBAL EVALUATION AT THE END OF DOUBLE-BLIND - PATIENTS WITH PRE-TREATMENT ENDOS. GRADE OF 3

POPULATION: INTENT-TO-TREAT
ASSESSMENT: 1=MARKED IMP., 2=MODERATE IMP., 3=MINIMAL IMP., 4=UNCHANGED, 5=DETERIORATED; LOWER SCORE IS BETTER

EVALUATION	PLACEBO N	PLACEBO %	CISAPRIDE 10MG N	CISAPRIDE 10MG %	CISAPRIDE 20MG N	CISAPRIDE 20MG %	OVERALL P-VALUE(1)	PAIRWISE TEST(1) P. VS 10	P. VS 20	10 VS 20
INVESTIGATOR'S GLOBAL ASSESS.										
MARKED IMPROVEMENT	9	32.1	6	33.3	8	57.1				
MODERATE IMPROVEMENT	3	10.7	3	16.7	3	21.4				
MINIMAL IMPROVEMENT	11	39.3	3	16.7	2	14.3				
UNCHANGED	3	10.7	3	16.7	0	0.0				
DETERIORATED	2	7.1	3	16.7	1	7.1				
NOT ASSESSED(2)	1	-	2	-	1	-				
TOTAL	28	100	18	100	14	100	0.024	0.649	0.017 BB	0.014 BB
PATIENT'S GLOBAL ASSESS.										
MARKED IMPROVEMENT	7	25.9	6	33.3	5	41.7				
MODERATE IMPROVEMENT	6	22.2	5	27.8	4	33.3				
MINIMAL IMPROVEMENT	8	29.6	2	11.1	2	16.7				
UNCHANGED	5	18.5	2	11.1	0	0.0				
DETERIORATED	1	3.7	3	16.7	1	8.3				
NOT ASSESSED(2)	2	-	2	-	3	-				
TOTAL	27	100	18	100	12	100	0.218	0.907	0.109	0.107

GLOBAL EVALUATION AT THE END OF DOUBLE-BLIND - PATIENTS WITH PRE-TREATMENT ENDOS. GRADE OF 3, 3, OR 4

INVESTIGATOR'S GLOBAL ASSESS.										
MARKED IMPROVEMENT	6	17.2	8	23.5	15	34.8				
MODERATE IMPROVEMENT	11	37.9	17	50.0	16	37.2				
MINIMAL IMPROVEMENT	9	31.0	4	11.8	8	18.6				
UNCHANGED	3	10.3	5	14.7	4	9.3				
DETERIORATED	1	3.4	0	0.0	0	0.0				
NOT ASSESSED(2)	2	-	2	-	3	-				
TOTAL	29	100	34	100	43	100	0.152	0.149	0.050 BB	0.803
PATIENT'S GLOBAL ASSESS.										
MARKED IMPROVEMENT	8	28.6	11	32.4	20	47.6				
MODERATE IMPROVEMENT	8	28.6	15	44.1	11	26.2				
MINIMAL IMPROVEMENT	7	25.0	4	11.8	8	19.0				
UNCHANGED	4	14.3	3	8.8	3	7.1				
DETERIORATED	1	3.6	1	2.9	0	0.0				
NOT ASSESSED(2)	3	-	2	-	4	-				
TOTAL	28	100	34	100	42	100	0.096	0.164	0.022 BB	0.674

: GLOBAL EVALUATION AT THE END OF DOUBLE-BLIND - PATIENTS WITH PRE-TREATMENT ENDOS. GRADE OF 4

INVESTIGATOR'S GLOBAL ASSESS.										
MARKED IMPROVEMENT	1	20.0	2	33.3	1	12.5				
MODERATE IMPROVEMENT	2	40.0	2	33.3	4	50.0				
MINIMAL IMPROVEMENT	1	20.0	1	16.7	2	25.0				
UNCHANGED	1	20.0	1	16.7	1	12.5				
DETERIORATED	0	0.0	0	0.0	0	0.0				
NOT ASSESSED(2)	1	-	1	-	1	-				
TOTAL	5	100	6	100	8	100	0.805	0.855	0.572	0.480
PATIENT'S GLOBAL ASSESS.										
MARKED IMPROVEMENT	1	25.0	3	50.0	3	37.5				
MODERATE IMPROVEMENT	1	25.0	2	33.3	2	25.0				
MINIMAL IMPROVEMENT	1	25.0	0	0.0	2	25.0				
UNCHANGED	1	25.0	0	0.0	1	12.5				
DETERIORATED	0	0.0	1	16.7	0	0.0				
NOT ASSESSED(2)	2	-	1	-	1	-				
TOTAL	4	100	6	100	8	100	0.411	0.180	0.388	0.895

(1) 'GENERALIZED COCHRAN-MANTEL-HAENSZEL TEST CONTROLLING FOR INVESTIGATOR. (RESPONSE SCORES USED IN THE TEST.)
(2) 'NOT ASSESSED' EVALUATION PATIENTS NOT INCLUDED IN THE ANALYSIS, TOTALS OR THE PERCENTAGES.

"P": TWO-SIDED P-VALUE <=0.10 WITH PLACEBO HAVING LOWER (BETTER) SCORES; "PP": P-VALUE <=0.05.
"A": TWO-SIDED P-VALUE <=0.10 WITH CISAPRIDE 10MG HAVING LOWER (BETTER) SCORES; "AA": P-VALUE <=0.05.
"B": TWO-SIDED P-VALUE <=0.10 WITH CISAPRIDE 20MG HAVING LOWER (BETTER) SCORES; "BB": P-VALUE <=0.05.

Table 81/1203
Repeated Measures Analysis Results For
Heartburn Intensity (Sponsor's Analysis)

Analysis#	Change From Baseline LSMEAN			2-sided p (Placebo vs)			
#1	Placebo	10 mg	20 mg	10	20	overall	10 +20
Day Investig	-1.6	-2.0	-2.8	.27	.002	.006	.014
Patient	-14.4	-20.3	-23.3	.097	.007	.022	.011
Night Investig	-2.1	-2.3	-3.4	.76	.014	.036	..10
Patient	-12.5	-29.9	-22.3	.035	.003	.007	.00.
#2							
Day Investig	-1.4	-2.0	-2.5	.127	.004	.01	.011
Patient	-13.9	-17.7	-20.9	.245	.027	.086	.052
Night Investig	-2.1	-2.3	-2.6	-	-	.462	.321
Patient	-12.3	-18.3	-19.2	.075	.032	.068	.023

Note: Pairwise comparison p-values are given only when the overall p-value is at least statitically significant at the 10% level.

Analysis#1=Analysis for patient with complete data adjusted for investigator.

Analysis#2=LOCF analysis adjusted for investigator.

Table 1c
Visits Schedule, Patient Dispositions & Demographics

Table 6. Schedule of Evaluations							
Assessment	Pre-Baseline	Selection Wk 0	Single-Blind Placebo Phase Baseline (2 wks)	Double-Blind Phase			
				Wk 4	Wk 6	Wk 8	Wk 10
-Symptoms (Inv.)		X	X	X	X	X	X
-Endoscopy		X					X
-Bernstein test		X					X
-Biopsy		X					X
-Manometry	X						X
-ECG			X				X
-pH probe			X				X
-Lab tests		X	X		X		X
-Diary completion			X	X	X	X	X
-Global evaluation							X

SUMMARY OF DISPOSITION OF PATIENTS

	CISAPRIDE		PLACEBO		TOTAL	
	EVAL	TOTAL	EVAL	TOTAL	EVAL	TOTAL
ENTERED(ALL CENTERS)	76	76	71	71	147	147
00005/171	5	5	5	5	10	10
BEHAR/122	10	10	8	8	18	18
CASTELL/123	11	11	12	12	23	23
OAR/124	13	13	12	12	25	25
SPECHLER/125	14	14	11	11	25	25
PELLICANO/851	11	11	10	10	21	21
CHAMPION/851	12	12	13	13	25	25
SUBGROUPS(ALL CENTERS)						
MODERATELY SEVERE HEARTBURN AT PRE-TREATMENT	51	51(122)	43	43(112)	94	94
WITH ULCERS AT PRE-TREATMENT	50	50	47	47	97	97
LESP <= 10 AT PRE-TREATMENT	51	51	48	48	99	99
PREMATURELY DISCONTINUED(ALL CENTERS)	7	7	6	6	13	13
REASON FOR DISCONTINUED						
ADVERSE EXPERIENCE	4	4	0	0	4	4
INELIGIBLE	0	0	1	1	1	1
INADEQUATE RESPONSE	0	0	2	2	2	2
LOST TO FOLLOW UP	0	0	1	1	1	1
CHOSE TO DISCONTINUE	2	2	1	1	3	3
UNCOOPERATIVE	1	1	1	1	2	2

SUMMARY OF DEMOGRAPHIC AND BACKGROUND DATA FOR INTENT-TO-TREAT POPULATION

PARAMETER	TREATMENT GROUP CISAPRIDE	TREATMENT GROUP PLACEBO	TOTAL	P-VALUE * TREATMENT	P-VALUE * INTERACTION
SEX					
MALE	58	54	112	0.89 **	
FEMALE	18	17	35		
RACE					
WHITE	71	66	137	0.46 **	
BLACK	3	5	8		
ORIENTAL	1	0	1		
AMERICAN INDIAN	1	0	1		
AGE(YEARS)					
N	76	71	147	0.56 ***	0.99 ***
MEAN	48.4	48.3	47.4		
STD.DEV.	14.4	15.7	15.0		
MEDIAN	47.5	47.0	47.0		
MINIMUM	22.0	18.0	18.0		
MAXIMUM	78.0	73.0	75.0		
GERD SYMPTOM DURATION(YEAR)					
N	76	71	147	0.45 ***	0.99 ***
MEAN	8.7	8.2	8.0		
STD.DEV.	9.6	8.8	9.2		
MEDIAN	5.3	5.0	5.0		
MINIMUM	0.5	0.5	0.5		
MAXIMUM	41.0	50.0	50.0		

* BETWEEN-TREATMENT COMPARISONS
** COCHRAN-MANTEL-HAENSZEL TEST
*** ANOVA MODEL INCLUDING TREATMENT, INVESTIGATOR, AND TREATMENT X INVESTIGATOR INTERACTION EFFECTS. (P-VALUE BASED ON TYPE III SS.)

Table 2c/ITT
Heartburn Intensity Evaluation Results

Study 121

POPULATION: INTENT-TO-TREAT
PHASE: DOUBLE-BLIND
ASSESSMENT: SEVERITY SCALE: 0-100 PT., 0=NONE, ... , 100=MOST SEVERE; LOWER SCORES ARE BETTER
SOURCE: PATIENT'S DIARY; AVERAGE OVER DAYS WITHIN BI-WEEKLY PERIOD

PARAMETER	CISAPRIDE N	CISAPRIDE LSMEAN(1)	CISAPRIDE DIFFERENCE FROM BASELINE LSMEAN(1)	CISAPRIDE DIFFERENCE FROM BASELINE P-VALUE(2)	PLACEBO N	PLACEBO LSMEAN(1)	PLACEBO DIFFERENCE FROM BASELINE LSMEAN(1)	PLACEBO DIFFERENCE FROM BASELINE P-VALUE(2)	ANOVA(3) P-VALUE TRT.	ANOVA(3) P-VALUE INT.
HEARTBURN SEV. - DAY										
BASELINE	74	37.0			68	38.1			0.93	0.22
D/B WEEK 2	74	31.9	-5.1	<0.01	68	33.8	-4.2	0.01	0.96	0.27
D/B WEEK 4	70	29.7	-8.8	<0.01	66	30.2	-9.1	<0.01	0.71	0.64
D/B WEEK 6	68	27.8	-9.3	<0.01	65	28.9	-8.9	<0.01	0.77	0.71
D/B WEEK 8	68	24.9	-12.2	<0.01	65	26.8	-11.1	<0.01	0.88	0.74
ENDPOINT	74	25.8	-11.2	<0.01	68	27.7	-10.4	<0.01	0.96	0.59
OVERALL	74	29.8	-8.0	<0.01	68	30.5	-7.6	<0.01	0.80	0.66
HEARTBURN SEV. - NIGHT										
BASELINE	74	27.6			68	22.0			0.13	0.39
D/B WEEK 2	74	20.9	-6.7	<0.01	68	19.4	-2.6	0.03	0.07CC	0.83
D/B WEEK 4	70	19.0	-8.9	<0.01	66	18.8	-3.6	0.03	0.07CC	0.64
D/B WEEK 6	68	15.7	-11.6	<0.01	65	19.2	-2.8	0.07	<0.01CC	0.65
D/B WEEK 8	68	14.3	-13.0	<0.01	65	17.9	-3.7	<0.01	<0.01CC	0.76
ENDPOINT	74	16.0	-11.6	<0.01	68	18.8	-3.2	<0.01	<0.01CC	0.59
OVERALL	74	18.4	-9.1	<0.01	68	19.0	-3.0	<0.02	<0.01CC	0.58

POPULATION: INTENT-TO-TREAT
PHASE: DOUBLE-BLIND
ASSESSMENT: SEVERITY SCALE: 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE; LOWER SCORES ARE BETTER
SOURCE: INVESTIGATOR'S CLINIC EVALUATION

PARAMETER	CISAPRIDE N	CISAPRIDE LSMEAN(1)	CISAPRIDE DIFFERENCE FROM BASELINE LSMEAN(1)	CISAPRIDE DIFFERENCE FROM BASELINE P-VALUE(2)	PLACEBO N	PLACEBO LSMEAN(1)	PLACEBO DIFFERENCE FROM BASELINE LSMEAN(1)	PLACEBO DIFFERENCE FROM BASELINE P-VALUE(2)	ANOVA(3) P-VALUE TRT.	ANOVA(3) P-VALUE INT.
HEARTBURN SEV. - DAY										
BASELINE	76	2.1			69	2.0			0.43	0.72
D/B WEEK 2	76	1.7	-0.3	<0.01	68	1.7	-0.3	<0.01	0.81	0.52
D/B WEEK 4	70	1.6	-0.5	<0.01	66	1.6	-0.4	<0.01	0.37	0.88
D/B WEEK 6	69	1.6	-0.4	<0.01	66	1.7	-0.3	<0.01	0.27	0.78
D/B WEEK 8	69	1.5	-0.5	<0.01	66	1.5	-0.5	<0.01	0.60	0.56
ENDPOINT	76	1.6	-0.5	<0.01	69	1.5	-0.5	<0.01	0.90	0.87
OVERALL	76	1.7	-0.4	<0.01	69	1.6	-0.4	<0.01	0.72	0.79
HEARTBURN SEV. - NIGHT										
BASELINE	76	1.8			69	1.8			0.94	0.78
D/B WEEK 2	76	1.4	-0.4	<0.01	68	1.5	-0.3	0.02	0.31	0.73
D/B WEEK 4	70	1.2	-0.6	<0.01	68	1.4	-0.4	<0.01	0.19	0.45
D/B WEEK 6	69	1.1	-0.8	<0.01	66	1.4	-0.4	<0.01	0.03CC	0.70
D/B WEEK 8	69	1.1	-0.8	<0.01	66	1.3	-0.5	<0.01	0.05CC	0.90
ENDPOINT	76	1.2	-0.7	<0.01	69	1.3	-0.5	<0.01	0.13	0.90
OVERALL	76	1.2	-0.8	<0.01	69	1.4	-0.-	<0.01	0.08C	0.87

(1) LEAST SQUARES MEANS ADJUST FOR UNEQUAL SAMPLE SIZE. THEY ARE EQUAL TO THE UNWEIGHTED AVERAGE OF INVESTIGATOR MEANS.
(2) TWO-SIDED BLOCK WILCOXON SIGNED RANK TEST, ADJUSTED FOR UNEQUAL SAMPLE SIZES, ON DIFFERENCE FROM BASELINE. (P-VALUE NOT GIVEN WHEN NUMBER OF CASES WITH CHANGE IS LESS THAN 3.)
(3) ANOVA MODEL ON RANKED DATA INCLUDING TREATMENT(TRT.), INVESTIGATOR, AND TREATMENT X INVESTIGATOR INTERACTION(INT.) EFFECTS. P-VALUE BASED ON TYPE III SS.(BASELINE P-VALUES BASED ON MEANS, OTHERS ON DIFFERENCES.)
"CC": TWO-SIDED P-VALUE <=0.10 WITH CISAPRIDE HAVING LOWER(BETTER) SCORES; "CC": P-VALUE <=0.05.
"PP": TWO-SIDED P-VALUE <=0.10 WITH PLACEBO HAVING LOWER(BETTER) SCORES, "PP": P VALUE <=0.05.

Global Evaluations: ITT

AT THE END OF DOUBLE-BLIND

POPULATION: INTENT-TO-TREAT
ASSESSMENT: 1=EXCELLENT, 2=GOOD, 3=FAIR, 4=POOR, 5=DETERIORATED;

EVALUATION	CISAPRIDE N	CISAPRIDE %	PLACEBO N	PLACEBO %	P-VALUE *
INVESTIGATOR'S ASSESSMENT					
EXCELLENT	7	9.5	1	1.5	
GOOD	30	40.5	23	33.8	
FAIR	22	29.7	21	30.8	
POOR	13	17.6	20	29.4	
DETERIORATED	2	2.7	3	4.4	
TOTAL	74	100%	68	100%	0.02 CC
PATIENT'S ASSESSMENT					
EXCELLENT	6	8.8	2	3.4	
GOOD	34	45.8	30	44.1	
FAIR	20	27.0	17	25.4	
POOR	13	17.6	15	22.1	
DETERIORATED	2	2.7	4	5.4	
TOTAL	74	100%	68	100%	0.21

* BASED ON GENERALIZED COCHRAN-MANTEL-HAENSZEL TEST CONTROLLING FOR INVESTIGATOR. (RESPONSE SCORES USED IN TEST.)
C: TWO-SIDED P-VALUE <= 0.10 WITH CISAPRIDE HAVING BETTER SCORES, "CC": P-VALUE <= 0.05.
P: TWO-SIDED P-VALUE <= 0.10 WITH PLACEBO HAVING BETTER SCORES, "PP": P-VALUE <= 0.05.

Table 3c/Subgroup
Heartburn Intensity Assessments Results

Summary of Symptom Severity Assessments

POPULATION: INTENT-TO-TREAT
PHASE: DOUBLE-BLIND
ASSESSMENT: SEVERITY SCALE: 0-100 PT., 0=NONE, ... , 100=MOST SEVERE; LOWER SCORES ARE BETTER
SOURCE: PATIENT'S DIARY; AVERAGE OVER DAYS WITHIN BI-WEEKLY PERIOD
SUBGROUP: PATIENTS WITH AT LEAST MODERATE HEARTBURN AT PRE-TREATMENT (> 30 ON 0-100 ANALOGUE SCALE) >= 4 TIMES/WEEK

	CISAPRIDE				PLACEBO				ANOVA(3) P-VALUE	
			DIFFERENCE FROM BASELINE				DIFFERENCE FROM BASELINE			
PARAMETER	N	LSMEAN(1)	LSMEAN(1)	P-VALUE(2)	N	LSMEAN(1)	LSMEAN(1)	P-VALUE(2)	TRT.	INT.
HEARTBURN SEV. - DAY										
BASELINE	50	45.6			41	51.1			0.47	0.13
D/B WEEK 2	50	38.5	-7.0	<0.01	41	44.7	-6.4	0.02	0.90	0.46
D/B WEEK 4	48	36.2	-9.5	<0.01	40	40.2	-11.0	<0.01	0.62	0.58
D/B WEEK 6	46	33.4	-11.8	<0.01	39	38.7	-12.5	<0.01	0.86	0.90
D/B WEEK 8	46	30.7	-15.0	<0.01	39	35.3	-15.3	<0.01	0.97	0.97
ENDPOINT	50	31.8	-13.7	<0.01	41	36.6	-14.4	<0.01	0.91	0.86
OVERALL	50	35.4	-10.1	<0.01	41	40.0	-11.0	<0.01	0.70	0.76
HEARTBURN SEV. - NIGHT										
BASELINE	50	36.3			41	31.8			0.34	0.43
D/B WEEK 2	50	28.1	-8.2	<0.01	41	28.2	-3.6	0.20	0.06C	0.34
D/B WEEK 4	48	25.4	-10.8	<0.01	40	26.4	-4.8	0.44	0.09C	0.72
D/B WEEK 6	46	21.9	-14.4	<0.01	39	29.5	-1.5	0.30	0.01CC	0.93
D/B WEEK 8	46	20.1	-15.6	<0.01	38	26.9	-4.0	0.03	0.07CC	0.90
ENDPOINT	50	22.4	-13.9	<0.01	41	28.1	-3.8	0.04	0.05C	0.97
OVERALL	50	25.1	-11.2	<0.01	41	28.2	-3.6	0.21	0.07CC	0.89

Summary of Investigator's Symptom Severity Assessments

POPULATION: INTENT-TO-TREAT
PHASE: DOUBLE-BLIND
ASSESSMENT: SEVERITY SCALE: 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE; LOWER SCORES ARE BETTER
SOURCE: INVESTIGATOR'S CLINIC EVALUATION
SUBGROUP: PATIENTS WITH AT LEAST MODERATE HEARTBURN AT PRE-TREATMENT (> 30 ON 0-100 ANALOGUE SCALE) >= 4 TIMES/WEEK

	CISAPRIDE				PLACEBO				ANOVA(3) P-VALUE	
			DIFFERENCE FROM BASELINE				DIFFERENCE FROM BASELINE			
PARAMETER	N	LSMEAN(1)	LSMEAN(1)	P-VALUE(2)	N	LSMEAN(1)	LSMEAN(1)	P-VALUE(2)	TRT.	INT.
HEARTBURN SEV. - DAY										
BASELINE	51	2.2			41	2.2			0.76	0.50
D/B WEEK 2	51	1.8	-0.4	<0.01	41	1.9	-0.3	0.03	0.72	0.97
D/B WEEK 4	48	1.6	-0.6	<0.01	41	1.9	-0.3	0.02	0.14	0.89
D/B WEEK 6	46	1.5	-0.7	<0.01	39	1.9	-0.2	0.13	0.06C	0.86
D/B WEEK 8	46	1.5	-0.7	<0.01	39	1.5	-0.6	<0.01	0.47	0.81
ENDPOINT	51	1.6	-0.6	<0.01	41	1.6	-0.4	<0.01	0.75	0.86
OVERALL	51	1.7	-0.5	<0.01	41	1.8	-0.4	0.03	0.31	0.88
HEARTBURN SEV. - NIGHT										
BASELINE	51	2.0			41	2.0			0.75	0.53
D/B WEEK 2	51	1.6	-0.4	<0.01	41	1.8	-0.4	0.04	0.76	0.77
D/B WEEK 4	48	1.4	-0.6	<0.01	41	1.8	-0.4	0.01	0.37	0.61
D/B WEEK 6	46	1.3	-0.7	<0.01	39	1.8	-0.4	<0.01	0.14	0.30
D/B WEEK 8	46	1.3	-0.8	<0.01	39	1.8	-0.4	0.09	0.08C	0.18
ENDPOINT	51	1.3	-0.7	<0.01	41	1.8	-0.4	0.11	0.14	0.23
OVERALL	51	1.4	-0.6	<0.01	41	1.8	-0.4	0.01	0.27	0.55

(1) "LEAST SQUARES MEANS ADJUST FOR UNEQUAL SAMPLE SIZE. THEY ARE EQUAL TO THE UNWEIGHTED AVERAGE OF INVESTIGATOR MEANS.
(2) TWO-SIDED WILCOXON SIGNED RANK TEST, ADJUSTED FOR UNEQUAL SAMPLE SIZES, ON DIFFERENCE FROM BASELINE. (P-VALUE NOT GIVEN WHEN NUMBER OF CASES WITH CHANGE IS LESS THAN 3.)
(3) ANOVA MODEL ON RANKED DATA INCLUDING TREATMENT(INT.), INVESTIGATOR, AND TREATMENT X INVESTIGATOR INTERACTION(INT.) EFFECTS. P-VALUE BASED ON TYPE III SS.(BASELINE P-VALUES BASED ON MEANS, OTHERS ON DIFFERENCES.)
"C": TWO SIDED P VALUE <=0.10 WITH CISAPRIDE HAVING LOW(BETTER) SCORES; "CC": P-VALUE <=0.05.
"P": TWO SIDED P-VALUE <=0.10 WITH PLACEBO HAVING LOW(BETTER) SCORES; "PP": P-VALUE <=0.05.

Table 4c/Subgroup
Heartburn Intensity Assessments Results

Summary of Symptom Severity Assessments from Diary Data

POPULATION: INTENT-TO-TREAT
PHASE: DOUBLE-BLIND
ASSESSMENT: SEVERITY SCALE: 0-100 PT., 0=NONE, ..., 100=MOST SEVERE; LOWER SCORES ARE BETTER
SOURCE: PATIENT'S DIARY; AVERAGE OVER DAYS WITHIN BI-WEEKLY PERIOD
SUBGROUP: PATIENTS WITHOUT ULCERS AT PRE-TREATMENT

PARAMETER	CISAPRIDE N	CISAPRIDE LSMEAN(1)	CISAPRIDE DIFFERENCE FROM BASELINE LSMEAN(1)	CISAPRIDE DIFFERENCE FROM BASELINE P-VALUE(2)	PLACEBO N	PLACEBO LSMEAN(1)	PLACEBO DIFFERENCE FROM BASELINE LSMEAN(1)	PLACEBO DIFFERENCE FROM BASELINE P-VALUE(2)	ANOVA(3) P-VALUE TRT.	ANOVA(3) P-VALUE INT.
HEARTBURN SEV. - DAY										
BASELINE	48	40.8			45	39.5				
D/B WEEK 2	48	37.5	-3.3	0.25	45	35.1	-4.4	0.14	0.51	0.30
D/B WEEK 4	46	33.7	-8.3	0.07	44	31.8	-8.5	<0.01	0.58	0.66
D/B WEEK 6	44	30.6	-10.2	<0.01	43	31.3	-7.6	0.02	0.80	0.80
D/B WEEK 8	44	28.5	-12.3	<0.01	43	28.7	-10.7	<0.01	0.80	0.91
ENDPOINT	48	29.3	-11.4	<0.01	45	29.3	-10.2	<0.01	0.87	0.63
OVERALL	48	32.8	-7.9	<0.01	45	32.0	-7.6	<0.01	0.75	0.53
HEARTBURN SEV. - NIGHT									0.71	0.70
BASELINE	48	28.6			45	19.7				
D/B WEEK 2	48	22.8	-6.7	<0.01	45	16.8	-3.7	0.09	0.05PP	0.91
D/B WEEK 4	46	18.9	-10.7	<0.01	44	14.5	-4.7	0.04	0.16	0.59
D/B WEEK 6	44	18.6	-13.8	<0.01	43	15.3	-3.2	0.07	0.10CC	0.81
D/B WEEK 8	44	17.2	-13.2	<0.01	43	15.5	-3.0	0.03	0.01CC	0.92
ENDPOINT	48	18.6	-11.0	<0.01	45	17.0	-2.7	0.05	0.05CC	0.80
OVERALL	48	19.9	-9.7	<0.01	45	16.8	-3.7	0.02	0.07C	0.75
									0.04CC	0.84

Summary of Investigator's Symptom Severity Assessments

POPULATION: INTENT-TO-TREAT
PHASE: DOUBLE-BLIND
ASSESSMENT: SEVERITY SCALE: 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE; LOWER SCORES ARE BETTER
SOURCE: INVESTIGATOR'S CLINIC EVALUATION
SUBGROUP: PATIENTS WITHOUT ULCERS AT PRE-TREATMENT

PARAMETER	CISAPRIDE N	CISAPRIDE LSMEAN(1)	CISAPRIDE DIFFERENCE FROM BASELINE LSMEAN(1)	CISAPRIDE DIFFERENCE FROM BASELINE P-VALUE(2)	PLACEBO N	PLACEBO LSMEAN(1)	PLACEBO DIFFERENCE FROM BASELINE LSMEAN(1)	PLACEBO DIFFERENCE FROM BASELINE P-VALUE(2)	ANOVA(3) P-VALUE TRT.	ANOVA(3) P-VALUE INT.
HEARTBURN SEV. - DAY										
BASELINE	50	2.1			48	2.1				
D/B WEEK 2	50	1.9	-0.2	<0.01	45	1.6	-0.4	<0.01	0.65	0.65
D/B WEEK 4	46	1.7	-0.5	<0.01	46	1.6	-0.5	<0.01	0.59	0.59
D/B WEEK 6	45	1.6	-0.5	<0.01	44	1.6	-0.4	<0.01	0.77	0.51
D/B WEEK 8	45	1.6	-0.5	<0.01	44	1.5	-0.6	<0.01	0.52	0.90
ENDPOINT	50	1.7	-0.4	<0.01	46	1.5	-0.6	<0.01	0.97	0.78
OVERALL	50	1.7	-0.4	<0.01	46	1.6	-0.5	<0.01	0.67	0.74
HEARTBURN SEV. - NIGHT									0.87	0.40
BASELINE	50	1.7			46	1.8				
D/B WEEK 2	50	1.4	-0.4	0.03	45	1.2	-0.4	0.05	0.52	0.66
D/B WEEK 4	46	1.3	-0.5	0.01	46	1.3	-0.4	<0.01	0.09	0.31
D/B WEEK 6	45	1.0	-0.8	<0.01	44	1.1	-0.5	<0.01	0.57	0.67
D/B WEEK 8	45	1.1	-0.7	<0.01	44	1.2	-0.4	0.02	0.11	0.84
ENDPOINT	50	1.2	-0.6	<0.01	46	1.2	-0.4	0.02	0.21	0.96
OVERALL	50	1.2	-0.5	<0.01	46	1.2	-0.4	<0.01	0.33	0.86
									0.26	0.60

(1) LEAST SQUARES MEANS ADJUST FOR UNEQUAL SAMPLE SIZE. THEY ARE EQUAL TO THE UNWEIGHTED AVERAGE OF INVESTIGATOR MEANS.
(2) TWO-SIDED BLOCK WILCOXON SIGNED RANK TEST, ADJUSTED FOR UNEQUAL SAMPLE SIZES, ON DIFFERENCE FROM BASELINE. (P-VALUE MAY GIVEN WHEN NUMBER OF CASES WITH CHANGE IS LESS THAN 3.)
(3) ANOVA MODEL ON RANKED DATA INCLUDING TREATMENT(INT.), INVESTIGATOR, AND TREATMENT X INVESTIGATOR INTERACTION(INT.) EFFECTS. P-VALUE BASED ON TYPE III SS (BASELINE P-VALUES BASED ON MEANS, OTHERS ON DIFFERENCES.)
"C": TWO-SIDED P-VALUE <=0.10 WITH CISAPRIDE HAVING LOW(BETTER) SCORES; "CC": P-VALUE <=0.05.
"P": TWO-SIDED P-VALUE <=0.10 WITH PLACEBO HAVING LOW(BETTER) SCORES; "PP": P-VALUE <=0.05.

Table 5c/ Subgroup

: SUMMARY OF SYMPTOM SEVERITY ASSESSMENTS FROM DIARY DATA

POPULATION: INTENT-TO-TREAT
PHASE: DOUBLE-BLIND
ASSESSMENT: SEVERITY SCALE: 0-100 PT., 0=NONE, ... , 100=MOST SEVERE; LOWER SCORES ARE BETTER
SOURCE: PATIENT'S DIARY; AVERAGE OVER DAYS WITHIN BI-WEEKLY PERIOD
SUBGROUP: PATIENTS HAVING MEAN LESP LESS THAN OR EQUAL TO 10 AT PRE-TREATMENT

PARAMETER	CISAPRIDE N	CISAPRIDE LSMEAN(1)	CISAPRIDE DIFFERENCE FROM BASELINE LSMEAN(1)	CISAPRIDE DIFFERENCE FROM BASELINE P-VALUE(2)	PLACEBO N	PLACEBO LSMEAN(1)	PLACEBO DIFFERENCE FROM BASELINE LSMEAN(1)	PLACEBO DIFFERENCE FROM BASELINE P-VALUE(2)	ANOVA(3) P-VALUE TRT.	ANOVA(3) P-VALUE INT.
HEARTBURN SEV. - DAY										
BASELINE	51	37.0			46	39.1			0.97	0.12
D/B WEEK 2	51	31.0	-6.0	0.04	46	36.1	-3.0	0.02	0.82	0.63
D/B WEEK 4	49	28.8	-8.3	<0.01	45	34.1	-5.6	<0.01	0.67	0.86
D/B WEEK 6	47	26.0	-10.3	0.01	45	33.7	-6.0	0.05	0.44	0.92
D/B WEEK 8	47	23.7	-12.6	<0.01	45	31.9	-7.8	0.02	0.35	0.84
ENDPOINT	51	25.7	-11.3	<0.01	46	31.7	-7.5	0.04	0.50	0.80
OVERALL	51	28.6	-8.4	<0.01	46	33.7	-5.4	0.02	0.86	0.87
HEARTBURN SEV. - NIGHT										
BASELINE	51	27.2			46	35.3			0.57	0.16
D/B WEEK 2	51	20.7	-6.6	<0.01	46	34.2	-1.1	0.05	0.04CC	0.29
D/B WEEK 4	49	18.8	-7.3	<0.01	45	33.4	-2.2	0.17	0.11	0.80
D/B WEEK 6	47	16.2	-9.8	<0.01	45	37.1	1.5	0.60	<0.01CC	0.67
D/B WEEK 8	47	13.7	-12.3	<0.01	45	35.4	-0.2	0.82	<0.01CC	0.51
ENDPOINT	51	16.5	-10.7	<0.01	46	35.0	-0.3	0.74	<0.01CC	0.20
OVERALL	51	19.2	-8.0	<0.01	46	34.7	-0.7	0.45	<0.01CC	0.15

: SUMMARY OF INVESTIGATOR'S SYMPTOM SEVERITY ASSESSMENTS

POPULATION: INTENT-TO-TREAT
PHASE: DOUBLE-BLIND
ASSESSMENT: SEVERITY SCALE: 0=NONE, 1=MILD, 2=MODERATE, 3=SEVERE; LOWER SCORES ARE BETTER
SOURCE: INVESTIGATOR'S CLINIC EVALUATION
SUBGROUP: PATIENTS HAVING MEAN LESP LESS THAN OR EQUAL TO 10 AT PRE-TREATMENT

PARAMETER	CISAPRIDE N	CISAPRIDE LSMEAN(1)	CISAPRIDE DIFFERENCE FROM BASELINE LSMEAN(1)	CISAPRIDE DIFFERENCE FROM BASELINE P-VALUE(2)	PLACEBO N	PLACEBO LSMEAN(1)	PLACEBO DIFFERENCE FROM BASELINE LSMEAN(1)	PLACEBO DIFFERENCE FROM BASELINE P-VALUE(2)	ANOVA(3) P-VALUE INT.	ANOVA(3) P-VALUE INT.
HEARTBURN SEV. - DAY										
BASELINE	51	2.1			47	2.0				
D/B WEEK 2	51	1.7	-0.4	<0.01	47	1.8	-0.2	0.02	0.48	0.69
D/B WEEK 4	49	1.6	-0.5	<0.01	46	1.7	-0.3	0.02	0.45	0.91
D/B WEEK 6	47	1.6	-0.6	<0.01	46	1.9	-0.1	0.43	0.79	0.91
D/B WEEK 8	47	1.4	-0.7	<0.01	46	1.7	-0.4	<0.01	0.07CC	0.46
ENDPOINT	51	1.5	-0.6	<0.01	47	1.7	-0.4	<0.01	0.09C	0.78
OVERALL	51	1.6	-0.5	<0.01	47	1.8	-0.2	0.10	0.13	0.84
HEARTBURN SEV. - NIGHT										
BASELINE	51	1.8			47	1.8				
D/B WEEK 2	51	1.5	-0.4	<0.01	47	1.7	-0.2	0.20	0.57	0.65
D/B WEEK 4	48	1.2	-0.6	<0.01	46	1.6	-0.3	0.07	0.36	0.44
D/B WEEK 6	47	1.0	-0.8	<0.01	46	1.7	-0.2	0.08	0.13	0.82
D/B WEEK 8	47	1.0	-0.8	<0.01	46	1.5	-0.4	0.02	0.01CC	0.96
ENDPOINT	51	1.1	-0.7	<0.01	47	1.5	-0.4	0.02	0.05CC	0.89
OVERALL	51	1.2	-0.6	<0.01	47	1.6	-0.3	0.04	0.05C	0.98

*(1) LEAST SQUARES MEANS ADJUST FOR UNEQUAL SAMPLE SIZE. THEY ARE EQUAL TO THE UNWEIGHTED AVERAGE OF INVESTIGATOR MEANS.
(2) TWO-SIDED BLOCK WILCOXON SIGNED RANK TEST, ADJUSTED FOR UNEQUAL SAMPLE SIZES, ON DIFFERENCE FROM BASELINE. (P-VALUE NOT GIVEN WHEN NUMBER OF CASES WITH CHANGE IS LESS THAN 5.)
(3) ANOVA MODEL ON RANKED DATA INCLUDING TREATMENT(TRT.), INVESTIGATOR, AND TREATMENT X INVESTIGATOR INTERACTION(INT.) EFFECTS. P-VALUE BASED ON TYPE III SS.(BASELINE P-VALUES BASED ON MEANS, OTHERS ON DIFFERENCES.)
"C": TWO-SIDED P-VALUE <=0.10 WITH CISAPRIDE HAVING LOWER(BETTER) SCORES; "CC": P-VALUE <=0.05.
"P": TWO-SIDED P-VALUE <=0.10 WITH PLACEBO HAVING LOWER(BETTER) SCORES; "PP": P-VALUE <=0.05.

Table 6c/Global Evaluations: Subgroup

. . GLOBAL ASSESSMENTS AT THE END OF DOUBLE-BLIND

POPULATION: INTENT-TO-TREAT
ASSESSMENT: 1=EXCELLENT, 2=GOOD, 3=FAIR, 4=POOR, 5=DETERIORATED;
SUBGROUP: PATIENTS WITH AT LEAST MODERATE HEARTBURN AT PRE-TREATMENT (> 30 ON 0-100 ANALOGUE SCALE) ++ 4 TIMES/WEEK

EVALUATION	CISAPRIDE N	CISAPRIDE %	PLACEBO N	PLACEBO %	P-VALUE *
INVESTIGATOR'S ASSESSMENT					
EXCELLENT	3	6.1	1	2.5	
GOOD	20	40.8	8	20.0	
FAIR	16	32.7	13	32.5	
POOR	8	16.3	15	37.5	
DETERIORATED	2	4.1	3	7.5	
TOTAL	49	100%	40	100%	0.02 CC
PATIENT'S ASSESSMENT					
EXCELLENT	2	4.1	1	2.5	
GOOD	21	42.8	14	35.0	
FAIR	15	30.6	9	22.5	
POOR	10	20.4	12	30.0	
DETERIORATED	1	2.0	4	10.0	
TOTAL	49	100%	40	100%	0.13

. GLOBAL ASSESSMENTS AT THE END OF DOUBLE-BLIND

POPULATION: INTENT-TO-TREAT
ASSESSMENT: 1=EXCELLENT, 2=GOOD, 3=FAIR, 4=POOR, 5=DETERIORATED;
SUBGROUP: PATIENTS HAVING MEAN LESP LESS THAN OR EQUAL TO 10 AT PRE-TREATMENT

EVALUATION	CISAPRIDE N	CISAPRIDE %	PLACEBO N	PLACEBO %	P-VALUE *
INVESTIGATOR'S ASSESSMENT					
EXCELLENT	3	6.0	0	0.0	
GOOD	23	46.0	16	34.0	
FAIR	16	32.0	14	29.8	
POOR	6	12.0	15	31.9	
DETERIORATED	2	4.0	2	4.[illegible]	
TOTAL	50	100%	47	[illegible]	<0.01 CC
PATIENT'S ASSESSMENT					
EXCELLENT	2	4.0	1	2.1	
GOOD	24	48.0	19	40.4	
FAIR	15	30.0	11	23.4	
POOR	7	14.0	14	29.8	
DETERIORATED	2	4.0	2	4.2	
TOTAL	50	100%	47	100%	0.10 C

POPULATION: INTENT-TO-TREAT
ASSESSMENT: 1=EXCELLENT, 2=GOOD, 3=FAIR, 4=POOR, 5=DETERIORATED;
SUBGROUP: PATIENTS WITHOUT ULCERS AT PRE-TREATMENT

EVALUATION	CISAPRIDE N	CISAPRIDE %	PLACEBO N	PLACEBO %	P-VALUE *
INVESTIGATOR'S ASSESSMENT					
EXCELLENT	5	10.4	1	2.2	
GOOD	19	39.6	13	28.9	
FAIR	14	29.2	14	31.1	
POOR	9	18.8	14	31.1	
DETERIORATED	1	2.1	3	6.7	
TOTAL	48	100%	45	100%	0.01 CC
PATIENT'S ASSESSMENT					
EXCELLENT	3	6.3	2	4.4	
GOOD	23	47.9	16	35.6	
FAIR	11	22.9	13	28.9	
POOR	11	22.9	11	24.4	
DETERIORATED	0	0.0	3	6.7	
TOTAL	48	100%	45	100%	0.08 C

* BASED ON GENERALIZED COCHRAN-MANTEL-HAENSZEL TEST CONTROLLING FOR INVESTIGATOR.
(RESPONSE SCORES USED IN TEST.)
C: TWO-SIDED P-VALUE < 0.10 WITH CISAPRIDE HAVING BETTER SCORES), "CC": P-VALUE <= 0.05.
P: TWO-SIDED P-VALUE < 0.10 WITH PLACEBO HAVING BETTER SCORES), "PP": P-VALUE <= 0.05.

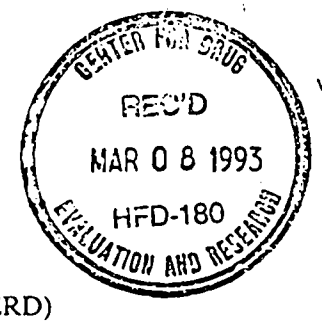
Table S1/121-5
Heartburn Intensity (Sponsor's Analysis)

	LSMEAN 10 mg - plac	2-sided p*
Day		
Invest.	-3.4	.605
Patient	-1.0	.884
Night		
Invest.	-13.1	.05
Patient	-21.9	.001

*=p-values based on ANOVA rank data

STATISTICAL REVIEW & EVALUATION
(ADDENDUM)

Date:



NDA #: 20-210

Drug Class: 1S

Applicant: Janssen Research Foundation

Drug: Cisapride (Propulsid)

Indication: Treatment of symptoms of gastroesophageal reflux disease (GERD)

This review is an addendum to the original statistical review of this NDA (# 20-210) dated March 26, 1992.

This document addresses the adjustments of p-values for multiple endpoints for the effectiveness of cisapride 10 mg in patients with GERD. The adjustments of p-values is done for two of the three studies (study #121-5 and study #1201) originally reviewed.

For study # 121-5, 26 endpoints (week 2, week 4, week 6, week 8, endpoint, overall and global for both patient and investigator daytime/ nighttime assessments), and for study # 1201, 22 endpoints (week 4, week 8, week 12, endpoint, overall and global for both patient and investigator daytime/ nighttime assessments) were considered for multiple endpoints adjustments.

The method used is an enhancement of the Tukey's method and was presented by Dr. Satya Dubey, Ph. D., at the Sixth Annual Meeting of the International Society for Clinical Biostatistician in Germany in 1985. The method uses the correlation coefficients among endpoints to adjust p-values. The method has the property that if the endpoints are fully uncorrelated, then this method reduces to the usual Bonferroni procedure; however, if endpoints are fully correlated, then no adjustment is necessary. The formula used for this method is shown at the bottom of Table-2. [The performance of this method is currently being evaluated using statistical simulation techniques.]

Table-1 and Table-2 (attached) summarize the results of these adjustments. Table-3 shows the (unadjusted) p-values for the third study (study # 1203).

A. J. Sankoh, Ph. D.
(Mathematical Statistician)

Table-1 Endpoints & P-Values in favor of Cisapride (Placebo vs Cisapride) Study 121-6

Endpoints	Cisapride 10 mg	Adjusted For None* E26 E14
Nighttime HB-diary: Wk 2	-6.7	.020 .130 .103
Wk 4	-8.9	.020 .126 .086
Wk 6	-11.6	.010 .053 .039
Wk 8	-13.0	.009 .033 .026
Endpoint	-11.6	.009 .044 .032
Overall	-9.1	.009 .039 .041
Daytime HB- Diary: Wk 2	-5.1	.960
Wk 4	-8.0	.710
Wk 6	-9.3	
Wk 8	-12.2	.880
Endpoint	-11.2	.960
Overall	-8.0	.800
Pat Global		.210
Nighttime HB- Invest: Wk 2	-.40	.310
Wk 4	-.60	.190
Wk 6	-.80	.030 .189 .134
Wk 8	-.80	.093 .274 .202
Endpoint	-.70	.110
Overall	-.60	.080 .368 .282
Daytime HB- Invest: Wk 2	-.30	.810
Wk 4	-.50	.370
Wk 6	-.40	.270
Wk 8	-.50	.600
Endpoint	-.50	.900
Overall	-.40	.720
Invest Global		.020 .128 .091

*: Sponsor's calculated 2-sided p-values; E26: 2-sided p-values adjusted for all 26 end points; E14: 2-sided p-values adjusted for nighttime end points and global evaluations

Table-2 Endpoints & P-Values in favor of Cisapride (Placebo vs Cisapride) Study 1201

Endpoints	Cisapride 10 mg	Cisapride 20 mg	Plac vs 10 mg	Plac vs 20 mg
Nighttime HB-diary: Wk 4	-18.0	-13.3	.044 .159*	.436
Wk 8	-24.2	-16.1	.234 .587	.542
Wk 12	-27.6	-20.7	.249 .596	.717
Endpoint	-24.3	-17.1	.290 .662	.556
Overall	-21.2	-15.1	.256 .595	.691
Daytime HB- Diary: Wk 4	-19.1	-10.8	.024 .095	.962
Wk 8	-25.9	-15.4	.128 .360	.402
Wk 12	-31.0	-21.2	.... .193	.779
Endpoint	-26.9	-17.2	.139 .390	.453
Overall	-22.7	-14.2	.145 .602	.485
Pat Global			.061 .749	.901
Nighttime HB- Invest: Wk 4	-2.4	-1.5	.010 .197	.906
Wk 8	-3.1	-2.1	.062 .767	.946
Wk 12	-3.8	-2.8	.010 .035	.479
Endpoint	-3.4	-2.1	.006 .021	.947
Overall	-2.9	-1.7	.020 .070	.773
Daytime HB- Invest: Wk 4	-1.8	-1.1	.126 .464	.624
Wk 8	-2.4	-1.5	.462 .920	.261
Wk 12	-3.0	-1.9	.057 .181	.882
Endpoint	-2.7	-1.4	.100 .306	.300
Overall	-2.3	-1.2	.200 .517	.188
Invest Global			.154 .974	.924

*: 2-sided p-values adjusted for 22 end points

Note: The adjusted p-values are calculated using the formula:

$$\alpha_i = 1 - (1 - \gamma_i)^{m_i}$$

$$m_i = k^{1 - r_{i.}}$$

$$r_{i.} = \sum_{i \neq j}^{k} \frac{r_{ij}}{k-1}$$

r_{ij} is the (i,j)th element of the correlation matrix, γ_i is the sponsor's p-value for the i^{th} end point and k is the number of end points, i=1,2, ... ,k, where k is the # of endpoints.

Table-3 Endpoints & P-Values in favor of Cisapride (Placebo vs Cisapride) Study 1283

Endpoints	Cisapride 10 mg	Cisapride 20 mg	Plac vs 10 mg	Plac vs 20
Nighttime HB-diary: Wk 4	-16.2	-14.1	.008	.034
Wk 8	-20.5	-22.3	.180	.020
Wk 12	-22.3	-26.4	.086	.003
Endpoint	-20.6	-23.0	.147	.029
Overall	-18.4	-19.0	.062	.036
Daytime HB- Diary: Wk 4	-14.4	-15.8	.079	.022
Wk 8	-21.9	-25.5	.189	.017
Wk 12	-23.5	-27.8	.159	.008
Endpoint	-20.6	-24.7	.339	.033
Overall	-17.8	-20.8	.230	.028
Pat Global			.269	.009
Nighttime HB - Invest: Wk 4	-1.9	-2.1	.347	.139
Wk 8	-2.4	-3.0	.882	.161
Wk 12	-2.7	-3.7	.803	.009
Endpoint	-2.7	-3.1	.744	.175
Overall	-2.3	-2.6	.573	.212
Daytime HB- Invest: Wk 4	-1.8	-2.0	.010	.002
Wk 8	-2.0	-2.9	.515	.011
Wk 12	-2.2	-3.3	.793	.011
Endpoint	-2.2	-2.9	.564	.028
Overall	-2.0	2.5	.111	.003
Invest Global			.458	.006

Statistical Review and Evaluation

Date: 3

CENTER FOR DRUG
RECD
JAN 16 1992
HFD-180
EVALUATION AND RESEARCH

NDA #: 20-210

Applicant: Janssen Research Foundation

Name of Drug: Propulsid (Cisapride) Tablets

Documents Reviewed: NDA submission volumes 33 and 29.
Data set supplied in floppy diskettes

I. Background

Two animal carcinogenicity studies (one in rats and one in mice) were included in this NDA submission. These two studies were intended to assess the carcinogenic potential of Propulsid in rats and mice when administered as a diet admixture to these animals for the major part of their lives. Dr. Chopra, HFD-180, who is the reviewing pharmacologist of this NDA, had requested the Division of Biometrics to perform the statistical review and evaluation of the two studies. The data used in the reviewer's independent analyses were supplied by the sponsor in floppy diskettes. This review has been discussed with Dr. Chopra.

II. The Rat Study

II.a. Design

The study consisted of four treatment groups in each sex. The Charles River SPF Wistar rats were used as experimental animals. Of the four groups, one served as control and the remaining three as treated groups. The dose levels 20, 40, and 80 mg/kg were administered to the low, medium, and high-dose groups, respectively. Each group had a size of 50 animals. The drug was administered to the animals as a diet admixture. The duration of the study was 107 weeks. All surviving animals were sacrificed for histopathological examinations at the end of study.

II.b. Sponsor's Analysis of the Rat Study

Survival Analysis The sponsor reported the following end-of-study mortality rates:

Mortality rates (in %)

	Control	Low	Mid	High
Male	38	54	60	60
Female	46	40	52	34

The sponsor tested for dose related positive trend in mortality by the methods of Peto et. al (Guidelines for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-Term Animal Experiments. In Long-Term and Short-Term Screening Assays for Carcinogens: A Critical Appraisal, International Agency for Research Against Cancer Monographs, Annex to Supplement 2, World Health Organization, Geneva, pp. 311-426, 1980). A statistically significant (one-tailed p=.011) dose-related increase in mortality was observed in male rats. A pairwise comparison by the chi-square test revealed a statistically significant increase ($p<.05$) in mortality in the mid and high dose groups during the last two months in male rats.

In female rats, no statistically significant (at .05 level) dose-related positive trend in mortality was present. Also none of the treated groups showed statistically significantly higher (at .05 level) mortality compared to the control group.

Tumor Data Analysis The sponsor followed the methods described in Peto et. al (1980). The tumor types that showed statistically significant positive dose-response relationship (trend) or statistically significantly increased tumor rate in a treated group relative to the control group are listed below.

Sex	Tumor type Tumor count#	p-value Trend	 pairwise (chi-square)
Male	kidney/lipoma (0,0,1,2)	.0264	
	pituitary/adenoma (8,14,18,11)	.0577	<.05 (C vs M)
Female	Mammary gland/ adenocarcinoma (2,10,5,5)	.31	<.05 (C vs L)

Tumor counts are out of 50 animals in each group.

Hence the only tumor type showing a statistically significant dose-related trend (at .05 level) is kidney/lipoma in males. In addition, pituitary/adenoma in mid-dose males, and mammary/adenocarcinoma in low dose females showed statistically significantly increased tumor rates relative to the respective control animals.

The sponsor has provided historical control tumor rates of pituitary/adenoma in males, and mammary/adenocarcinoma in

The phrase "(positive) dose-response relationship/trend" refers to the (increasing) linear component of the effect of treatment, and not necessarily to a strictly increasing mortality or tumor rate as dose increases.

females. This data is reproduced in Appendix A.

II.c. Reviewer's Analysis of the Rat Study

The reviewer independently performed survival and tumor data analyses. For survival data analyses, the methods described by Cox, D.R. (Regression models and life tables, Journal of the Royal Statistical Society, B, 34, 187-220, 1972), by Gehan. E. (A generalized Wilcoxon test for comparing arbitrarily singly-censored samples, Biometrika, 52, 203-223, 1965) and by Tarone, R. (Tests for trend in life table analysis, Biometrika, 62, 679-682, 1975) were used. The methods applied in tumor data analyses are those described by Peto et al. (1980) and the methods of age-adjusted exact permutation trend test and age-adjusted Fisher exact test.

The data used in reviewer's analyses were provided by the sponsor in floppy diskettes.

Survival Analysis The intercurrent mortality rates are given in Table 1. The end-of-experiment survival rates for males are 38% (control), 54% (low), 60% (medium), and 60% (high). In the females they are 46% (control), 40% (low), 52% (medium), and 34% (high). For the purpose of visual comparison, the Kaplan-Meier survival curves are plotted in figures 1, and 2, respectively, for males and females.

The four survival curves were tested for homogeneity by both the Cox test and the Wilcoxon test. No statistically significant differences (at two-tailed .05 level) among them were observed in either sex. However, a statistically significant (two-tailed p=.036) positive dose-response trend in intercurrent mortality in males was detected. Also, by pairwise comparison, the mid and the high dose males showed a statistically significantly higher mortality relative to the control group. The p-values of the tests applied in survival analyses are given in Table 2.

Tumor Data Analysis The sponsor classified tumor types as 'fatal' or 'incidental'. Following Peto et al. (1980), the reviewer applied the death-rate method for fatal tumors, and the prevalence method for incidental tumors in testing for a positive dose-response relationship (trend) in tumor rates. A combined analysis was performed when a tumor type was observed in both contexts. For tumor types with 25 or less occurrences across treatment groups, an exact permutation trend test was used. The scores assigned to the control, low, mid, and high dose groups were the actual dose levels 0, 20, 40, and 80 mg/kg, respectively. The time intervals (in weeks) used in these tests are, 0-52, 53-80, 81-95, 96-107, and terminal sacrifice. In addition to trend test, age-adjusted Fisher exact tests comparing a treated group with the control group were also performed. The tumor types tested, the tumor rates, and the p-values of the tests are listed in Table 3.

The tumor types that showed a statistically significant finding

(at .05 level) by any of the tests are listed below.

Sex/Tissue/Tumor Type/ /Tumor count[2]	p-value (right-tailed) of test[1] Trend	Fisher Exact Test C,L	C,M	C,H
MALE				
Kidney/Lipoma (0,0,1,2)	<u>.0493</u>*	-	>.20	>.10
Pituitary/Adenoma (8,14,18,11)	>.20	<u>.043</u>	<u>.013</u>	>.10
Pituitary/Adenoma+ Adenocarcinoma (8,15,18,11)	>.20	<u>.028</u>	<u>.013</u>	>.10
FEMALE				
Mammary Gland/Adenocarcinoma (2,10,5,5)	.39	<u>.0137</u>	>.10	>.10
Thyroid/Adenoma+ Adenocarcinoma (0,3,4,2)	.23	>.10	<u>.045</u>*	>.10

1 p-values showing statistical significance are underlined. A '-' indicates a zero count in control versus a zero count in the treated group.
C,L=Control vs. Low; C,M=Control vs. Mid; C,H=Control vs. High.

2 Tumor counts are out of 50, 50, 50, and 50 animals in control, low, mid, and high-dose groups, respectively.

The p-values superscripted with an asterisk(*) will be considered as yielding statistically significant results after adjustment for multiple testing by Haseman's rule. (<u>Haseman's rule</u>. Tumor types with an spontaneous tumor rate of no more than one percent should be tested at .05 level, otherwise the level should be set at .01. Haseman, J.K. (1983), A Reexamination of False-Positive Rates for Carcinogenesis Studies, <u>Fundamental and Applied Toxicology</u>, 3:334-339.) It should be noted, however, that Haseman's rule is an ad-hoc procedure for reducing false-positive rates in multiple testing, and should not be taken very rigidly. The findings of statistical significance must be judged in combination with other scientific evidence in order to make inference on their biological significance.

III. <u>The Mouse Study</u>

III.a. <u>Design</u>

The study consisted of four treatment groups in each sex. The Charles River SPF Albino Swiss mice were used as experimental

animals. Of the four groups, one served as control and the remaining three as treated groups. The dose levels 20, 40, and 80 mg/kg were administered to the low, medium, and high-dose groups, respectively. Each group had a size of 50 animals. The drug was administered to the animals as a diet admixture. The duration of the study was 84 weeks. All surviving animals were sacrificed for histopathological examinations at the end of study.

III.b. Sponsor's Analysis of the Mouse Study

Survival Analysis The sponsor reported the following end-of-study mortality rates:

Mortality rates (in %)

	Control	Low	Mid	High
Male	46	48	34	32
Female	60	38	42	50

The sponsor also reported a one-tailed p-value of .986 in testing for a positive dose-response trend in mortality in males by the methods of Peto et. al (1980). Hence, while the dose-related positive trend in mortality was not statistically significantly positive, there was statistically significant negative trend (one-tailed p=.014).

In female rats, no statistically significant (at .05 level) dose-related trend (in either direction) in mortality was present.

Tumor Data Analysis The sponsor performed both dose-response trend test and Fisher exact test on the tumor incidence data. No statistically significant (at .05 level) results were reported.

III.c. Reviewer's Analysis of the Mouse Study

The reviewer independently performed survival and tumor data analyses. For survival data analyses, the methods described by Cox, D.R., (1972), by Gehan. E. (1965) and Tarone, R. (1975) were used. The methods applied in tumor data analyses are those described by Peto et al. (1980) and the methods of age-adjusted exact permutation trend test and age-adjusted Fisher exact test. The data used in reviewer's analyses were provided by the sponsor in floppy diskettes.

Survival Data Analysis The intercurrent mortality rates are given in Table 4. It is seen that the end-of-experiment survival rates for males are 54% (control), 52% (low), 66% (medium), and 68% (high). In the females they are 40% (control), 62% (low), 58% (medium), and 50% (high). For the purpose of visual comparison, the Kaplan-Meier survival curves are plotted in figures 3, and 4.

for males and females, respectively.

The four survival curves were tested for homogeneity by both the Cox test and the Wilcoxon test. No statistically significant differences (at two-tailed .05 level) among them were observed in either sex. However, a statistically significant (two-tailed p=.036) negative dose-response trend in intercurrent mortality in males was detected. Also, by pairwise comparison, the pairs (C,H), and (L,H) in males, and (C,L) in females showed statistically significant differences in intercurrent mortality. The p-values of the tests applied in survival analyses are given in Table 5.

Tumor Data Analysis The sponsor classified tumor types as 'fatal' or 'incidental'. Following Peto et al. (1980), the reviewer applied the death-rate method for fatal tumors, and the prevalence method for incidental tumors in testing for a positive dose-response relationship (trend) in tumor rates. A combined analysis was performed when a tumor type was observed in both contexts. For tumor types with 25 or less occurrences across treatment groups, an exact permutation trend test was used. The scores assigned to the control, low, medium and high-dose groups were the actual dose levels 0, 20, 40, and 80 mg/kg, respectively. The time intervals (in weeks) used in these tests are, for males, 0-52, 53-65, 66-75, 76-84, and terminal sacrifice. In addition to trend test, age-adjusted Fisher exact tests comparing a treated group with the control group were also performed. The tumor types tested, tumor rates, and the p-values of the tests are listed in Table 6.

None of the tumor types tested showed statistically significant findings (at .05 level) by any of the tests in either sex.

Hepatocytic Neoplasia in male mice The incidence of this neoplasia was recorded in NDA vol. 29, page 52-06497, with rates 11/49 (C), 11/50 (L), 12/50 (M), and 19/50 (H), but was not included in the data set supplied in the floppy diskettes. These rates show a statistically significant dose-related trend with a p-value of .028.

IV. Evaluation of validity of the of the mouse study

The results of the reviewer's analysis show that in the mouse study there is no statistically significant positive dose-response relationship or increased tumor rate in a treated group relative to the control group in any of the tumor types tested. However, before concluding that the drug is not carcinogenic in mice, it is important to look into the following two issues as have been pointed out in the paper by Haseman (Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies, Environmental Health Perspectives, Vol. 58, pp 385-392, 1984):

(i) Were enough animals exposed, for a sustained period of time, to the risk of late developing tumors?

(ii) Were dose levels high enough to pose a reasonable tumor challenge to the animals ?

There is no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with fifty animals per treatment group.

The following are some rules of thumb regarding these two issues as suggested by experts in this field: Haseman (Issues in carcinogenicity testing: Dose selection, Fundamental and Applied Toxicology, Vol. 5, pp 66-78, 1985) has done an investigation in which he gathered data from 21 studies using Fischer 344 rats and B6C3F1 mice conducted at the National Toxicology Program (NTP). He found that, on an average, approximately 50% of the animals in the high dose group survived the two-year study period. Also, in a personal communication with Dr. Karl Lin of the Statistical Application and Research Branch, Division of Biometrics, Haseman suggested that, as a rule of thumb, a 50% survival of the 50 initial animals in the high dose group, between weeks 80-90, would be consider as a sufficient number and adequate exposure.

In addition Chu, Cueto and Ward (Factors in the evaluation of 200 national cancer institute carcinogen bioassay, Journal of Toxicology and environmental Health. Vol. 8, pp 251-280, 1981), suggested that "To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year."

It appears, from these three sources, that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk.

Regarding the question of adequacy of dose levels, it is generally accepted that the high dose should be close to the MTD (maximum tolerated dose). In the paper of Chu, Cueto and Ward (1981), the following criteria are mentioned for dose adequacy:

i) "A dose is considered adequate if there is a detectable weight loss of up to 10 % in a dosed group relative to the controls."

ii) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."

iii) "In addition, doses are considered adequate if the dosed animals show a slightly increased mortality compared to the controls."

In another paper, Gart, Chu and Tarone (Statistical issues in interpretation of chronic bioassay tests for carcinogenicity, Journal of the National Cancer Institute, 62, 957-974, 1979) stated that the mean body weight curves over the entire study period should be taken into consideration in conjunction with the

survival curves when adequacy of dose levels is to be examined. In particular, "Usually, the comparison should be limited to the early weeks of a study when no or little mortality has yet occured in any of the groups. Here a depression of the mean weight in the treated groups is an indication that the treatment has been tested on levels at or approaching the MTD."

We will now examine the validity of the Propulsid mouse carcinogenicity study, in the light of the above guidelines. The following are summary survival data of the high dose group.

	End of 52 weeks	End of 84 weeks
Male	100%	68%
Female	96%	50%

By the criteria mentioned above, the number of animals and the duration of exposure will be considered adequate.

The mean body weight curves are depicted in Fig. 5 (which is a reproduction from NDA vol. 29, p. 52-06442). Also, the decrements in weight are given in Table 7.

It is seen, from Fig. 5 males, that from week 10 to the end of the study the mean high dose weights for the treated males are always lower than those of the control group. In addition, (from Table 7), the decrements in weight (at study end) relative to the control group are 13.6%, 9%, and 13.6% in low, mid, and high dose males, respectively. Hence, according to the criteria described above, the dose levels in males will be considered adequate, the high dose being close to the MTD.

In the females, it is seen from Fig. 5 females, that the mean body weight curve for the high dose stayed almost always above that of the control group, and there was a 13% increment (Table 7) in the mean high dose weight at study end relative to the control group. In addition, the high dose mortality is 10% lower than that of the control group (Table 4). Hence, according to the criteria described above, the high dose will not be considered as reaching the MTD.

V. Summary

In this review, the phrase "(positive) dose-response relationship/trend" refers to the (increasing) linear component of the effect of treatment, and not necessarily to a strictly increasing mortality or tumor rate as dose increases.

The Rat Study The reviewer independently performed survival and tumor data analyses of the rat study. A statistically significant positive dose-response trend (at .05 level) in intercurrent mortality in males was detected. Also, by pairwise

comparison, the mid and high dose males suffered statistically significantly higher (at .05 level) intercurrent mortality relative to the control group. These findings agree with those of the sponsor.

In tumor data analysis, the reviewer applied both the age-adjusted exact permutation trend test and the age-adjusted Fisher exact test. The tumor types showing statistically significant findings are the following:

Sex/Tumor type Tumor count	p-value	
MALE		
Kidney/Lipoma (0,0,1,2)	.0493*	(Trend)
Pituitary/Adenoma (8,14,18,11)	.043 .013	(C vs. L) (C vs. M)
Pituitary/Adenoma+ Adenocarcinoma (8,15,18,11)	.028 .013	(C vs. L) (C vs. M)
FEMALE		
Mammary Gland/Adenocarcinoma (2,10,5,5)	.0137	(C vs. L)
Thyroid/Adenoma+ Adenocarcinoma (0,3,4,2)	.045*	(C vs. M)

Tumor counts are out of 50, 50, 50, and 50 animals in control, low, mid, and high-dose groups, respectively. The p-values attached with an asterisk(*) will be considered as yielding statistically significant results after adjustment for multiple testing by Haseman's rule.

The Mouse Study The reviewer independently performed survival and tumor data analyses of the mouse study. A statistically significant negative dose-response trend (at .05 level) in intercurrent mortality in males was detected. Also, by pairwise comparison, statistically significant differences in intercurrent mortality were observed between the pairs (C vs. H), and (L vs. H) in males, and (C vs. L) in females. These findings agree with those of the sponsor.

In tumor data analysis, the reviewer applied both the age-adjusted exact permutation trend test and the age-adjusted Fisher exact test. In the males, hepatocytic neoplasia (with rates 11/49 (C), 11/50 (L), 12/50 (M), and 19/50 (H) showed a statistically significant dose-related trend (p=.028). None of the tumor types tested in females revealed statistically significant findings (at .05 level) by any of the tests.

The mouse study was evaluated for its validity based on body weight and mortality data. The duration of exposure to the drug was found to be adequate for both males and females. However, only the males, and not the females, would be considered to have been challanged by an MTD.

Mirza W. Ali, Ph.D.
Mathematical Statistician

Concur: Karl K. Lin 1/6/92
Karl K. Lin, Ph.D., Group Leader, SARB

cc: Original NDA # 20-210
HFD-180/Dr. Fredd
HFD-180/Dr. Chopra
HFD-180/Dr. Choudary
HFD-710/Chron
HFD-715/Chron
HFD-715/Dr. Lin
HFD-715/Dr. Ali
HFD-502/Dr. Weissinger
HFD-715/DRU 2.1.1, Propulsid (Cisapride), Janssen Research Foundation
HFD-715/Diskette MALI-2/Propulsid.w51

TABLE 1
INTERCURRENT MORTALITY RATES
THE RAT STUDY

SEX	TIME(WKS)	CONTROL	LOW	MEDIUM	HIGH
MALE					
	0 - 52	0/ 50 (0.00)	1/ 50 (2.00)	0/ 50 (0.00)	0/ 50 (0.00)
	53- 80	5/ 50 (10.00)	6/ 49 (14.00)	6/ 50 (12.00)	8/ 50 (16.00)
	81- 95	6/ 45 (22.00)	8/ 43 (30.00)	14/ 44 (40.00)	9/ 42 (34.00)
	96- 107	8/ 39 (38.00)	12/ 35 (54.00)	10/ 30 (60.00)	13/ 33 (60.00)
	TERM. SACR	31/ 50 (62.00)	23/ 50 (46.00)	20/ 50 (40.00)	20/ 50 (40.00)
FEMALE					
	0 - 52	2/ 50 (4.00)	1/ 50 (2.00)	1/ 50 (2.00)	1/ 50 (2.00)
	53- 80	4/ 48 (12.00)	4/ 49 (10.00)	5/ 49 (12.00)	5/ 49 (12.00)
	81- 95	6/ 44 (24.00)	8/ 45 (26.00)	7/ 44 (26.00)	6/ 44 (24.00)
	96- 107	11/ 38 (46.00)	7/ 37 (40.00)	13/ 37 (52.00)	5/ 38 (34.00)
	TERM. SACR	27/ 50 (54.00)	30/ 50 (60.00)	24/ 50 (48.00)	33/ 50 (66.00)

NOTE: EXCEPT THE TERM. SACR. ROW, AN ENTRY OF THIS TABLE =NUMBER OF ANIMALS DYING OR SACRIFICED IN THE TIME INTERVAL/NUMBER OF ANIMALS ENTERING THE TIME INTERVAL. AN ENTRY IN PARENTHESIS = CUMULATIVE MORTALITY RATE;I.E. CUMULATIVE PERCENT OF ANIMALS DYING UP TO THE END OF THE TIME INTERVAL. AN ENTRY IN THE TERM. SACR. ROW = NUMBER OF ANIMALS SURVIVING TO TERMINAL SACRIFICE / INITIAL NUMBER OF ANIMALS. AN ENTRY IN PARENTHESIS IN THIS ROW = PERCENT OF ANIMALS (OF THE INITIAL NUMBER) SURVIVING TO TERMINAL SACRIFICE.

Table 2
Results of Intercurrent Mortality
(Survival) Data Analyses
The Rat Study

Sex	Groups Compared	Two-tailed p-value of test		
		Cox	G-B	Tarone trend
Male	C,L,M,H	.10	.11	.036* (+)
	C,L	.18	.18	
	C,M	.036*	.029*	
	C,H	.040*	.034*	
	L,M	.50	.35	
	L,H	.51	.39	
	M,H	.97	.95	
Female	C,L,M,H	.37	.46	.40 (-)
	C,L	.68	.57	
	C,M	.66	.61	
	C,H	.36	.34	
	L,M	.31	.27	
	L,H	.72	.67	
	M,H	.13	.14	

G-B Gehan-Breslow test.
\+ Increasing trend in intercurrent mortality.
\- Decreasing trend in intercurrent mortality.
* Statistically significant at .05 level.

Table 3
Results of Tumor Data Analysis
The Rat Study

Sex/Tissue/Tumor Type/ /Tumor count[2]	p-value (right-tailed) of test[1]			
	Trend	Fisher Exact Test		
		C,L	C,M	C,H
MALE				
Hematopoietic System/ Hematopoietic System Tumor (2,1,2,5)	.0587	>.5	>.20	>.10
Kidney/Lipoma (0,0,1,2)	<u>.0493</u>	-	>.20	>.10
Pituitary/Adenoma (8,14,18,11)	>.20	<u>.043</u>	<u>.013</u>	>.10
Pituitary/Adenoma+ Adenocarcinoma (8,15,18,11)	>.20	<u>.028</u>	<u>.013</u>	>.10
Thyroid/Adenocarcinoma (1,2,1,4)	.18	>.10	>.20	>.10
FEMALE				
Kidney/Tubular Adenoma (0,0,0,1)	>.10	-	-	>.10
Mammary Gland/Adenocarcinoma (2,10,5,5)	.39	<u>.0137</u>	>.10	>.10
Ovary/Mixoma (0,0,0,1)	>.10	-	-	>.10
Pituitary/Schwannoma (0,0,0,1)	>.10	-	-	>.10
Thyroid/Adenoma (0,2,3,2)	.14	>.10	>.10	>.10
Thyroid/Adenoma+ Adenocarcinoma (0,3,4,2)	.23	>.10	<u>.045</u>	>.10

1 p-values were obtained by age-adjusted tests. For a total tumor count of 25 or less p-values were obtained by age-adjusted exact test. A '-' indicates a zero count in control versus a zero count in the treated group. p-values yielding statistically significant results are underlined.

2 Tumor counts are out of 50, 50, 50, and 50 animals in control, low, medium, and high-dose groups, respectively.

TABLE 4
INTERCURRENT MORTALITY RATES
THE MOUSE STUDY

SEX	TIME(WKS)	CONTROL	LOW	MEDIUM	HIGH
MALE					
	0 - 52	6/ 50 (12.00)	2/ 50 (4.00)	4/ 50 (8.00)	0/ 50 (0.00)
	53- 65	9/ 44 (30.00)	10/ 48 (24.00)	6/ 46 (20.00)	3/ 50 (6.00)
	66- 75	6/ 35 (42.00)	7/ 38 (38.00)	4/ 40 (28.00)	8/ 47 (22.00)
	76- 84	2/ 29 (46.00)	5/ 31 (48.00)	3/ 36 (34.00)	5/ 39 (32.00)
	TERM. SACR	27/ 50 (54.00)	26/ 50 (52.00)	33/ 50 (66.00)	34/ 50 (68.00)
FEMALE					
	0 - 52	9/ 50 (18.00)	6/ 50 (12.00)	2/ 50 (4.00)	2/ 50 (4.00)
	53- 65	7/ 41 (32.00)	3/ 44 (18.00)	6/ 48 (16.00)	6/ 48 (16.00)
	66- 75	6/ 34 (44.00)	4/ 41 (26.00)	6/ 42 (28.00)	10/ 42 (36.00)
	76- 84	8/ 28 (60.00)	6/ 37 (38.00)	7/ 36 (42.00)	7/ 32 (50.00)
	TERM. SACR	20/ 50 (40.00)	31/ 50 (62.00)	29/ 50 (58.00)	25/ 50 (50.00)

NOTE: EXCEPT THE TERM. SACR. ROW, AN ENTRY OF THIS TABLE ≐NUMBER OF ANIMALS DYING OR SACRIFICED IN THE TIME INTERVAL/NUMBER OF ANIMALS ENTERING THE TIME INTERVAL. AN ENTRY IN PARENTHESIS = CUMULATIVE MORTALITY RATE;I.E. CUMULATIVE PERCENT OF ANIMALS DYING UP TO THE END OF THE TIME INTERVAL. AN ENTRY IN THE TERM. SACR. ROW = NUMBER OF ANIMALS SURVIVING TO TERMINAL SACRIFICE / INITIAL NUMBER OF ANIMALS. AN ENTRY IN PARENTHESIS IN THIS

Table 5
Results of Intercurrent Mortality
(Survival) Data Analyses
The Mouse Study

Sex	Groups Compared	Two-tailed p-value of test		
		Cox	G-B	Tarone trend
Male	C,L,M,H	.15	.08	.036* (-)
	C,L	.99	.82	
	C,M	.27	.20	
	C,H	.08	.024*	
	L,M	.26	.25	
	L,H	.069	.024*	
	M,H	.72	.41	
Female	C,L,M,H	.10	.10	.50 (-)
	C,L	.039*	.032*	
	C,M	.08	.054	
	C,H	.29	.17	
	L,M	.86	.81	
	L,H	.36	.37	
	M,H	.54	.48	

G-B Gehan-Breslow test.
\+ Increasing trend in intercurrent mortality.
\- Decreasing trend in intercurrent mortality.
* Statistically significant at .05 level.

Table 6
Results of Tumor Data Analysis
The Mouse Study

Sex/Tissue/Tumor Type/ /Tumor count[2]	p-value (right-tailed) of test[1] Trend	Fisher Exact Test C,L	C,M	C,H
MALE				
Kidney/Adenoma (0,0,0,1)	>.10	-	-	>.10
Liver/Hemangioendothelioma (1,1,1,3)	.19	>.20	>.20	>.10
Hemangioendothelioma(all tissues combined) (2,1,1,3)	>.10	>.50	>.50	>.20
Liver/Hepatocytic Carcinoma (3,7,6,6)	.30	.20	>.20	>.20
Lung/Primary Lung Tumor(benign) (6,5,8,11)	.11	>.50	>.20	>.10
Lung/Primary Lung Tumor(malignant) (6,3,8,3)	>.20	>.50	>.20	>.50
Lung/Primary Lung Tumor(ben.+malg.) (12,8,16,14)	>.20	>.50	>.20	>.20
Small Intestine/ Adenocarcinoma (0,0,0,1)	>.10	-	-	>.10
Soft tissue/Sarcoma (0,0,0,1)	>.10	-	-	>.10
Testis/Leydig Cell Tumor (1,2,0,2)	>.10	>.10	>.50	>.10

Table 6 continued on the following page

Table 6 (continued from previous page)

Sex/Tissue/Tumor Type/ /Tumor count[2]	p-value (right-tailed) of test[1]			
	Trend	Fisher Exact Test		
		C,L	C,M	C,H
FEMALE				
Mammary Gland/Adenocarcinoma (1,3,5,4)	.16	>.20	.13	>.10
Ovary/Adenoma (0,0,0,1)	>.10	-	-	>.10
Thyroid/Adenoma (0,0,0,1)	>.10	-	-	>.10
Uterus/Leiomyosarcoma (1,2,0,3)	>.10	>.20	>.50	>.20

1 p-values were obtained by age-adjusted tests. For a total tumor count of 25 or less p-values were obtained by age-adjusted exact test. A '-' indicates a zero count in control versus a zero count in the treated group. p-values yielding statistically significant results are underlined.

2 Tumor counts are out of 50, 50, 50, and 50 animals in control, low, medium, and high-dose groups, respectively.

TABLE 7
DECREMENTS IN WEIGHT
THE MOUSE STUDY

Sex	Group	Weight (in grams) Last Week	Weight Decrement (%)
Male			
	Control	22.00	0.00
	Low	19.00	-13.64
	Medium	20.00	-9.09
	High	19.00	-13.64
Female			
	Control	15.00	0.00
	Low	18.00	20.00
	Medium	16.00	6.67
	High	17.00	13.33

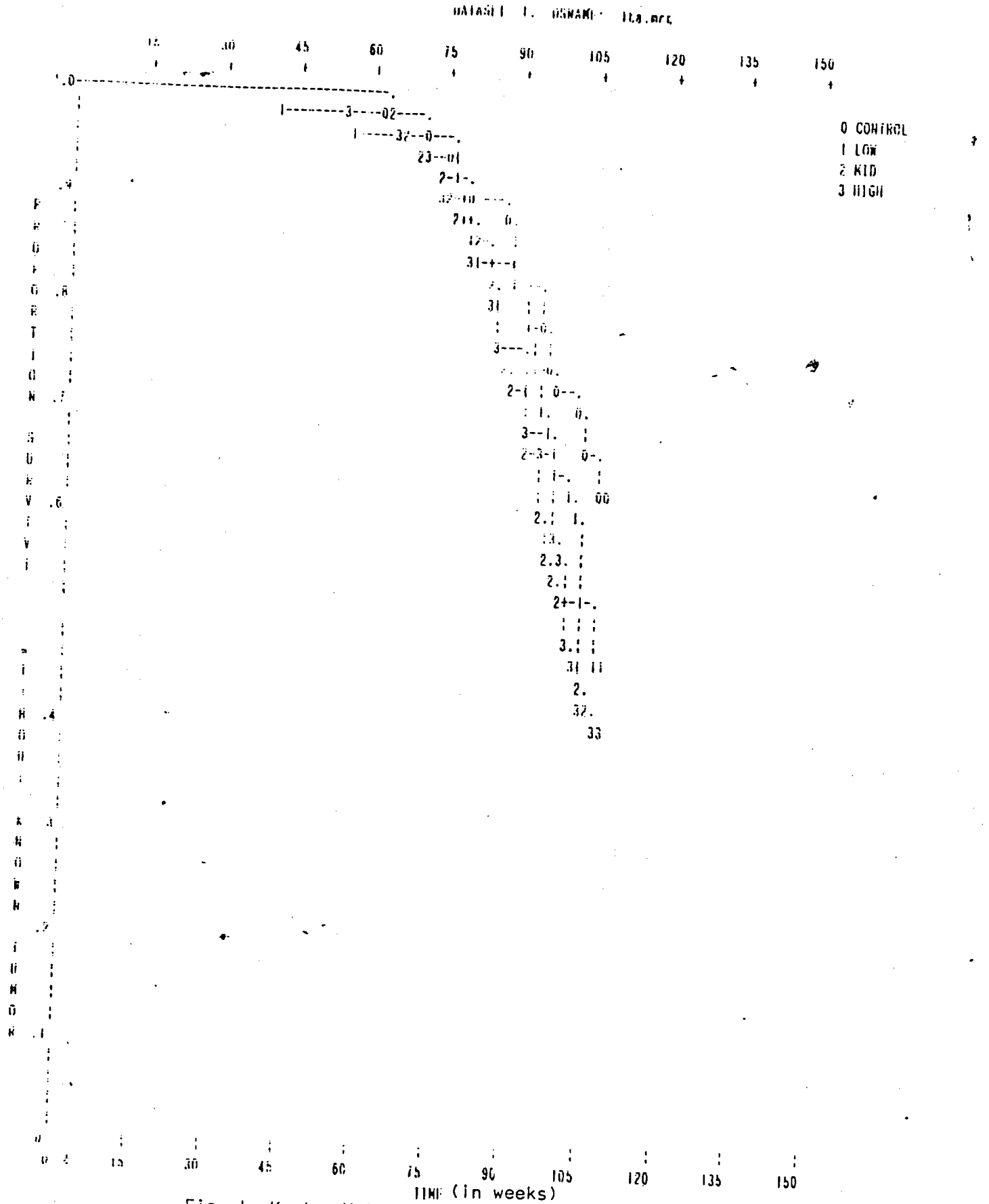


Fig. 1. Kaplan-Meier Survival Curves: Male Rats

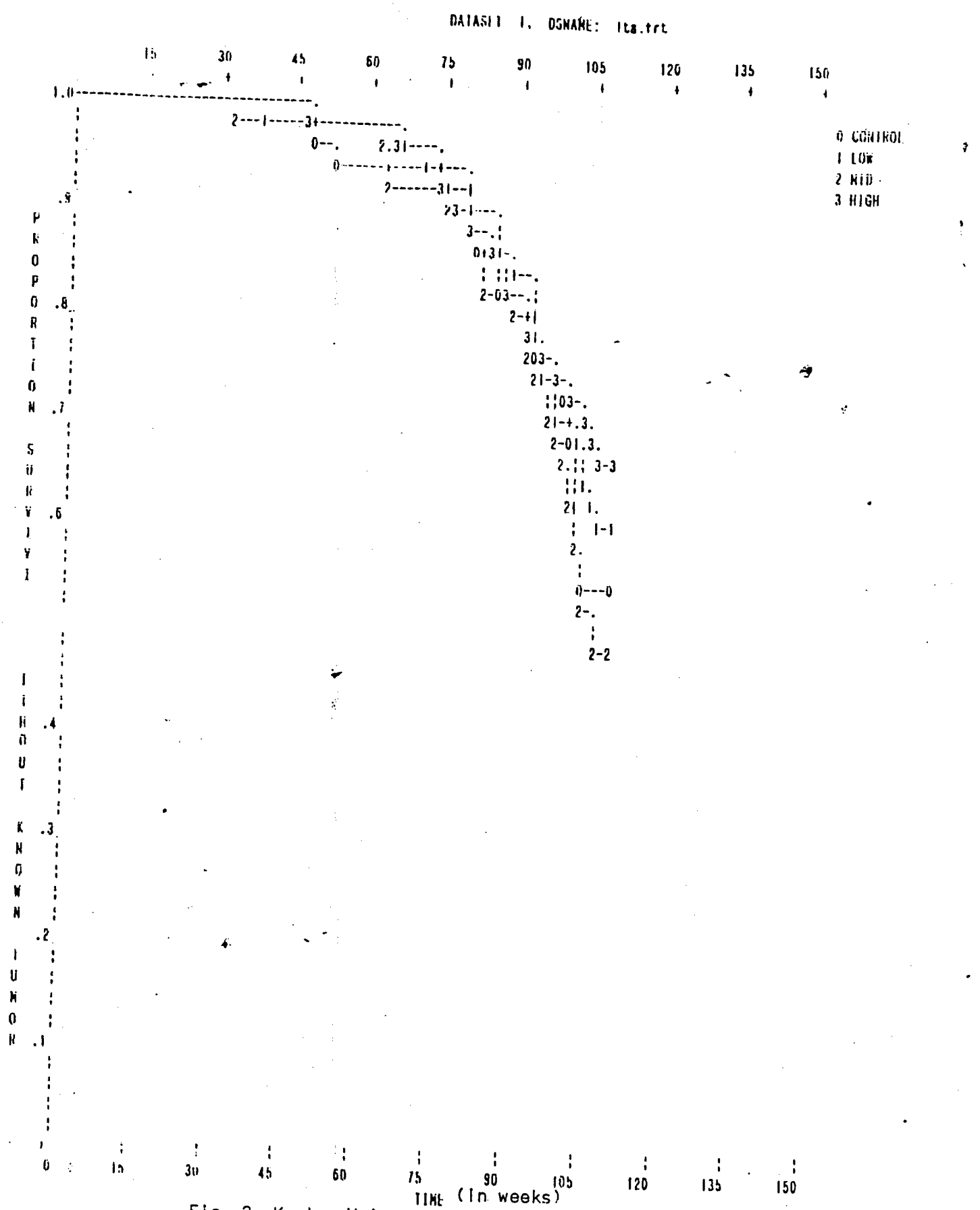


Fig. 2. Kaplan-Meier Survival Curves: Female Rats

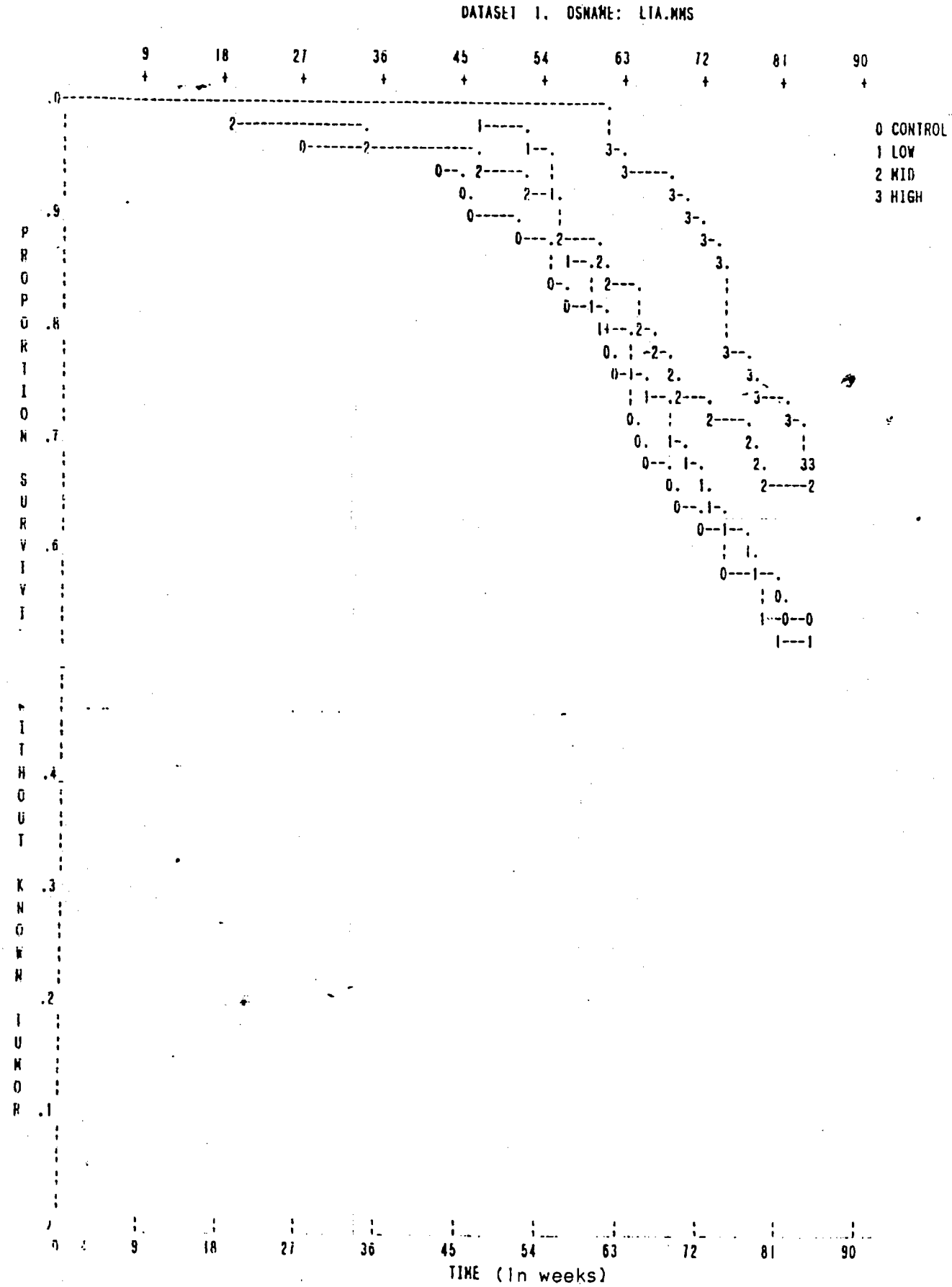


Fig. 3, Kaplan-Meier Survival Curves
Male Mice

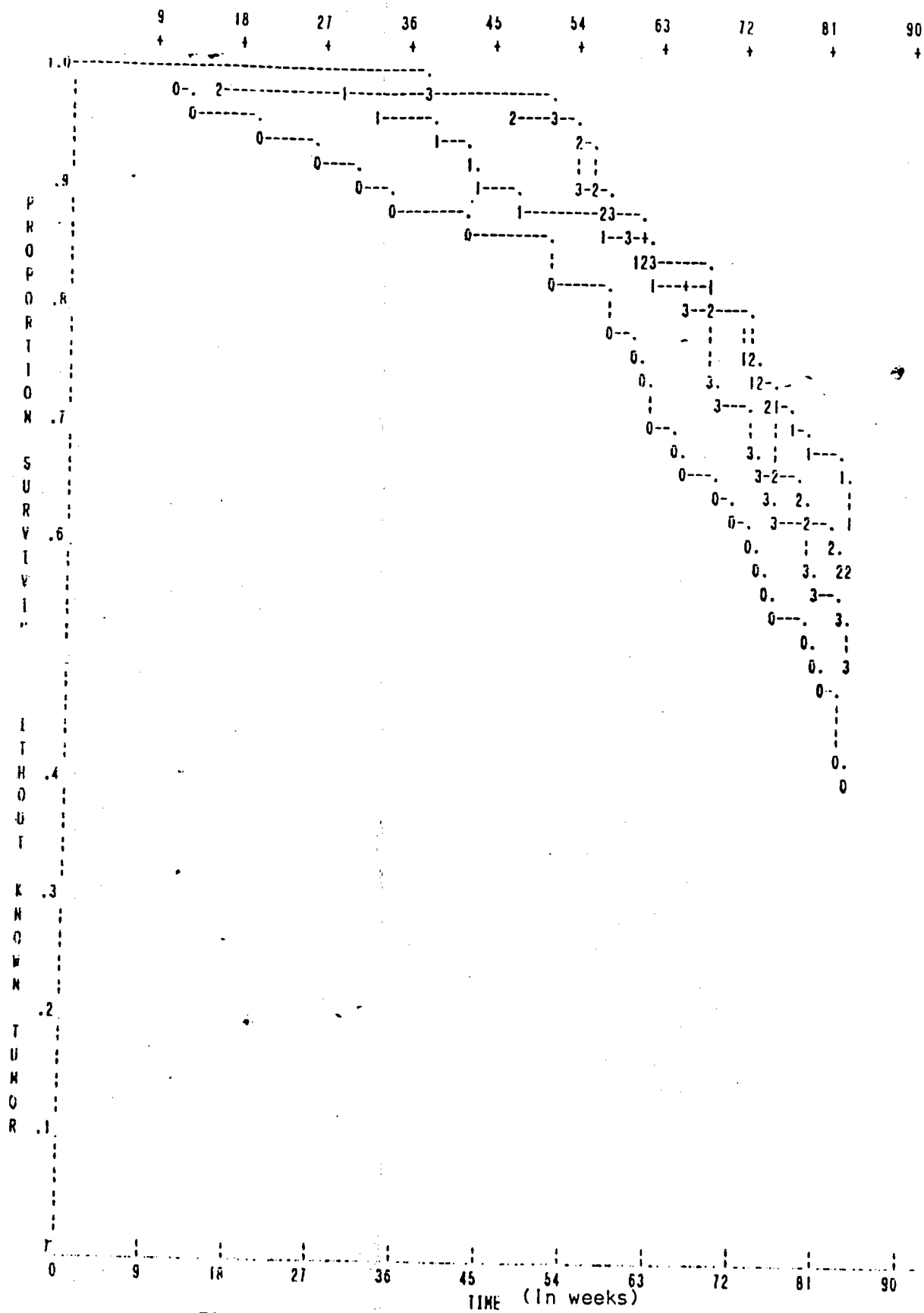


Fig. 4. Kaplan-Meier Survival Curves: Female Mice

JANSSEN PHARMACEUTICA NV
Department of toxicology

EXPERIMENT: 1987
Carcinogenicity study
R 51619 - FOOD - MICE - 18 MONTH

| WEIGHT GAIN |
| Mean values per dosage group in g |

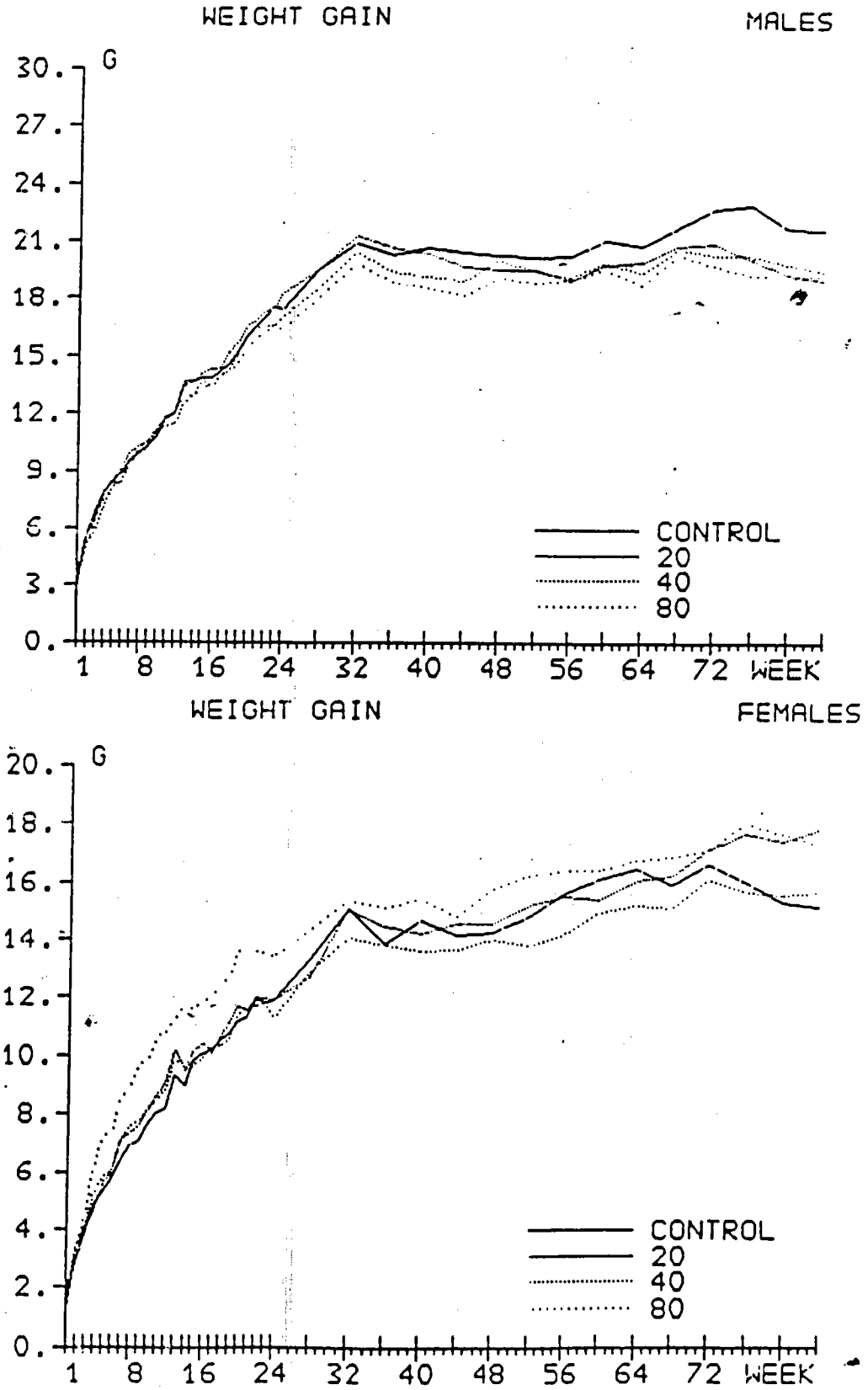


Fig. 5. Mean Body Weight Curves

APPENDIX A

Hisfofical control tumor rates for pituitary adenoma in male rats, and mammary gland adenocarcinoma in female rats.

	Male pituitary adenoma	Female Mammary Gland adenocarcinoma
Historical control data (period 1985 - 1990)		
(see also addendum to the report)		
Exp. No.1155	**19/47**	**9/50**
Exp. No.1214	**15/49**	**4/50**
Exp. No.1230	**9/48**	**5/50**
Exp. No.1307	**13/49**	**5/50**
Exp. No.1317	**11/50**	**2/50**
Exp. No.1335	**12/50**	**3/50**
Exp. No.1450	**10/49**	**4/50**
Exp. No.1309	**4/48**	**5/50**
Exp. No.1650	**15/50**	**7/50**

Statistical Review and Evaluation
(Addendum)

NDA #: 20-210

Date: MAR 26 1992

Applicant: Janssen Research Foundation

Name of Drug: Propulsid (Cisapride) Tablets

I. Background

A report of statistical review and evaluation of the rat and mouse carcinogenicity studies was issued by the Division of Biometrics on Jan. 13, 1992. A typographical error was detected in that review report. The error is corrected in this addendum.

II. Correction

On page 3, under the paragraph "Survival Analysis", the paragraph segment

> The end-of-experiment survival rates for males are 38% (control), 54% (low), 60% (medium), and 60% (high). In the females they are 46% (control), 40% (low), 52% (medium), and 34% (high).

should be replaced by

> The end-of-experiment survival rates for males are 62% (control), 46% (low), 40% (medium), and 40% (high). In the females they are 54% (control), 60% (low), 48% (medium), and 66% (high).

Mirza W. Ali, Ph.D.
Mathematical Statistician

Concur: Karl K. Lin, Ph.D., Group Leader, SARB 3/25/92

cc: Original NDA # 20-210
HFD-180/Dr. Fredd
HFD-180/Dr. Chopra
HFD-180/Dr. Choudary
HFD-710/Chron
HFD-715/Chron
HFD-715/Dr. Lin
HFD-715/Dr. Ali
HFD-502/Dr. Weissinger
HFD-715/DRU 2.1.1, Propulsid (Cisapride), Janssen Research Foundation
HFD-715/Diskette MALI-2/Propulsid.adn

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 27 1992
HFD-180

Statistical Review and Evaluation
(Addendum)

NDA #: 20-210

Date: APR 22 1992

Applicant: Janssen Research Foundation

Name of Drug: Propulsid (Cisapride) Tablets

I. Background

A report of statistical review and evaluation of the rat and mouse carcinogenicity studies was issued by the Division of Biometrics on Jan. 13, 1992. Dr. Chopra requested that an additional combined analysis of liver/hepatocytic neoplasia, hepatic neoplastic nodule, and hepatocytic carcinoma be performed. The results of this additional analysis are reported in this addendum.

II. Combined analysis of liver/hepatocytic neoplasia, hepatic neoplastic nodule, and hepatocytic carcinoma.

This analysis is based on the data supplied by the sponsor in floppy diskettes. In this data set there was no entry under liver/hepatocytic neoplasia for any of the four sex/species experiments. Hence the analyses are for combined hepatic neoplastic nodule, and hepatocytic carcinoma.

Sex/Species	Incidence	Trend test p-value
male mice	(11/50,11/50,12/50,19/50)	0.088
female mice	(1/50,1/50,1/50,1/50)	>.20
male rat	(9/50,6/50,5/50,5/50)	>.20
female rat	(14/50,6/50,7/50,7/50)	>.20

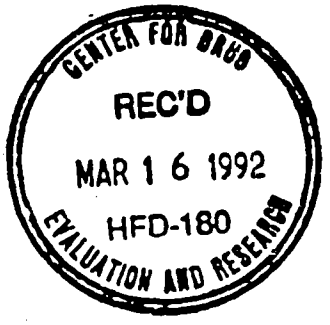
It is to be noted (as mentioned in the original review report) that the sponsor has recorded the entries (11/49,11/50,12/50, 19/50) under hepatocytic neoplasia in male mice on page 52-06497, vol. 29. The p-value of .028 reported on page 6 of the review report under hepatocytic neoplasia was computed from these four incidences, and hence was not adjusted for differences in survival. On the other hand, the p-values reported above are obtained from survival adjusted tests.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 24 1992
HFD-180

Mirza W. Ali, Ph.D.
Mathematical Statistician

Concur: Karl K. Lin, Ph.D., Group Leader, SARB 4/16/92

cc: Original NDA # 20-210
HFD-180/Dr. Fredd
HFD-180/Dr. Chopra
HFD-180/Dr. Choudary
HFD-710/Chron
HFD-715/Chron
HFD-715/Dr. Lin
HFD-715/Dr. Ali
HFD-502/Dr. Weissinger
HFD-715/DRU 2.1.1, Propulsid (Cisapride), Janssen Research Foundation
HFD-715/Diskette MALI-2/Propulsid.adn



M E M O R A N D U M

(REV)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: MAR 13 1992

FROM: I. Jerome Abramson, Ph.D. 3.13.92
Environmental Assessment Officer HFD-102

THRU: P. G. Vincent, Ph.D. 3.13.92

SUBJECT: Environmental Concerns-- NDA 20-210 Propulsid
(Cisapride) TABLETS Janssen Research Foundation

1C Stamp Date: 12-20-91

TO: K. Johnson/M. Adams HFD-180

The Center has reviewed carefully the environmental assessment (EA) for the subject NDA.

Please convey the following information to Janssen:

1. The information submitted in the application is inadequate and, therefore, it is deficient and not reviewable [21 CFR 25.22(b)].

2. Reference is made to 21 CFR 25.31a. Parts 1-6 were addressed adequately, however, parts 7-11 and 14 were either not addressed or were submitted inadequately to complete an EA review.

   Part 15 was not addressed; there were no test data, protocols, calculations, or estimations of substances expected to enter the environment.

Information submitted in part #7 was more appropriate for presentation in parts #5 and #15.

Parts #8-#11 were indicated to be "Reserved". This is inadequate, not comprehensive, and not acceptable to the EA Officer. No matter the circumstance, each part must be explained and adequate reasons provided as to the reasons why a firm indicates that parts of the EA report are not applicable.

3. The company labelled correctly part #15 as "Appendices". This section should have addressed data, experimental design, LC_{50}, sample calculations, however, this section contained location maps, syntheses, master batch records which were not appropriate in part #15.

On March 05, 1992, the EA Officer spoke by telephone to Maria Geigel, Director of Technical Regulatory Affairs [(908) 524-9483]. She was informed of the deficiences. She informed me that she was a recent hire by Janssen brought aboard to address the aforementioned inadequacies. The EA Officer informed Ms. Geigel that the EA should be approached with diligence and should be both complete and comprehensive according to 21 CFR 25.31a. She informed me that she would correct the inadequacies.